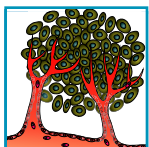


ION CHANNELS IN CANCER: ARE CANCER HALLMARKS ONCOCHANNELOPATHIES?

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Prevarskaya N, Skryma R, Shuba Y. Ion Channels in Cancer: Are Cancer Hallmarks Oncochannelopathies? *Physiol Rev* 98: 559–621, 2018. Published February 7, 2018; doi:10.1152/physrev.00044.2016.—Genomic instability is a primary cause and fundamental feature of human cancer. However, all cancer cell genotypes generally translate into several common pathophysiological features, often referred to as cancer hallmarks. Although nowadays the catalog of cancer hallmarks is quite broad, the most common and obvious of them are 1) uncontrolled proliferation, 2) resistance to programmed cell death (apoptosis), 3) tissue invasion and metastasis, and 4) sustained angiogenesis. Among the genes affected by cancer, those encoding ion channels are present. Membrane proteins responsible for signaling within cell and among cells, for coupling of extracellular events with intracellular responses, and for maintaining intracellular ionic homeostasis ion channels contribute to various extents to pathophysiological features of each cancer hallmark. Moreover, tight association of these hallmarks with ion channel dysfunction gives a good reason to classify them as special type of channelopathies, namely oncochannelopathies. Although the relation of cancer hallmarks to ion channel dysfunction differs from classical definition of channelopathies, as disease states causally linked with inherited mutations of ion channel genes that alter channel's biophysical properties, in a broader context of the disease state, to which pathogenesis ion channels essentially contribute, such classification seems absolutely appropriate. In this review the authors provide arguments to substantiate such point of view.

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I. INTRODUCTION

Various ion species are asymmetrically distributed between extracellular and intracellular milieu as well as among various lipid membrane-confined cellular compartments. Ion channels are integral membrane proteins that contain an aqueous pore through which, when it is open, certain ions can move freely between these compartments (208). Redistribution of ions among cellular compartments as a result of channels' opening can affect a plethora of cellular processes and functions ranging from electrical excitation to locomotion. Among these processes also are those that are crucial for maintaining normal tissue homeostasis, such as cell proliferation, migration, and apoptosis. Thus aberrant channels' expression and/or function can impair these processes driving the transformation of normal cells into malignant

derivatives that exhibit uncontrolled multiplication and spreading, which are hallmarks of cancer (201).

The first direct hints that ion channels may be important for carcinogenesis came in the late 1980s, early 1990s with observations that cancer cell lines display unusual patterns of ion channel functional expression and that pharmacological blockade of some channels can inhibit cancer cell growth (26, 285, 378, 379, 486, 543). These findings stimulated significant interest to the field, and since then intense research not only confirmed the role of ion channels in defining pathological features of major cancer hallmarks (411), but provided solid evidences that, in fact, these hallmarks can be viewed as pathological states largely caused by disturbed expression and/or function of certain ion channels. Such view is in line with the definition of channelopathy (see sect. IIB), although to emphasize specific relevance to cancer the use of the term *oncochannelopathy* would be more appropriate. This review provides the current state of knowledge on the role of ion channels in cancer in the context of oncochannelopathies. In fact, categorizing cancer as channelopathy (304) and ion channels that support malignant behaviors of tumor cells as “oncochannels” (229) has already been proposed; however, given the variety of cancer types and

pathophysiological features involved, such categorizing requires more precise elaboration.

Except for the introduction and conclusions, this review consists of five principal chapters (sects. II–VI). In the first of them (sect. II), we provide a concise description of ion channels' classification as well as their roles as determinants of channelopathies and propose a definition of the term *oncochannelopathy*. Next (sect. III), we demonstrate how ion channel deregulation in cancer impairs key cellular processes, calcium signaling, cell volume regulation, membrane potential regulation, mechanosensitivity, and microenvironment regulation and how this promotes malignant transformation as well as cancer hallmarks and eventually translates into oncochannelopathy. We also focus on oncogenic roles of ion channels, which are unrelated to their ion permeation functions (sect. IV). A separate section (sect. V) is dedicated to examining the examples of some channels' anticancer functions. And, finally, we evaluate how understanding of ion channels' contribution to carcinogenesis may help to advance cancer treatment (sect. VI). Although each cancer type as well as the type and manner of certain ion channels involvement in its hallmarks are quite specific, in the review along with the description of original data and key findings we attempted to make some generalizations as well as to point to some uncertainties or unresolved issues.

The field of ion channel involvement in cancer-related processes became so popular that PubMed search for articles whose title/abstract contains various variations of terms *cancer* and *ion channel* provides 5,944 hits (as of 12/12/2016), which with all the wish cannot be covered in one review. Therefore, in many instances the authors have been forced to cite the most recent special reviews and apologize if somebody's original work has not been mentioned.

II. ION CHANNELS IN HEALTH AND DISEASE

A. General Classification of Ion Channels

The studies of the 1950s and 1960s of electrical excitability and synaptic transmission (209, 255) provided the basis for initial classification of ion channels onto two broad classes, voltage-gated channels (VGC) and ligand-gated channels (LGC). Within the VGC class, different channel types were distinguished by ion species which they most selectively passed through (sodium, potassium, calcium, chloride), while within the LGC class according to the nature of signaling molecule (ligand), which activated them (e.g., acetylcholine, glutamate, GABA, glycine, serotonin) (208). As LGCs simultaneously acted as receptors of those signaling molecules, they were also often called respective receptors.

Widespread introduction into research practice of the revolutionary electrophysiological technique called “patch-

clamp” in the early 1980s enabled studying of ionic currents through single channels (198). This immediately revealed a high degree of channel functional inhomogeneity even within the channel types with common ion selectivity or ligand sensitivity, which prompted the introduction of additional levels of their classification. A good example of such classification is represented by voltage-gated calcium channels (VGCC), which based exclusively on functional studies using patch-clamp technique were subdivided into L, N, P/Q, R, and T type (72).

However, a real explosion in the number of ion channel types came with application of molecular biology techniques to the cloning of their genes. In fact, the cloning and followed up structure-functional studies revealed that ion channels are most often represented not by a single membrane protein, but by multiple proteins called subunits, which assemble together in the plasma membrane in a way to form transmembrane pore. So, in modern terms, when somebody talks about ion channels, in fact, most often only a channel subunit is meant. The era of ion channel cloning not only essentially broadened the nomenclature of traditional VGCs and LGCs, but also opened up the whole new classes of channels with principally different gating mechanisms. The latter now include physical (light, temperature, pressure, tonicity) and chemical (pH, Po_2 , pollutants, culinary spices) characteristics of the environment, as well as intracellular factors, such as level of ATP, status of organelles, presence of second messengers, etc. Essential information on the current status of ion channels classification and basic properties is presented in “The concise guide to pharmacology 2015/16” (5–7). To refer to the complete set of ion channels expressed in the whole organism, tissue, cell type, or pathological state, the term *channelome* was coined in analogy to the widely accepted “genome”, “proteome”, “metabolome”, while the branch of science aimed at characterization of the ion “channelome” is referred to as “channelomics”.

B. What Is Channelopathy?

With cloning of ion channel genes and application of genetic linkage analysis to several human congenital diseases, it became obvious that many of these diseases are causally linked to the mutations of ion channels genes. Such linkage was first established in the early 1990s between the inherited human disorders of skeletal muscle contraction, myotonia congenita, and hypercalemic periodic paralysis and mutations in gene encoding skeletal muscle voltage-gated sodium channel (VGSC) (414). At about the same time, the term *sodium channelopathy* was introduced to distinguish this type of disorders (522). Shortly after, it became clear that this term can be extended to the inherited heart rhythm disturbances, variety of inherited epilepsy syndromes, and rare painful neuropathies, as all of them resulted from respective VGSC gene mutations and consequent alterations

in biophysical properties of sodium channel (169). Nowadays, the catalog of channelopathies is no longer restricted to sodium ones, but encompasses almost all known channel genes and diseases of almost all organs and systems of the human body resulting from their dysfunction (254). Querying the PubMed database with specific article title word “channelopath*” yields 274 of review articles only (as of October 2016), covering the whole spectrum of channelopathies from such relatively rare inherited kidney defect as Bartter’s syndrome (prevalence 1/1,000,000) to such relatively frequent respiratory genetic disorder as cystic fibrosis (prevalence 1/3,000).

Furthermore, if classically channelopathies were considered to be exclusively linked with inherited mutations of ion channel genes that alter channel’s biophysical properties, then now this view is getting reevaluated towards inclusion of pathological states resulting from altered normal channel gene expression, autoimmune damage, aberrations in synthesis of ion channel protein(s), their posttranslational modifications, membrane trafficking of channel subunits, and/or in situ regulation of ion channel function (106). It is also becoming increasingly clear that because of multiple cellular compensatory and rescue mechanisms, disruption of a single channel type may not always produce definitive pathological phenotype, and often malfunction of similar channels or channels constituting functional unit (e.g., Ca^{2+} -selective and Ca^{2+} -dependent ones) may be required for such phenotype to occur.

G. Is Cancer a Channelopathy?

According to the definition by World Health Organization (WHO), “cancer is a generic term for a large group of diseases characterized by the rapid creation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjoining parts of the body and spread to other organs.” As such, cancer represents one of the major health problems to the humanity, currently responsible for ~8.2 million deaths each year (i.e., estimated 13% of all deaths worldwide), with an expected 70% increase in new cases over the next 2 decades (<http://www.who.int/cancer/en/>). Genomic instability is a primary cause and fundamental feature of human cancer. When genetic alterations ranging from spontaneous or environmentally induced mutations to chromosomal aberrations override the potential of cell’s repair mechanisms, normal cells transform into malignant derivatives with uncontrolled multiplication and spreading which can radically reshape tissue homeostasis.

Over 100 cancer types exist (<http://www.who.int/cancer/en/>), each of which is characterized by specific molecular markers, gene-expression profiles, patterns of genomic alteration and, consequently, requiring unique diagnosis and treatment. Despite such heterogeneity, though, all cancer cell genotypes generally translate into several common

pathophysiological features, often referred to as cancer hallmarks characterizing malignant transformation. Initially proposed by Hanahan and Weinberg (201) in their seminal review, these cancer hallmarks included the following: 1) self-sufficiency in growth signals, 2) insensitivity to growth suppressors, 3) resistance to programmed cell death (apoptosis), 4) replicative immortality, 5) sustained angiogenesis, and 6) tissue invasion and metastasis. Although recent progress in understanding cancer pathophysiology has widened cancer hallmarks catalog (202), and new additions to it are possible, those that were initially defined still represent the most intrinsic and obvious features of neoplastic growth. As any of these hallmarks represents an integral part of oncogenic transformation, in the opinion of the authors of this review, they can be regarded as separate oncopathologies.

No doubt that it is much more likely that the primary reason for cancer onset would be mutations in the oncogenes or tumor suppressor genes, which are directly involved with cell division or cell death, then in any other gene potentially affected by genomic instability. However, as cancer progresses, these other genes may contribute to the development of one or more cancer hallmarks and, thus, promote the transition to more aggressive cancer phenotype. And those genes must not necessarily be mutated, as it is sufficient that just normal functionality of their products would be impaired. Such impairment may result from adaptation- or epigenetically-evoked switches in gene expression as well as from irregularities in synthesis, posttranslational processing, or regulation of product proteins.

Among genes affected during oncogenic transformation it is inevitable that those encoding ion channels are present. For instance, microarray-assisted expression profiling of ion channel genes in breast cancer (265), lung adenocarcinoma (264), and glioma (514) has identified 30, 37, and 18 ion channel genes, respectively, to be differentially expressed as compared with normal tissues to contribute to various extents to pathophysiological features of each cancer hallmark (411). Since the late 1980s when the first indications on ion channels involvement in cancer-related processes have emerged, numerous evidences have been accumulated that this contribution becomes especially prominent to such cancer hallmarks as unrestricted proliferation, evasion of apoptosis, neovascularization, tissue invasion, and metastasizing (for recent reviews, see Refs. 27, 35, 48, 113, 152, 291, 447). Tight association of these hallmarks with ion channels dysfunction gives us a good reason to classify them as special type of channelopathies, namely, oncochannelopathies (FIGURE 1, A and B). Although the relation of cancer hallmarks to ion channels dysfunction differs from classical definition of channelopathies, as disease states causally linked with inherited mutations of ion channel genes that alter channel’s biophysical properties, in a broader context of the disease state, to which pathogenesis

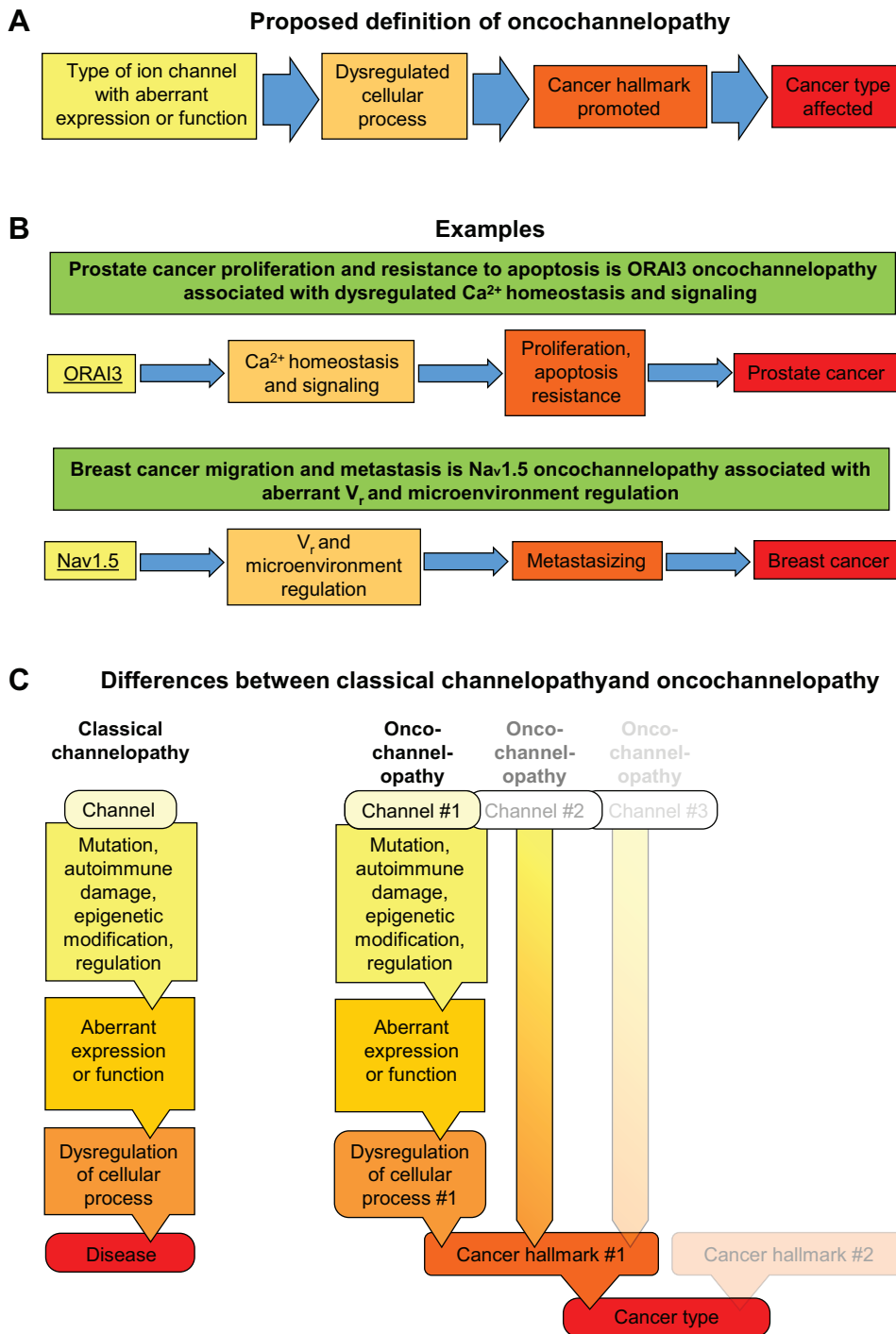


FIGURE 1. Proposed definition of oncochannelopathy. It is proposed that cancer hallmark for each particular cancer type is regarded as oncochannelopathy of specific channel(s), which aberrant expression/function contributes to this hallmark via dysregulation of certain cellular processes (A; i.e., Ca^{2+} signaling, volume regulation, membrane potential regulation, mechanosensitivity, microenvironment regulation, etc.). Examples of application of such definition to prostate and breast cancers are shown in B with the complete list presented in TABLE 1. C: depiction of the differences in definition of classical channelopathy and oncochannelopathy. The features that need to be mentioned to define channelopathy are depicted in round-corner boxes.

ion channels essentially contribute, such classification seems absolutely appropriate. Furthermore, cancer hallmarks do not appear all at once in each neoplasm, but rather develop gradually one after the other or in certain combinations, as oncogenesis progresses to more and more aggressive cancer phenotype. This gives another argument to treat them as separate pathological conditions dependent on ion channels dysfunction. Finally, classification of the above-mentioned cancer hallmarks as oncochannelopathies is further justified by the possibility to control their pathophysiological features through pharmacological or siRNA-

mediated influences on ion channels (14, 284), which provides new opportunities for cancer treatment. Regarding cancer hallmarks as oncochannelopathies departs from classical definition in one more essential aspect, namely, each cancer hallmark commonly depends on malfunction of not just one channel type, but of multiple channels, whereas classical channelopathies are traditionally viewed as one channel diseases (FIGURE 1C).

The suffix *pathy* is derived from Ancient Greek *πάθος* (páthos, “suffering”) and in modern connotations can be

used to reflect feelings (e.g., sympathy, antipathy), as well as damage, disease, or abnormality (e.g., neuropathy, psychopathy, sociopathy). Each of the cancer hallmarks is not a disease on its own, but a pathophysiological abnormality that contributes to the disease (i.e., cancer). Thus, if accepted, the meaning of the term *oncochannelopathy* in relation to cancer would have to be broadened to characterize not only the disease as a whole, as it takes place for traditional channelopathies, but also individual specific pathophysiological features of the disease (FIGURE 1C). Furthermore, even in classical channelopathies, the channel affected first disrupts certain cellular process (e.g., excitability, osmoregulation, plasticity), which only on the whole organism level translates into disease.

To be regarded as oncochannelopathy, the pathological involvement of ion channel(s) must be demonstrated not only in the *in vitro* experimental settings on certain cancer cell line(s), but also in the *in vivo* animal models and primary human cancer cells and tissues. The studies which lack such complex approach cannot be considered as providing sufficient evidence for claimed involvement.

III. ION CHANNEL-DEPENDENT CELLULAR FUNCTIONS CRUCIAL FOR MALIGNANT TRANSFORMATION

Opening of plasma membrane ion channels is tightly regulated by their intrinsic gating mechanisms, which in turn are controlled by the presence of specific endogenous or exogenous physical or chemical factors. When open, ion channels selectively pass through certain ion species down its electrochemical gradient which affects such basic cellular characteristics as 1) membrane potential due to generation of transmembrane ionic current, 2) cell volume due to coupled transmembrane movement of water to compensate for altered intracellular tonicity, and 3) the state of intracellular signaling pathways due to changes in ion-effector molecule(s) interaction(s). Depending on the total number of ion channels per cell and the density of their distribution on cell surface membrane, ion fluxes associated with their activation may produce global or local, spatially restricted changes in these characteristics.

Orderly changes in membrane potential, cell volume, and intracellular Ca^{2+} signaling not only accompany, but critically determine, normal progression of key to cells fate processes, such as proliferation, differentiation, apoptosis, and motility (240, 278, 455, 476). Any perturbations in these orderly changes resulting from ion channel(s) dysfunction would seriously impair cell proliferation, differentiation, apoptosis, and/or motility and promote the development of one or more oncochannelopathy in the form of certain cancer hallmark(s).

A. Ca^{2+} Signaling

Calcium is a universal signaling ion regulating a plethora of cellular processes and functions including those that determine whether the cell has to live, multiply, move, or die (31, 53). All Ca^{2+} signaling events take place in the cytosol, which to provide proper background for their occurrence must maintain very low basal level of Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$), normally around 10^{-7} M. Only under such conditions any small increases of $[\text{Ca}^{2+}]_i$ above that level in combination with the activity of high-affinity Ca^{2+} -sensing effectors (kinases, proteases, phosphatases, transcription factors, Ca^{2+} -binding proteins) would have signaling significance. But that is not enough. To be able to affect multiple processes, $[\text{Ca}^{2+}]_i$ increases must be encoded in space and time in such a way that their spatial and temporal characteristics would be unique for each process they regulate. To account for these requirements, three other compartments, extracellular space, endoplasmic reticulum (ER), and mitochondria, participate in Ca^{2+} signaling by serving the purpose for excess cytosolic Ca^{2+} removal as well as for needed Ca^{2+} supply. Circulation of Ca^{2+} between these compartments and cytosol determines cellular Ca^{2+} homeostasis and is supported by a molecular Ca^{2+} -handling toolkit consisting of active energy-dependent Ca^{2+} transporters, Ca^{2+} -permeable ion channels, Ca^{2+} -binding and storage proteins, and Ca^{2+} -dependent effectors. Coordinated in space and time, activation of these components, in fact, underlies creation of cytosolic Ca^{2+} signal with spatiotemporal pattern required for any specific purpose, often taking intricate forms of calcium oscillations, waves, sparks, spikes, flickers, etc. Deregulation of this toolkit leads to the disruption of normal Ca^{2+} homeostasis and Ca^{2+} signaling resulting in a number of pathological states including most of the cancer hallmarks (36, 53, 409). There are a number of excellent recent reviews showing how remodeling of Ca^{2+} homeostasis and Ca^{2+} signaling promotes malignant transformation (322, 343, 409, 413, 423, 466). Therefore, here we only focus on what changes in Ca^{2+} -permeable channels take place to turn normal Ca^{2+} homeostasis and signaling into oncogenic one.

1. Classes of Ca^{2+} -permeable ion channels

Ca^{2+} -permeable channels are passive structures in a sense that they pass Ca^{2+} only down its electrochemical gradient without consuming any energy, as active Ca^{2+} transporters, Ca^{2+} ATPases, and Na^+ - Ca^{2+} exchangers do. Therefore, when open (i.e., activated), these channels operate as Ca^{2+} suppliers to the cytoplasm from the places where its concentration is much higher, namely, extracellular space and intracellular ER Ca^{2+} store. Consistent with this, there are two classes of Ca^{2+} -permeable channels, plasma membrane (PM) and ER membrane ones.

PM Ca^{2+} -permeable channels in turn consist of seven major subclasses distinguished by the principal mechanism of

their activation: 1) VGCC (in unifying nomenclature designated as Ca_v) (74), 2) LGC (380), 3) store-operated channels (SOC) (408), 4) transient receptor potential (TRP) channels (504), 5) second messenger-operated channels (SMOC) (212), 6) acid-sensing ion channels (ASIC) (257), and 7) mechano-gated channels (416).

Ca_v channels are responsible for Ca^{2+} entry mostly in the excitable cells, such as neurons as well as neuron-like and various types of muscle cells. They open during membrane depolarization, and Ca^{2+} influx through them couples electrical excitation with activation of specific cell response(s). The appearance of Ca_v channels commonly manifests cancer cell differentiation towards electrically excitable phenotype (324), although they are also found in multiple cancers with no apparent excitability correlation (58, 515). Ca^{2+} -permeable LGC include the members of Cys-loop, glutamate, and purinergic P2X ionotropic receptor families (380). Their primary function is to mediate fast chemical synaptic transmission in the nervous system, while their Ca^{2+} permeability is important for regulating synaptic plasticity (380). Extracellular ATP-activated P2X channels are also distributed outside the nervous system, where they play a number of important functions (360), including oncogenic ones (426). Many of the TRP-channel family members, especially those that constitute the group of thermal receptors (often referred to as thermo-TRP, TRPA1, TRPM8, TRPV1–4), have their endogenous and exogenous chemical ligands as well (504), and in that respect can be also regarded as LGC.

SOC is a generic name for the channel underlying the major Ca^{2+} entry mechanism in nonexcitable cells, termed store-operated Ca^{2+} entry (SOCE) (408). This type of channel opens only when ER Ca^{2+} store becomes depleted thereby providing SOCE necessary for store refilling as well as for signaling purposes. There are many cell-specific SOC phenotypes, with the one having the highest Ca^{2+} selectivity, first described in the cells of immune system, known under the name calcium release-activated channel (CRAC) (217). From a molecular standpoint, SOC is represented by ORAI1 protein-based PM channel whose opening is regulated by ER membrane-localized stromal interaction molecule 1 (STIM1) or 2 (STIM2), serving as intraluminal Ca^{2+} sensors (52, 408, 457). ORAI1-based PM channels can be also constitutively activated in a store-independent manner via protein-protein interaction with Golgi apparatus secretory pathway Ca^{2+} -ATPase (SPCA2) (149).

Ca^{2+} -permeable members of the mammalian TRP-channel family are widely distributed in various tissues and cell types where they participate in the sensing of endogenous and exogenous stimuli of various modalities (temperature, osmolarity, membrane stretch, pH, second messengers, irritating chemicals, pollutants) (504). Members of canonical

TRPC subfamily as well as TRPV6 tend to partner with ORAI1 proteins via several interaction mechanisms to create diverse noncanonical SOCE phenotypes in different cell types (83, 420).

SMOC is a generic name for the channels mainly from TRP or ORAI families whose activation is regulated by second messengers derived in response to certain GPCR stimulation. In addition to TRPC3 and TRPC6 (212), classical examples of Ca^{2+} -selective SMOC are represented by arachidonate-regulated (ARC) (488) and leukotriene C_4 (LTC_4)-regulated (LRC) (563) channels whose structures are based on heteromultimeric assembly of ORAI1 and homologous to it ORAI3 subunits, and whose activation depends on GPCR-stimulated derivation of arachidonic acid (AA) and its metabolite, LTC_4 .

Mechanical stimulus, resulting from deformation of plasma membrane lipid bilayer, is an important factor modulating the activity of many channel types, especially those from TRP and ASIC families (416). However, recently a novel family of mammalian ion channels, termed PIEZO, has been discovered whose two members, PIEZO1 and PIEZO2 (also known as FAM38A and FAM38B), membrane stretch represents the primary activating stimulus (95, 214, 416, 511). These Ca^{2+} -permeable channels are differentially expressed in various mechanosensitive tissues and cell types, and their pathophysiological roles are only beginning to be understood.

Ca^{2+} -permeable channels of the ER membrane are less diverse and are classified according to the two major mechanisms of Ca^{2+} mobilization from the ER: 1) Ca^{2+} -induced Ca^{2+} release (CICR) and 2) agonist-induced GPCR-dependent release. CICR is mediated via ER membrane Ca^{2+} release channels, termed ryanodine receptors (RyR). RyR is a homotetramer for which three subunits, RyR1 (primarily skeletal muscle), RyR2 (primarily cardiac), and RyR3 (ubiquitous), encoded by homologous genes have been identified (500). Its major physiological ligand is intracellular Ca^{2+} per se (that is where the name CICR came from), but it also can be activated via protein-protein interaction with some members of Ca_v family, and by cytoplasmic messenger cyclic ADP-ribose (cADPR). Agonist-induced, GPCR-dependent Ca^{2+} release involves another type of ER Ca^{2+} release channels, called inositol trisphosphate (IP_3) receptors (IP_3R). IP_3R can be homo- or heterotetramer consisting of three subunits, $\text{IP}_3\text{R1}$, $\text{IP}_3\text{R2}$, $\text{IP}_3\text{R3}$, encoded by homologous genes. Its activation requires binding of the diffusible second messenger, IP_3 , which is derived from phospholipase C (PLC)-catalyzed breakdown of inositol phospholipids. As many of plasma membrane GPCR operate via PLC stimulation, IP_3R -mediated Ca^{2+} release represents the major component of agonist-controlled Ca^{2+} signaling.

In addition, Ca^{2+} liberation mechanism from endosomes and lysosomes relies on a novel class of endolysosomally localized nicotinic acid adenine dinucleotide phosphate (NAADP)-sensitive two-pore channels (TPCs) (393). Locally released Ca^{2+} from endolysosomes can be further coupled to the release from ER via CICR, thereby inducing global calcium signals.

2. Oncogenic alterations in Ca^{2+} signaling

As was already mentioned, Ca^{2+} regulates both the processes associated with cell's life cycle as well as those leading to its death. There is, however, a principal difference in Ca^{2+} signaling aimed to support these processes. It had been noted that intracellular Ca^{2+} signals regulating life-related processes, proliferation, differentiation, migration, or secretion are usually structured in space and time. They occur either as global cytosolic calcium oscillations, propagate through the cell in the form of Ca^{2+} waves, or appear as short-lived local events commonly called Ca^{2+} sparks, spikes, or flickers (387). In order for calcium signal to convey information, it must be efficiently decoded which typically involves effectors with multiple Ca^{2+} binding sites and frequency decoding properties, such as nuclear factor of activated T cells (NFAT), NF- κB , Ca^{2+} /calmodulin kinase II (CaMKII), mitogen-activated protein kinase (MAPK), and calpain (456, 494). It is likely that more effective linkage of remodeled Ca^{2+} signals to proliferation and migration of cancer cells may at least in part be explained by better correspondence of their frequency to the natural activation and/or turnaround frequencies of Ca^{2+} -dependent effectors.

In contrast to life processes, cell death pathway usually involves global, sustained $[\text{Ca}^{2+}]_i$ increases (Ca^{2+} overload) due to excessive calcium entry from extracellular space and release from ER store, commonly accompanied by the long-lasting decrease in the ER calcium content ($[\text{Ca}^{2+}]_{\text{ER}}$) and enhanced mitochondrial calcium uptake (372). Remodeling of normal Ca^{2+} signaling during oncogenic transformation may provide advantage to one or more of the above processes at the expense of others and shift the balance between life and death towards the developments of cancer hallmarks, and perturbations in Ca^{2+} -permeable channels play key roles in such deregulation. For instance, in cancer cells, as in most nonexcitable cell types, the major Ca^{2+} entry pathway is represented by SOCE. If for any reason SOC expression decreases, this immediately reduces the chances for global cytosolic Ca^{2+} overload and probability to undergo apoptosis, resulting in the development of apoptosis resistance (497, 499). However, a significant departure from this general paradigm is possible if spatial organization of SOC or any other type of Ca^{2+} -permeable channel is such that they become a part of signaling complexes with preferred access to Ca^{2+} -dependent effectors involved in the regulation of cell cycle or adhesion. In such a case, any increase in the channel expression and/or

activity may promote cell proliferation or motility up to the extent when their normal control will no longer be possible.

A) PROLIFERATION. Oncogenic, pro-proliferative channel functions can be well illustrated on the example of ORAI3 protein which is known to participate in ARC-channel formation (488). In prostate cancer cells ARC-mediated Ca^{2+} influx is involved in the AA-stimulated cell proliferation due to its preferred coupling with Ca^{2+} /calcineurin-dependent transcription factor, NFAT (**FIGURE 2**, blue color). However, ORAI3 overexpression, which takes place during prostate cancer transition to more aggressive phenotype, promotes the development of not just one, but simultaneously two cancer hallmarks, enhanced proliferation plus resistance to apoptosis (130). As studies have shown, this occurs due to preferred ORAI1-ORAI3 multiheteromerization over ORAI1 multihomomerization, and shifting the balance in prostate cancer cells Ca^{2+} entry pathways from ORAI1-based SOC to ORAI1/ORAI3-based ARC. Since downregulation of ORAI1-mediated SOCE represents the factor of apoptosis resistance (154), whereas ARC-mediated Ca^{2+} influx promotes proliferation, such ORAI3-dependent switch positions this channel-forming protein as an oncogenic one in prostate cancer (130). Thus two cancer hallmarks, unrestricted proliferation and evasion of apoptosis, can be viewed as ORAI3 oncochannelopathies in prostate cancer (**TABLE 1**).

ORAI3 involvement in the formation of Ca^{2+} entry pathways and its role in conferring cancer hallmark is cancer type specific. For instance, ORAI3 overexpression was documented in breast cancer cells, in which it was shown to be a part of noncanonical SOC (143, 144, 346) rather than any kind of SMOC. In breast cancer cells, increased ORAI3-dependent SOCE supported proliferation, apoptosis resistance, and migration in an estrogen receptor-dependent manner via the mechanisms involving phosphorylation of extracellular signal-regulated kinase (ERK1/2), focal adhesion kinase (FAK), as well as stimulation of NFAT transcriptional activity (346) (**FIGURE 2**, blue color). Correlation of ORAI3 expression with elevated noncanonical SOCE and enhanced proliferative activity was also described for non-small-cell lung adenocarcinoma, in which control of proliferation and cell cycle progression via ORAI3-dependent SOCE is realized via Akt phosphorylation pathway (18). These results suggest that despite possible differences in details and mechanisms, proliferation and apoptosis resistance can be classified as ORAI3 oncochannelopathies for the number of cancers (**TABLE 1**).

Switching to highly proliferative state requires remodeling of Ca^{2+} entry and Ca^{2+} release pathway to favor activation of the Ca^{2+} -dependent effectors and transcription factors promoting hypertrophic growth via induction of the expression of the G_1 and G_1/S phase transition cyclins (D and E) and associated cyclin-dependent kinases (CDK4 and

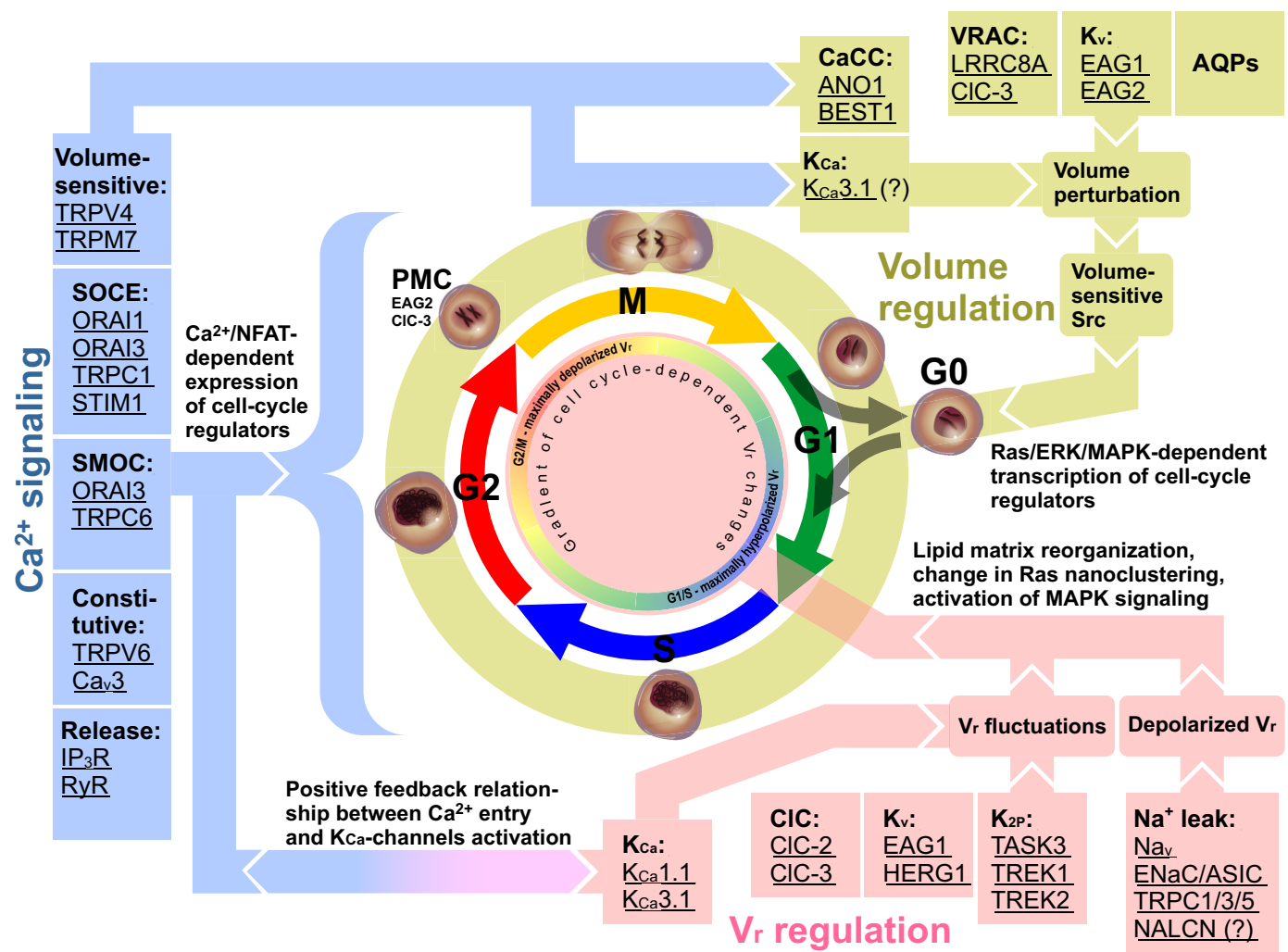


FIGURE 2. Contribution of ion channels to proliferation and cell cycle progression of cancer cells. The names of ion channels, which were shown to promote cell cycle progression and proliferation of different types of cancer cells via Ca²⁺ signaling (color coded in blue), resting membrane potential regulation (V_r, pink), and cell volume regulation (olive), are presented in rectangular boxes by underlined font with respective classes of ion channels specified in bold; question mark near channel's name indicates insufficient information. Arrows show the sequence of events with cellular processes affected presented in round-corner boxes and end results specified near the terminal arrows. The gradient of cell cycle-dependent V_r changes are color-coded in the middle of the diagram with blue corresponding to maximal hyperpolarization and red to maximal depolarization. PMC, premitotic condensation. See mentions of **FIGURE 2** in the text for details and explanations.

CDK2) (423). Several types of Ca²⁺ entry and Ca²⁺ release channels have been implicated in such remodeling in various cancer types (**FIGURE 2**, blue color). Among them are ORAI1 and STIM1 SOC components (78, 136, 218, 260, 308, 420, 558, 569); TRP members TRPV6 (44, 136, 289, 290, 420), TRPC1, TRPC3, TRPC4 and TRPC6 (15, 19, 85, 117–119, 247, 458, 460, 485, 487, 557), TRPM2 (556), TRPM6/7 (117, 190, 475, 554, 560); Ca_v family members (58, 381, 562); as well as IP₃R (436, 481) and RyR (3) ER release channels. Most of the relevant data, however, were obtained by comparing respective channels mRNA expression in normal and cancer tissues and assaying proliferative activity of related cancer cell lines in the in vitro setting in response to pharmacological or siRNA-mediated impairment of channels function and/or expression.

With no evidence for the in vivo tumor behaviors, channel(s) involvement in the proliferation may turn out to be circumstantial due to interaction with other, more critical components of the molecular Ca²⁺-handling toolkit, thereby preventing proliferation of certain cancer cells to be automatically declared as specific Ca²⁺-permeable channel oncochannelopathy.

So far, the bulk of evidence and availability of in vivo modeling allow to regard with high degree of confidence prostate cancer proliferation as TRPV6 oncochannelopathy (420) (**TABLE 1**). TRPV6 is highly Ca²⁺-selective channel predominantly expressed in the gastrointestinal tract, where it mediates transepithelial Ca²⁺ absorption (114). TRPV6 expression is also found in kidney, bone, pancreas,

Table 1. List of major oncochannelopathies

Ion Channel With Aberrant Expression or Function	Cellular Process(es) Dysregulated	Cancer Hallmark(s) Promoted	Cancer Type Affected	Reference Nos.
ANO1 (TMEM16A)	Volume regulation	Proliferation (?), migration, invasion, and metastasis	Prostate, HNSCC, lung	133, 245, 309, 433
AQP1	Volume regulation	Apoptosis resistance, TEC migration, and angiogenesis	RCC, melanoma, breast	139, 227, 357, 435
AQP8/9	Volume regulation	Apoptosis resistance	HCC	235
ASIC1	Microenvironment (pH) sensitivity	Migration and invasion	HCC	248
		Proliferation, migration	GBM	431
		Invasion and metastasis	Breast	193
ASIC2a/ASIC3	Microenvironment (pH) sensitivity	?	ACC	550
Ca _v 1.1/Ca _v 1.3	Ca ²⁺ signaling: CCE	Migration, invasion, and metastasis	Breast	237
CLC-3	Volume regulation	Migration and invasion	Glioma	101
IP ₃ R	Ca ²⁺ signaling: ER filling, ER-mitochondria crosstalk	Proliferation, survival	All types of cancer	69, 492
K _{2P} 2.1 (TREK1)	V _r regulation and driving force for Ca ²⁺ entry	Proliferation	Prostate	512, 561
K _{2P} 3.1 (TASK1)	Microenvironment (P _{O₂} , pH) sensitivity	Proliferation, apoptosis resistance	NSCLC	292
K _{2P} 9.1 (TASK3)	V _r regulation and driving force for Ca ²⁺ entry	Proliferation	Breast, lung, colorectal	259, 348, 391, 474
K _{Ca} 1.2 (BK)	V _r regulation and driving force for Ca ²⁺ entry	Migration	Breast	164
K _{Ca} 2.2 (SK2)	Volume regulation, V _r regulation, and Ca ²⁺ entry	Proliferation	Melanoma	483
K _{Ca} 2.3 (SK3)	V _r regulation and driving force for Ca ²⁺ entry	Migration and metastasis	Breast, colon	76, 189, 406
K _{Ca} 3.1 (IK)	Volume regulation	Migration and invasion	Glioma	107
	Volume regulation, V _r regulation, and Ca ²⁺ entry	Proliferation	Melanoma	483
	V _r regulation, Ca ²⁺ entry in TEC	TEC proliferation	Colon	183, 266
K _v 10.1 (EAG1)	V _r regulation, protein-protein interaction	Proliferation	Multiple cancers	177, 374
	V _r regulation and driving force for Ca ²⁺ entry	Migration and metastasis	Breast	199
	Protein-protein interaction	Angiogenesis via AF release by tumor cells	Cancer nonspecific	126
K _v 10.2 (EAG2)	Volume regulation	Proliferation, migration, and metastasis	Medulloblastoma	224, 225
K _v 11.1 (HERG)	V _r regulation, protein-protein interaction	Proliferation	Multiple cancers	282
	?	Invasion and metastasis	Colorectal	281
	V _r regulation and protein-protein interaction	Angiogenesis via AF release by tumor cells	Colorectal	97
Na _v 1.5	V _r regulation, microenvironment (pH) regulation, protein-protein interaction	Invasion and metastasis	Breast, colon, ovarian	54, 55, 166, 174, 220
Na _v 1.6	?	Invasion	Cervical cancer	207
Na _v 1.7	V _r regulation, Na ⁺ entry	Invasion	Breast, prostate, cervical, NSCLC	2, 64, 428
ORAI1	Ca ²⁺ signaling: SOCE	Migration and metastasis	Breast	76
ORAI1/TRPC1	Ca ²⁺ signaling: SOCE	Migration and metastasis	Colon	189
ORAI3	Ca ²⁺ signaling: SMOC	Proliferation, apoptosis resistance	Prostate	130

Continued

Table 1.—Continued

Ion Channel With Aberrant Expression or Function	Cellular Process(es) Dysregulated	Cancer Hallmark(s) Promoted	Cancer Type Affected	Reference Nos.
	Ca ²⁺ signaling: noncanonical SOC	Proliferation, apoptosis resistance, migration	Breast, SCLC	18, 143, 144, 346
PIEZO1	Ca ²⁺ signaling, mechanosensitivity	Migration	Breast	300
PIEZO2	Ca ²⁺ signaling and mechanosensitivity in TEC	Angiogenesis via TEC proliferation, migration, and tube formation	Glioma	546
TRPC4	Ca ²⁺ signaling in tumor cells: SMOC, CCE	Angiogenesis via AF release by tumor cells	RCC	503
TRPC6	Ca ²⁺ signaling: SMOC, CCE	Migration and invasion, angiogenesis	Glioblastoma	85
	Ca ²⁺ signaling: SMOC, noncanonical SOC	Proliferation, apoptosis resistance	HCC	136, 530
TRPM2	Ca ²⁺ signaling	Apoptosis resistance, prosurvival autophagy	Neuroblastoma	79
TRPM3	Ca ²⁺ signaling	Prosurvival autophagy	ccRCC	197
TRPM7	Ca ²⁺ signaling	Proliferation	Breast	191
	Ca ²⁺ signaling	Proliferation, migration, and invasion	Ovarian	517
	Protein-protein interaction, mechanotransduction	Migration and metastasis	Breast	191, 333
	[Mg ²⁺] _i homeostasis and signaling	Migration and invasion	Pancreatic	434, 552
TRPV2	Ca ²⁺ signaling: CCE	Migration	Breast	164
		Invasion and metastasis	Prostate	341
TRPV4	Ca ²⁺ signaling in TEC	Angiogenesis	Breast, RCC	153
	Ca ²⁺ signaling and mechanosensitivity in TEC	Angiogenesis	Multiple cancers	4, 489
TRPV6	Ca ²⁺ signaling: CCE	Proliferation	Prostate	289, 420
STIM1	Ca ²⁺ signaling: SOCE	Proliferation, migration, angiogenesis	Cervical	78
STIM1/ORAI1	Ca ²⁺ signaling: SOCE	Migration, invasion, and metastasis	Breast, melanoma, glioblastoma, ccRCC	260, 345, 473, 549
STIM1/ORAI1/TRPC1	Ca ²⁺ signaling in EPC: SOCE	Angiogenesis	RCC	314, 338
VRAC	Volume regulation	Proliferation	All types of cancer	211, 395
VRAC (LRRC8A/D)	Volume regulation, Pt drug uptake	Apoptosis resistance	All types of cancer, ovarian	211, 395, 405

Oncochannelopathies are presented in accordance with the definition proposed in **FIGURE 1** and are grouped by channel type. Channels are ordered alphabetically. Only channels whose involvement has been demonstrated in primary human cancer tissue, in clinicopathological studies, or in the in vivo animal cancer xenograft models are presented. Question marks indicate lack or insufficient information. ACC, adenoid cystic carcinoma; AF, angiogenic factors; CCE, constitutive Ca²⁺ entry; GBM, glioblastoma multiforme; EPC, endothelial progenitor cells; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; SCLC, small cell lung cancer; SMOC, second messenger-operated channel; TEC, tumor endothelial cells.

prostate, mammary, sweat, and salivary glands, with its levels becoming especially high in a number of common human carcinomas, prostate, breast, thyroid, colon, and ovarian (290, 570). The most attention, however, oncogenic potential of TRPV6 received in prostate cancer. According to the most recent data TRPV6 whose de novo expression correlates with prostate cancer Gleason score, translocates to the plasma membrane in an ORAI1/TRPC1-mediated, SOCE-dependent manner to contribute to Ca²⁺ entry pathway (420) specifically linked to NFAT activation (289) (**FIGURE 2**, blue color). This translocation involves

Ca²⁺/Annexin I/S100A11 signaling and represents part of Ca²⁺-handling toolkit remodeling to promote prostate cancer cells proliferation. Overexpression of TRPV6 in prostate cancer cells used for tumor explanting in nude mice increased tumor growth in vivo by specifically enhancing prostate cancer cells proliferation (420).

Indirect involvement of ORAI1/TRPC1-mediated SOCE in the pro-proliferative actions of TRPV6 potentially allows viewing prostate cancer proliferation also as ORAI1/TRPC1 oncochannelopathy; however, because of the sec-

ondary role of these channel-forming proteins, such view is rather questionable. On the contrary, proliferation of cervical cancer cells has more right to be regarded as SOCE, and more specifically as STIM1 oncochannelopathy (TABLE 1). Indeed, STIM1 was found overexpressed in 71% of early-stage cervical cancers, and its silencing inhibited cervical cancer cells SOCE and proliferation by cell-cycle arrest in S and G₂/M phases (FIGURE 2, blue color) via the mechanism involving increasing p21 protein and a decreasing Cdc25C protein levels (78). Furthermore, interference with STIM1 expression or SOCE blockade inhibited tumor growth in severe combined immunodeficiency (SCID) mice subcutaneously inoculated with cervical cancer cells (78).

Proliferation of lung cancer cells largely depends on TRPC subfamily members (247, 482). In non-small-cell lung carcinoma (NSCLC) cells, epidermal growth factor (EGF)-stimulated proliferation was found to be accompanied by Ca²⁺ signaling whose oscillatory component depended on Ca²⁺ entry similar to SOCE, but mediated by TRPC1 (FIGURE 2, blue color). Such signaling was necessary for G₀/G₁ transition, cyclins D1 and D3 expression, EGF receptor phosphorylation, and activation of PI3K/Akt and MAPK downstream pathways. EGF-induced Ca²⁺ signaling involving TRPC1 not only stimulated proliferation, but also facilitated EGF receptor activation in a positive-feedback manner, suggesting that TRPC1 plays a role in Ca²⁺-dependent amplification of EGF-stimulated cell proliferation (482). Nevertheless, lack of data from human tissues and in vivo animal modeling makes it premature to classify SCLC cell proliferation as TRPC1 oncochannelopathy.

In the primary human prostate cancer epithelial cells, proliferation in response to agonist-induced α 1-adrenergic receptor stimulation was shown to involve oscillatory Ca²⁺ signaling dependent on store-independent Ca²⁺ entry via TRPC6 channel (487). This channel acted as diacylglycerol (DAG)-activated SMOC, Ca²⁺ entry through which was selectively coupled to nuclear translocation of Ca²⁺/calcineurin-dependent NFAT (FIGURE 2, blue color).

B) EVASION OF APOPTOSIS. Apoptosis is an orderly physiological process of disposal of unwanted cells that completed their life cycle and are no longer necessary. It is imperative for maintaining normal tissue homeostasis by supporting the balance between formation of new cells and elimination of shabby old ones. Apoptosis can be initiated either by extrinsic or intrinsic mechanisms. In the first case it involves extracellular ligands (produced mainly by activated macrophages), acting on cell surface death receptors of the tumor necrosis factor (TNF) superfamily, whereas in the second case it is associated with intracellular stress response to multiple detrimental insults (181). Although irrespective of the initiation phase, all types of apoptosis eventually require recruitment of caspases, cysteine proteases executing a cell

death program, it is the intrinsic mechanism in which engagement of caspase cascade is Ca²⁺ dependent.

Ca²⁺-dependent mechanisms of apoptosis have been well defined and are illuminated in a plethora of excellent reviews (e.g., Refs. 131, 372, 404). Contingently they can be separated onto three closely related Ca²⁺-dependent pathways, mitochondrial, cytosolic, and ER-dependent, which in turn rely on function of numerous Ca²⁺-handling molecules, including Ca²⁺-permeable channels. Cytosolic Ca²⁺ overload resulting from massive Ca²⁺ entry and/or release represents a common starting point engaging one or more of these pathways. On the one hand, [Ca²⁺]_i overload promotes mitochondrial Ca²⁺ uptake, and excessive Ca²⁺ accumulation within the mitochondria induces mitochondrial permeability transition (MPT). This results in the releasing of mitochondrial apoptogenic factors, cytochrome *c* (Cyt-*c*) and apoptosis-inducing factor (AIF), into the cytoplasm which in turn activate death-executing caspase cascade (175, 498). The release of apoptogenic factors from mitochondria is regulated by pro- and anti-apoptotic members of Bcl-2 family of proteins (507). On the other hand, initial [Ca²⁺]_i overload may also directly activate crucial Ca²⁺-dependent pro-apoptotic effectors, such as calcium/calmodulin (CaM)-dependent phosphatase, calcineurin, which can promote apoptosis by regulating the activity of pro-apoptotic member of Bcl-2 family member, Bad (520) or NFAT transcription factor (419), DNA-degrading endonucleases (459), and Ca²⁺-activated cysteine proteases of calpain family (12, 283). Finally, sizable and continuous reduction of the ER Ca²⁺ content ([Ca²⁺]_{ER}) due to massive Ca²⁺ releases and/or compromised Ca²⁺ uptake may induce ER stress response and activation of caspase-12, which is associated with the ER and is specifically involved in apoptosis that results from ER stress (418).

Thus, to acquire resistance to apoptosis, cancer cells must remodel their Ca²⁺-handling toolkit in a way that would diminish the chances of cytosolic Ca²⁺ overload and enhance tolerance to the prolonged reductions of the ER intraluminal Ca²⁺ content (FIGURE 3, top left). In androgen-independent, apoptosis-resistant prostate cancer cell phenotypes, such remodeling was shown to involve downregulation of SOCE (497, 499) due to decreased expression of ORAI1 (154) or STIM1 (32) SOC components and adaptation of the ER to the conditions of reduced Ca²⁺ storage and uptake (FIGURE 3, top left). The latter was achieved by downregulated expression of ER luminal Ca²⁺-binding/storage protein, calreticulin, and ER membrane Ca²⁺ uptake pump, SERCA2b, along with enhanced expression of the ER-resident anti-apoptotic Bcl-2 protein that likely contributes to the increased Ca²⁺ leak from the ER (497, 499). Partial ER Ca²⁺ store depletion and associated apoptosis resistance was also described in human colon carcinoma cells versus normal human mucosa cells (458). However, in this case, the critical event in Ca²⁺ re-

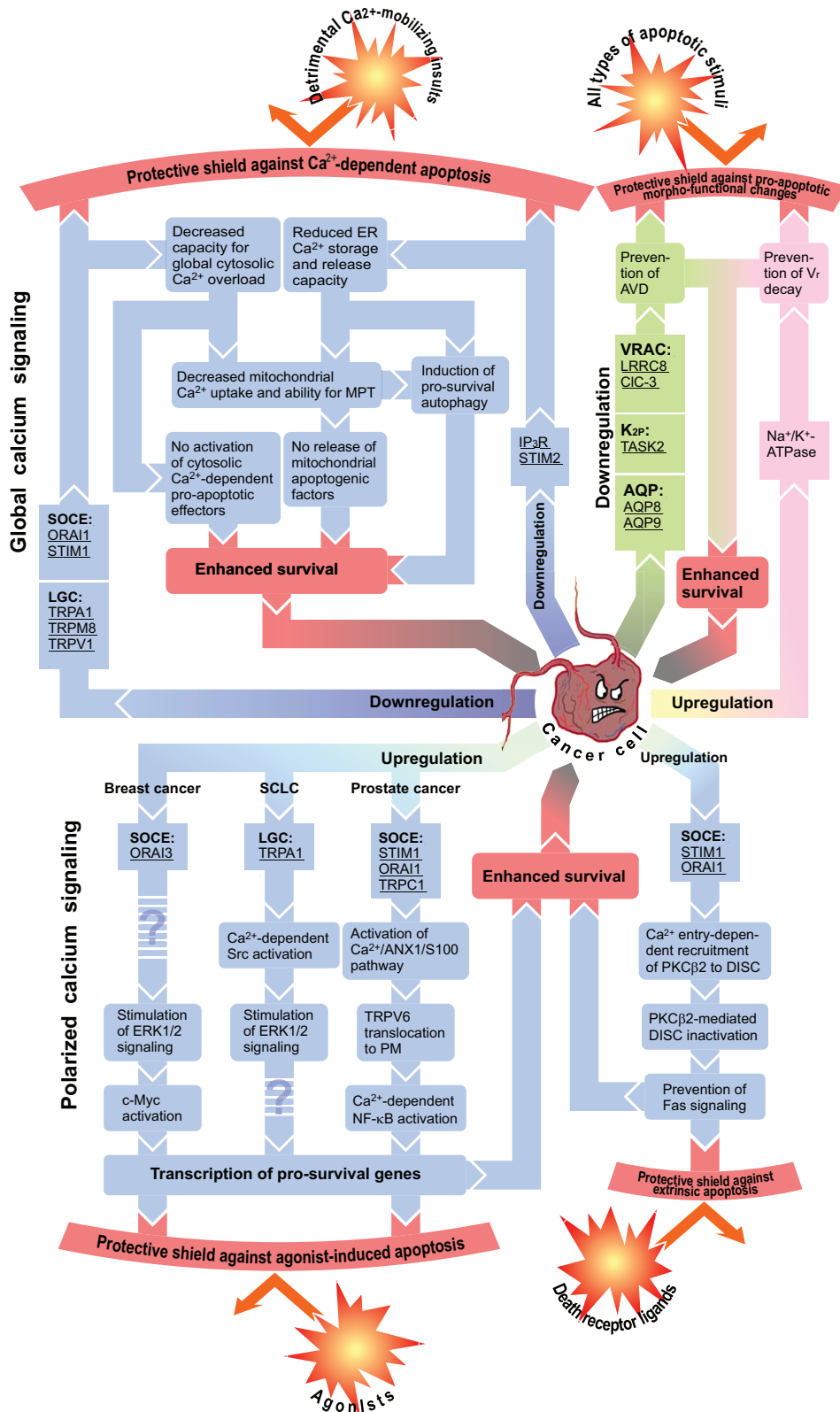


FIGURE 3. Events through which ion channels participate in conferring enhanced survival of cancer cells. The names of ion channels implicated in enhanced survival are presented in rectangular boxes by underlined font with respective classes of ion channels specified in bold. Arrows show the sequence of events with cellular processes affected presented in round-corner boxes. Dashed arrow with question mark indicates the presence of additional, not defined intermediary process. Events associated with Ca^{2+} signaling are presented in blue, with cell volume regulation in olive and with resting membrane potential (V_r) regulation in pink. AVD, apoptotic volume decrease; ER, endoplasmic reticulum; MPT, mitochondrial permeability transition; SCLC, small cell lung cancer. See mentions of **FIGURE 3** in the text for details and explanations.

modeling in colon cancer could be downregulation of the ER intraluminal Ca^{2+} sensor, STIM2, whose function is important for basal $[\text{Ca}^{2+}]_{\text{ER}}$ maintenance (52) (**FIGURE 3**, top left). Interestingly, along with pro-survival reduction of $[\text{Ca}^{2+}]_{\text{ER}}$, as a consequence of STIM2 underexpression, hu-

man colon carcinoma cells exhibited not decreased, but increased non-canonical SOCE mainly due to a reciprocal elevation in TRPC1 expression, which in turn contributed to enhanced proliferation (458). These data position STIM2 as important player in colon carcinogenesis, how-

ever, lack of human tissue studies and animal modeling do not provide sufficient grounds to call colon carcinoma cells evasion of apoptosis as STIM2 oncochannelopathy. Overexpression of certain Ca^{2+} -permeable channels by cancer cells may serve the purpose of reducing the significance of Ca^{2+} -dependent ER-stress response in initiation of apoptosis by providing alternative to SOC Ca^{2+} entry pathways to sustain ER store refilling.

Except global anti-apoptotic perturbations in Ca^{2+} homeostasis, Ca^{2+} -handling toolkit undergoes specific remodeling to favor interactions of Ca^{2+} with Ca^{2+} -dependent pro-survival effectors or signaling pathways. This remodeling, however, is rather cancer type-specific involving variety of molecular players (**FIGURE 3**, *bottom left*). As was already mentioned, breast cancer tissues and cell lines are characterized by elevated expression of ORAI3 protein, which contributes to non-canonical SOCE (143, 144, 346). Correspondingly, ORAI3-dependent Ca^{2+} influx was shown to enhance breast cancer cell viability through lowering the ratio of pro-apoptotic Bax to anti-apoptotic Bcl-2 proteins (143) most likely by controlling expression and activity of c-Myc transcription factor in a Ca^{2+} -dependent manner (144) (**FIGURE 3**, *bottom left*). The chemosensory TRPA1 ion channel, which is normally present mostly in sensory neurons, unexpectedly, was found to be functionally expressed in tumor samples of small cell lung cancer (SCLC) patients and SCLC cell lines (441). Ca^{2+} entry through this channel stimulated ERK1/2 via Src- and Ca^{2+} -dependent mechanism promoting SCLC cells survival and resistance to apoptosis in serum withdrawal assays (441) (**FIGURE 3**, *bottom left*). Plasma membrane translocation of the highly oncogenic TRPV6 channel, which is a part of prostate cancer cells Ca^{2+} -handling toolkit remodeling, was found by itself to be Ca^{2+} -dependent through ORAI1-TRPC1/Annexin I/S100A11 pathway (420). Consequent TRPV6-mediated Ca^{2+} entry promoted prostate cancer cells survival most likely by engaging NF- κ B transcription factor, which is indirectly regulated by calcium and which induces the expression of genes that are known to confer resistance to apoptosis (420) (**FIGURE 3**, *bottom left*).

Furthermore, extrinsic apoptotic signaling through the TNF death receptors family member, FasR (also known as CD95, APO-1), exhibits Ca^{2+} dependence as well (258, 538). In particular, polarized ORAI1/STIM1-mediated SOCE within CD95-colocalized microdomain was shown to be crucial for preventing formation of death-inducing signaling complex (DISC), and downstream transmission of the apoptotic signal in T-leukemic cell lines (258). ORAI1-mediated localized Ca^{2+} influx was necessary for recruiting the Ca^{2+} -dependent protein kinase C (PKC) β 2 to the DISC which holds the complex in an inactive status, preventing caspase activation (258) (**FIGURE 3**, *bottom right*). Thus, if in the global context activation of SOCE and ensuing elevation of $[\text{Ca}^{2+}]_i$ is a potent catalyst of cell death, than in

the event of its spatial restriction to death receptor signaling complexes it may have anti-apoptotic significance. Although this phenomenon was suggested to provide a lag phase in the early steps of the CD95 signal to prevent accidental cell death (258), its role in cancer deserves attention.

Given that MPT and the release of mitochondrial apoptogenic factors is quite sensitive to IP_3R -mediated Ca^{2+} mobilization due to privileged IP_3R to mitochondria communication in the ER-mitochondrial contact sites (68, 69, 480), downregulation of IP_3R expression and/or activation represents important measure that cancer cells can employ to increase their survival (**FIGURE 3**, *top left*). Indeed, such mechanism was implicated in apoptosis resistance of glioblastoma cells associated with increased protein kinase B (PKB) activity (479) and acquired cisplatin resistance of bladder cancer cells (492). In glioblastoma cells PKB-mediated IP_3R phosphorylation was shown to be responsible for inhibiting IP_3R function and concomitant reduction of Ca^{2+} flux from the ER to mitochondria (479), whereas in bladder cancer cells cisplatin-induced downregulation of $\text{IP}_3\text{R1}$ expression underlined the effect (492). In addition, IP_3R is the target for the ER resident anti-apoptotic Bcl-2 protein, which can directly interact with IP_3R to suppress its activation and prevent pro-apoptotic Ca^{2+} elevation (182, 430).

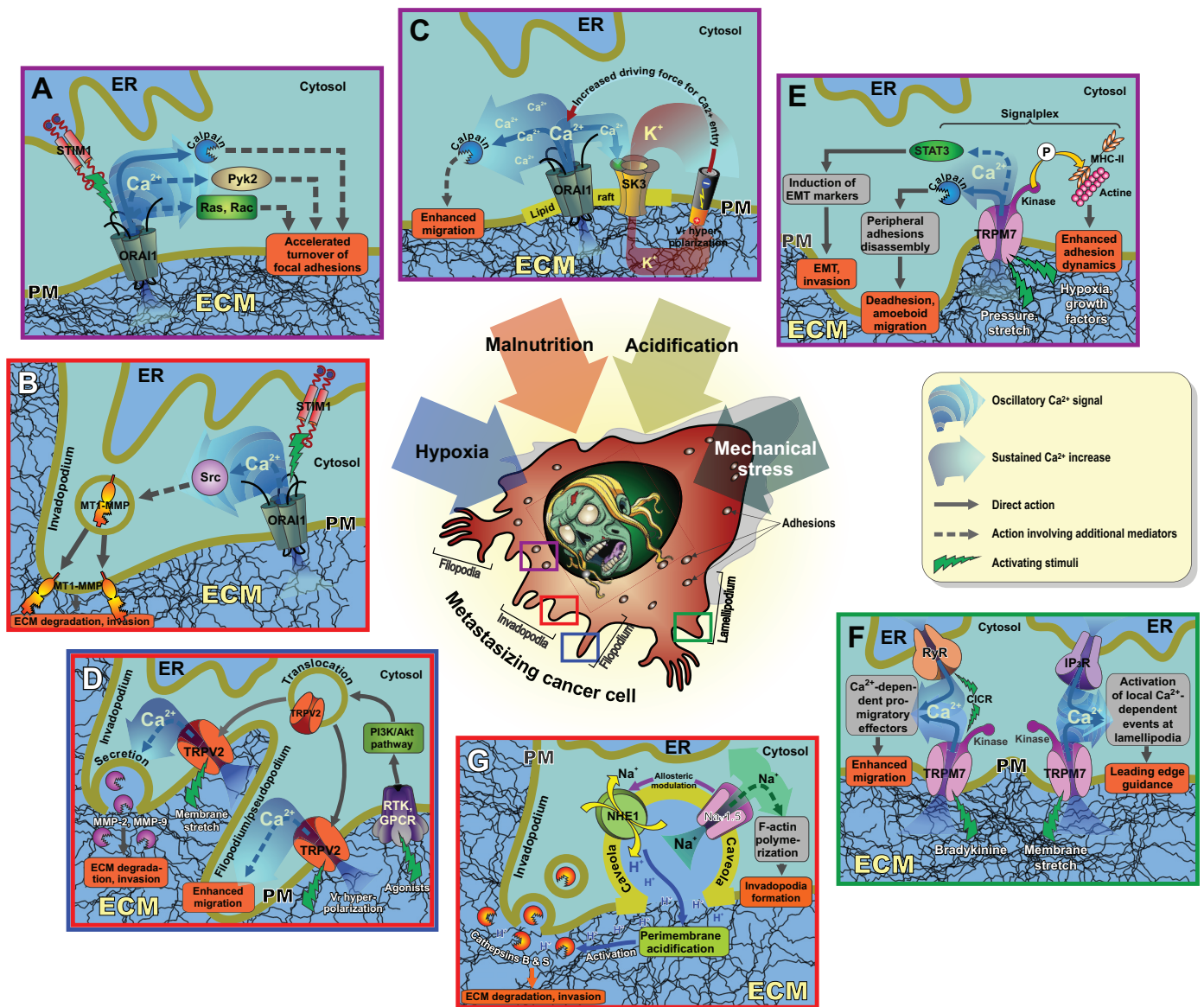
Furthermore, efficient mitochondrial respiration and maintenance of normal cell bioenergetics requires basal mitochondrial Ca^{2+} uptake supported by constitutive low-level IP_3R -mediated ER-mitochondria Ca^{2+} signaling, and lack of such signaling activates prosurvival autophagy (67, 68). Thus any impairment of IP_3R function and/or regulation in cancer cells may disrupt IP_3R -mediated ER-mitochondria crosstalk and activate autophagy as additional pro-survival mechanism (see also sect. III E 2A). Given the universal nature of IP_3R -dependent Ca^{2+} signaling mechanisms, the available data suggest that apoptosis resistance of all types of cancers can be regarded as IP_3R oncochannelopathy.

C) MIGRATION AND METASTASIS. It is not the primary tumor, but its invasion to the neighboring organs and dissemination through the circulation to the remote sites and tissues throughout the body in the form of metastasis which makes cancers so dangerous and deadly. Malignant cells become highly invasive by gaining two key properties: 1) the possibility for enhanced migration and 2) the ability to efficiently cleanse their way through extracellular matrix (ECM) by proteolytic degradation of its components. The first property is achieved through molecular machinery of migration enabling faster formation and disassembling (i.e., turnover) of physical linkages between cytoskeleton and ECM, called focal adhesions (FA), through which mechanical force and regulatory signals are transmitted (116). The second property results from upregulated synthesis and secretion of matrix metalloproteinases (MMPs), zinc-dependent endopep-

tidases that cleave various types of ECM proteins (57). Acquisition of both properties by cancer cells involves substantial remodeling of Ca^{2+} -handling toolkit (77, 412).

SOC components ORAI1 and STIM1 appeared to be among the most critical determinants of cancer cells migration and metastasis (FIGURE 4, A–C). This was first demonstrated for the human breast cancer cells serum-induced migration in vitro and explanted tumor metastasis in mice (549). In breast cancer cells, ORAI1/STIM1-dependent Ca^{2+} influx was necessary for enhanced assembly and disassembly (i.e., turnover) of focal adhesions via the mechanism involving activation of small GTPases, Ras and Rac

(549) (FIGURE 4A). EGF-stimulated migration and invasion of cervical cancer cells, which are characterized by elevated STIM1 expression, was shown to be associated with $[\text{Ca}^{2+}]_i$ oscillations that to occur required enhanced STIM1/ORAI1-mediated SOCE (78). The resultant Ca^{2+} signaling engaged Ca^{2+} -dependent protease calpain, as well as Ca^{2+} -regulated cytoplasmic protein tyrosine kinase, Pyk2, which regulate the focal-adhesion dynamics of migratory cervical cancer cells (78) (FIGURE 4A). The requirement of STIM1/ORAI1-dependent Ca^{2+} signaling was also demonstrated for glioblastoma multiforme invasion (345), melanoma invasion and metastasis (473), and clear cell renal cell carcinoma migration (ccRCC) (260), allowing metastasis



sizing in general to be regarded as STIM1/ORAI oncochannelopathy (**TABLE 1**). In melanoma cells, for instance, STIM1/ORAI1-mediated SOCE was necessary to support generation of $[Ca^{2+}]_i$ oscillations, which promoted invasive behaviors by orchestrating invadopodium assembly and ECM degradation (473). The data showed that oscillatory Ca^{2+} signaling facilitated invadopodial precursor assembly via Src activation and regulated proteolytic activity of individual invadopodia through recycling of ECM-degrading membrane type 1 matrix metalloproteinase (MT1-MMP, otherwise known as MMP-14), to the plasma membrane (473) (**FIGURE 4B**). Although constitutive increase of $[Ca^{2+}]_i$ was also able to enhance Src activation, in fact, such increase inhibited invadopodia formation and melanoma invasion, suggesting that Ca^{2+} signaling in the form of temporal Ca^{2+} oscillations with STIM1/ORAI1 involvement is specifically required for effective coordination of invasive behaviors and ECM degradation (473).

Pro-metastatic significance of SOCE can be facilitated by colocalization of its components with $K_{Ca2.3}$ (SK3) Ca^{2+} -activated K^+ channel in plasma membrane glycolipoprotein microdomains called lipid rafts (76, 189). In breast cancer cells, lipid rafts provided platform for the feedback interaction of $K_{Ca2.3}$ with ORAI1 (76) and in colon cancer cells with ORAI1/TRPC1 (189) to increase constitutive Ca^{2+} entry and cell migration via activation of Ca^{2+} -dependent protease calpain (76, 189) (**FIGURE 4C**). The data suggested that such complexes might only function within rafts and that removal of any of the partner channel suppresses the whole machinery. Intriguingly, no evidence was obtained on the involvement of ORAI1 partner STIM1 in breast cancer cells (76), but in colon cancer cells STIM1 activation by ER Ca^{2+} store depletion was required to facilitate ORAI1/TRPC1 recruitment into $K_{Ca2.3}$ -containing lipid rafts (189). Confirmation of channels' interaction in human breast cancer clinical samples and in metastasizing of transplanted tumor in animal model (76) indicates that breast cancer and likely colon cancer metastasis can be classified as $K_{Ca2.3}$ -ORAI1 oncochannelopathy (**TABLE 1**).

Migration and metastasis of cancer cells have been shown to depend also on Ca^{2+} influx through several Ca^{2+} -permeable TRP family members. Among them canonical TRPC1 (46, 105) and TRPC6 (85), Mg^{2+} - and stretch-regulated channel with kinase domain, TRPM7 (333, 517, 552), cold/menthol-sensitive TRPM8 (368, 536, 553), and heat-activated TRPV2 (164, 311, 340, 341, 375). However, a number of questions regarding the mechanism(s) of their involvement still remain unanswered.

TRPM7 has been shown to be abundantly expressed in a variety of human carcinoma cells, and because of its stretch-dependent mode of activation was proposed to be a part of a mechanosensory complex adopted by cancer cells to drive metastasis formation (for more details, see sect. IIID2).

TRPV2 was initially identified as a noxious heat ($>45^\circ\text{C}$) thermosensor, although subsequent studies revealed its much more complex pharmacological and physiological profile (400). TRPV2's most potent chemical agonist is cannabidiol, the dominant nonpsychoactive phytocannabinoid from cannabis extract, whereas endogenously its function is primarily regulated by translocation from the ER to PM in response to PI3K-activating ligands and mechanical stress (400) (**FIGURE 4D**). Androgen-resistant prostate cancer cells are characterized by de novo TRPV2 expression (341). Lysophospholipids by engaging PI3K signaling can induce TRPV2 translocation to the PM where constitutive channel activity maintains elevated $[Ca^{2+}]_i$ to promote prostate cancer cells invasive features (340, 341). The latter were manifested by both enhanced prostate cancer cell migration and expression of invasion markers MMP-2, MMP-9, and cathepsin B (341) (**FIGURE 4D**). Promotion of prostate cancer and urothelial cancer cells invasive phenotype by adrenomedullin (AM) was shown to depend on TRPV2 as well (375). AM is a 52-amino acid regulatory peptide expressed in a variety of malignant tissues. It acts as a mitogenic factor via specific surface receptors linked to PI3K signaling. It was shown that AM induces prostate cancer and urothelial cancer cell adhesion, migration, and invasion through FAK and integrin $\beta 1$ activation accompanied by TRPV2 translocation to plasma membrane and associated increase in resting $[Ca^{2+}]_i$ (375).

In a panel of human breast cancer cell lines (MCF7, MDA-MB-435s, MDA-MB-231), PI3K/AKT-mediated recruitment of TRPV2 in response to pro-migratory and pro-metastatic factors (in this case antimicrobial peptide LL-37 associated with malignancy in various cancers and acting in a cancer type-specific manner via multiple PM receptors of unrelated structures) was found to be specifically targeted to PM of pseudopodia (164), cytoplasm-filled projections involved in amoeboid-type motility of mesenchymal cells. Ca^{2+} entry through pseudopodia-localized TRPV2 induced $[Ca^{2+}]_i$ increase and cell migration. Owing to TRPV2 mechanosensitivity, local mechanical tensions occurring in pseudopodia could further enhance TRPV2 activation (164) (**FIGURE 4D**). Furthermore, the data suggested that within pseudopodia, TRPV2 may be colocalized with $K_{Ca1.1}$ (BK) Ca^{2+} -activated K^+ channel to provide a positive-feedback loop for Ca^{2+} entry (164).

Overall, confirmation of the in vitro studies in the in vivo animal experimentation and primary cancer tissues enable categorizing prostate cancer (341) and breast cancer (164) invasion and migration as TRPV2 oncochannelopathy (**TABLE 1**).

Formation of signaling complexes that include Ca^{2+} -permeable channel was also demonstrated to be important for promoting metastatic behaviors of glioma cells (105). In glioma cells, Ca^{2+} -permeable TRPC1 was shown to colo-

calize with CLIC-3 Cl^- -channels on caveolar lipid rafts (caveolin protein-rich, invagination-shaped lipid rafts), especially on the cells' processes (105). Gliomas are attracted in a chemotactic manner to EGF which induces TRPC1 accumulation in the leading edge, stimulates channel function, and enhances directional migration (46). It was concluded that by being colocalized with TRPC1 and exhibiting Ca^{2+} dependence of activation, CLIC-3 operates downstream TRPC1 to convert $[\text{Ca}^{2+}]_i$ elevations into shape and volume changes required for facilitated migration (105) (see also sect. IIIB2c).

Notch signaling is a conserved cell-cell communication mechanism involving physical interactions between the Notch surface receptors (known as Notch1–4 in mammals) and the membrane-bound ligands located on adjacent cells. In multiple tissues it links the fate of neighboring cells through transcriptional control of differentiation, proliferation, and apoptosis, but alterations in the Notch pathway can lead to tumorigenesis (361). It has been shown that in primary samples from human glioblastoma multiforme (GBM) and GBM-derived cell lines, hypoxia induces TRPC6 expression in a manner dependent on Notch1 signaling (85). Consequent increase in TRPC6-mediated Ca^{2+} entry and sustained $[\text{Ca}^{2+}]_i$ elevation promoted the development of the aggressive GBM phenotype featured by enhanced GBM cells migration in a Matrigel-based invasion assay under hypoxic conditions (85). GBM cells proliferation and proangiogenic potential were enhanced as well. Mechanistically, all oncogenic effects of TRPC6 in GBM cells under hypoxia were linked to the activation of the Ca^{2+} /calceinurin/NFAT pathway (85). Immunohistochemical detection of marked TRPC6 expression in human GBM specimens compared with its much lower expression in the corresponding brain regions of age-matched normal subjects (85) suggests that GBM migration and invasion may correspond to TRPC6 oncochannelopathy (TABLE 1).

Oncogenic potential of cold/menthol-sensitive TRPM8 channel in general and its role in cancer cells migration and invasion in particular is ambiguous and seems to depend on the cancer type (551). Promigratory effects of TRPM8 channel activation were documented in glioblastoma cells (536), squamous carcinoma cells (368), pancreatic adenocarcinoma (553), breast cancer cells (307), and osteosarcoma (564), whereas in prostate cancer cells TRPM8 displays anti-metastatic properties (187) (see also sect. V). In squamous carcinoma cells, menthol increased $[\text{Ca}^{2+}]_i$ due to both TRPM8-mediated Ca^{2+} entry and Ca^{2+} release, and this augmented cell motility and cell invasion via induction of MMP-9 (368). Overexpression of TRPM8 in breast cancer cells increased metastatic potential by promoting epithelial-mesenchymal transition (EMT) via activating AKT glycogen synthase kinase-3 β (GSK-3 β) pathway (307).

Just as this review was close to completion, an interesting link between localized increases in $[\text{Ca}^{2+}]_i$ at the tips of filopodia, the actin-rich finger-like frontal migratory protrusions, and activation of L-type VGCCs (i.e., Ca_v1), particularly of skeletal muscle-type $\text{Ca}_v1.1$ (gene symbol *CACNA1S*) and neuronal-type $\text{Ca}_v1.3$ (gene *CACNA1D*), was established in breast and pancreatic cancer cell lines (237). Targeting these channels with classical Ca^{2+} -channel antagonists, many of which are clinically approved for other applications, impairs filopodia formation and inhibits cancer cell invasion. The data suggested that integrin activation and integrin signaling through Src kinase stimulates L-type VGCCs to cause Ca^{2+} influx and $[\text{Ca}^{2+}]_i$ increase at filopodia tips. Higher $[\text{Ca}^{2+}]_i$ in turn activates μ -calpain (i.e., calpain-1) which contributes to the directional cell motility via filopodia stabilization and focal adhesion maturation (237). The expression of L-type VGCCs in cancer cell lines and clinical tissue samples as well as their engagement in motility and invasion appeared quite unexpected given that their activation requires membrane depolarization usually achievable only in electrically excitable tissues. In this regard it was proposed that activation of Ca_v1 in cancer cells is facilitated by their more depolarized resting membrane potential (V_r) compared with normal cells (more details on V_r in cancer cells, see sect. IIIC) (237). Although these results still require thorough verification in other systems, they suggest that at least breast cancer cells motility, invasion, and metastasis can be tentatively regarded as $\text{Ca}_v1.1/\text{Ca}_v1.3$ oncochannelopathy (TABLE 1).

D) ANGIOGENESIS. Both local endothelial cells (ECs) and endothelial progenitor cells (EPCs), recruited from bone marrow, have been implicated in the angiogenic switch, which is ultimately triggered by a plethora of growth factors released by cancer cells (70). The most important of these factors is vascular endothelial growth factor A (VEGF-A), which acts to activate ECs within and nearby the growing tumor as well as leads to EPC mobilization into the circulation. Thus Ca^{2+} -handling toolkit remodeling in tumors must provide for both enhanced release of proangiogenic growth factors by cancer cells and facilitated response of ECs to these factors.

VEGF expression and secretion is generally linked to activation of transcription factors of the hypoxia-inducible factors (HIF) family aimed to stimulate angiogenesis as part of adaptive response to compensate for insufficient oxygen supply characteristic of tumor microenvironment (for more details, see sect. IIIE). Various members of canonical TRP-channel subfamily (TRPC) were implicated in these processes (FIGURE 5, top left).

VEGF release by human breast cancer cells as well as the extent of angiogenesis in breast cancer tumor xenografts was shown to parallel the development of resistivity to chemotherapy (i.e., doxorubicin) (567). TRPC5 channel

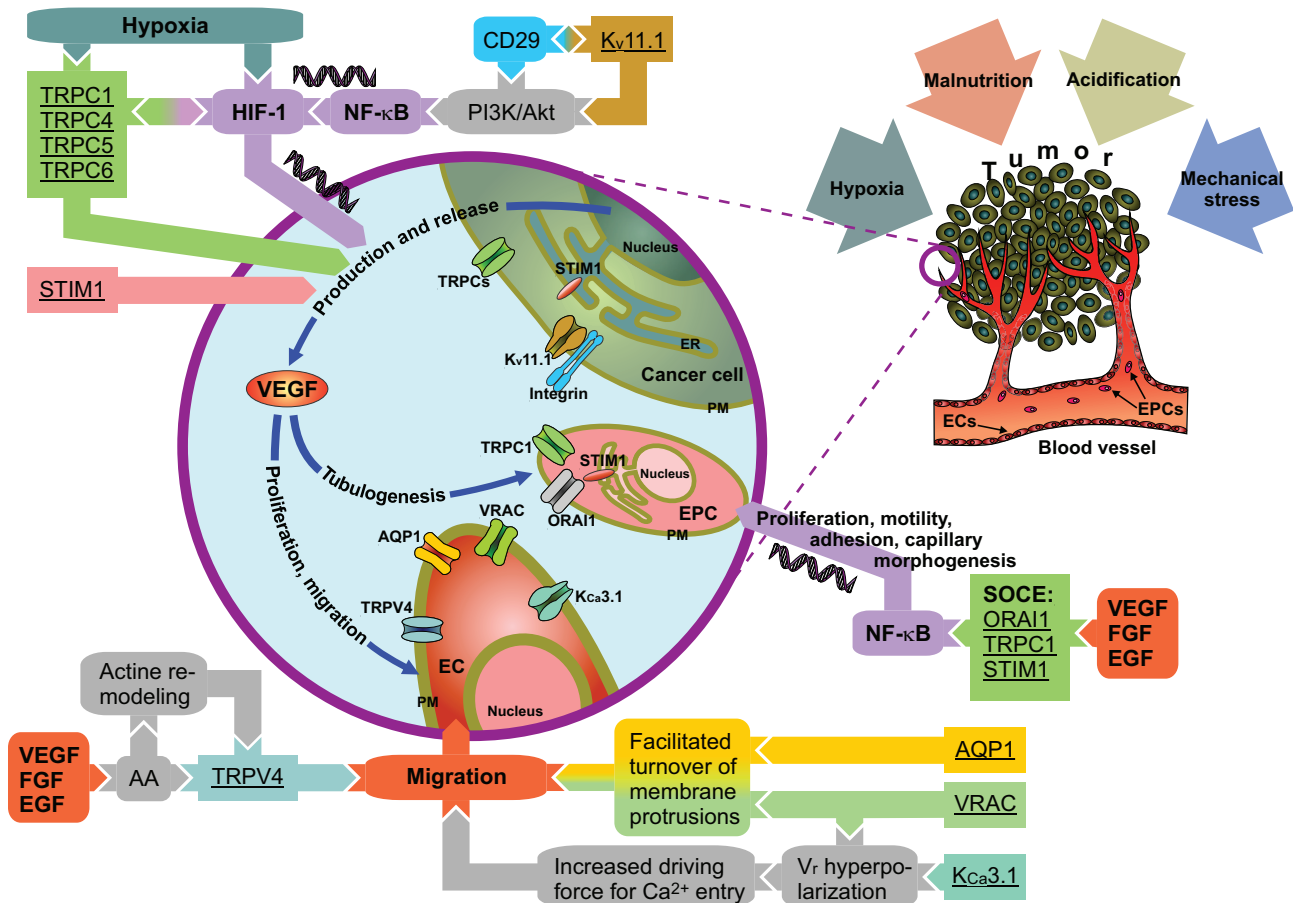


FIGURE 5. Ion channel dependence of tumor angiogenesis. *Right:* artistic depiction of tumor cells with their vascular arborization. *Left:* enhanced view of the encircled area that includes cancer cell, tumor endothelial cell (EC), and endothelial progenitor cell (EPC) along with their ion channels contributing to tumor angiogenesis. Diagrams around enhanced view show the modes of channels involvement in angiogenesis with arrows indicating the sequence of events and double-headed arrows indicating interaction or mutual regulation. In the diagrams, the names of ion channels are presented by underlined font in rectangular boxes of the same color as depicted channels. All other effectors, steps, and processes are specified in round-corner boxes of different colors. DNA symbols indicate transcriptional regulation. AA, arachidonic acid; ER, endoplasmic reticulum; PM, plasma membrane. See mentions of **FIGURE 5** in the text for details and explanations.

played an essential role in angiogenesis in breast cancer during chemotherapy by regulating VEGF release. TRPC5 activation induced downstream accumulation of HIF-1 α in the nucleus and VEGF transcription, which promoted tumor angiogenesis (567). Enhanced proangiogenic potential of human GBM under hypoxic conditions was linked to Notch1-dependent overexpression of TRPC6 channel (85) (for more details, see sect. IIIA2c). This was evidenced by the ability of culture medium harvested from hypoxic GBM cells to induce tube formation by ECs *in vitro* only when their TRPC6 expression was intact (85). However, the nature of proangiogenic factor released by GBM cells thanks to TRPC6 activity was not identified. Hypoxia-stimulated VEGF expression in U-87 MG malignant glioma cell line specifically required TRPC1 channel (516). Normoxic U-87 MG cells expressed several TRPC members, TRPC1/3/4/5, but transition to hypoxia along with the enhancement of VEGF on mRNA and protein levels downregulated all of

them, except TRPC1. Knock-down of TRPC1 prevented VEGF expression associated with hypoxia (516).

Angiogenic switch during renal cell carcinoma (RCC) progression was shown to involve not only inactivation of the von Hippel-Lindau (VHL) tumor suppressor, stabilization of HIF-1, and increase in VEGF (for more details, see sect. IIIA2b), but also diminished secretion of the angiogenesis inhibitor thrombospondin-1 (TSP1) (503). It appeared that loss of TSP1 is associated with profound decrease in the expression of Ca²⁺-permeable TRPC4 channel in RCC cells (503). The data indicated that absence of TRPC4-mediated Ca²⁺ influx in RCC leads to TSP1 misfolding and its retrograde transport to the ER, thus contributing to angiogenic switch during RCC progression.

Altogether, the above examples indicate that angiogenic switch in most of the malignancies prompting tumor cells to

begin enhanced production and release of VEGF is associated with remodeling of their Ca^{2+} -permeable channelome to favor the expression of various TRPC channels (**FIGURE 5**, *top left*). Apparently, expression of these channels and Ca^{2+} influx mediated by them are optimally linked to HIF-1 activation and VEGF secretion. A somewhat different picture, though, was described in cervical cancer whose several hallmarks, including secretion of proangiogenic VEGF-A, were shown to depend on upregulated expression of STIM1, the ER Ca^{2+} sensor that triggers SOCE (78) (**FIGURE 5**, *top left*). Subcutaneous injection of cervical cancer cells with variable STIM1 levels in SCID mice revealed direct correlation of tumor size, local spread, and angiogenesis with STIM1 content (78) (see also sect. IIIA2c). Production of VEGF-A by cervical cancer cells was proportional to STIM1 expression as well, implicating Ca^{2+} signaling involving STIM1 in cervical tumor angiogenesis via VEGF-A (78) and positioning cervical cancer angiogenesis as STIM1 oncochannelopathy (**TABLE 1**).

Literature survey indicates that Ca^{2+} -permeable channelome of ECs includes at least 14 members of TRP-channel family as well as all SOC components that are involved in a wide range of vascular functions, including tone, permeability, mechanosensing, remodeling, etc. (reviewed in Ref. 349). Tumor-derived ECs essentially differ from their normal counterparts in gene expression profiles and functional levels. However, of numerous TRPs, so far only TRPV4 has been implicated in the malignant angiogenesis.

Arachidonic acid (AA) is one of the second messengers mediating the action of proangiogenic growth factors, such as FGF and VEGF (151). AA-induced proliferation and organization of vessel-like structures in vitro by ECs obtained from human breast carcinomas were shown to involve Ca^{2+} entry via TRPV4 (151, 153) (**FIGURE 5**, *bottom left*). Furthermore, TRPV4 expression and Ca^{2+} influx in response to AA or selective TRPV4 agonist 4 α -phorbol 12,13-didecanoate (4 α PDD) were found significantly elevated in tumor-derived ECs as compared with normal ECs, and this correlated with higher tumor-derived ECs migration in wound-healing assays (153). In addition to possible activating effect of AA on TRPV4 channel (526), AA also increased TRPV4 surface expression by inducing remodeling of the actin cytoskeleton (153). AA and its metabolites participate in signaling pathways that lead to the activation of GTPases such as Rac and Rho, ultimately resulting in actin remodeling, whereas TRPV4, as polymodal sensor of a wide array of stimuli, including cell volume and mechanical stress, is known to interact with actin for its activation and membrane translocation (28, 29, 140, 533) (see also sect. IIIB1). Although no in vivo evidences were presented, the use of primary human breast and renal carcinomas-derived ECs (153) allows classifying angiogenesis of these types of tumors as TRPV4 oncochannelopathy (**TABLE 1**).

Quite intriguingly, recent study on tumor-derived ECs from a transgenic adenocarcinoma mouse prostate (TRAMP) model provided opposite results (4). This type of tumor-derived ECs exhibited not enhanced, but reduced TRPV4 expression and function compared with normal ECs, which resulted in their aberrant mechanosensitivity towards ECM stiffness, increased migration, and abnormal angiogenesis (4) (see also sects. IIID2 and V). Lack of TRPV4 correlated with overactivation of Rho/Rho-associated protein kinase (ROCK) pathway, known to link mechanical cues to cytoskeletal structures (489).

The reason for such discrepancy is not clear, but it may be in part explained by different tumor models used in the respective studies whose microenvironments may differentially affect TRPV4 expression in tumor-derived ECs, and/or by different types of ECs migratory behaviors TRPV4 channel was involved in (i.e., AA-stimulated vs. mechano- and ECM stiffness-dependent). At any rate, these results further highlight the specificity of each cancer and unique role of every channel in its hallmarks.

EPCs are generally recruited from the bone marrow to the sites of acute tissue injury to sustain vascular regeneration via neovascularization. However, homing and retention of EPCs within solid tumors can also support angiogenic switch, although this depends on tumor type, stage, and location. The growth and tubulogenesis of human EPCs is driven by VEGF-evoked intracellular Ca^{2+} oscillations involving SOCE, with downstream effector eventually being NF- κ B transcription factor (338) (**FIGURE 5**, *bottom right*). SOCE in EPCs is mediated by the interaction between the ER Ca^{2+} -sensor STIM1 and plasma membrane ORAI1 and TRPC1 channels (338). EPCs derived from peripheral blood of renal cellular carcinoma (RCC) patients (RCC-EPCs) are characterized by dramatic remodeling of their Ca^{2+} toolkit consisting in the reduction of $[\text{Ca}^{2+}]_{\text{ER}}$ and downregulation of IP₃R expression, along with the augmented expression of SOC constituents, STIM1, ORAI1 and TRPC1, and upregulated of SOCE (314, 338). The larger SOCE correlated with in vitro RCC-EPCs proliferation and tube formation in the medium enriched with the cocktail of growth factors as well as with higher abundance of circulating EPCs in RCC patients. Surprisingly, it was found that VEGF lost the ability of eliciting proangiogenic $[\text{Ca}^{2+}]_i$ oscillations and NF- κ B activation in RCC-EPCs. It was suggested that tumor EPCs express defective VEGF receptor, but the presence of other growth factors, such as bFGF and EGF, may sustain RCC-EPCs proliferation through SOCE activation (338). Altogether this prompted the conclusion that ORAI1 and TRPC1 may be more promising targets for anti-angiogenic treatments compared with just inhibition of VEGF signaling (338) and permits RCC angiogenesis to be classified as STIM1/ORAI1/TRPC1 oncochannelopathy (**TABLE 1**).

B. Cell Volume Regulation

During its lifespan, under normal physiological conditions, a cell constantly exchanges ions, nutrients, metabolites, and other solutes with extracellular milieu, resulting in perturbations of intracellular osmolarity. Such exchange becomes especially intense during progression of active physiological processes of cell division, differentiation, secretion, endocytosis, transcellular transport, and apoptosis (210, 395). Loss or gain of intracellular solutes during physiological activities is associated with osmotically obliged transmembrane flow of water via specialized plasma membrane pores called aquaporins (AQP) (234, 506), which necessarily promotes cell swelling or shrinkage. If they last too long or reach extreme values, the changes in cell volume can induce irreversible cell damage. Thus, to prevent massive influx/efflux of water and associated dramatic, potentially harmful changes in volume, a cell must develop regulatory mechanisms that counteract the net flow of water. Such mechanisms, termed regulatory volume decrease (RVD) and regulatory volume increase (RVI) (210), involve extrusion or uptake of the most abundant physiological ions, Na^+ , K^+ , and Cl^- , or nonessential organic osmolytes to balance gain or loss of essential solutes, thereby reducing or even preventing influx/efflux of water and limiting changes of cell volume in size and time.

Cell volume regulation in the form of RVD or RVI is also necessary to counteract volume perturbations associated with the shifts in extracellular osmolarity. Such shifts can take place under certain physiological conditions, such as intestinal epithelial cells are exposed to during water intake or kidney medullar cells are experiencing during antidiuresis, but most importantly they accompany a variety of pathological states. Among the latter are hypoxia/ischemia, diabetes-associated hyperglycemia, alkalosis, ketoacidosis and electrolyte disorders, hypernatremia, hyponatremia, hyperkalemia, and hypokalemia (301).

RVD and RVI are based on the activation of several types of ion channels and transporters linked to AQP-mediated efflux/influx of water. RVD is primarily dependent on the increase in the net efflux of Cl^- , K^+ , organic osmolytes, and water, whereas RVI involves the net gain of osmolytes and water via activation of Na^+ - K^+ - 2Cl^- cotransport, Na^+/H^+ exchange, and nonselective cation channels (210). In glioma cells, for instance, the latter is represented by amiloride-sensitive heteromeric channel composed of αENaC , γENaC , and ASIC1 subunits from closely related epithelial sodium channel (ENaC) and acid-sensitive ion channel (ASIC) families (432) (for more on ASIC channels, see sect. III E1).

1. Ion channels important for cell volume regulation

Although phenomenologically changes in cell volume produce changes in mechanical tension of plasma membrane,

ion channels involved in cell volume regulation are generally distinguished from those that can be activated by other forms of mechanical stimuli. To determine experimentally if a specific ion channel possesses cell volume-dependent mode of activation, a cell is usually exposed to the extracellular solution with altered tonicity, and functional response in the form of membrane current or fluorescence of ion-sensitive dye, associated with channel activation, is measured. On the contrary, activation of mechanosensitive ion channels, which will be discussed in more detail in section III D1, is commonly assessed by means of electrophysiology or fluorescence microscopy under isotonic conditions in response to mechanical stimuli applied to the plasma membrane in the form of hydraulic shock (i.e., sudden switch from static to moving extracellular solution and vice versa), local pressure (touch) to the cell surface by means of blunted glass microneedle, membrane stretch via cell-attached suction glass micropipette, and change in plasma membrane microcurvature using lipid bilayer-modifying agents (416). The presence of mechanical mode of channel activation does not warrant its sensitivity to cell volume and vice versa (e.g., Refs. 200, 321). This implies that the transduction mechanisms of volume changes to channel activation must be unique involving not only plasma membrane, but also other structures and/or messengers within the cell, including intracellular messengers, phosphorylation, cytoskeletal reorganization, Ca^{2+} -signaling, changes in macromolecular crowding, signaling via integrins, and receptor tyrosine kinases (RTKs).

One of the key channels displaying distinct volume-dependent mode of activation and playing pivotal role in RVD is the so-called volume-regulated anion channel (VRAC), also known as volume-sensitive outwardly rectifying (VSOR) anion channel or volume-sensitive organic osmolyte/anion channel (VSOAC) (211, 396, 397). VRAC is an anion channel which under physiological conditions is mostly permeable to Cl^- . It is widely distributed in essentially all vertebrate cell types in which Cl^- membrane current associated with its activation ($I_{\text{Cl,swell}}$) can be experimentally induced by hypotonic cell swelling. Although the classical way of VRAC activation remains hypotonic challenge, the current similar to $I_{\text{Cl,swell}}$ can be also activated under isotonic conditions by the reduction of intracellular ionic strength (510), by extracellular ATP via P2Y receptors (299, 521), by intracellular ROS generated in response to the variety of insults (305, 450, 501, 502), and by sphingolipids (59, 421). Since in mammals the osmolality of the extracellular fluid is maintained in a narrow range around 300 mosmol/l, and in vivo hypotonic conditions can be rarely achieved, these modes of VRAC activation are likely to be of major physiological and/or pathological importance.

The long and turbulent quest for VRAC molecular identity has recently culminated in identification of ubiquitously expressed, but poorly characterized, four putative trans-

membrane domain protein with multiple COOH-terminal leucine-rich repeats, LRRC8A (leucine-rich repeats-containing 8A, gene symbol *LRRC8A*), as the likely pore-forming subunit of VRAC (415, 513) (reviewed in Refs. 243, 396, 397). Since LRRC8A appeared to be a protein required for transmembrane anion flux in response to cell swelling, it was also named SWELL1 (415). The presence of LRRC8A in the cells was mandatory for activation of membrane current with all the signature properties of VRAC-mediated $I_{Cl,swell}$, including activation by low intracellular ionic strength (415). LRRC8 family of proteins, in addition to LRRC8A, includes four other homologs, LRRC8B-E (genes *LRRC8B-E*), distantly related to pannexins (1, 269). As long as LRRC8A was present, manipulations with LRRC8B-E expression levels affected $I_{Cl,swell}$ amplitude and inactivation kinetics up to its complete abolition in the cells with all four homologs knockout (513), suggesting that native VRAC may be a heteromer, in which LRRC8A represents obligatory subunit.

Of other types of Cl^- -permeable channels, the Ca^{2+} -activated ones (CaCCs) can contribute to RVD by taking advantage of the fact that cell volume perturbations are associated with changes in $[Ca^{2+}]_i$ (211, 250, 270). In terms of the abundance of false candidates, the history of search for CaCC molecular identity quite resembled that of VRAC. It eventually led to the identification of TMEM16A protein, the member of transmembrane 16 (TMEM16) family of proteins with no homology to any known channel, as representing CaCC molecular origin (66, 444, 545). Because TMEM16A is an eight transmembrane domains protein which displays an anionic channel permeation, it also received name anoctamin 1 (ANO1) reflecting these particular features (545). One more CaCC phenotype, considered to be most specific to human retinal pigment epithelium (RPE), is represented by bestrophin 1 (BEST1), a member of bestrophin family of integral membrane proteins encoded in human by four paralogous genes (*BEST1-4*, the name reflects “Best disease,” a juvenile form of macular degeneration associated with disease-causing *BEST1* mutations) (204, 270). Moreover, recently the evidences have been provided that BEST1 may be a crucial component of VRAC function in human RPE cells and in mouse sperm (335).

In addition to anion channels, a number of K^+ -selective ones have been shown to exhibit cell swelling-dependent mode of activation, thereby participating in RVD, although the mechanisms underlining the volume sensitivity of these channels are not always understood. In view of the fact that in most cell types hyposmotic cell swelling is consistently accompanied by the increase in cytosolic Ca^{2+} concentration (330), one of such mechanisms may be related to direct or indirect control of channel's activation by intracellular Ca^{2+} , whose increase may occur in a cell type-specific manner as a result of release or entry (389). There are three major subfamilies of Ca^{2+} -activated K^+ channels (K_{Ca})

classified based on their unitary conductance to big-conductance $K_{Ca}1.1$ (also called BK, Slo or MaxiK, gene *KCNMA1*), small-conductance $K_{Ca}2.1-3$ (SK1-3, gene *KCNN1-3*) and intermediate-conductance $K_{Ca}3.1$ (IK, gene *KCNN4*) (527). Basically all individual members of these subfamilies were implicated in swelling-induced, Ca^{2+} -dependent K^+ efflux and associated RVD in various cell types (150, 429, 519). Increased K^+ permeability due to activation of K_{Ca} channels would result in membrane hyperpolarization, thereby increasing the driving force for Ca^{2+} entry and further activating K_{Ca} channels in a positive-feedback manner to enhance RVD.

K^+ efflux participating in volume regulation in different cell types was also shown to involve a number of Ca^{2+} -independent channel types mostly from voltage-gated (K_v) and background, 2P-domain (K_{2P}) K^+ channel families. For instance, both genetic and pharmacological data implicated $K_v1.3$ (gene *KCNA3*) and $K_{2P}5.1$ (also known as TASK2, gene *KCNK5*) channels in the osmoregulation and RVD of T lymphocytes (43). $K_v1.3$ was shown to contribute to the increased K^+ efflux underlying the late phase of lymphocyte apoptosis and its lack or downregulation conferred resistance to apoptosis (reviewed in Ref. 478). The data suggested, though, that $K_v1.3$ is also targeted to mitochondria inner membrane where it may regulate programmed cell death through physical interaction with pro-apoptotic Bax protein (478). Voltage-gated $K_v1.5$ (gene *KCNA5*) and background TASK2 have been implicated in RVD by spermatozoa (94). Sensitivity to the variations in cell volume was also demonstrated for voltage-gated $K_v7.1$ channel (gene *KCNQ1*) (188, 276, 484). In *Xenopus* oocytes, expression system coupling of $K_v7.1$ to cell volume changes was shown to occur through interactions between the cytoskeleton and the NH_2 terminus of the channel protein (188), whereas in rat hepatocytes cytoskeletal rearrangement translated to channel activation through involvement of protein kinase C (PKC) (277). Compelling evidence point to the background TASK2 ($K_{2P}5.1$) channel as playing a prominent role in osmotic volume regulation in epithelial tissues with significant levels of its expression (24, 358). The primary stimulus for TASK2 activation is extra- and intracellular alkalinization, but the channel activity can be modulated by cell volume and inhibited by direct G protein $\beta\gamma$ -subunit interaction (88). The identity of cell volume sensor and its coupling to TASK2 activation during RVD remain elusive. Extracellular alkalinization secondary to the activation of Cl^-/HCO_3^- exchanger, altered G protein modulation or tyrosine kinase-dependent phosphorylation during cell volume changes have been proposed as possible mechanisms (88). Cell volume sensitivity was also demonstrated for $K_v10.2$ (EAG2, gene *KCNH5*) channel, which appeared to be involved in cell cycle-dependent regulation of cell volume dynamics during proliferation of medulloblastoma cells (224) and highly oncogenic $K_v10.1$ (EAG1, gene *KCNH1*) channel,

which was implicated in the enhancement of RVD and proliferation of colonic carcinoma cells (462).

Ion channels from TRP family are nonselective, and their activation under normal negative V_r would provide influx rather than efflux of cations. Thus involvement of these channels in swelling-induced RVD would be expected to occur via elevations of $[Ca^{2+}]_i$ with subsequent activation of downstream effectors rather than due channel's direct ion-transporting function. Of TRP members, vanilloid 4 (TRPV4) is one of the most implicated in cell volume regulation (29, 376). TRPV4 was identified as the mammalian ortholog of the *C. elegans* osmosensory channel protein, OSM-9, which led to its initial designations as vanilloid receptor-related osmotically activated channel (VR-OAC) or OSM9-like transient receptor potential channel, member 4 (OTRPC4) (303, 469), although subsequent studies revealed that this channel acts as multimodal integrator of a variety of stimuli including heat, fatty acid metabolites, endocannabinoids, hypotonicity, and mechanical stress (140, 533). In terms of how TRPV4 senses hypotonic challenge, at least three mechanisms have been suggested: 1) hypotonicity-dependent TRPV4 tyrosine phosphorylation by volume-sensitive tyrosine kinases of the Src family (93, 541), 2) functional interaction between TRPV4 and cytoskeletal F-actin (28), and 3) direct or indirect coupling to aquaporins (30, 249, 306). RVD responses to changes in osmolality and associated elevation of intracellular Ca^{2+} due to TRPV4 activation often involve consequent activation of K^+ efflux via K_{Ca} potassium channels (147, 150).

Aside of TRPV4, several other TRP members have been shown to exhibit cell volume dependence of activation and contribute to certain extent to the volume regulatory response. Among these channels are heat- and capsaicin-sensitive TRPV1 (448); heat- and cannabidiol-sensitive TRPV2 (351); TRPM3 (186); Ca^{2+} -, Mg^{2+} -, and divalent trace metal-permeable, serine/threonine α -kinase domain-containing TRPM7 (34, 362), TRPC6 (461), and TRPP2 (342).

Finally, indispensable for volume regulation are water-permeable channels AQPs which provide the pathway for selective transmembrane movement of water molecules, but are impermeable for ions and other solutes (233, 506). The AQP family of water channel-forming proteins in humans consists of 13 members (AQP0-12) of which AQP0-2, -4, -5, -6, and -8 are water selective, while others can also transport glycerol and some other solutes, which is why they were termed aquaglyceroporins (AQP3, -7, -9, -10) and supraaquaporins (AQP11, -12). Each AQP consists of six transmembrane α -helical domains with its own water pore, but in the cell membranes they assemble into homotetramers.

2. Ion channel-dependent impairment of cell volume regulation in cancer and its implication for cancer hallmarks

Three processes, proliferation, apoptosis, and migration, involve global or local alterations in cell volume. As all of these processes are strictly Ca^{2+} dependent, it would be difficult to delineate the role of Ca^{2+} -permeable channels in their dysregulation in cancer cells via specific impairment of cell volume from the participation of these channels in Ca^{2+} signaling. Therefore, in this section we will consider only Ca^{2+} -impermeable channels that exhibit volume-dependent mode of activation or are activated downstream of cytosolic Ca^{2+} rise.

A) PROLIFERATION. Proliferation is generally associated with increases in cell volume and can be inhibited by cell shrinkage (129, 210, 395). Such dependence is obvious even from general considerations, given that to produce two daughter cells of constant average size the size of mother cell first must double before it divides. Moreover, from the moment of cell division up to the time when cell is ready to divide again, its volume is gradually increasing (e.g., Ref. 11). In view of the fact that cell volume is controlled via coupled transmembrane fluxes of water and osmolytes, the expression and/or activities of ion channels participating in these processes must undergo cyclical changes, as cells progress through the division cycle. If highly cooperative fluxes of nutrients, ions, and water go out of balance this can modify the intracellular concentration of enzymes and cofactors involved in cell cycle progression and alter the rate of proliferation.

Proliferating cells maintain an ability to recover from osmotic swelling during progression through the whole cell cycle, although this ability and the capacity for RVD do not remain constant and are actively modulated at various phases. In mouse fibroblasts the lowest density of VRAC-mediated $I_{Cl,swell}$ and compromised ability for RVD were detected in the phases in which cells experienced the strongest volume perturbations, namely, the cells of the largest size approaching mitosis, the cells in the M-phase, and the new daughter cells formed just after cell division (125). Quite different cell cycle dependence of $I_{Cl,swell}$ and RVD was documented in nasopharyngeal carcinoma cells, in which both the magnitude of $I_{Cl,swell}$ and RVD capacity maintained at the highest level in G_1 phase, decreased in S phase, but increased again in M phase (82). Pharmacological inhibition of VRAC-mediated $I_{Cl,swell}$ caused nasopharyngeal carcinoma cells to arrest in G_0/G_1 phase (82). Suppression of the cell cycle progression following pharmacological VRAC blockade due to cell cycle arrest in the G_0/G_1 phase was also shown in other cell types, suggesting that this channel may be constitutively active in dividing cells and that its activity is particularly important for the G_1/S checkpoint progression (449, 535).

However, depending on cancer cell type, the dependence of cell volume regulation on cell cycle may vary. In Ehrlich Lettre ascites carcinoma (ELA) cells, for instance, the increase in intracellular Na^+ and Cl^- concentrations accompanied with enhanced water uptake and cell swelling were detected in S phase (263). Moreover, in glioma cells whose RVD was shown to largely rely on $I_{\text{Cl,swell}}$ activation (138, 417), a large rapid and regulated decrease in cell volume before M phase, termed premitotic condensation (PMC), was documented (196). The mechanism behind this process involved the outwardly directed movement of Cl^- via VRACs constitutively activated in M phase followed by water efflux similar to that employed during RVD (196). Activation of ClC-3 voltage-gated Cl^- channels (195) via Ca^{2+} -dependent mechanisms mediated by Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII) ClC-3 phosphorylation was also implicated in this process (100).

Overall, the available data suggest that VRAC is a critical determinant of volume regulation during cell cycle progression, and its blockade induces proliferation arrest. In cancer cells, VRAC-mediated $I_{\text{Cl,swell}}$ and capacity for RVD are strengthened. In this respect, proliferation of all types of cancer cells can be potentially regarded as VRAC oncochannelopathy. However, the involvement of VRAC in various phases of cell cycle may be cancer cell type specific, depending on the levels of its constitutive activation and/or sensitivity to the rate and magnitude of volume perturbations. Regulation of constitutive VRAC function under isotonic conditions during certain phases of the cell cycle may be supported by such factors as altered intracellular ionic strength, ROS, and ATP (396). In addition, VRAC activation is dependent on protein tyrosine phosphorylation (454) and Ca^{2+} entry via SOC (294) which also can contribute to the extent of its constitutive engagement.

The exact mechanisms of how changes in cell volume translate in the events controlling cell cycle progression in normal and cancer cells remain elusive. In this context, the role of cell volume-sensitive cytoplasmic protein tyrosine kinases of Src family (93) that regulate a number of signaling pathways involved in tumor cells behaviors, including proliferation via the Ras/ERK/MAPK pathway (261), can be suggested. ERK1/2 activation has been reported to take place in a large variety of cell types after hyposmotic cell swelling in a calcium-dependent and independent manner (61, 210, 442).

The evidences on ANO1- or BEST1-mediated CaCC involvement in dysregulated proliferation of cancer cells via specific impairment of cell volume regulation during cell cycle progression are extremely sparse, despite that these channels were implicated in a number of cancer hallmarks (TABLE 1), including proliferation, and ANO1 gene amplification has been reported in several malignancies (133, 211, 245, 270, 309). The same is true about K^+ channels

that display cell volume-dependent mode of activation (see sect. IIIB1). It has been shown, though, that in head and neck squamous cell carcinoma (HNSCC) ANO1 knockdown induces an accumulation of cells in G_0/G_1 and a concomitant decrease in the S/G_2 phase (133) and that ANO1 regulates proliferation of human pancreatic cancer-derived cell line, CFPAC-1, at the G_1/S transition of the cell cycle (463). It was also demonstrated that colonic carcinoma cells, which due to spontaneous transformation acquire fast growing phenotype, exhibit stronger cell swelling and more potent RVD compared with slow growing ones (462). This was associated with overexpression of EAG1 ($\text{K}_{\text{v}10.1}$) K^+ and BEST1 Cl^- channels, which prompted the conclusion that both channels participate in the volume control during the mitotic cell cycle (462). Moreover, the presence of EAG1 and BEST1 in fast-growing phenotype of colonic carcinoma cells enhanced their intracellular Ca^{2+} signaling (462). As both intracellular Ca^{2+} and cell volume control are essential for the mitotic cell cycle, these results provided a mechanism for the proliferative role of EAG1 and BEST1 (462).

Another example for the role of K^+ channels in proliferation through volume control was described in medulloblastoma (MB), the most common type of pediatric malignant primary brain tumor. In MB cells, a close relative of EAG1, EAG2 ($\text{K}_{\text{v}10.2}$), was found to exhibit high plasma membrane localization in late G_2 phase and during the course of mitosis, leading to substantial increase in EAG2-mediated noninactivating outward K^+ current in dividing versus quiescent cells. EAG2 knockdown resulted in striking increase of MB cells volume and cell cycle arrest in late G_2 phase and prevented premitotic condensation, indicating that EAG2 promotes MB cells proliferation specifically via regulating cell volume dynamics (224, 225). Interestingly, in its such action EAG2 was recently found to cooperate with $\text{K}_{\text{Ca}4.2}$ (gene symbol *KCNT2*, alternative names Slick, Slo2) K^+ channel (225), which structurally belongs to Ca^{2+} -activated K^+ channel family, but is activated by intracellular Na^+ and Cl^- , rather than Ca^{2+} , and is inhibited by ATP (527). The fact that EAG2 knockdown or pharmacological blockade not only impaired MB cell growth in vitro, but also reduced tumor burden in vivo and enhanced survival in xenograft studies (224, 225), provides sufficient grounds to classify MB cells proliferation as EAG2 oncochannelopathy (TABLE 1).

Aquaporins play prominent roles in defining some of cancer hallmarks, especially enhanced migration and angiogenesis (382). However, despite cell volume perturbations during cell cycle progression inevitably evoke transmembrane water fluxes, the AQP's involvement in cancer cells proliferation goes beyond their water-transporting function, and novel, water transport-unrelated mechanisms are possible. For instance, it was shown that pro-proliferative function of AQP5 in colon cancer and lung cancer is realized through

its interaction with the ERK1/2 signaling (253, 559) and of AQP3 in skin tumors via facilitated glycerol transport required for cellular energetics and lipid synthesis (203).

B) APOPTOSIS RESISTANCE A major hallmark of apoptosis is normotonic shrinkage of cells, called apoptotic volume decrease (AVD), which starts before cell fragmentation and is believed to be necessary to facilitate cell dismantling into apoptotic bodies and to counteract cell swelling and lysis that may occur otherwise (for review, see Ref. 339). In the cells exhibiting AVD, facilitation of RVD is always observed, suggesting that AVD is caused by normotonic activation of K^+ and Cl^- channels that are normally involved in RVD under hypotonic conditions (318, 339, 366, 367). Moreover, the apoptotic cell death can be rescued by preventing AVD. Thus, to escape from apoptosis, cancer cells inhibit shrinkage by preventing loss of K^+ and Cl^- or by increasing ion uptake through Na^+/H^+ exchange (NHE1) and $Na^+/2Cl^-/K^+$ cotransporter (NKCC1) (271, 279). Indeed, exposure of apoptosis-resistant strain of Ehrlich ascites tumor cells (EATC) to anticancer drug cisplatin was shown to induce less pronounced multistep AVD process and decreased caspase 3 activation compared with the wild type, drug-sensitive strain (407). EATC were also characterized by smaller VRAC-mediated $I_{Cl,swell}$ compared with the wild-type cells, and the differences in cisplatin-induced apoptotic events between the two strains could be abolished by the high-affinity VRAC (and CaCC) inhibitor NS3728 (407). Furthermore, inhibition of TASK2 K^+ channel in EATC by clofilium also suppressed AVD and caspase activation in a manner similar to NS3728, suggesting that apoptosis resistance could be circumvented by maneuvers leading to the enhancement of either VRAC-mediated chloride or TASK2-mediated potassium permeability (407).

In fact, the significance of VRAC in conferring AVD and sensitivity to apoptosis of cancer cells was most documented on the example of anticancer, platinum-based chemotherapeutics cisplatin, which induces apoptosis via DNA damage. In a number of cancer cell types, cisplatin-induced apoptosis, AVD, and caspase-3 activity correlated with the magnitude of VRAC-mediated $I_{Cl,swell}$ and vice versa, the cells in which this current was small or absent showed high resistance to cisplatin (233, 287, 337). Thus VRACs not only regulate cell volume, but may influence anti-cancer drug responsiveness of tumors. Identification of LRRC8 proteins as essential VRAC components (415, 513) led to the realization that its significance in regulating tumor cell responsiveness to platinum-based chemotherapeutics may be more complex than initially anticipated. It was established that LRRC8A/LRRC8D-containing VRACs play dual role in tumor drug sensitivity by being necessary not only for AVD and progression of apoptosis, but also for mediating cisplatin/carboplatin uptake, in which the presence of specifically LRRC8D subunit appeared critical for conferring the highest VRAC's permeability to platinum-

based drugs (405). Analysis of ovarian cancer patients survival with a low tumor expression of *LRRC8A* or *LRRC8D* versus the remaining patients have shown that *LRRC8A* expression had no influence on survival, whereas patients with a low *LRRC8D* gene expression displayed a significantly reduced survival (405). These findings significantly heighten the importance of VRAC (or more correctly its absence) as a determinant of cancer cell resistance to apoptosis allowing to regard it as LRRC8A/LRRC8D onco-channelopathy (**TABLE 1**).

In conflict with this general paradigm, however, were the findings in prostate cancer cells whose apoptosis resistance was associated with overexpression of antiapoptotic Bcl-2 oncoprotein. In these cells VRAC-mediated $I_{Cl,swell}$ and capacity for RVD were found not down-, but upregulated (295). Similar effects of Bcl-2-conferred apoptosis resistance on RVD and VRAC function were detected in other cell types, including human cervical cancer cell lines (451). It was concluded from these studies that Bcl-2-induced upregulation of $I_{Cl,swell}$ would strengthen the ability of the cells to handle proliferative volume perturbations and promote their survival through the advantage on growth, metabolism, and a better ability to handle stress. The involvement of specific interactions (direct or indirect) of Bcl-2 and VRAC in such pro-survival effects were ruled out, as similar augmentation of VRAC-mediated $I_{Cl,swell}$ and RVD strengthening was also observed in neuroendocrine differentiated prostate cancer cells whose apoptosis resistance is not associated with Bcl-2 overexpression (293). Thus it is possible that VRAC may play divergent roles in cancer cell evasion of apoptosis. On the one hand, decrease in normotonic VRAC activity is required to hamper AVD and progression to apoptosis, but, on the other hand, upregulation of VRAC would contribute to the tighter control of volume constancy under various stress conditions to improve overall survival rates. It cannot be excluded that the described pro-survival effects may be specifically associated with ClC-3 Cl^- channel. This channel exhibits cell volume-dependent mode of activation, which made it one of the molecular candidates for VRAC (211, 396, 397), and its expression and function in apoptosis-resistant prostate cancer cell phenotypes paralleled the size of $I_{Cl,swell}$ (293, 295). In this respect, it would be interesting to verify the involvement in these effects of the newly identified VRAC components from LRRC8 family. Since VRAC function can be inhibited by SOCE (294), another factor that may contribute to higher VRAC-mediated $I_{Cl,swell}$ and RVD in apoptosis-resistant cancer cell phenotypes is the reduction of this inhibition (293, 295) due to the fact that in such cell phenotypes SOCE becomes downregulated (154, 410, 497, 499).

Activation of pro-apoptotic enzymes requires AVD supported by rapid, AQP-mediated water efflux. Thus, to confer apoptosis resistance, cancer cells must elaborate mech-

anism(s) reducing such efflux. Consistent with this, expression of AQP8 and AQP9 was found significantly decreased in animal (rat) model of hepatocellular carcinoma (HCC) versus normal liver (235). An inherent resistance of hepatic tumor cells to apoptotic stimuli [transforming growth factor (TGF)- β or serum withdrawal] was associated with compromised transmembrane water movement in response to hyposmotic challenge, in contrast to normal hepatocytes, which readily responded to such challenge by AQP-dependent water movement and underwent cell death following apoptotic stimulation (235). Positive correlation between high AQP1 expression and better outcome was established for primary renal cell carcinomas (RCC), with RCC patients showing high AQP1 levels presenting significantly better survival rates than those with low expression (227). Overall, these results allow to classify apoptosis resistance of at least HCC and RCC as AQP oncochannelopathy (**TABLE 1**). In many instances, though, not lower, but higher levels of some AQPs were linked to the increased apoptosis resistance of cancer cells, in which case the mechanisms different from water transport and volume regulation were implicated (219, 272, 452).

CJ MIGRATION AND METASTASIS. Cell movement is based on dynamic alterations in shape involving continuous cycles of frontal protrusions and rear retractions. In addition to cytoskeletal mechanisms, such alterations are supported by local volume perturbation driven by transmembrane fluxes of osmotically determinative K^+ and Cl^- ions accompanied by inflow/outflow of water (445). A number of K^+ - and Cl^- -permeable channels have been implicated in the enhanced migratory behaviors of various types of cancer cells via specific facilitation of cell shape and cell volume perturbations (103, 493). Activation of these channels is often secondary to $[Ca^{2+}]_i$ changes that are intrinsic to migratory cells and involves Ca^{2+} -dependent intermediaries translating intracellular Ca^{2+} signal into channel activity. An essential part of the relevant data was obtained in malignant gliomas which are highly invasive brain cancers with very dismal prognosis (101). Among the ion channels that have been implicated in Ca^{2+} -dependent glioma cells shape and volume changes, facilitating cell movement, are intermediate-conductance Ca^{2+} -activated K^+ channel, $K_{Ca3.1}$ (or IK), and voltage-gated $ClC-3$ Cl^- channel whose Ca^{2+} -dependent activation is regulated through CaMKII phosphorylation (102–104, 107, 317, 493). Ca^{2+} entry required for $ClC-3$ activation was shown to rely on TRPC1 channels that colocalize with $ClC-3$ on caveolar lipid rafts of glioma cell processes (105).

In glioma cell protrusions, $ClC-3$ also clusters with MMP-2 to jointly regulate migratory and invasive behaviors of glioma cells (317). Chlorotoxin (CTX), a 36-amino-acid peptide from scorpion *Leiurus quinquestriatus* venom, which was initially thought to be $ClC-3$ inhibitor, effectively blocks glioma cells migration (101, 109, 317). However,

relentless search for CTX receptor revealed that CTX most likely does not bind to channel directly, but instead, it binds to MMP-2 (115). This causes endocytosis of the whole complex to deplete cell-surface $ClC-3$ (317). The 10-fold higher $ClC-3$ expression in glioblastoma compared with the non-malignant brain tissues (102) together with the importance of this channel for tumor cells infiltration allows regarding malignant glioma cell migration as $ClC-3$ oncochannelopathy (**TABLE 1**).

To support electroneutrality, Cl^- efflux in glioma cells is balanced by the efflux of K^+ mainly via Ca^{2+} -activated $K_{Ca1.1}$ and $K_{Ca3.1}$ channels, which thus also support continuous changes of cell shape and volume required for migration (101). The fact that the specific $K_{Ca3.1}$ blocker TRAM-34 reduces in vivo infiltration of gliomas xenografted into the brain of SCID mice (107) suggests that glioma cell migration can be also viewed as $K_{Ca3.1}$ oncochannelopathy (**TABLE 1**).

The experimental approach to identifying Cl^- -permeable channel linked to migratory behaviors of cancer cells commonly consisted in comparison of biophysical properties of respective Cl^- current with signature properties of known Cl^- channel phenotypes (i.e., VRAC or CaCC) along with utilization of their pharmacological inhibitors whose specificity, however, remains highly questionable. For instance, glioma cells were shown to have resting Cl^- conductance under isotonic conditions whose biophysical properties resembled those of VRAC-mediated $I_{Cl,swell}$ (417). During glioma cell movement and accompanied changes in cell shape, spontaneous activation of this current was detected, while the use of the nonspecific Cl^- channel inhibitor 5-nitro-2–3-phenylpropylamino benzoic acid (NPPB) suppressed the current and reduced chemotactic migration of glioma cells in migration assays (417). Based on these results, it was suggested that $I_{Cl,swell}$ contributes to cell shape and volume changes required for glioma cell migration through brain tissue (417). On the other hand, in the RVI process, which helps to restore glioma cell volume following shrinkage while migrating through the narrow interstices of the brain, Na^+ influx through heteromeric, Na^+ -selective ENaC/ASIC channel was implicated (432).

The importance of Cl^- -selective channels, and in particular $ClC-3$, in migration and invasion was further confirmed on the example of human hepatocellular carcinoma. Combination of tamoxifen pharmacology and siRNA-mediated $ClC-3$ knockdown revealed that migration of highly metastatic human hepatocellular carcinoma MHCC97H cells is proportional to their RVD capacity and required activation of $I_{Cl,swell}$, which in turn appeared to depend on $ClC-3$ expression (320). These results further highlighted the general significance of $ClC-3$ in promoting cancer cells migration via mediation of Cl^- current and facilitation of cell shape and volume changes, although whether $ClC-3$ activa-

tion is linked to volume changes directly, as potential molecular component of cell-specific VRAC, or indirectly via changes in $[Ca^{2+}]_i$ requires elucidation for each cancer cell type.

Ca^{2+} -dependent mechanisms of migratory behaviors of cancer cells involve also the molecular CaCC counterpart ANO1. ANO1 expression is amplified in a number of common human malignancies, including head and neck squamous cell carcinoma (HNSCC), gastrointestinal stromal tumors (GIST), parathyroid tumors, ovarian tumors, as well as breast, pancreatic, gastric, and uterine cancers (524). Moreover, ANO1 amplification and expression has been suggested as a marker for distant metastasis in HNSCC (20). Expression of ANO1 strongly correlated with the magnitude of Ca^{2+} -activated Cl^- currents in HNSCC cells, their ability to regulate volume, cell motility, and cell migration in wound healing and in real time migration assays, prompting the conclusion that ANO1 can contribute to the metastatic progression in HNSCC via facilitated regulation of the cell volume that promotes cell migration (433). The significance of ANO1 in supporting cell migration, but not proliferation, was also demonstrated in pancreatic ductal adenocarcinoma (PDAC) cells. In these cells ANO1 expression and function in mediation of CaCC current was found significantly higher compared with normal human pancreatic ductal epithelium-derived cells, whereas ANO1 knockdown greatly reduced PDAC cells migration in wound healing assay (440).

Cell volume-driven locomotion mechanism established more than two decades ago (238, 446) and recently generalized as “osmotic engine model” (468) postulates that in addition to the cytoskeletal “migration machinery,” directional cell movement requires polarized distribution of ion channels and aquaporins in the cell membrane to create a net inflow of water and ions at the cell leading edge and a net outflow of water and ions at the trailing edge, causing net cell displacement. Consistent with this, EAG2 K^+ channel, which promotes medulloblastoma (MB) cells proliferation via regulating cell volume dynamics, was also found to facilitate cell motility due to its specific enrichment at the trailing edge of migrating MB cell, and EAG2 knockdown was able to impair medulloblastoma metastasis in a xenograft model (225). Thus, along with proliferation, MB cell migration can be also considered EAG2 oncochannelopathy associated with volume regulation (TABLE 1). The notion on preferential clustering of the activity of K^+ channel to the rear end of migrating cell comes yet from the studies in the model system of transformed Madin-Darby canine kidney cells (MDCK-F), which lose epithelial apical-basolateral polarization and instead become polarized in the direction of migration (446).

In agreement with “osmotic engine model,” polarized, AQP-dependent changes in cell shape that accompany cell motility have been documented in many studies (382, 435).

Overexpression of several AQPs in different types of human cancer has been linked to the enhanced migratory behaviors, metastasizing and invasion, although in many cases the mechanisms outside the water transport have been implicated. In prostate cancer cells, pro-migratory and pro-invasive function of AQP3 was shown to involve ERK1/2 activation resulting in the increased expression and secretion of matrix metalloproteinase-3 (MMP-3) (81). The involvement of ERK1/2 pathway has been also implicated in the mechanism of proliferative and metastatic action of AQP5 in colon cancer, with the odds of liver metastasis being more than three times higher in colon cancer patients with positive versus negative AQP5 expression (253). Induction of MMP-2 and downregulation of cell-to-cell adhesion molecules was implicated in the mechanism of AQP4-dependent glioblastoma cells migration and invasion (120). Moreover, growth factors (EGF, FGF) promote migration of cancer cells by inducing AQPs expression (65, 228, 298, 312). Thus the role of AQPs in cancer cells migration and metastasis is highly specific in terms of cancer type, AQP family members involved, and possible mechanisms.

D) ANGIOGENESIS. Angiogenesis requires migration, differentiation, and proliferation of endothelial cells (EC), and angiogenic factors produced and released by cancer cells act as endothelial cell mitogens. In fact, angiogenesis inducers, vascular endothelial growth factor A (VEGF-A), basic (bFGF also known as FGF2 or FGF- β) and acidic (aFGF or FGF1) fibroblast growth factors, platelet-derived growth factor (PDGF), interleukin 8 (IL-8), platelet-activating factor (PAF), etc., promote the formation of new blood vessels by stimulating proliferation and migration of EC (70). In this respect, the role of ion channels in regulation of EC proliferation and migration via control of cell volume is hardly different from other types of epithelial cells (359).

EC express VRAC with biophysical properties similar to those in most other cell types (359). Endothelial cell swelling is one of the earliest hallmarks of angiogenesis, and using chemically distinct VRAC inhibitors was shown to attenuate the formation of new blood vessel in various in vitro settings (319), as well in vivo animal experimentation (571) (FIGURE 5, bottom right). Antiangiogenic effect of VRAC inhibitors suggests that EC VRACs may be characterized by certain levels of basal activation under isosmotic conditions thereby also contributing to the maintenance of V_r . As the latter determines the driving force for Ca^{2+} entry through Ca^{2+} -permeable channels, this can provide an additional mechanism through which VRAC may influence angiogenesis.

Specific to vascular endothelia is AQP1 water channel which increases cell membrane water permeability and promotes tumor angiogenesis by facilitating EC migration through polarized water transport and rapid turnover of cell membrane protrusions at the leading edge (139, 357,

435) (**FIGURE 5**, bottom right). AQP1-null mice are characterized by decreased expression of the endothelial marker Factor VIII and reduced vascularity of subcutaneously implanted melanoma (357, 435), validating AQP1 as a proangiogenic protein and tumor vascularization as AQP1 oncochannelopathy (**TABLE 1**).

C. Cell Membrane Potential Regulation

Cell membrane potential (V_m) is vital characteristic of any living cell. Its size defines the operation of active membrane transporters and functional state of ion channels, the driving force for the entry of the key signaling ion Ca^{2+} , and cell response to extracellular ligands. The size of V_m at any given time is determined by the concentrations of unevenly distributed between extracellular and intracellular sides of the membrane key physiological ions and membrane permeability to each of these ions (P_i), which in turn depends on which ion channel(s) are open (208). It can be quantitatively estimated using Goldman-Hodgkin-Katz (GHK) equation, which considers all these parameters (208). Depending on cell type and the set of ion channels expressed, V_m can take any values in the range of -100 to $+50$ mV (usually referred to as physiological range); however, positive values are only attainable in the electrically excitable cells, such as neurons and various types of muscle cells, and only during brief periods of action potential (AP) generation. Most of the time, however, cells sit at the so-called resting membrane potential (V_r) whose negative values range from -90 to -30 mV. Terminally differentiated muscle cells and neurons typically have relatively hyperpolarized (i.e., negative) V_r of -90 to -60 mV compared with nonexcitable cells whose V_r is maintained at more depolarized (i.e., less negative) level of -50 to -30 mV (544). The size of the V_r is determined by membrane channels that are constitutively open or the opening of which is regulated on a relatively long timescale by various physical and chemical factors, whereas transient changes of V_m during AP generation depend on ion channels characterized by fast mode of gating (i.e., opening and closing), which is also strongly dependent on the size of V_m per se (i.e., voltage-gated channels, VGC).

1. Ion channels important for cellular electrogenesis

In view of the fact that transmembrane ionic current due to opening of any type(s) of ion channel will affect V_m , it is inevitable that all known channels to a variable extent participate in cellular electrogenesis. However, there are types of ion channels for which involvement in the V_r maintenance and V_m changes represent their dominant functions. Among these channels primarily are those that are highly selective to the three most abundant physiological ions, K^+ , Na^+ , and Cl^- : various types of K^+ channels, voltage-gated (K_v) (194), calcium-activated (K_{Ca}) (527), inwardly rectifying (K_{ir}) (268) and two-pore domain ($\text{K}_{2\text{P}}$) (178); voltage-

gated Na^+ channels (Na_v) (73); and voltage-gated Cl^- channels of ClC family (464). Of these channels, K^+ - and Cl^- -selective ones primarily contribute to the maintenance of the V_r , and its regulation by various factors, such as state of intracellular metabolism, the presence of intracellular second messengers, $[\text{Ca}^{2+}]_i$, pH, membrane stretch, and xenobiotics, whereas the presence of Na_v channels typically confers excitability phenotype. The size of the V_r and its sensitivity to various modulatory factors may also largely depend on Na^+ - and Ca^{2+} -selective cationic channels from TRP family displaying constitutive activity or acting as multimodal sensors of diverse physical and chemical stimuli (134, 231).

2. Deregulation of cellular electrogenesis in cancer

Tumor cells escape many of the controls and restrains that regulate various processes in normal cells. In particular, deregulation of ionic homeostasis leading to higher intracellular Na^+ ($[\text{Na}^+]_i$) and Cl^- ($[\text{Cl}^-]_i$) concentrations is one of characteristic features associated with oncogenesis (63). This in turn causes cancer cells to have more depolarized V_r compared with normal counterparts (323, 544). Moreover, depolarized V_r in cancer cells no longer becomes just a mere reflection of impaired balance of ionic concentrations, but turns into an active factor in promoting cancer hallmarks. Model experiments in *Xenopus laevis* embryos have shown that melanoma-like tumorigenesis induced by 4-nitroquinolin-1-oxide (4NQO) carcinogen is accompanied by an embryo-wide depolarization, whereas artificially forcing V_r to negative values by preinjecting the embryos with mRNA encoding for a hyperpolarizing $\text{K}_{\text{ir}}4.1$ K^+ channel or by pharmacological manipulations on endogenous Cl^- channels significantly reduces susceptibility to tumorigenesis in response to oncogene (Xrel3 or KRASG12D) treatment (313). Thus depolarized and hyperpolarized V_r can be viewed as causative and protective factors, respectively, in tumor induction and progression largely independently of ion channels involved.

A) PROLIFERATION. During cell cycle progression, V_r , similarly to cell volume, undergoes fluctuations (41, 537); however, the mean values of the V_r in cancer cells still remain more depolarized compared with the respective normal cells (544). Moreover, the cells at resting state, G_0 , can be induced to enter cell-division cycle just by virtue of V_m depolarization (544). Although the mechanisms linking V_m to cell proliferation are still poorly characterized, just because of the requirement to be sensitive to V_m they must involve either reorganization of plasma membrane (PM) lipid matrix under V_m changes, activation of membrane-associated signaling proteins whose conformational state is governed by voltage drop across their molecule, or entry of universal signaling ion, Ca^{2+} , the driving force for which is dependent on V_m . In this respect, it was recently shown that V_m depolarization promotes nanoscale reorganization of phosphatidylserine and phosphatidylinositol 4,5-bisphosphate

(PIP₂) on the inner leaflet of the PM (566). This in turn facilitates nanoclustering of PM-bound K-Ras due to electrostatic interactions with phosphatidylserine to markedly amplify K-Ras-dependent mitogen-activated protein kinase (MAPK) signaling, which plays a crucial role in key cellular processes, including proliferation (566) (**FIGURE 2**). Conversely, V_m hyperpolarization disrupts K-Ras nanoclustering and inhibits MAPK signaling (566).

A number of ion channels show variation of expression or activity at various phases of the cell cycle, thereby contributing to V_r fluctuations. Typically, in most of the cells, V_r undergoes hyperpolarization at G₁/S checkpoint before S phase initiation owing to K⁺ efflux through various K⁺ channels (537), followed by depolarization at G₂/M phase transition before entering mitotic M phase due to increased Cl⁻ efflux (41, 495, 544) (**FIGURE 2**). The fact that diverse K⁺-channel blockers can induce proliferation arrest (537) suggests that contribution of specific K⁺-channel types to V_r hyperpolarization at G₁/S checkpoint and its changes in cancer is cell type and context dependent.

The magnitude of K⁺ conductance is the major determinant of the V_r in basically all excitable and nonexcitable cells: the bigger K⁺ conductance is, the more hyperpolarized V_r is established. In view of the fact that V_r in cancer cells is on average more depolarized compared with normal counterparts (41, 544), it seems paradoxical that in most cases it is not deficit, but abundance of certain K⁺ channel(s), which theoretically would favor V_r hyperpolarization, contributes to the enhanced proliferation of cancer cells (544). This paradox can be explained if one considers that changes in K⁺ channel expression in cancer cells occur on the background of considerable Na⁺ resting leak rising [Na⁺]_i and driving V_r to more depolarized values, and excepts the model in which K⁺ channels act not just as passive determinants of the V_r during cell cycle, but play an active role in synchronization of V_r hyperpolarization with other cell cycle regulatory processes at G₁/S checkpoint (537). Such requirement would limit the types of relevant K⁺ channels only to those whose activity can be appropriately controlled by other cell cycle regulatory signals in a feedback manner to provide proliferative advantages (537). In addition, biophysical properties of many K⁺ channels implicated in cancer endow them only limited capacity for V_r hyperpolarization. Finally, membrane polarization is not the only factor underlying K⁺ channel-dependent proliferative behaviors of cancer cells, and the mechanisms associated with 1) modulation of a driving force for Ca²⁺ entry which is V_m function, 2) cell volume regulation, and 3) K⁺ permeation-independent protein-protein interactions (226, 296, 496) should be considered. Thus it is not always possible to make a clear-cut distinction whether pro-proliferative oncogenic effects of ion channel is solely linked to V_r changes, or other factors contribute as well.

Among the K⁺ channel types whose overexpression has been most implicated in proliferation of various cancer cells are voltage-gated K_v10.1 (EAG1, human gene *KCNH1*) (374) and K_v11.1 (HERG1, human gene *KCNH2*) (16, 241, 282), background K_{2p}2.1 (TREK1, human gene *KCNK2*), K_{2p}9.1 (TASK3, gene *KCNK9*) and K_{2p}10.1 (TREK2, gene *KCNK10*) (386, 398, 512, 534, 561), Ca²⁺-dependent K_{Ca}1.1 (BK, Slo or MaxiK, gene *KCNMA1*) (42, 162, 347, 363), and K_{Ca}3.1 (IK, gene *KCNN4*) (142, 274), although the involvement of some other members from these groups was documented as well (reviewed in Refs. 226, 385, 496) (**FIGURE 2**).

The significance of K_v10.1, also commonly known as ether-a-go-go-1 (EAG1), in promoting cancer cells proliferation was established in 1999 (383) and since then it remains the focus of oncology as genuine oncogenic channel. It was believed that K_v10.1 is only present in the central nervous system, but its expression becomes significantly elevated in up to 80% of human tumors (206). Recent data, however, show that K_v10.1 is also present in healthy cells, but its expression is temporally restricted to a premitotic period in which its activity is important for ciliary disassembly (437). Oncogenic potential of K_v10.1 was proven by a variety of approaches in a number of experimental and clinical models, including channel overexpression and silencing in primary cancer cells and cell lines, xenograft tumors, and human cancer tissue biopsies (reviewed in Ref. 374). Blocking K_v10.1 function using specific antibody inhibits the ability of cancer cells to form colonies in vitro and reduces in vivo growth of human breast and pancreatic tumors implanted in SCID mice (177). However, nonconducting K_v10.1 mutants are still able to influence proliferation and tumorigenesis (126, 205, 496), suggesting that ion permeation is not a prerequisite for oncogenesis (see sect. IV for conduction-independent oncogenic channel functions). K_v10.1 expression is transiently regulated in a cell cycle-dependent manner by the E2F1 transcription factor which is released upon inactivation of retinoblastoma protein (pRb) growth suppressor to facilitate G₂/M progression (495). Since pRb/E2F1 complex is disrupted in cancer, this explains why K_v10.1 is often upregulated in cancer cell lines and clinical tumor specimens (495). In normal cells, K_v10.1 expression during G₂/M phases was shown to promote ciliary disassembly which is required for cells to divide (437). The latter effect involved K_v10.1 K⁺ permeation, suggesting that it could be associated with local hyperpolarization of the primary cilium (437).

K_v11.1 (HERG1, sometimes referred to as simply HERG) channel is best known for mediating key hyperpolarizing K⁺ current of cardiac action potential I_{Kr}, whose deficiency causes one of the forms of congenital and acquired (i.e., drug-induced) electrocardiographic long-QT syndrome (LQTS) (438). In tumor cell lines of various lineage, high levels of K_v11.1 transcripts and K⁺ current whose biophys-

ical and pharmacological properties corresponded to I_{K_r} were first documented in 1998 (37). On the contrary, cells representing the normal counterparts of the tested tumors lacked $K_v11.1$ and instead expressed other K^+ channel types (37). In view of the fact that biophysical properties of $K_v11.1$ channel (i.e., time and voltage dependence of activation and inactivation) endow it only a limited hyperpolarization power on the V_r compared with other K^+ channels, particularly K_{ir} ones, this led to essentially depolarized V_r in tumor cells compared with normal cells (37).

Further studies firmly established aberrant $K_v11.1$ expression on mRNA and protein levels in cells originating from virtually all solid tumors and hematologic malignancies with no essential presence in noncancerous cells, making this K^+ channel a biomarker of malignant transformation (reviewed in Refs. 16, 241, 282, 373). Although similarly to $K_v10.1$, the tumorigenic actions of $K_v11.1$ often involve K^+ conduction-independent mechanisms due to functional interaction with partner proteins within plasma membrane macromolecular signaling complexes (see sect. IV), its proliferative effects can be explained by passage of K^+ current and modulation of V_r . In this respect it should be mentioned that human tumor cell lines (neuroblastoma, rhabdomyosarcoma, colon carcinoma, mammary carcinoma, monoblastic leukemia) as well as primary human tumors (primary myeloid leukemias) in addition to the full-length $K_v11.1$ isoform, originally called HERG1, express on their plasma membrane also NH_2 terminus truncated HERG1b isoform displaying activation at more depolarized V_m (96). Plasma membrane expression of isoforms appeared to be strongly cell cycle dependent, with HERG1 being upregulated in G_1 phase and HERG1b in the S phase, thereby allowing attribution of cell cycle-dependent V_r fluctuation to the alterations in HERG1b/HERG1 ratio (96). Surprisingly, in the estrogen receptor-negative (ER^-) mammary gland adenocarcinoma cell lines (i.e., SKBr3 or MDA-MB-231) it was not inhibition, but prolonged stimulation, of HERG1 with its activator NS1643 that caused cell cycle arrest in the G_0/G_1 phase and induced the development of a senescence-like phenotype (280). This result prompted the conclusion that HERG1 activity is essential for the G_1 to S transition, but such transition may require some optimal level of channel activation, and both under- and hyperactivation cause cell cycle arrest in G_0/G_1 (280).

There are other examples when pro-proliferative effects of specific K^+ channels in certain types of cancer were shown to be specifically mediated via V_r changes. For instance, proliferation inhibition of MCF-7 breast cancer cells via G_0/G_1 cell cycle arrest caused by the nonspecific K^+ channel inhibitor quinidine involved both depolarization of the V_r and the inhibition of ATP-sensitive K^+ channel (K_{ATP}) currents, supporting the notion on primary role of V_r changes rather than volume regulation in anti proliferative action of quinidine (518).

Expression of the background $K_{2p9.1}$ (TASK3, *KCNK9*) K^+ channel is amplified in breast, lung, colorectal, and ovarian cancers (232, 259, 348). Systemic administration of specific monoclonal anti- $K_{2p9.1}$ antibody effectively inhibits growth of human lung cancer xenografts and murine breast cancer metastasis in mice (474). Heterologous overexpression of dominant-negative, K^+ -impermeable $K_{2p9.1}$ mutant, in contrast to the wild-type $K_{2p9.1}$, did not confer on cells oncogenic features, including proliferation in low serum, resistance to TNF-induced apoptosis, and tumorigenicity in nude mice (398), suggesting that generation of $K_{2p9.1}$ -mediated background K^+ current that contributes to the V_r is required for oncogenesis. In colorectal cancer tissue samples, the level of $K_{2p9.1}$ protein expression correlated with tumor stage and lymph node metastasis, with no mutations in *KCNK9* gene having been detected (259). It was suggested that $K_{2p9.1}$ might modulate cancer cell growth through controlling V_r and ensuing driving force for Ca^{2+} entry (391). $K_{2p9.1}$ and its close relative $K_{2p3.1}$ (TASK1), both of which can be inhibited by acidic extracellular pH, have been suggested as candidate channels facilitating the passage of glioma cells through the hyperpolarization-dependent G_1/S cell-cycle checkpoint (213). Suppression of respective pH-sensitive K^+ conductance by acidic pH depolarized glioma cells inhibiting cell division.

Yet another background K^+ channel, $K_{2p2.1}$ (TREK1, *KCNK2*), is highly expressed in prostate cancer specimens and prostate cancer-derived cell lines, but not in normal prostate or in benign prostatic hyperplasia (512, 558). Proliferation of prostate cancer cells directly correlated with the presence of functional $K_{2p2.1}$ channel. As in the event of $K_{2p9.1}$ (398), $K_{2p2.1}$ -mediated K^+ current and proliferation of prostate cancer cells could be reduced by heterologous overexpression of K^+ -impermeable dominant negative $K_{2p2.1}$ mutant (512), suggesting K^+ conduction requirement. TREK1 knockdown in PC-3 prostate cancer cells induces G_1/S phase cell cycle arrest (561), favoring the hypothesis that pro-proliferative effects of $K_{2p2.1}$ are based on supporting background K^+ current to maintain appropriate V_r during cell cycle progression.

Contribution to cell cycle-dependent growth of bladder cancer cells via regulation of V_r was also documented for $K_{2p10.1}$ (TREK2, *KCNK10*) channel (386) (FIGURE 2) whose activation is regulated by microenvironmental insults such as mechanical stress or change in pH. TREK2 silencing led to cell cycle arrest G_0/G_1 phases (386).

The role of Ca^{2+} -dependent K^+ channels in cancer cells proliferation is closely linked to Ca^{2+} signaling through their functional coupling to the sources of intracellular Ca^{2+} for activation (347) and increasing driving force for Ca^{2+} entry via various TRP channels or SOCs (142, 274). In prostate cancer cells, pro-proliferative significance of $K_{Ca1.1}$ (BK) was shown to be associated with setting V_r at

a level enabling steady-state Ca^{2+} “window current” (i.e., current through voltage-gated channels at V_m , which are sufficient to partially activate channels, but insufficient to fully inactivate them) through $\text{Ca}_v3.2$ T-type VGCC (162). However, $\text{K}_{\text{Ca}3.1}$ can promote proliferation also independently of K^+ permeation, V_r hyperpolarization, and increasing driving force for Ca^{2+} entry by directly interacting with ERK1/2 and JNK signaling pathways (336), emphasizing cell type specificity of the effects and cautioning from any kind of generalizations.

Overall, although the role of K^+ channels in V_m -dependent control of cancer cells proliferation is undeniable, because of the multiplicity of channels involved, multimodality of the effects of K^+ -channel activation and often lack of sufficient mechanistic data it is difficult to regard enhanced proliferation of certain type of cancer as specific K^+ -channel oncochannelopathy associated with V_m changes. Indeed, just only in the proliferation of prostate cancer cells, Ca^{2+} -activated $\text{K}_{\text{Ca}1.1}$ (42, 162) and $\text{K}_{\text{Ca}3.1}$ (274) as well as background $\text{K}_{2p2.1}$ (512, 561) channels were implicated, each of which has specific biophysical properties, regulates V_r in response to diversr factors, and supports different mechanisms of V_r translation into pro-proliferative response. So far, probably only background $\text{K}_{2p9.1}$ and $\text{K}_{2p2.1}$ channels would conform to the required criteria (TABLE 1).

Changes in Cl^- conductance during cell cycle are primarily linked to the regulation of cell volume, particularly to the process known as premitotic condensation (PMC), an obligatory step in cell replication functionally related to nuclear condensation (196, 493). The same changes in Cl^- conductance would obviously contribute to the V_r depolarization as well, which represents a common characteristic feature of G_2/M phase transition (41, 544). Indeed, it was reported that PMC of glioma cells is accompanied by a sizable V_r depolarization in the M phase due to significantly larger NPPB- and DIDS-sensitive Cl^- membrane currents, as compared with the growth phase cells (195). The reduction of glioma cell volume and V_r was shown to be accomplished by Cl^- efflux specifically through plasma membrane ClC-3 Cl^- channels, which hypothetically are caused to open by either actin rearrangements, occurring at the onset of mitosis (195), or in a Ca^{2+} -dependent manner (100). The same mechanism is supposed to be shared among normal and malignant cells, with the latter taking advantage of deregulated Cl^- gradient and overexpression of specific Cl^- channels to drive rapid volume and V_r changes, as the means of accelerating progression through mitosis and enhancing proliferative capacity. Indeed, it was demonstrated that in dividing fibroblasts at M phase the protein level of ClC-2 channel undergoes upregulation, while its mRNA level remains rather stable during the whole cell cycle (565). The data indicated that preferential expression of ClC-2 protein in the M phase is most likely regulated at the post-

transcriptional level, and its rapid decrease immediately after cell division is explained by ubiquitination and proteasomal degradation at around the M phase exit (565). Thus the contribution of different Cl^- channels and the mechanisms of their engagement in PMC and accompanying V_r depolarization are likely to be cell type specific. Limited availability of relevant data for various cancers so far prevents considering enhanced proliferation of any of them as specific Cl^- channel oncochannelopathy linked to V_m deregulation.

As was already mentioned, generally depolarized V_r in cancer cells is explained by substantial resting Na^+ leak to which “window current” through Na_v channels essentially contributes (e.g., Ref. 64), and whose aberrant expression represents one of the distinguishing features of malignant transformation (160, 425). However, despite established role in setting depolarized V_r , molecular biological or pharmacological manipulations on Na_v channels expression and function rarely interfered with cancer cell proliferation, but rather impacted other cancer hallmarks, especially migration and invasion (to be discussed in sect. IIIB2c). VGSCs are most likely not the only contributors to the resting Na^+ conductance driving V_r of cancer cells to depolarized values. For instance, malignant glioma cells express a heteromeric cation channel complex composed of closely related epithelial sodium channel (ENaC) and acid-sensitive (ASIC) channel family members, αENaC , γENaC , and ASIC1 , which is responsible for the constitutive, Na^+ -carried, amiloride-sensitive current not present in normal astrocytes or low-grade gliomas (431). Impairment of this Na^+ current by ASIC1 pharmacological blockade or knockdown reduced glioma cells migration and proliferation by inducing cell cycle arrest in the G_0/G_1 phase (431). Extracellular Na^+ and normal channel activity were required for downregulating cyclin-dependent kinases inhibitors, $p21^{\text{Cip1}}$ and $p27^{\text{Kip1}}$, and for ERK1/2 phosphorylation to support proliferation (431). Although constitutive Na^+ permeability would inevitably contribute to depolarized V_r of glioma cells, changes in V_r were not implicated in these phenomena.

Depolarized V_r of glioma cells was also shown to depend on constitutive activity of nonselective TRPC1 , TRPC3 , TRPC5 , and TRPC6 cationic channels whose pharmacological blockade by SKF96365 or GdCl_3 caused V_r hyperpolarization by ~ 10 mV (45). Chronic treatment of glioma cells with TRPC blockers induced almost total proliferation inhibition by cell cycle arrest in G_2 and M phase, resulting in incomplete cell divisions and appearance of multinucleate, enlarged cells (45). Although the effects of TRPC channels blockade were attributed to the impairment of TRPC-mediated Ca^{2+} influx and Ca^{2+} signaling essential for activation of cytokinesis (i.e., division of cytoplasmic constituents, aside from the nuclear events of mitosis) (45), it is likely that in glioma cells TRPC channels also partici-

pate in the obligatory maintenance of depolarized V_r during G_2/M phase transition (FIGURE 2).

A viable candidate for providing Na^+ leak driving V_r of cancer cells to depolarized values and increasing their $[Na^+]_i$ could also be the so-called Na^+ -leak channel (NALCN, reviewed in Ref. 92) (FIGURE 2). NALCN is a structural homolog of Na_v1 and Ca_v1 channels, which is predominantly expressed in neurons where it regulates V_r and neuronal excitability (315). However, *NALCN* gene was found among 16 significantly mutated genes in a patients of early (stages I and II) sporadic pancreatic ductal adenocarcinoma (38). Furthermore, genotyping of advanced-stage NSCLC patients revealed single-nucleotide polymorphisms (SNPs) associated with poor prognosis located in the genomic *NALCN* region (288). These results position NALCN as potentially oncogenic channel, although further studies are necessary to determine mechanisms and modes of its involvement.

B) EVASION OF APOPTOSIS. Like it is with proliferation, changes in V_r during apoptosis are inextricably linked to changes in cell volume, and both are dependent on ionic fluxes across the plasma membrane and intracellular ionic homeostasis. Triggering of receptor-induced, stress-induced, or drug-induced apoptosis initiates the chain of specific alterations in ionic conductances leading to V_r depolarization, which thus becomes an early event during apoptosis (49, 157, 279). Normotonic cell shrinkage and dehydration, known as apoptotic volume decrease (AVD; see also sect. IIIB2B), are another characteristic feature in early apoptotic process (279, 339). An efflux of K^+ , as predominant intracellular cation, accompanied by the exit of obliged water is necessary for AVD (50). To ensure overall electroneutrality, efflux of K^+ is balanced by loss of Cl^- , with activation of various K^+ and Cl^- channels participating in cell shrinkage (271). Apoptosis is also characterized by inactivation $Na^+-K^+-ATPase$ (sodium-potassium pump) (49, 377), which normally provides for asymmetric, energy-dependent Na^+ and K^+ distribution from both sides of the plasma membrane. Enhanced K^+ efflux along with $Na^+-K^+-ATPase$ inactivation leads to the decrease of $[K^+]_i$ and increase of $[Na^+]_i$, which is the primary reason for V_r depolarization (377). Although the importance of $[K^+]_i$ in creating a specific low- K^+ intracellular microenvironment favoring the apoptosome formation and activation of death executing caspases and endonucleases is well established (279), relatively little is known about the contribution of Na^+ in the regulation of cell death. The data suggest that $[Na^+]_i$ increase not only determines cell size, but also participates in controlling the initial signaling of the cell death cascade (377).

Another typical feature of apoptotic cells is lowered intracellular pH largely, but not only due to measurable permeability of some Cl^- channels to HCO_3^- whose exit leads to

cytosolic acidification (279). Decreased cytosolic pH represents another favorable microenvironmental factor for caspases and endonucleases activation (279).

The role of V_r depolarization per se during apoptosis remains elusive. It is still not clear whether it is just a mere reflection of altered ionic balance during apoptosis, or if it bears a specific signaling role. V_r hyperpolarization as well as K^+ and Cl^- channel blockers can prevent shrinkage as well as cell death (529). Notably, overexpression of the common antiapoptotic Bcl-2 protein in human lymphoma and leukemia cell lines resulted in significant V_r hyperpolarization accompanied by enhanced cell survival in response to irradiation (173). Depolarization of the V_r of Bcl-2-overexpressing cells by exposure to high extracellular KCl made them significantly more sensitive to irradiation-induced cell death, suggesting that hyperpolarization is one of the mechanisms by which Bcl-2 confers apoptosis resistance (173). The data indicated that hyperpolarized V_r in Bcl-2-overexpressing cells is in part linked to the upregulated $Na^+-K^+-ATPase$ activity (173, 377).

Thus, to escape apoptosis, malignant cells must counteract shrinkage and V_r depolarization by downregulating the channels responsible for K^+ and Cl^- efflux, as already discussed in section IIIB2c. However, the available data suggest that the role of K^+ and Cl^- channels underexpression in conferring cancer cells apoptosis resistance is mainly realized via dysregulation of AVD, whereas evasion of apoptosis due to promotion of hyperpolarized V_r is likely mediated by the enhanced $Na^+-K^+-ATPase$ activity (377) (FIGURE 3, top right).

C) MIGRATION AND METASTASIS. Several mechanisms have been implicated in the effects of V_r depolarization on the cytoskeleton dynamics (reviewed in Ref. 445): 1) voltage-dependent activation of $ERK \rightarrow GTP/GDP$ exchange factor (GEF-H1) \rightarrow Rho \rightarrow Rho-kinase signaling pathway leading to myosin light chain phosphorylation; 2) regulation of the actin polymerization/depolymerization ratio and thus cell stiffness via direct sensing of transmembrane electrical field by submembranous actin network; and 3) control of the activity of voltage-dependent enzymes such as the phosphoinositide phosphatase $Ci-VSP$, a member of the PTEN family of phosphatidylinositol phosphatases which regulates PIP_2 supply for the actin modulator, cofilin, or for ion channels involved in cell migration. Which of these mechanisms participates in the promotion of enhanced migration of cancer cells is still an open issue.

Of membrane conductances that determine depolarized V_r of cancer cells, the Na^+ one is probably the most implicated in cancer cells migration and metastasis, while aberrant expression Na^+ -selective VGSCs of Na_v1 family represents one the most prominent feature of this cancer hallmark (160, 425). Given the importance of Na_v1 channels in tu-

mor biology, below we briefly outline some of their molecular characteristics necessary to understand their oncogenic functions.

Na_v1 family of channel-forming α 1-subunits consists of nine members, Na_v1.1 to Na_v1.9 (human genes *SCN1A* to *SCN5A* and *SCN8A* to *SCN11A*), each of which possesses all structural elements to function as stand-alone VGSC (73). They are differentially expressed in various tissues with those that are highly sensitive to the classical VGSC blocker tetrodotoxin (TTX, in nM range), are broadly represented in the CNS (Na_v1.1..Na_v1.3 and Na_v1.6), peripheral neurons (Na_v1.7), and skeletal muscle (Na_v1.4); and those that exhibit TTX-sensitivity in micromolar range are primarily restricted to cardiac muscle (Na_v1.5) and sensory neurons (Na_v1.8, Na_v1.9) (73). Besides well-characterized canonical roles of Na_v channels in generation and propagation of AP in excitable cells, their functional expression was documented in numerous normal nonexcitable cells (glial, endothelial, immune, fibroblasts, osteoblasts, keratinocytes), where they were proposed to perform noncanonical functions in regulating cell fate processes (proliferation, survival, migration, differentiation) as well as supporting some homeostatic and functional responses (endosome acidification, phagocytosis, podosome formation) (40).

Although Na_v1 α 1-subunits are self-sufficient in sustaining VGSC function with all the biophysical features characteristic of this channel type, these properties can be further tuned by multifunctional signaling molecules commonly known as VGSC auxiliary β -subunits (354, 369). Four VGSC β -subunits, β 1 to β 4, encoded by four, *SCN1B* to *SCN4B* genes, respectively, have been identified. All of them consist of a single α -helical transmembrane domain with extracellular NH₂ and intracellular COOH terminus. The extracellular NH₂-terminal region of β -subunits contains a single V-type immunoglobulin (Ig) domain found in many immune system proteins and cell-adhesion molecules (CAMs), indicating that in addition to modulating Na_v1 they can be engaged in adhesive interactions similar to those of integrins, cadherins, and selectins (354, 369). *SCN1B* gene is expressed in two developmentally regulated splice variants, β 1 and β 1B, of which the latter shares the NH₂-terminal part including Ig domain with β 1, but lacks downstream COOH-terminal transmembrane region. It was suggested that β 1B may function as soluble and secreted cell adhesion molecule involved in neurite outgrowth in embryonic brain (394).

The first evidence on the presence of VGSC-mediated currents (I_{Na}) in some cancer cell lines (i.e., leukemic, SCLC) appeared yet in the late 1980s (285, 379, 543); however, it took another 8 yr to realize that I_{Na} represents an integral part of malignant transformation associated with invasion and metastasis first in prostate cancer (185) and then in other cancers (159, 166, 184, 220, 424, 428).

Simultaneous expression of mRNAs for multiple Na_v channel subtypes in various cancers is commonly observed; however, the bulk of evidence indicates that it is Na_v1.5, Na_v1.6, and Na_v1.7 that are the most widely distributed oncogenic channels, which sole or combined overexpression and function at plasma membrane promotes invasive and metastatic behaviors. In particular, TTX-insensitive, cardiac-type Na_v1.5 was found upregulated in breast, colon, and ovarian cancers (158, 166, 220), TTX-sensitive neuronal Na_v1.6 in cervical cancer (207), and Na_v1.7 in prostate, breast, cervical, and NSCLC cancers (2, 121, 158, 207, 424, 428). Importantly, Na_v1.5 and Na_v1.7 in cancer cells are represented by their developmentally regulated embryonic/neonatal splice variants, consistent with the concept of embryonic genes reexpression in cancer cells (123, 158). Biophysical properties of neonatal Na_v1.5 are modified in a way enabling it to pass greater Na⁺ influx compared with the primary isoform (371). As shown in NSCLC, Na_v1.7 channel expression at mRNA, protein, and functional levels to promote cellular invasion is controlled at transcriptional level by epidermal growth factor (EGF) and EGF receptor (EGFR) signaling via the ERK1/2 pathway (64).

In addition to Na_v1 α 1-subunits, expression of auxiliary, non-pore-forming β -subunits and especially of β 1, was found upregulated in cancer (86, 122, 174, 355). β 1 expression levels in breast cancer cell lines directly correlated with the size of I_{Na} , cell adhesiveness, and appearance of processes, but inversely correlate with cell migration, suggesting that β 1 performs both Na_v1.5-modulating and CAM-like functions in breast cancer cells (86). Upregulated β 1 expression on mRNA and protein levels in breast cancer specimens compared with healthy tissue was associated with enhanced tumor growth and metastasis in vivo as well as with the extension of neurite-like processes on breast cancer cells (355). It was suggested that β 1 enhances metastatic behaviors of breast cancer cells by promoting outgrowth of processes via a trans-homophilic adhesion (i.e., binding between CAMs on opposing surfaces) similar to mechanism(s) of neuronal migration in embryonic brain (355).

The association of VGSCs with prometastatic behaviors of cancer cells is unquestionable; however, how these channels interact with molecular machinery of migration and invasion to promote such behaviors is much less clear, and several mechanisms are considered (35, 425). As VGSCs are indispensable for electrical excitability, the first possibility which comes to mind is that conferring excitability phenotype may be the primary reason. However, for the cell to be excitable (i.e., to support AP generation), the presence of I_{Na} is not sufficient; to make this current available, it must also have fairly hyperpolarized V_r and a set of voltage-gated K⁺ currents to provide for AP repolarization, the features not present in cancer cells. Moreover, the properties of volt-

age-dependent activation and inactivation of cancer cell-specific Na_v1 channels are such that they are able to create small steady-state inward current in the window of membrane potentials around cancer cells' V_r (correspondingly called "window current"). This current promotes V_r depolarization as well as leads to the increase in $[\text{Na}^+]_i$ and decrease in transmembrane Na^+ gradient (64, 174, 424). So far, the bulk of evidence suggests that it is mainly Na^+ influx and/or protein-protein interactions rather than V_r depolarization that are important for conferring invasive phenotype. In particular, $\text{Na}_v1.5$ function has been shown to be responsible for intra- and extracellular pH changes that favor higher activity of cathepsins, external matrix-digesting proteases involved in breast cancer cells invasiveness (54, 55, 174). This mechanism, however, can be regarded as more relevant to the microenvironmental factors; therefore, it will be discussed in greater detail in section III E2c. Nevertheless, the involvement of V_r depolarization in proinvasive Na_v1 action is also likely. In colon cancer cells, $\text{Na}_v1.5$ activity and ensuing depolarization were implicated in the transcriptional induction of invasion-related genes through protein kinase A (PKA), Rap1B, MEK, ERK1/2 signaling pathway (220, 221). In breast cancer cells, $\text{Na}_v1.5$ localization and function is predominantly confined to caveolae, dynamic lipid raft platforms at the plasma membrane for protein clustering, which also provide restricted space for diffusion of ionic fluxes (55). It was suggested that such $\text{Na}_v1.5$ -mediated Na^+ fluxes could be responsible for local changes in membrane potential to modulate F-actin polymerization and invadopodia formation (54) (**FIGURE 4G**), consistent with previous findings that V_r depolarization can be directly sensed by the submembranous actin network to regulate the actin polymerization/depolymerization ratio and decrease cell stiffness (62). Overall, the available data strongly suggest that invasion and metastasis of the majority of human cancers can definitely be regarded as Na_v1 oncochannelopathy; however, the extent and manner of its specific association with V_m changes remain uncertain (**TABLE 1**).

Of other highly Na^+ -selective channels that may contribute to the depolarized V_r of cancer cells, the expression of acid-sensitive ASIC1a was found significantly upregulated in HCC tissues compared with the adjacent normal tissues, and in HCC with postoperative metastasis compared with nonmetastatic one (248). ASIC1a silencing in HCC cell lines inhibited migration and invasion, although whether or not this involved changes in V_r was not determined (248). It was suggested that acidic extracellular tumor microenvironment may promote migration and invasion of HCC cells via enhancement of ASIC1a activation and expression (248). Without direct implication of V_r changes, ASIC1 subunit-containing channel, responsible for the basal, amiloride-sensitive Na^+ current, was also shown to participate in the regulation of glioma cell migration (431). The function of this channel appeared to be important for pro-

liferation as well, and both channel-dependent oncogenic effects involved ERK1/2 phosphorylation, a key signaling event controlling migration and proliferation of multiple cancer cells (431).

Surprisingly, not only V_r -depolarizing, Na^+ -conducting, but also V_r -hyperpolarizing, K^+ -conducting channels were implicated in promigratory and proinvasive behaviors of cancer cells. However, in the event of K^+ channels, the effects seem to be almost exclusively mediated by increased driving force for Ca^{2+} entry and associated Ca^{2+} signaling. Indeed, the member of Ca^{2+} -activated K^+ channel family, apamin-sensitive $\text{K}_{\text{Ca}2.3}$ (SK3), was found to be present in highly metastatic breast cancer cell lines (i.e., MDA-MB-435s) and breast cancer biopsies, but not in non-tumor breast tissues (406). Cells expressing $\text{K}_{\text{Ca}2.3}$ displayed high $[\text{Ca}^{2+}]_i$, which could be decreased by apamin treatment. Manipulations on $\text{K}_{\text{Ca}2.3}$ expression level or functional activity have shown that by regulating V_r and $[\text{Ca}^{2+}]_i$ $\text{K}_{\text{Ca}2.3}$ participates in the promotion of breast cancer cells migration, but not proliferation (76, 406). Furthermore, $\text{K}_{\text{Ca}2.3}$ activation in MDA-MB-435s cells is functionally coupled to Ca^{2+} entry through ionotropic purinergic P2X_7 receptor-channel ($\text{P2X}_7\text{R}$) (242). $\text{P2X}_7\text{R}$ per se is considered as potential cancer cell biomarker expressed at unusually high levels in several tumors (426). In breast cancer cells, interaction between two oncogenic channels, $\text{K}_{\text{Ca}2.3}$ and $\text{P2X}_7\text{R}$, enhanced promigratory morphological features (i.e., appearance of extensions) and increased cell migration (242).

Strong upregulation of $\text{K}_{\text{Ca}2.3}$ channel protein was also detected in melanoma cell lines, but not in normal melanocytes (75). The presence of functional $\text{K}_{\text{Ca}2.3}$ hyperpolarized melanoma cells V_r and promoted cell motility, whereas its pharmacological inhibition by apamin or shRNA-mediated knockdown depolarized V_r and decreased cell motility (75). Interestingly, melanoma cells also expressed another member of Ca^{2+} -activated K^+ channel family, $\text{K}_{\text{Ca}3.1}$, but its pharmacological inhibition had no effect on cell motility despite depolarizing V_r (75). It was hypothesized that $\text{K}_{\text{Ca}2.3}$ uniqueness in regulation melanoma cell motility may arise from its spatial distribution at cell protrusions, where it may selectively interact with Ca^{2+} entry channels within specialized signaling complexes (75). In fact, formation of such complexes has been demonstrated. In breast cancer cells, $\text{K}_{\text{Ca}2.3}$ was shown to associate with ORAI1 (76) and $\text{P2X}_7\text{R}$ (242), whereas in colon cancer cells with ORAI1/TRPC1 (186), and in both cancers these complexes tend to spatially segregate in lipid-rafts microdomains (see **FIGURE 4C**). From these examples, it is possible to conclude that enhanced migration of at least some cancers (i.e., breast, colon, and melanoma) can be considered as $\text{K}_{\text{Ca}2.3}$ oncochannelopathy associated with V_m changes (**TABLE 1**).

Although K^+ -conducting function of $K_v10.1$ does not seem to be the primary reason for its carcinogenic potential (see sect. IV), there is evidence that in breast cancer cells oncogenic function of $K_v10.1$ involves V_r hyperpolarization and concomitant increase of driving force for ORAI1-mediated Ca^{2+} entry, which specifically promotes cell migration without affecting cell proliferation (199). Establishment of an invasive phenotype in colorectal cancer cells both in vitro and in vivo was shown to directly correlate with $K_v11.1$ (HERG1) channel mRNA and protein expression as well as with K^+ current-conducting functional activity (281).

DJ ANGIOGENESIS. Neoplastic cells themselves serve as production and releasing points for VEGF-A, which promotes the formation of new blood vessels by stimulating proliferation and migration of EC, as well as for a number of alternative angiogenic factors participating in the angiogenic switch (70). On the other hand, EC proliferation and migration in response to angiogenic factors requires intracellular Ca^{2+} signaling involving both Ca^{2+} release and Ca^{2+} entry mechanisms. By keeping hyperpolarized V_r , chloride and potassium channels provide the driving force for Ca^{2+} entry and thus play an important role in regulating ECs behaviors.

Of K^+ -permeable channels, the $K_v11.1$ (HERG1) one was shown to contribute to malignancy by promoting VEGF secretion in high-grade astrocytomas (i.e., glioblastoma multiforme, GBM) (326), colorectal cancer (97, 99), and myeloid leukemia cells (99), stimulating neoangiogenesis. In colorectal cancer cells, the release of proangiogenic VEGF-A was shown to depend on $K_v11.1$ channel via quite complex multistep mechanism involving 1) functional engagement of β_1 subunit of integrin receptors (also known as CD29, hereafter CD29) by cell adhesion; 2) association between CD29 and $K_v11.1$ leading to strong potentiation of $K_v11.1$ -mediated current; 3) phosphorylation of p85 subunit of phosphatidylinositol-3-kinase (PI3K) and its association with CD29/ $K_v11.1$ to produce a single macromolecular CD29/ $K_v11.1$ /PI3K complex whose phosphorylation depends on both integrin activation and $K_v11.1$ K^+ -conducting function; 4) induction by CD29/ $K_v11.1$ /PI3K complex of Akt activation with subsequent NF- κ B-mediated transcription of hypoxia inducible factors (HIF); and 5) HIF-dependent upregulation of transcriptional activity of *VEGFA* gene and VEGF-A production (97) (**FIGURE 5, top**). Although this mechanism postulates the requirement of $K_v11.1$ -mediated K^+ current, the significance of K^+ efflux and ensuing V_r changes are not fully defined, with activity-dependent protein-protein interactions likely presenting the major mechanism. Angiogenic effects of $K_v11.1$ were confirmed in the in vivo animal model classifying colorectal cancer angiogenesis as $K_v11.1$ oncochannelopathy (**TABLE 1**). In myeloid leukemia and colorectal cancer cell lines, membrane expression of $K_v11.1$ channel, formation of CD29/ $K_v11.1$ complex, activation of the PI3K/Akt pathway, and VEGF secretion were shown to be controlled by

sigma-1 receptor (Sig1R, human gene *SIGMAR1*) (99), still enigmatic stress-activated ER-localized chaperone involved in the remodeling of Ca^{2+} homeostasis and electrical properties of cancer cells to promote their survival and aggressiveness (98), adding additional complexity to this proangiogenic mechanism.

Stimulation of VEGF secretion linked to HIF induction was also shown to depend on $K_v10.1$ (EAG1) K^+ channel expression in cancer cells (126). Preventing $K_v10.1$ channel ion conduction in the cells used to induce tumors in SCID mice failed to completely abolish tumor formation, suggesting the involvement of K^+ permeation-independent mechanisms. It was proposed that $K_v10.1$ favors tumor progression through increased VEGF-mediated angiogenesis under hypoxia characteristic of tumor microenvironment (126).

In addition to the excess of proangiogenic signals within tumor tissue, facilitated responsiveness of ECs to these signals is important for malignant angiogenesis. Several types of ion channels can contribute to such responsiveness. For instance, bFGF and VEGF were reported to specifically upregulate functional expression of $K_{Ca3.1}$ (IK) intermediate conductance Ca^{2+} -activated K^+ channel in human umbilical vein ECs (HUVEC) and human microvascular ECs (HMVEC) (183). The presence of $K_{Ca3.1}$ promoted mitogen-induced EC proliferation and angiogenesis in vivo most likely by hyperpolarizing V_r and enhancing the electrochemical driving force for Ca^{2+} influx (**FIGURE 5, bottom right**). Pharmacological $K_{Ca3.1}$ inhibitors abolished bFGF- or VEGF-induced cell proliferation in vitro and vascularization of Matrigel plugs in vivo, suggesting that $K_{Ca3.1}$ controls angiogenesis via ECs proliferation and that selective blockade of endothelial $K_{Ca3.1}$ may represent a useful strategy to prevent tumor, particularly a colonic one, angiogenesis (183, 266). As was already mentioned (see sect. IIIB2D), inhibition of spontaneous formation of microvessels and tubular structures by HMVECs in various in vitro assays could be also achieved by structurally distinct blockers of volume-regulated anion channels (VRAC) (319). The data suggested that VRAC activity may be important not only for ECs proliferation, but also for other steps of the angiogenic cascade, including migratory, adhesive, and matrix-degrading abilities of the angiogenic ECs. Here again, the involvement of background VRAC activity in angiogenesis was explained by the increase of the driving force for Ca^{2+} entry and concomitant changes in $[Ca^{2+}]_i$ (319) (**FIGURE 5, bottom right**). Importantly, chlorotoxin (CTX), a scorpion venom-derived peptide inhibitor of Cl^- conductance in glioma cells and glioma invasion (see also sect. IIIB2c) (109), and its synthetic derivatives TM-601, CA4, and CTX-23 were shown to bind to proliferating vascular ECs in vitro and to have anti-angiogenic activity both in vitro and in vivo (236, 540). However, given that Cl^- conductance similar to glioma cells has not been identified in ECs, the mechanisms of these anti-angiogenic functions remain unclear.

Most likely they involve inhibition of MMP-2, which represents important aspect of pharmacological CTX profile (109, 115, 236).

D. Mechanotransduction

Sensing mechanical stimuli and generating mechanical force are the properties characteristic to various extents to all cell types, making these properties the most basic in all living uni- and multicellular organisms. Malignant transformation is associated with dramatic changes in intratumoral mechanical strain. Cancer cells and ECs within an expanding tumor experience excessive compressive and shear forces due to increased extracellular matrix (ECM) stiffness and high interstitial pressure heightened by the growth against the constraining stroma. Such forces could stimulate proliferative, migratory, and invasive behaviors of cancer cells via a mechanosensitive ion channel in their plasma membrane (25) as well influence tumor angiogenesis (4). On the other hand, migratory and invasive behaviors requires generating mechanical force involving cytoskeletal and adhesion machinery in which mechanosensitive ion channels play the role of feedback sensors.

1. Mechanosensitive ion channels

As was already mentioned (see sect. IIIB1), cell reaction to plasma membrane stretch resulting from changes in cell volume is considered to be phenomenologically and mechanistically distinct from membrane deformation occurring in response to mechanical insults of other modalities, such as shear stress, local touch, local pressure, and changes in lipid bilayer microcurvature. Consequently, volume-regulated ion channels, which were discussed in section IIIB1, are generally distinguished from the so-called mechanosensitive ion channels whose activation is modulated by aforementioned mechanical insults (416); however, the properties of volume sensitivity and mechanical sensitivity are not mutually exclusive, and some channels can exhibit both. Since all types of mechanical stimulation eventually result in plasma membrane stretch, ion channels that respond to such stimulation are often referred to as stretch-activated channels (SAC) or mechanically gated channels (MGC). In fact, functional properties of basically all known ion channels can be to various extents affected by membrane stretch. However, only those of them that are endowed with specific mechanosensitive gating mechanism and whose activation (i.e., open probability) in response to mechanical insult can generate sufficient membrane current to induce distinct cellular response can be attributed to the class of stretch-activated ion channels. The representation of this class of channels by individual types throughout the animal kingdom is species specific, and in mammals the members of four channel families, ENaC/ASIC (370), TRP (310), K_{2P} (56), and PIEZO (214, 511), have been suggested as candidates to the class of stretch-activated channels. In addition, transmem-

brane channel-like proteins 1 and 2 (TMC1 and TMC2), tetraspan membrane protein of hair cell stereocilia (TMHS), and transmembrane inner ear expressed protein (TMIE) are considered as components of the hair cell mechanotransducer complex (416).

Stretch-activated members of all but K_{2P} channel families are rather nonselective cationic channels displaying variable permeability to Ca^{2+} . Therefore, their activation can do both, depolarize V_r and induce Ca^{2+} entry, which is crucial for triggering and maintaining $[Ca^{2+}]_i$ signals regulating cell response(s). On the other hand, stretch-activated representatives of K_{2P} channel family are K^+ selective, which is why they regulate cellular responses via setting up V_r values. It should be mentioned, however, that many channels, which exhibit membrane stretch-dependent mode of activation, are often characterized by multiplicity of activation mechanisms, meaning that they can react to several physical and/or chemical stimuli of which membrane stretch is not the sole one. Only for PIEZO1 and PIEZO2 whose cloning strategy was specifically designed to identify mechano-gated channels (95), membrane stretch seems to represent the primary activating mechanism.

2. Ion channels as determinants of tension-effect relationships in cancer

Carcinogenesis is accompanied by ever-increasing mechanical strain within tumor which can exaggerate all aspects of malignant behaviors, including growth, metastasizing, angiogenesis, and treatment responsiveness. The most obvious cancer hallmark in which stretch-activated ion channels may be critically involved is tissue invasion and metastasis, as it is associated with enhanced migratory behaviors of cancer cells requiring creation of repetitive local tensions in the plasma membrane. Without their ability to move, tumor cells would not be able to metastasize. Depending on tumor microenvironment and cell morphology, cancer cells employ different patterns of migratory behaviors. The fastest types of migration, referred to as amoeboid type and mesenchymal type, are characteristic of cells migrating individually or within the loose streams, and having round or elongated (spindle-like) morphologies in the absence of significant cell-cell and cell-matrix interactions, whereas stronger cadherin-mediated cell-cell and integrin-mediated cell-ECM interactions promote slower, collective-type migration characteristic of cells retaining distinct epithelial morphology (reviewed in Refs. 91, 161). However, irrespective of cell morphology and adherence strength, a cell's locomotion requires protrusive activity necessarily involving membrane stretch.

Stretch-activated Ca^{2+} -permeable channels are thought to be important transducers of local mechanical stress into $[Ca^{2+}]_i$ signal (127, 286, 350). Indeed, several types of TRP members that exhibit stretch-dependent mode of activation, such as TRPC1 (141, 148), TRPV1 (523), TRPV4 (153,

329, 523), and TRPM7 (333, 528) have been implicated in the adhesive and migratory behaviors of various cells, including cancer ones. While many of the relevant studies were performed on non-tumor cells, and conclusions regarding mechanosensitivity of certain TRP members are still quite controversial (e.g., Ref. 180), interpolation of the obtained results to cancer cells can be instructive in terms of future directions. For instance, TRPC1 channel was implicated in the mechanisms causing pressure-induced activation of tumor-associated pancreatic stellate cells (PSCs) (148). These cells form dense fibrotic stroma in pancreatic ductal adenocarcinoma (PDAC) which further contributes to elevated pancreatic tissue pressure. Another Ca^{2+} -permeable TRP member, TRPM7, was shown to mediate pressure-induced Ca^{2+} entry and $[\text{Ca}^{2+}]_i$ rise in human bone marrow mesenchymal stem cells (MSCs), which is required for mechanostimulated osteogenesis (539). In analogy with this finding and in view of elevated intratumoral pressure, one can assume that similar pressure-induced TRPM7 activation and concomitant Ca^{2+} signaling may be important for promoting mesenchymal-epithelial transition (MET) and clonal outgrowth of circulating tumor cells, exiting the bloodstream to form micrometastases. In fact, the significance of TRPM7 in the opposite process of epithelial-mesenchymal transition (EMT), by which tumor microenvironment signals trigger epithelial cells to lose their polarity and cell-cell adhesion to adopt migratory and invasive properties, has been suggested (111). In MDA-MB-468 breast cancer cells, EMT induction by EGF specifically involved transient TRPM7-mediated increase of $[\text{Ca}^{2+}]_i$ followed by STAT3 phosphorylation and expression of the EMT marker vimentin (111) (FIGURE 4E). It was also shown that TRPM7 overexpression in HEK-293 cells induces cell rounding and loss of cell adhesion (470), which is quite reminiscent of cancer cells transition to amoeboid- and mesenchymal-type morphologies. The data indicated that this occurs due to preferred TRPM7 localization to the peripheral adhesion complexes with m-calpain, a member of calpain family of Ca^{2+} -dependent protease specifically implicated in focal adhesion disassembly and deadhesion (470). It was concluded that TRPM7-mediated Ca^{2+} influx into peripheral adhesion complexes, presumably resulting from local membrane deformations, regulates cell adhesion by controlling m-calpain activity (FIGURE 4E).

Stretch-dependent mode of TRPM7 activation was specifically implicated in the flicker-like $[\text{Ca}^{2+}]_i$ surges at the leading lamella of migrating fibroblasts (528). These flickers occurred due to interaction of TRPM7-mediated Ca^{2+} entry and IP_3R -mediated Ca^{2+} release and were imperative to guide migration towards a chemoattractant (528) (FIGURE 4F, right). Since local membrane tensions at the front are common to all migrating cells, similar TRPM7-dependent mechanism may take place also in cancer cells, although the end result may depend on the proximity of Ca^{2+} -dependent effectors, which may be cancer type specific. Moreover,

given the unique functional properties of TRPM7, such as permeation not only to Ca^{2+} , but also to Mg^{2+} , inhibition by intracellular Mg^{2+} and Mg-nucleotide complexes (i.e., Mg-ATP), and possession of COOH-terminal domain with intrinsic serine/threonine kinase activity (509), generation of stretch-activated Ca^{2+} influx may represent only one mechanism in much broader range of TRPM7 effects. In particular, an essential role in TRPM7-mediated control of cytoskeletal organization, adhesion dynamics, and cell migration belongs to its kinase domain-dependent phosphorylation of the components of actomyosin complex independent of ion-conducting function (see sect. IV; reviewed in Ref. 509).

TRPM7 expression is positively correlating with metastasizing of several primary tumors and in vitro migration of respective cancer cells (TABLE 1), including breast cancer (191, 333), pancreatic adenocarcinoma (434, 552), nasopharyngeal carcinoma (80), ovarian cancer (517), and lung cancer (165). In breast cancer cell lines, TRPM7 was proposed to be a part of mechanosensory complex driving metastasis formation by modifying focal adhesion number, cell-cell adhesion, and polarized cell movement primarily through its kinase activity and myosin IIA heavy chain (MHC-II) phosphorylation (191, 333) (FIGURE 4E, right). In pancreatic adenocarcinoma cell lines, in which both cell migration and intracellular Mg^{2+} levels depended on TRPM7 expression, and which impaired migration due to TRPM7 knockdown could be restored by elevation of extracellular Mg^{2+} , TRPM7 was suggested to regulate migration by Mg^{2+} -dependent mechanisms due its Mg^{2+} permeation, although the events downstream of Mg^{2+} entry remain to be elucidated (434). Only in nasopharyngeal carcinoma cells Ca^{2+} signaling involving basal or bradykinin-stimulated Ca^{2+} influx via TRPM7 and Ca^{2+} release from ER via RYRs by a CICR mechanism was shown to be required for cell migration (80), although specifically stretch-dependent mode of TRPM7 activation was not implicated (FIGURE 4F, left). Thus, despite being formally mechanosensitive, TRPM7 in cancer cells realizes its promigratory and metastatic functions via diversity of mechanisms among which stretch-activated Ca^{2+} entry may not even be the primary one.

Formation of structurally and functionally abnormal tumor vasculature, in addition to the action of soluble angiogenic stimuli (e.g., VEGF), is largely dependent on continuous remodeling of extracellular matrix (ECM) elasticity under the influence of various intratumoral factors. Tumor ECs form abnormal vessels because they lose their ability to sense and respond to these physical cues by exhibiting aberrant mechanosensitivity towards ECM stiffness (171). It was shown that tumor-derived ECs from transgenic adenocarcinoma mouse prostate (TRAMP) model display lower levels of mechanosensitive TRPV4 channel expression and reduced TRPV4-mediated Ca^{2+} influx compared with nor-

mal mouse ECs (4). Spreading of ECs on gelatin gels of increasing stiffness inversely correlated with TRPV4 expression levels, suggesting the requirement of TRPV4 for conferring mechanosensitivity of ECs towards ECM. In addition, vessel malformations and growth of xenograft tumors were enhanced in TRPM4-knockout versus wild-type mice (4). Altogether, these results prompted the conclusion that TRPV4 is critical mechanosensing channel in modulating tumor angiogenesis and that absence of TRPV4 can lead to tumor ECs spreading, migration, and abnormal angiogenesis. Mechanistically, TRPV4 was proposed to act as endogenous mechanosensing upstream regulator of Rho/ROCK signaling pathway involved in proadhesive and promigratory behaviors with lower TRPV4 expression and activity overstimulating Rho/ROCK signaling (489). TRPV4 is one of the rare examples when it is not excess, but deficiency of Ca^{2+} -permeable channel which promotes cancer hallmark. Given structural and functional homogeneity of endothelial cells, it would not be unreasonable to qualify most tumor angiogenesis as TRPV4 oncochannelopathy linked to aberrant mechanosensitivity (TABLE 1).

Comparison of biophysical properties of endogenous mechanoactivated currents in malignant MCF-7 breast cancer cell line with biophysical fingerprints of heterologously expressed PIEZOs allowed to conclude that these currents are likely mediated by PIEZO1 (i.e., FAM38A) channel function (300). In addition, MCF-7 cells expressed significantly higher endogenous PIEZO1 mRNA levels compared with the nonneoplastic MCF-10A cells, a model cells for normal mammary gland, which also lacked mechanoactivated current. Motility and velocity of MCF-7, but not of MCF-10A cells could be suppressed by tarantula spider *Grammostola spatulata* mechanotoxin 4 (GsMTx-4), which is specific blocker of mechanoactivated channels, including those from PIEZO family. Finally, high level of PIEZO1 mRNA expression in the primary tumor turned to be associated with significantly shorter survival times of breast cancer patients (300), underscoring oncogenic roles of PIEZO1 in breast cancer most likely via promotion of migration, invasion and metastatic propagation.

PIEZO1 has been also implicated in gastric cancer cell migration with PIEZO1 knockdown decreasing migratory capacity of gastric cancer cell lines in the in vitro assays by downregulating the expression of β_1 -subunit of integrin (i.e., CD29) (547). However, these effects were attributed to PIEZO1 partnership and interaction with trefoil factor family-1 (TFF1) protein, a protein specific to mucus-secreting cells with the function in mucosal protection and repair through stimulation of cell migration into the lesion area. PIEZO1 and TFF1 partnership was required for regulating the expression of integrin subunits (547); however, no evidence on the involvement of PIEZO1 mechanosensitive channel function was presented. PIEZO1 has also been shown to reside in the ER membrane and to regulate β_1 -

integrin affinity in mechanosensitive channel-independent manner (331). In highly aggressive SCLC cell lines much lower PIEZO1 level compared with normal lung epithelial cells was implicated in β_1 -integrin inactivation and promotion of rapid, anchorage-independent, amoeboid-type SCLC cells migration (331). It cannot be excluded that deficit of PIEZO1 also contributes to cell rounding and ultimately to amoeboid-type migration by impairing the ability of a cancer cells to sense their environment through the loss of mechanosensory input.

Yet another PIEZO family member, PIEZO2, was recently shown to play a significant role in promotion of glioma development (546) primarily through promotion of angiogenesis (TABLE 1). PIEZO2-depleted glioma cells, used for subcutaneous tumor implantation in nude mice, displayed substantially reduced tumorigenic potential featured by increased tumor cell death, depressed tumor cell proliferation, decreased tumor vascular density, and vascular leakage. In independent experiments on human umbilical vein ECs (HUVECs) PIEZO2 knockdown decreased HUVECs basal $[\text{Ca}^{2+}]_i$ levels, migration, and tube formation, while in coculture systems with glioma cells, PIEZO2-depleted HUVECs inhibited glioma cells proliferation, migration, and invasion. Finally, it was established that mechanistically effects of PIEZO2 are associated with Ca^{2+} -dependent upregulation of Wnt11 expression and secretion by ECs, which by acting in an autocrine manner enhanced angiogenic potential of ECs via β -catenin-dependent signaling (546).

Overall, the roles of mechanosensitive PIEZOs in cancer hallmarks is far from being elucidated. From what is already known, it is likely to be cancer type-specific and involving several mechanisms and signaling pathways.

Of 15 mammalian K_{2P} K^+ -channel family members (178), only 3, $\text{K}_{2P2.1}$ (TREK1), $\text{K}_{2P4.1}$ (TRAAK), and $\text{K}_{2P10.1}$ (TREK2), have been shown to display distinct membrane stretch-dependent mode of activation (56). In addition to being mechanosensitive, the activity of these channels can be modulated by a number of other physical and chemical stimuli including lipids, polyunsaturated fatty acids (PUFAs), temperature, phosphorylation, and pH, making them polymodal convertors of various signals into changes of cell's V_r (56, 392). Analysis of the online cancer microarray database revealed that of mechanosensitive K_{2P} members, $\text{K}_{2P4.1}$ does not show altered expression in cancers (534). Of the remaining two, $\text{K}_{2P2.1}$ overexpression and function was implicated in abnormal prostate cancer cells proliferation (512, 561), whereas $\text{K}_{2P5.1}$ was found to be important for 17β -estradiol-induced proliferation of estrogen receptor α positive (ER^+) breast cancer cell lines (8). Furthermore, in bladder cancer cell lines, $\text{K}_{2P10.1}$ expression specifically correlated with the size of membrane K^+ currents in response to the known physiological channel-

activating stimuli, including mechanical stretch of plasma membrane, arachidonic acid (AA), and intracellular acidification (386). siRNA-mediated $K_{2P10.1}$ knockdown in bladder cancer cells resulted in V_r depolarization and suppression of proliferation through cell-cycle arrest at the G_0/G_1 phase (386). Overall, the data suggest that carcinogenic significance of mechanosensitive K_{2P} channels is mainly realized via regulation of V_r during proliferation in response to tumor intrinsic and microenvironmental factors affecting channels activation; however, specific contribution of stretch-dependent mode of activation is hard to discern.

E. Microenvironment Regulation

Solid tumors provide complex, heterogeneous local microenvironment for cancer cell growth, survival, and motility whose major features include elevated interstitial pressure, acidic pH, low nutrient levels, insufficient and fluctuating oxygen supply, continuous remodeling of ECM elasticity, excess of soluble growth signals, and deficiency of growth inhibitory signals (161, 216). The structural elements of tumor microenvironment include ECM and stromal cells, with the former being composed of proteoglycans, hyaluronic acid, and fibrous proteins (collagen, fibronectin, laminin), and the latter represented by fibroblasts, adipocytes, ECs, and various types of immune cells (531). Cancer progression is strongly influenced by reciprocal tumor-stroma interactions, and cancer cells play an active role in the recruitment and metabolic reprogramming of stromal cells as well as in the dynamic remodeling of ECM to create a favorable background for sustaining tumor growth. In view of high intratumoral pressure, special importance in such interactions belong to mechanosensitive channels (see sect. IIID).

Malnutrition and low oxygenation (hypoxia) due to abnormal vasculature inadequate in meeting the oxygen and nutrient demands often aggravated by the low hematocrit of cancer patients are believed to be the most critical deficiencies within tumors, which trigger a number of prosurvival responses that eventually cause tumor cells to exhibit resistance to cancer therapies. Autophagy and activation of transcription factors of the hypoxia-inducible factors (HIF) family are key to these prosurvival responses. Autophagy is a cellular pathway that normally controls lysosomal-dependent degradation and recycling of damaged or superfluous proteins and organelles. However, in cancer, autophagy turns into an alternative, “self-digestion-sustained” energy source, helping cancer cells to withstand metabolic stress (reviewed in Refs. 163, 328, 532). HIFs, on the other hand, become activated in response to a drop in partial oxygen pressure to hypoxic levels, thereby linking low oxygen condition to expression of a panel of genes that assist cells to adapt to hypoxic environment (e.g., glycolysis enzymes to catalyze O_2 -independent ATP synthesis, VEGF to promote angiogenesis) (reviewed in Refs. 21, 112).

Another important feature of the tumor microenvironment is extracellular acidosis, which is a consequence of the high rate of glycolysis in cancer cells, leading to the production of glycolytic byproducts, lactate and H^+ (108, 477). To compensate for such production, cancer cells develop redundant mechanisms for facilitated lactate and H^+ efflux, eventually resulting in the maintenance of alkaline intracellular and acidic extracellular pH in tumor cells compared with normal ones (108, 477).

1. Ion channels as sensors of microenvironmental cues (PO_2 , pH, mechanical stress)

There are two ways that ion channels can be involved in promoting cancer hallmarks associated with microenvironmental conditions within tumor. First of all, ion channels can act as direct sensors of such conditions converting environmental cues into some kind of cancer cells' response. Alternatively, expression or activity of certain types of ion channel(s) may be a part of secondary cancer cells' adaptive reaction to the microenvironmental changes. In the first case, ion channels must be endowed with the gating mechanism capable of sensing specific physical or chemical parameter of the microenvironment, whereas in the second case ion channel may be of any type provided that its function enhances cancer cell's adaptive potential.

Ion channels whose activity is regulated by mechanical stress due to changes in cell volume or localized deformations of plasma membrane as well as their oncogenic significance were discussed in section III, *B* and *D*; therefore, here we only focus on pH- and O_2 -sensitive channels.

pH and O_2 , similarly to mechanical stress, can be considered as universal nonspecific stimuli, to which to a certain extent all channels are sensitive via protonation of an amino acid side chains, oxidative phosphorylation or O_2 -dependent synthetic and degradation mechanisms. Several members of voltage-gated (K_v), background (K_{2P}), and Ca^{2+} -activated (K_{Ca}) K^+ channel families can be specifically inhibited by hypoxia, inducing depolarization and in such a way participating in the transduction of hypoxic stimuli in specialized oxygen-sensing cells (179, 390, 525). Of these channels, the background $K_{2P3.1}$ (TASK1) one is also highly sensitive to the blockade by external protons (390), making it an important regulator of cell V_r in response to both hypoxia and acidification. However, protons can depolarize V_r not only by inhibiting K^+ -selective channels, but also by activating a completely different set of Na^+ - and Ca^{2+} -permeable ones, acid-sensing ion channels (ASICs). Mammalian ASICs comprise a group of at least six channel-forming protein subunits, ASIC1a-b, ASIC2a-b, ASIC3, and ASIC4, arising from alternative splicing of four genes (ASIC1–4) and structurally belonging the broader family of degenerin/epithelial Na^+ channel (DEG/ENaC) proteins (reviewed in Ref. 252). All, but ASIC2b and ASIC4, subunits can assemble into homo- or heterotrimeric structures

to form proton-activated, amiloride-inhibited cationic channels with variable pH sensitivity, $\text{Na}^+/\text{Ca}^{2+}$ permeability, and characteristics of activation and desensitization. ASIC2b alone is not operable as homomer, but can influence channel properties in heteromeric assemblies with other subunits, whereas ASIC4 does not exhibit any functional significance. ASIC1 was shown to complex also with ENaC subunits to produce channel with unique gating, ion conduction, and pharmacology essential for the maintenance of the glioma cell phenotype (e.g., Refs. 332, 431). ASICs are preferentially distributed in the nervous system where they modulate synaptic transmission and neuronal excitability in a pH-dependent manner, but their expression is also found in other cell types, taste receptors, hair cells, different cells in the retina, vascular myocytes, endothelial cells, and immune cells, in which they mediate cell responsiveness to acidification as well as to unconventional stimuli (i.e., stretch).

As part of polymodal nature of TRP channel activation, some of their representatives exhibit sensitivity to the acidic pH (504). In particular, protons can potentiate the responsiveness of heat-sensitive TRPV1 channels to the extent that moderate acidification ($\text{pH} \leq 5.9$) per se becomes an activating stimuli at normal physiological temperatures and in the absence of any chemical agonists (490). The basal activity of mechanosensitive, intracellular MgATP-regulated and kinase domain-containing TRPM7 channel can be also upregulated by acidification of the extracellular milieu to $\text{pH} \leq 6$ (246), suggesting that TRPM7 may play a role under acidic pathological conditions.

2. Changes in microenvironment in cancer

Autophagy and activation of HIF are key cellular pro-survival responses triggered by deficient nutrients and O_2 supply, characteristic of tumor microenvironment.

A) MALNUTRITION AND AUTOPHAGY. The role of autophagy in cancer progression is rather ambiguous. On the one hand, it is a potent defensive mechanism against initiation and development of tumors at early stages, but, on the other hand, by representing a key pathway in adaptation to stress, it can also promote the survival and malignization of established tumors at later stages. At cancer onset, autophagy opposes malignant transformation due to 1) degradation of oncogenic proteins, 2) elimination of the endogenous sources of potential mutagens and prevention of genomic instability, 3) disposal of defective mitochondria and normalization of bioenergetics, 4) confinement of inflammatory responses, and 5) promotion of proliferative arrest (cell senescence) and specific form of autophagic cell death (163). However, once malignant transformation has occurred, autophagy turns from cancer foe into cancer ally by helping tumor cells to 1) adapt to the O_2 - and nutrient-deficient conditions and evade apoptosis in response to intrinsic and microenvironmental pro-apoptotic signals, 2) develop resistance to ther-

apy-induced cell death, 3) sustain tumor relapse by cancer cells driven to the state of dormancy or senescence by anticancer therapy, and 4) support EMT (163).

Autophagy is a lysosomal trafficking pathway which in its most common form, lacking selectivity towards the type of sequestered material, is referred to as macroautophagy. It is based on the formation of matter-encapsulating membrane vesicles called autophagosomes, which deliver unnecessary cytoplasmic content to lysosomes. The autophagy machinery in mammalian cells involves activation of over 20 autophagy-related (Atg-related) proteins and is highly regulated through the action of various kinases, phosphatases and GTPases (reviewed in Refs. 275, 422). Autophagy initiation is critically governed by the mammalian target of rapamycin (mTOR) kinase, acting within the multiprotein mTOR complex 1 (mTORC1). mTORC1 plays a role of sensor of various stress stimuli (growth factors, starvation, calcium, hypoxia, oxidative stress, low energy), and in the absence of those keeps the autophagosome formation cascade under basal inhibition. mTORC1 is in turn negatively regulated by AMP-activated protein kinase (AMPK), which when activated (i.e., under low ATP/AMP ratio indicative of unfavorable cellular energetics) phosphorylates mTORC1 components to remove its restraining control on autophagosome formation and induce autophagy. Rise of intracellular Ca^{2+} leads to phosphorylation and activation of AMPK via Ca^{2+} /calmodulin-dependent kinase kinase- β (CaMKK- β , also known as CaMKK2), whereas activated AMPK in turn inactivates mTORC1 to initiate accumulation of autophagosomes (222). Thus $[\text{Ca}^{2+}]_i$ elevations can serve as an important macroautophagy regulator via CaMKK- β /AMPK/mTORC1 signaling pathway, and components of Ca^{2+} -handling toolkit can be viewed as viable determinants for influencing oncogenesis through the control of autophagy.

Within the Ca^{2+} -handling toolkit, IP_3R Ca^{2+} release channel of the ER deserves special attention in the context of autophagy, as it not only contributes to $[\text{Ca}^{2+}]_i$ rises through Ca^{2+} mobilization, but its function is important for maintaining cellular bioenergetics. Indeed, constitutive low-level IP_3R -mediated Ca^{2+} siphoning from the ER to the mitochondria within ER-mitochondria contact sites is a prerequisite for efficient mitochondrial respiration (67). Disruption of such IP_3R -dependent ER-mitochondria Ca^{2+} signaling was shown to reduce ATP production and activate AMPK to promote autophagy as a pro-survival mechanism (67, 68). Notably, autophagy induced by deficiency in IP_3R expression and/or function, although correlating with enhanced AMPK activity, does not seem to involve canonical mTORC-dependent pathway (67, 68). In practical terms, induction of autophagy, as a specific form of cell death, via IP_3 depletion and interruption of IP_3R -mediated ER-to-mitochondria Ca^{2+} transport, was shown to underlie sensitizing effect of valproic acid (VPA) to chemothera-

peutic agents (i.e., doxorubicin) in the treatment of lymphoma (244). Moreover, tumorigenic cancer cells more than normal cells depend on constitutive IP₃R-mediated ER-to-mitochondria Ca²⁺ transfer for their survival (69), potentially providing opportunities for selective therapeutic targeting.

Another mechanism via which the components of Ca²⁺-handling toolkit can interfere with autophagy involves specific interactions of the Atg-related protein Beclin-1 (human gene *BECN1*, ortholog of the yeast *Atg6*). Beclin-1 is part of a multiprotein Beclin-1 complex, acting as a platform for recruiting other Atg proteins to the process of autophagosome biogenesis (275, 422). Beclin-1 contains conserved Bcl-2 homology-3 (BH3) domain shared by several pro- and antiapoptotic members of Bcl-2 family of proteins (297). The presence of this domain in Beclin-1 structure is necessary and sufficient for binding of antiapoptotic, BH-multi-domain Bcl-2 or Bcl-X_L proteins to Beclin-1, which down-regulates autophagy function. In contrast, pro-apoptotic, BH3-only proteins (i.e., those containing only a single BH3 domain, such as Bad) can competitively disrupt the interaction between Beclin-1 and Bcl-2/Bcl-X_L to liberate Beclin-1 from its Bcl-2/Bcl-X_L-conferred inhibition and trigger autophagy (297). Thus Beclin-1 and Bcl-2 protein interactions provide the basis for the interdependence and direct correlation between autophagy and apoptosis. In view of the recognized function of antiapoptotic Bcl-2 proteins in the control of ER, mitochondria and plasma membrane Ca²⁺ transport involved in cell death and survival (507), this gives another dimension on how deregulation of Ca²⁺-handling toolkit in cancer can contribute to both processes. Notably, BH4 domain of Bcl-2 mediates its interaction with IP₃R on the ER to inhibit IP₃R-mediated Ca²⁺ release and ensuing propensity to Ca²⁺-dependent apoptosis (430). Furthermore, Beclin-1 interactome may include IP₃R as well: it has been proposed that Atg-related Beclin-1, antiapoptotic Bcl-2 and Ca²⁺-releasing IP₃R can enter into a trimolecular interaction in which Bcl-2 plays a role of bonding moiety, and IP₃R acts as autophagy suppressor by virtue of its abundance independent of its Ca²⁺-releasing function and subcellular localization (508).

Remodeling of Ca²⁺ homeostasis in cancer keeps ER under constant stress due to a decrease in its Ca²⁺ content and ensuing perturbations in the ER lumen environment. Although ER stress is potentially a pro-apoptotic factor (418), it can also trigger autophagy through the unfolded protein response (UPR) signaling, as part of pro-survival mechanism (223, 364). Overall, the dependence of autophagy on Ca²⁺ and molecular components of Ca²⁺-handling toolkit is multifactorial, and the significance of each mechanism in malignant transformation may be cancer cell type and context specific, as well as be determined by the prevalence of specific microenvironmental triggers.

Senescence, a state in which cells stop to divide, is one of the primary defense responses against neoplastic transformation caused by oncogenes activation or tumor suppressor genes inactivation, which irreversibly arrests the growth of affected cells (reviewed in Ref. 170). Autophagy, as a pro-survival stress response, is required for efficient establishment of the oncogene-mediated senescence phenotype (555). Although senescent cells do not proliferate, they still maintain the so-called senescence-associated secretory phenotype (SASP), enabling them to release into the microenvironment a wide range of pro-inflammatory and mitogenic factors that may influence the growth and/or survival of neighboring cells in a paracrine manner. If the SASP involves autophagy, it may support disease relapse and reduce the efficacy of anticancer therapy (170). The role of ion channels and Ca²⁺ homeostasis in the crosstalk of the two processes in cancer is only beginning to unfold, and the related mechanisms still await their deciphering (146).

Aside from aforementioned IP₃Rs, Ca²⁺-permeable channels that have been implicated in autophagy regulation in various cells include: TRPs from several subfamilies, canonical (TRPC) TRPC1 (472), mucolipin (TRPML), TRPML1 and TRPML3 (262, 505), vanilloid (TRPV) TRPV1 (145), melastatin (TRPM) TRPM3 (197) and TRPM7 (365) as well as endolysosomal two-pore channels (TPC) (168). Of these channels, TRPMLs and TPCs, as being primarily localized to the endolysosomal compartments, were proposed to modulate autophagic flux on the level of autophagosome-lysosome fusion, whereas others via Ca²⁺ influx and ensuing increases in [Ca²⁺]_i (reviewed in Ref. 267, 471).

Clear cell renal cell carcinoma (ccRCC) is a malignant kidney cancer distinguished by early loss of VHL tumor suppressor leading to the accumulation of HIF (about VHL and HIF; see sect. III E2B) and induction of HIF-response genes, promoting tumor growth (197). Human kidney is a rich source of osmolarity-sensitive, spontaneously active member of melastatin TRP-channel family, TRPM3, which is implicated in the regulation of renal Ca²⁺ homeostasis (186), and whose expression is upregulated in ccRCC. It was shown that TRPM3 contributes to ccRCC growth by providing Ca²⁺, and potentially Zn²⁺ influx to stimulate pro-survival autophagy (197). Studies revealed that TRPM3-mediated Ca²⁺ influx stimulates autophagy via CaMKK2/AMPK signaling with upstream activation of essential for early steps of autophagosome biogenesis Atg-related ULK1 protein (human gene *ULK1*, ortholog of the yeast *Atg1*), but without mTOR involvement (197). Furthermore, the whole process appeared under the negative control from two types of microRNA, mir-204 and mir-214, whose expression is in turn regulated by VHL with loss of VHL resulting in the loss of both miRs and activation of autophagic pathway (197). Thus escape from VHL tumor suppressor control contributes to the growth of ccRCC via activation of TRPM3-dependent autophagy. Although in

vivo data are still missing, given the relative specificity of TRPM3 to human kidney ccRCC can be tentatively viewed as TRPM3 oncochannelopathy associated with pro-survival autophagy induction (TABLE 1).

Overall, the information on specific remodeling of cellular channelome in cancer-related autophagy is still quite limited. Pro-survival basal autophagy in metastatic melanoma cell lines (M16, M28, and JG) was shown to be supported by the activity of $\text{Ca}_v3.1$ and $\text{Ca}_v3.2$ T-type VGCCs, as several of their chemically unrelated pharmacological blockers or si-RNA-mediated silencing inhibited the constitutive autophagy and promoted apoptosis via induction of ER stress (110). It was suggested that T-type VGCCs-mediated Ca^{2+} influx in melanoma cells is required for autophagolysosomes formation, and its decrease would impair the turnover of autophagic vesicles (110). Interestingly, in another melanoma cell line (A375), but not in nontransformed skin cells, the $\text{K}_v11.3$ K^+ -channel (alias HERG3, gene *KCNH7*), which is a close relative of oncogenic $\text{K}_v11.1$ (HERG1), was proposed as a novel mediator of pro-survival autophagy, contributing to cellular senescence (401). The data suggested that stimulation of $\text{K}_v11.3$ with its NS1643 agonist leads to activation of AMPK via yet unknown mechanism to initiate both autophagy and cellular senescence in which autophagy serves as a survival mechanism (401).

B) HYPOXIA AND HIF. HIF is a heterodimeric complex of an oxygen-sensitive HIF- α and stable HIF- β subunits of which HIF-1 α and HIF-1 β represent the most conserved and ubiquitous isoforms. Under normoxic conditions, HIF-1 α binds to VHL, which targets it for proteasomal destruction.

Overexpression of HIF-1 α and loss of VHL in melanoma cells under hypoxic conditions were shown to be responsible for the transient increase in mRNA levels of Ca^{2+} -activated $\text{K}_{\text{Ca}2.2}$ (SK2) and $\text{K}_{\text{Ca}3.1}$ (IK) K^+ channels, which in turn correlated with enhanced cell proliferation (483). K_{Ca} channel blockers, charybdotoxin (ChTX) and apamin, prevented hypoxic cell proliferation, indicating that the mechanism linking HIF-dependent transcriptional activity and malignant melanoma cells proliferation under hypoxic conditions involves activation of these channels, leading to either perturbations in cell volume regulation during cell cycle progression or increased driving force for Ca^{2+} entry (483).

Although hypoxia represents the primary insult for HIF-1 activation, cancer cells can employ a number of nonhypoxic stimuli for activating HIF-1 complex to enhance malignant features even under normal oxygen levels, or normoxia (273). A member of canonical subfamily of TRP channels, TRPC6, is weakly expressed in normal hepatocytes, but becomes highly expressed in liver carcinoma samples, promoting cell proliferation (136). Moreover, in HCC

cells, the development of multidrug resistance (MDR), EMT, HIF-1 signaling, and DNA damage repair were all shown to be Ca^{2+} dependent requiring sustained TRPC6-mediated $[\text{Ca}^{2+}]_i$ increase with STAT3 activation downstream TRPC6/ Ca^{2+} signaling (530).

Interesting interplay between TRPM2 channel and HIF-1 α or -2 α (HIF-1/2 α) function was recently described in neuroblastoma cells (79). $\text{Ca}^{2+}/\text{Na}^+/\text{K}^+$ -permeable TRPM2 channel is known as being activated by free intracellular ADP-ribose (ADPR), which is produced in the mitochondria or by the enzyme poly(ADPR) polymerase (PARP) in response to oxidative stress (155). Suppression of TRPM2 function in neuroblastoma cells due to overexpression of its dominant negative short splice isoform was shown to decrease HIF-1/2 α and increase VHL mRNA levels, reduce expression of HIF-1/2 α target pro-survival and proangiogenic proteins, decrease cell viability, increase sensitivity to doxorubicin, and contain the growth of xenograft tumors in nude mice (79). Antitumor effects of compromised TRPM2 activation could be reverted by gain of HIF-1/2 α function, suggesting that TRPM2 is important for tumor growth and for cell viability and survival through modulation of HIF-1/2 α signaling (79).

$\text{K}_{2p3.1}$ (TASK1, *KCNK3*) K^+ channel is known to be hypoxia and pH inhibited (see sect. III E1); therefore, its activation in oxygen-deficient and acidic tumor microenvironment should be limited. Consistent with this, $\text{K}_{2p3.1}$ was found to be even significantly underexpressed across the several common human cancer types (534). Nevertheless, different NSCLC cell lines demonstrate variable levels of TASK1 expression, and in those of them which displayed a high level of expression, a pH- and hypoxia-inhibited K^+ current typical of TASK1 could be detected (292). This current contributed to the hyperpolarized cell's V_r , and its presence was associated with enhanced apoptosis resistance and proliferation rate of NSCLC cells (292). It was suggested that TASK1 might act as a pH and hypoxia sensor, facilitating proliferation NSCLC cells in well-perfused tumor areas with higher oxygen levels and normal pH. The data suggested that TASK1 channel might regulate NSCLC cell apoptosis and proliferation by promoting Na^+ gradient-driven nutrient transport across the plasma membrane which depends on the V_r setup by TASK1 activity (292).

C) ACIDIFICATION. The low pH of the extracellular microenvironment is known to promote tumor growth and metastasis. However, in view of the fact that protons can hardly be regarded as selective ligands, the way of how the tumor cells sense the acidic signal to activate appropriate response may be cancer type specific. Proton-gated cationic channels from ASIC family (see sect. III E1) are probably the best candidates for this role, as by being Na^+ and Ca^{2+} permeable they can directly transform the decrease of extracellular pH into depolarization and Ca^{2+} influx. Indeed, elevated ex-

pression and function of ASIC1 channel was implicated in the regulation of glioma cell proliferation and migration (431), in HCC cell migration and invasion (248), and in the pathogenesis of breast cancer (193) in response to acidic microenvironment. In the event of glioma cells, ASIC1 activation was shown to engage ERK1/2 signaling (431), whereas in breast cancer ASIC1-mediated Ca^{2+} influx appeared to be critical for acidosis-induced generation of reactive oxygen species, downstream activation of NF- κ B transcription factor, and tumor cell invasion (193). Interrogation of the Cancer Genome Atlas breast invasive carcinoma data set indicated that alterations of ASIC1 alone or combined with other four ASIC genes are significantly correlated with poor patient survival. Furthermore, ASIC1 inhibitors could cause a significant reduction of tumor growth and tumor load (193).

Functional expression of various ASICs, which apparently signal microenvironmental acidosis, is also characteristic of adenoid cystic carcinoma (ACC) cells and primary tumor tissues, but not of normal human salivary gland epithelial cells (550). Electrophysiological and pharmacological data suggested that ACC cells predominantly contain ASIC2a and 3a subunits composing heteromeric channel.

In addition to directly signaling acidic microenvironment in cancer cells to promote their malignant features, ASICs expressed in nociceptive sensory afferents can essentially contribute to the induction of cancer-related hyperalgesia, and in particular bone pain, which is one of the most common complications in cancer patients with bone metastases. Cancer colonization in bone causes aggressive bone destruction due to increased number of osteoclasts, a type of large, acid-secreting multinucleated bone cells that normally break down bone tissue for the purpose of bones maintenance, repair, and remodeling. It was shown that bone metastasis are associated with strong acidification of adjacent microenvironment due to abnormal increase in osteoclast number. This in turn causes bone pain due to enhanced expression of ASIC1a and ASIC1b in the ipsilateral dorsal root ganglions (DRGs) at relatively stable levels of ASIC3 and TRPV1 (353).

Ion channels may not only help cancer cells to sense and react to acidic microenvironment, but also to actively promote such microenvironment. Tumor cells extrude the excess protons mainly through the Na^+/H^+ exchanger type 1 (NHE1) (60, 316) with NHE1 activity and ensuing extracellular acidification being mostly localized to focal adhesion nanodomains as well as to invadopodia to promote both migration (316) and invasion (60) of tumor cells. It was shown that activity of highly prometastatic $\text{Na}_v1.5$ VGSC in MDA-MB-231 breast cancer cells leads to a perimembrane acidification accompanied with an intracellular alkalinization through $\text{Na}_v1.5$ functional interaction with NHE1 (54, 55, 174) (FIGURE 4G). Such pH changes in turn

render the secreted cathepsins, which are predominant pH-dependent ECM-digesting proteases in MDA-MB-231 cells, more active, thereby promoting cells' invasiveness. The data suggested that $\text{Na}_v1.5$ and NHE1 may form functional complexes in caveolin-1-containing lipid rafts of invadopodia (54, 55). It was also shown that independently of its regulation of NHE-1 activity, $\text{Na}_v1.5$ could also modulate F-actin polymerization and invadopodia formation via Src kinase activity (54, 55) (FIGURE 4G).

Noteworthy, invadopodia are similar in structure and function to osteoclast podosomes responsible for bone degradation, and extracellular acidification is central to podosome action (60). Metastases leading to overall bone loss due to osteoclast activity are classified as osteolytic, whereas those resulting in the excessive bone deposition are considered osteoblastic. It was suggested that interaction of breast and prostate cancer cells with the bone microenvironment could influence $\text{K}_{\text{Ca}2.3}$ (SK3) channel activity, which by amplifying ORAI1-mediated Ca^{2+} entry could promote formation of osteolytic metastatic lesions (76), although the mechanisms of this phenomenon remain unclear.

D) EXTRACELLULAR ATP. Another critical parameter of tumor microenvironment is relatively high concentration of extracellular ATP ($>100 \mu\text{M}$), which in normal tissues remains very low (hardly exceeding $1 \mu\text{M}$) (399, 426). The sources of high extracellular ATP in tumors include cancer cells per se which actively secrete ATP, but most importantly ruptured cells undergoing necrosis in response to various detrimental insults such as pressure or hypoxic injury (426). Extracellular ATP in turn may act in autocrine/paracrine manner via various surface purinergic receptors to initiate intracellular signaling important for oncogenesis or to serve as a source of an immunosuppressive agent, adenosine (13, 124). Several purinergic receptors both metabotropic (P2Y) and ionotropic (P2X) have been implicated in the promotion and/or progression of cancer (124, 426). However, of all these receptors ionotropic P2X_7 ($\text{P2X}_7\text{R}$) one has drawn the most attention, as its strong overexpression in multiple tumors positions it as potential cancer cell biomarker (426). Biophysical properties of $\text{P2X}_7\text{R}$ are such that it can support cationic influx upon prolonged activation that is lethal to the cell. However, in reality, $\text{P2X}_7\text{R}$ involvement in cancer-related processes appeared multifactorial and often contradictory, indicating possible differential modulation of its biophysical properties and functional significance depending on tumor type, tumor stage, tumor microenvironment, and host-tumor interaction. In addition, $\text{P2X}_7\text{R}$ can exist in several splice variants exhibiting both structural and functional peculiarities that may be of importance in the cancer (426). It is likely that a moderate level of constitutive $\text{P2X}_7\text{R}$ activation promotes cancer hallmarks by affecting ER and mitochondrial Ca^{2+} concentration and Ca^{2+} signaling, whereas its excessive stimulation in combination with certain endogenous or exogenous microenvironmental

factors may induce cancer cell death and thus can be anticancerous. For instance, in human pancreatic ductal adenocarcinoma (PDAC) cell lines that express higher P2X₇R protein compared with “normal” human pancreatic duct epithelial cell lines, it was directly shown that P2X₇R overactivation by high concentrations of ATP or specific agonists exerts cytotoxic effects causing necrotic cell death (172). At the same time, moderate P2X₇R activity under basal conditions and with low agonist concentrations supported oncogenic behaviors, proliferation, migration, and invasion of PDAC cells, and pharmacological P2X₇R inhibition could reduce these behaviors (172). P2X₇R is also markedly expressed on mRNA and protein levels in highly invasive MDA-MB-435s human breast cancer cell line, but not in noncancerous mammary cell lines (242). In MDA-MB-435s cells, however, P2X₇R overstimulation by high concentrations of ATP (up to 3 mM) appeared not detrimental, but strongly enhanced MDA-MB-435s cells migration and invasion through ECM (242). The latter effect was associated with P2X₇R-dependent release of ECM-degrading proteases, cysteine cathepsins, although underlying mechanisms remain poorly understood (242). This phenomenon may represent an escape strategy developed by some types of cancer cells (in this case the breast cancer ones) to flee the lethal high level of ATP and P2X₇R-mediated cell death via promotion of P2X₇R-dependent invasion of new niches (427). It was formulated as the “run or die hypothesis” postulating that while some tumor cells can die from stressful intratumoral factors; those that are the most invasive would escape and be selected (427).

IV. BEYOND THE ION PERMEATION: CONDUCTION-INDEPENDENT FUNCTIONS OF ION CHANNELS IN CANCER

Aside from their ability to conduct ions, ion channels, as integral membrane proteins, can enter into various types of protein-protein interactions with other proteins, thereby providing an additional, noncanonical mechanism for their physiological and pathological actions (251). Those proteins, which stay in the permanent functional coupling with the channel, are commonly referred to as partner proteins or auxiliary (accessory) subunits; however, there are many proteins whose interaction with the channel is cell type and/or context dependent. The fact that conformational state of the channel is determined by the presence of activating or regulatory stimuli provides additional degree of specificity to such interactions. Noncanonical channel-protein interactions leading to a distinct cellular response can be also facilitated by the formation of local signaling complexes within plasma membrane microdomains. The classical example of permeation-independent function of ion channel is the role of Ca_v1.1 VGCC as voltage sensor in excitation-contraction coupling of skeletal muscle, when in response to PM depolarization it induces Ca²⁺ release through protein-protein interaction with RyR (22).

Of ion channels for which nonconducting mechanisms were most implicated in their oncogenic functions are K_v10.1 (EAG1) (126), K_v11.1 (HERG1) (403) K⁺ channels, and Ca²⁺-, Mg²⁺-permeable, α -kinase domain-containing TRPM7 (509), although the list of ion channels that were shown to regulate cell fate in permeation-independent manner is much broader (e.g., Ref. 336).

Noncanonical, permeation-independent oncogenic effects of K_v10.1 were demonstrated by experimentation with the channel mutants bearing mutations in the pore region rendering them nonconducting, but preserving the ability to undergo conformational changes associated with gating (126, 205). Despite being devoid of K⁺ current-conducting function, when expressed in cell lines these mutants were able to increase p38 MAP kinase activity, promoting proliferation (205), and to interfere with the HIF-1 α control pathway, leading to the increase in HIF-1 α expression and upregulation of HIF-1 α target genes (126). In the latter case, K_v10.1 mutant-expressing cell lines showed increased VEGF secretion, and when implanted into SCID mice promoted xenograft tumor vascularization. This prompted the conclusion that K_v10.1 favors tumor progression through increased angiogenesis under the hypoxia characteristic of tumor microenvironment (126), and justifying tumor angiogenesis to be regarded as K_v10.1 oncochannelopathy (**TABLE 1**). Although K_v10.1 ion conduction was not required for the above effects, conformational changes normally accompanying gating remained important for inducing K_v10.1-mediated tumorigenic signal. In particular, it was suggested that pro-proliferative p38 MAPK-activating K_v10.1 signaling is limited to channels in a specific closed conformation, determined by the position of voltage sensor (205).

In the event of oncogenic K_v11.1 (HERG1) channel, its most important interaction partner appeared to be β_1 subunit of integrins, transmembrane receptors that mediate cell-cell and cell-ECM adhesion thereby regulating cell motility, proliferation, differentiation, and apoptosis (403). K_v11.1 channels are physically linked to integrin β_1 subunits (also known and further referred to as CD29) to form K_v11.1/CD29 complex localized in specific plasma membrane lipid raft microdomains, caveolae (84). Within this complex, CD29 engagement by cell adhesion can activate K_v11.1, which in turn by complexing in a channel activity-dependent manner with other signaling proteins, such as FAK (84) and PI3K/Akt (97) can initiate their downstream signaling. Assembly of a macromolecular CD29/K_v11.1/PI3K/Akt signaling complex in colorectal cancer cells was shown to induce HIF, thereby promoting production and release of proangiogenic VEGF-A by cancer cells (97). This allows colorectal cancer angiogenesis to be qualified as K_v11.1 oncochannelopathy (**TABLE 1**), although whether K_v11.1 involvement is solely based on conformational

change of the channel protein or the current flow is also required still remains an open issue.

The member of TRP channel family, TRPM7, except typical structural attributes of ion channel contains intracellular COOH-terminal α -kinase domain (509). Permeation-independent modes of oncogenic TRPM7 function are thought to be specifically linked to this domain. In particular, TRPM7 kinase-activity was shown to be important for the regulation of cytoskeletal organization, adhesion dynamics, and cell motility via the myosin II heavy chain (MHC-II) phosphorylation (89, 334) (**FIGURE 4E, right**). Moreover, recent mass-spectrometry studies on TRPM7 immune complexes from N1E-115 neuroblastoma cells indicate that TRPM7 may be a part of a large cytoskeletal multiprotein complexes, termed signalplexes, composed of the proteins mostly involved in cell protrusion dynamics and adhesions formation (334). Literature search and microarray-based gene expression analysis have shown that ~55% of these proteins are associated with cancer progression and metastasis formation (334). It was suggested that TRPM7 may function to anchor and maintain the integrity of signalplex with its kinase domain and ion permeation modulating the activity of cytoskeletal components within this signaling complex (334) (**FIGURE 4E, right**).

TRPM7 is expressed on mRNA and protein levels in primary breast cancer tissue samples, and high TRPM7 expression at the time of diagnosis predicts poor prognosis and therapy outcome in breast cancer patients (333). It is also expressed in both estrogen receptor-negative (ER⁻, i.e., MDA-MB-231) and positive (ER⁺, i.e., MCF-7) human breast cancer cells, and its presence confers higher metastatic potential on implanted tumors in a mouse xenograft models of human breast cancer (333). TRPM7 knockdown in invasive ER⁻ MDA-MB-231 cells strongly increased the number of cell-substrate focal adhesions, especially in the cell's periphery, and interfered with the ability of cells to migrate toward a serum gradient without affecting cells proliferation and viability (333). Noteworthy, TRPM7 knockdown in noninvasive, ER⁺ MCF-7 human breast cancer cells predominantly affected cell-cell rather than cell-substrate adhesion, which was evident by increased area of adherens junctions (i.e., cell-cell contacts) and their enrichment with E-cadherin (333). Moreover, by using wild-type and kinase domain-truncated forms of TRPM7 it was shown that migration of ER⁻ breast cancer cells (MDA-MB-231 and MDA-MB-435S) specifically involves TRPM7 kinase domain-mediated MHC-II phosphorylation (**FIGURE 4E, right**) and not channel permeation-dependent changes in Ca²⁺ or Mg²⁺ homeostasis (191). Thus it is tempting to speculate that estrogen receptor status of breast cancer cells may determine the preferred mechanism of promigratory and metastatic TRPM7 action (i.e., kinase dependent vs. permeation dependent) as well as the targets of such ac-

tion (i.e., focal adhesions vs. adherens junctions). Overall, breast cancer cell migration and metastasis can be classified as TRPM7 oncochannelopathy (**TABLE 1**), although the contributions of kinase and channel activity-dependent mechanisms may be cancer type- and context-specific requiring assessment in each particular case.

Just recently it was reported that the product of *SCN4 β* gene, a β 4 auxiliary β -subunit of voltage-gated Na_v1 channels (for more about β -subunits, see sect. IIIC2c), can function as metastasis-suppressor in breast cancer independently of its Na_v1-channel modulating properties (47). β 4 is expressed in normal breast epithelial cells, but disappears in high-grade primary and metastatic tumors. Reduced β 4 expression increases RhoA activity and potentiates cell migration and invasiveness, primary tumor growth and metastatic spreading, by promoting amoeboid-mesenchymal phenotype (47). β 4 metastasis-suppressing properties required intact intracellular COOH-terminal region, suggesting involvement of protein-protein interactions in the mechanism of its action.

V. ION CHANNELS' ANTICANCER FUNCTIONS

Surprisingly, there are a number of instances when overexpression or hyperactivation of certain channels had a protective significance against the development of certain cancer hallmarks with channels acting as tumor suppressors. The classical example is represented by the founding member of melastatin subfamily of TRP channels (TRPM), TRPM1, whose loss is an important diagnostic and prognostic marker for primary cutaneous melanoma (132, 192). It appeared that *TRPM1* gene encodes two transcripts, mRNA of TRPM1 channel per se (coded by the exons) and miR-211 (coded by the sixth intron) which exhibits tumor suppressor functions. It was proposed that while TRPM1 channel regulates melanogenesis and Ca²⁺ homeostasis, miR-211 acts as a tumor suppressor gene controlling multiple pathways to inhibit melanoma invasion (192). Downregulation of *TRPM1* promotes melanoma aggressiveness due to decrease in miR-211 for which loss of TRPM1 protein represents an excellent marker. Furthermore, three other TRPM members, TRPM2/M7/8, are also implicated in tumor-suppressing regulation of melanocytic behaviors: TRPM2 is capable of inducing melanoma apoptosis and necrosis, TRPM7 can act as protector and detoxifier in both melanocytes and melanoma cells, and TRPM8 can mediate agonist-induced melanoma cell death (192).

Growth inhibiting potential was also ascribed to canonical TRP members, TRPC4/C5. Activation of these channels by Englerin A, a guaiane sesquiterpene isolated from the bark of the African plant *phyllanthus engleri* which is positioned as TRPC4/C5 agonists, was shown to inhibit proliferation

of a subset of TRPC4/C5-expressing cancer cell lines across many cell lineages (71). However, the mechanism(s) by which TRPC4/C5-mediated Ca^{2+} influx and membrane depolarization lead to growth inhibition remains unclear. TRPC4 also appeared to oppose angiogenic switch in RCC by enabling secretion by RCC cells of angiogenesis-inhibiting factor, thrombospondin-1 (TSP1) (503). Lack of TRPC4 renders RCC cells angiogenic by preventing them from TSP1 secretion.

Capsaicin is an active pungent component of chili peppers and is a chemical agonist of heat-activated, highly Ca^{2+} -permeable TRPV1 channel. Capsaicin as well as some other dietary phytochemicals have anticancer activity potentially involving a number of cellular mechanisms (90). In glioma and urothelial cancer cells, anticancer effects of capsaicin were specifically linked to TRPV1 activation (9, 10, 439) with similar effects demonstrated by endovanilloids, endogenous fatty acid from the group of ethanolamides with agonistic activity on TRPV1 (467). TRPV1 activation was shown to trigger apoptosis via at least three mechanisms: 1) Ca^{2+} influx through PM-localized TRPV1 with subsequent dissipation of mitochondrial transmembrane potential and release of apoptogenic factors (9), 2) induction of TRPV1 clustering and colocalization with Fas/CD95 death receptor (10), and 3) via ER stress owing to TRPV1 localization in the ER membrane and TRPV1-mediated Ca^{2+} release (467).

Among the nonclassical targets of capsaicin to induce apoptosis in gastric cancer cells (87) as well in SCLC cell lines and human SCLC cell xenografts (283) was also shown to be TRPV6. In both cancers, capsaicin-activated, TRPV6-mediated $[\text{Ca}^{2+}]_i$ increase was implicated in initiation of apoptosis with subsequent involvement of JNK/p53 and calpain pathways in gastric cancer and SCLC, respectively (87, 283). These results indicate that although TRPV6 is commonly known to be a highly oncogenic channel whose constitutive activity promotes proliferation (290), strong TRPV6 overactivation can induce apoptosis. Thus, depending on cancer type and context, both inhibition and activation of TRPV6 can be beneficial.

Beneficial effects of activation of yet another heat-sensitive channel, TRPV2, for which, however, the principal chemical agonist is not capsaicin, but cannabidiol, a major nonpsychoactive phytocannabinoid, were demonstrated for urothelial carcinoma cells (542), glioblastoma cells (352), multiple myeloma cells (344), and triple-negative breast cancer cells (135). These data establish TRPV2 as one of the targets in general anticancer efficacy of cannabidiol in several types of cancer (327), although the involvement of TRPV2 in tumor growth and progression is much more complex and multifactorial (302) (see sect. IIIA2c and **TABLE 1**).

Mechanosensitive TRPV4 channel is required for conferring normal EC strain-induced reorientation and mechanosensitivity which is important for normal vascular formation and patterning. It was shown that tumor-derived ECs exhibit lower levels of TRPV4 expression, reduced TRPM4-mediated Ca^{2+} influx, and aberrant mechanosensitivity to ECM promoting defective angiogenesis (4). Vessel malformations and growth of xenograft tumors inversely correlated with TRPV4 expression levels, indicating that lack of this channel is a key factor in determining tumor EC dysfunction, and any maneuvers leading to its enhancement have normalizing anti-angiogenic significance (4).

A protective role against prostate cancer cells proliferation, migration, and xenograft tumor angiogenesis was shown to belong to cold/menthol-sensitive TRPM8 channel (176, 548, 568). In fact, TRPM8 was first identified as the product of prostate-specific gene overexpressed in prostate cancer (491) even before its classical function as cold receptor in sensory neurons was established. TRPM8 expression is androgen-dependent and undergoes complex changes with prostate cancer progression being maximal at the initial androgen-dependent stages of the disease and minimal in aggressive, androgen-independent prostate cancer (39). Although antiproliferative significance of TRPM8 still remains questionable, the fact that any maneuvers leading to the enhancement in channel expression and/or activation consistently suppress prostate cancer cell migration suggests a protective role against metastasis (187). Suppression of the migration of PC-3 androgen-independent prostate cancer cells due to TRPM8 overexpression was shown to involve inactivation of FAK (548), hinting to the mechanism of TRPM8 coupling to the migratory machinery.

Overall, the available data suggest that for each channel, and especially for Ca^{2+} -permeable ones, certain incremental levels of channel activity exist by which it supports either normal cellular function or promotes malignant features. However, increasing channel activation even further by specific agonists induces Ca^{2+} overload which is detrimental for any cell. Thus specific channel agonists may be as useful anticancer agents as specific channel blockers. In fact, anti-neoplastic activity of D-3263 hydrochloride, an enteric-coated selective TRPM8 agonist developed by Dendreon Corporation, on prostate cancer is supposed to result from TRPM8-mediated increase in Ca^{2+} and Na^+ entry, the disruption of calcium and sodium homeostasis, and the induction of cell death in TRPM8-expressing tumor cells. In 2009 it underwent a Phase 1, dose escalation study evaluating safety and pharmacokinetics in subjects with advanced solid tumors (<https://clinicaltrials.gov/ct2/show/NCT00839631>) showing no major toxicity and stabilization of the disease in men with advanced prostate cancer.

VI. PERSPECTIVES FOR CANCER TREATMENT

The involvement of ion channels in cancer hallmarks is nowadays indisputable. For some types of cancer this involvement is so profound that certain hallmark(s) can be defined as specific oncochannelopathy. However, despite identification of ion channel(s) whose altered expression and/or function promote certain malignant phenotype(s) and frequent optimistic claims in the literature that these channel(s) can serve as promising therapeutic target(s), not many of pharmacological agents acting on ion channels can be actually taken through the complete drug development process.

To be used as a therapeutic target in cancer, the channel must conform to the several important criteria: 1) display very limited expression in normal tissues, 2) be strongly overexpressed in tumor(s), and 3) have highly selective non-toxic ligand(s) with minimum adverse effects. In fact, there is no channel that conforms to all criteria. Most of the channels implicated in cancer hallmarks are ubiquitously expressed in different tissues, and their pharmacological targeting in cancer is likely to produce significant toxicity to normal cells. In addition, for many channels involved in cancer hallmarks, selective pharmacological tools are still not available. Among the rare encouraging examples is the peptide inhibitor of highly oncogenic Ca^{2+} -permeable TRPV6 channel, SOR-C13, developed by Soricimed Biopharma Inc., which recently underwent a Phase 1 clinical trial aimed at evaluating the safety and tolerability of the drug in patients with solid tumor cancers (<https://clinicaltrials.gov/ct2/show/study/NCT01578564>). SOR-C13 represents a short 13-amino acid COOH-terminal portion of soricidin, a 54-amino acid paralytic peptide from the submaxillary saliva glands of the northern short-tailed shrew (*Blarina brevicauda*), which was shown to act as highly specific ($\text{IC}_{50} = 14 \text{ nM}$) TRPV6 blocker (51, 465). Suppression of TRPV6-mediated Ca^{2+} influx is crucial for inhibiting Ca^{2+} -activated transcription factor NFAT and concomitantly NFAT-dependent tumor cell growth, proliferation, and metastases in TRPV6-rich tumor cells.

In view of high metastatic potential of VGSCs (see sect. IIIC2c) and the ability of local anesthetic agents to inhibit thereof (156), the Phase 3 trial has been initiated to assess the in vivo potential of infiltrating local anesthetics, such as lidocaine, to decrease the dissemination of cancer cells during surgery in operable breast cancer as well as to improve the disease-free interval and long-term survival (<https://clinicaltrials.gov/ct2/show/NCT01916317>) (TABLE 2).

Sometimes effective pharmacological agents targeting ion channels and cancer hallmark(s) associated with them can be found among pharmacological classes with apparently unrelated specificity. This opens up the whole new avenue in anticancer pharmacology associated with repurposing of

FDA-approved drugs for treatment of other conditions as anticancer agents (252) (TABLE 2). This is especially true with respect to K^+ channels of K_v10 (EAG) and K_v11 (ERG) subfamilies, which include highly oncogenic $\text{K}_v10.1$ (EAG1) and $\text{K}_v11.1$ (HERG1) channels, and whose members generally display a high degree of pharmacological promiscuity. For instance, bioinformatics-based approaches helped to reinvent tricyclic antidepressants, imipramine and promethazine, which act as nonspecific EAG1 blockers (167) as growth inhibitors of SCLC, pancreatic neuroendocrine tumors, and Merkel cell carcinoma (239). Treatment with tricyclic antidepressants (amitriptyline) to relieve depression appeared effective in significantly prolonging overall survival of patients with brain metastases from different carcinomas or with glioblastoma multiforme (GBM) compared with patients not receiving such therapy, and this beneficial effect was tentatively attributed to EAG1 inhibition (325). Recently an FDA-approved antipsychotic drug, thioridazine, was identified as a novel EAG2 channel blocker with potent efficacy in reducing intracranial xenograft medulloblastoma growth and metastasis (225). Moreover, a case report was presented of repurposing thioridazine to treat a human patient with metastasized medulloblastoma, although it was cautioned that prolonged treatment with escalating doses can cause considerable side effects associated with marked emotional lability and depression (225). Another recent example is provided by FDA-approved antihypertensive agents from the class of calcium channel blockers (amlodipine, felodipine, manidipine, cilnidipine), which were shown to possess remarkable potency in inhibiting filopodia formation, directional migration, and invasion of breast and pancreatic cancer cells (237).

Usefulness of the idea of repurposing of FDA-approved drugs can be further illustrated on the example of Na_v1 channel blocking agents. Na_v1 channels are commonly overexpressed in various cancers conferring metastatic phenotype (see sect. IIIE2c); therefore, any drug whose mechanism of action involves suppression of Na_v1 activation would also have welcomed beneficial anticancer “side effects.” Indeed, antiepileptic drug phenytoin and antiarrhythmic drug ranolazine indicated for the treatment of chronic angina can inhibit breast cancer cell invasiveness in vitro and growth and metastasis of breast cancer xenografts in vivo (128, 356), whereas local anesthetics lidocaine (221) and ropivacaine (23) demonstrated anti-invasion and antimetastatic effects on colon cancer cells.

Ca^{2+} -activated $\text{K}_{\text{Ca}3.1}$ (IK) K^+ channel (historically known as Gardos channel after György Gárdos who in 1958 first described characteristic channel activity in human erythrocytes) associates with poor prognosis of many cancers (see TABLE 1); therefore, safe $\text{K}_{\text{Ca}3.1}$ inhibitor would potentially present valuable anticancer therapeutic. Senicapoc (ICA-17043), a novel inhibitor of Gardos channel, limits solute

Table 2. Some of the examples of potential repurposing of FDA-approved drugs or drugs undergoing clinical trials for other conditions as anticancer agents

Drug	FDA-Approved or Clinically Tested		Cancer Repurposing			Reference Nos.
	Primary target(s)	Usage/condition	Cancer-relevant target(s)	Cancer hallmark(s) affected	Cancer type(s) effective	
Amitriptyline	Serotonergic, dopaminergic, adrenergic, cholinergic systems	Tricyclic antidepressant	K _v 10.1 (EAG1)	Metastasis	GBM	325
DHP Ca-channel antagonists: amlodipine, cinnidipine, felodipine, manidipine	Ca _v 1	Antihypertensive	Ca _v 1.1, Ca _v 1.3	Migration, invasion	Breast, pancreatic	337
		Tricyclic antidepressant	K _v 10.1 (EAG1)	Proliferation, apoptosis resistance	SCLC, pancreatic, MCC	239
Imipramine	Serotonergic, dopaminergic, adrenergic, cholinergic systems	Tricyclic antidepressant				
Lidocaine	Na _v 1.5, Na _v 1.7	Local anesthetic, antiarrhythmic	Na _v 1.5	Invasion, metastasis	Breast, colon	221, https://clinicaltrials.gov/ct2/show/NCT01916317
Phenytoin	Na _v 1	Antiepileptic	Na _v 1.5	Proliferation, invasion, metastasis	Breast	356
Promethazine	Serotonergic, dopaminergic, adrenergic, cholinergic, histaminergic systems	Neuroleptic, antihistamine	K _v 10.1 (EAG1)	Proliferation, apoptosis resistance	SCLC, pancreatic, MCC	239
Ranolazine	Na _v 1	Antiarrhythmic, chronic angina	Na _v 1.5	Invasion, metastasis	Breast	128
Ropivacaine	Na _v 1.7	Local anesthetic	Na _v 1.5	Invasion, metastasis	Colon	23
Senicapoc	K _{Ca} 3.1 (IK, Gardos)	Sickle cell anemia	K _{Ca} 3.1 (IK, Gardos)	Proliferation, migration, and invasion	Colon, melanoma, glioma	17, 107, 183, 266, 483
Thionidazine	Serotonergic, dopaminergic, adrenergic systems	Antipsychotic	K _v 10.2 (EAG2)	Metastasis	MB	225

Drugs are ordered alphabetically. DHP, dihydropyridine, GBM, glioblastoma multiforme; MB, medulloblastoma; MCC, Merkel cell carcinoma; SCLC, small cell lung cancer.

and water loss by sickle red blood cell to preserve their hydration and survival. It has been proposed for use in sickle cell anemia (SCA) (17). The drug has been tested in Phase 2 clinical trials for SCA and has been found safe and well tolerated at all doses studied (<https://clinicaltrials.gov/show/NCT00040677>). Thus repurposing this well-studied safe drug may potentially provide a promising strategy for cancer treatment.

Except traditional pharmacological tools, novel siRNA- and antisense oligonucleotide-based therapies should be considered to enable selective ion channel targeting only in tumors. In this respect, it is important to identify not only primary channel isoform, but most importantly its cancer-specific splice variant(s) involved in cancer hallmark. Progress in elaboration of effective, reliable, and nontoxic gene transfer technologies (256) makes such strategies feasible.

Disruption of intracellular ionic homeostasis due to massive influx of Na^+ or Ca^{2+} is detrimental to any cell through elimination of V_r , induction of osmotic shock, and/or causing Ca^{2+} overload. Therefore, utilizing in vivo gene transfer technologies for selective expression in cancer cells of “killer channels” that due to intrinsic properties and/or mutations lack specific gating (i.e., opening and closing in response to certain stimuli) and remain constitutively open may provide another promising strategy of anticancer therapy. Indeed, bacterial and other types of channel-forming toxins, cytolysins, are Nature’s most potent biological weapons (388). Potential effectiveness of such strategy was demonstrated by using mutated, constitutively active mammalian degenerin channel (MDEG, currently known as ASIC2), which when functionally expressed induces massive Na^+ influx into cells, causing cell ballooning and bursting (215). Intraperitoneal injection of the expression vector containing coding sequence of such mutant under control of gastric cancer-specific carcinoembryonic antigen (CEA) promoter into CEA-producing gastric cancer cells in a mouse peritoneal dissemination model was shown to increase animal survival rate to 85% from 0% survival in control (215).

Using light-gated ion channels of channelrhodopsin (ChR) family (443) in the capacity of “killer channels” potentially provides an attractive opportunity for cancer cell-destroying ion fluxes to be controlled through channels’ photoactivation (402). To circumvent the problem of nontransparency of most of the mammalian tissues to visible light (the wild-type channelrhodopsin ChR2 is activated by blue light with maximum at wavelength 480 nm), recently a strategy was proposed when photoactivated bioactive molecules (i.e., ChR2) are used in combination with biocompatible nanoparticles made of scintillator (phosphor) material (33, 453). The latter can absorb highly penetrable X-ray and in response reemit visible light. Thus, when scintillator-based nanoparticles are introduced to the required site deep inside

the body to be present in the vicinity of cancer cells expressing channelrhodopsin, the latter can be activated by focusing X-ray beam on that site. Importantly, such strategy can potentially be used not only with ChR2, but also with other photosensitive bioactive molecules, especially from the class of caged compounds (137), and it is not limited to cancer, but may find lots of other applications when remote, noninvasive, selective in vivo pharmacological control of organs, tissues, and cells deep inside the body is required (453).

Oncogenic ion channels with limited background expression in normal tissues and strong overexpression in tumors due to their cell-surface accessibility represent viable targets for antibody-based therapies. For instance, it was shown that a specific monoclonal antibody which inhibits function of highly oncogenic $\text{K}_v10.1$ potassium channel can effectively restrict cancer cell proliferation and reduce tumor growth in animal models with no significant side effects (i.e., neurotoxicity) (384). In addition, even if anti-channel antibodies do not produce functional effects, they could be used as carriers for radionuclides, toxic molecules, or nanoparticles.

Remarkably, ion channels may be important players also in radiation therapy, representing the key component in most of the anti-cancer treatment strategies (230). By damaging the targeted cells, ionizing radiation triggers a plethora of stress responses including activation of various ion channels. Activation of the so-called radiosensitizing channels, such as TRPM2 or TRPV1, may amplify ionizing radiation-induced insults, while activation of some others may confer intrinsic radioresistance (230). Among the latter are TRPV5/6-like nonselective cation and $\text{K}_v3.4$ voltage-gated K^+ channels whose activation induces cell cycle arrest and DNA repair, enabling tumor cells to survive radiation therapy (230). Further understanding of the mechanisms underlying radiogenic ion channel modifications might help to develop new strategies for the tumor radiosensitization.

VII. CONCLUSIONS

Despite an obvious progress achieved over the past two decades in realization that cancer hallmarks can be viewed as oncochannelopathies, this field of cancer research is still very young compared with classical oncology. Not all aspects of oncogenic channel functions are fully understood for different types of cancer and not all results obtained in the in vitro experimentation and even in vivo animal modeling can be easily transferred to human cancer. In fact, all such results require validation in human subjects. It is necessary to establish whether actual mutations can underlie oncogenic properties of the channels in certain types of cancer and if so what impact on channel function they may have. This will provide further solid arguments to regard cancer hallmarks and maybe even certain cancer types as a

whole as oncochannelopathy. Cancer hallmarks commonly depend on dysregulation of several channels. But is there a hierarchy of these channels and cellular processes they are involved in? If so, would it be possible to arrive at a single most important channel that regulates a certain process via which it dictates the onset and progression of the whole hallmark? Understanding cancer hallmarks and cancer types as specific oncochannelopathies will definitely help to focus efforts on discovery of new oncogenic mechanisms and unconventional strategies for cancer treatment.

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DISCLOSURES

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