Cellular and Molecular Biophysics

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Corso di laurea in LM Biotecnologie Industriali- LM Fisica

Cell volume regulation and H2O transports across the membrane

UNIVERSITÀ DI TORINO
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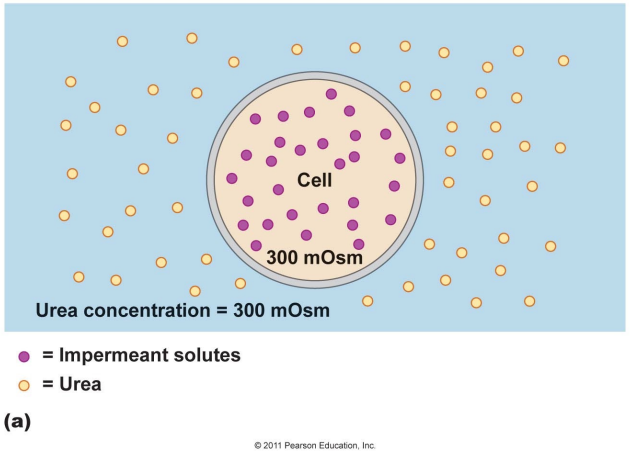
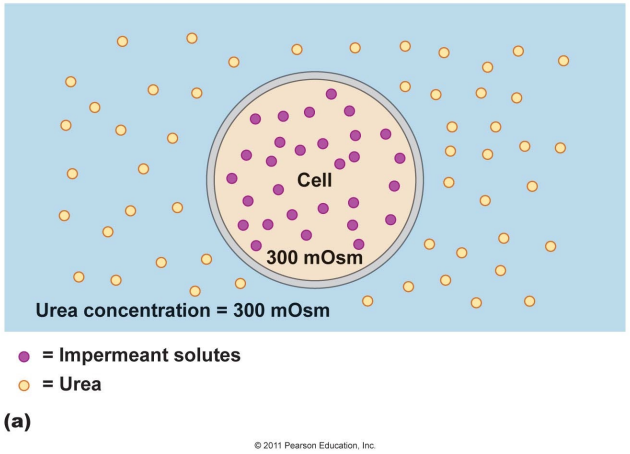
CELL VOLUME REGULATION

- Celle membranes are quite permeable to H_2O
- H_2O fluxes are determined by Osmotic Pressure differences: every misbalance of osmolality intra or extracellular is followed by H_2O fluxes across cell membranes with the consequent changes in volume



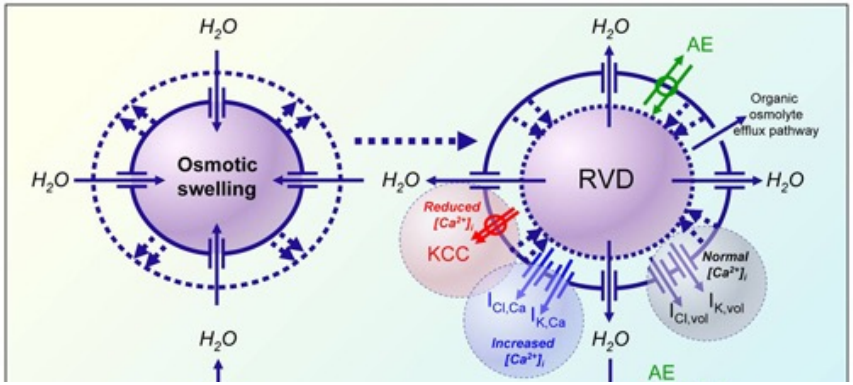
CONTROLLO DEL VOLUME CELLULARE

- Most of the mammals cells are exposed to extracellular fluids with constant osmolarity. However alterations of such osmolarity can be observed in several physiopathological conditions.
- Cells developed several regulatory mechanisms of cell volume involving membrane transports and metabolism



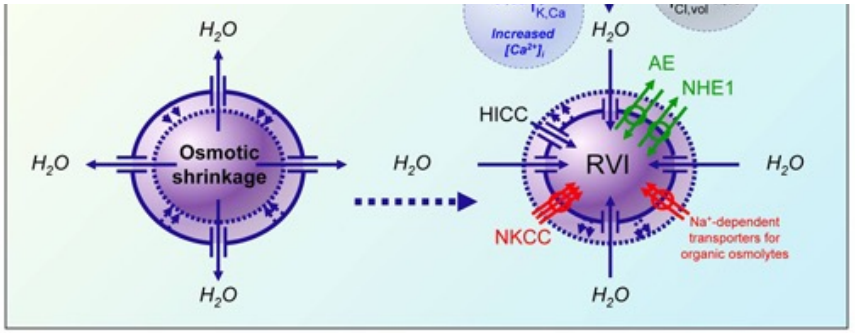
CELL VOLUME REGULATION

- Most cell types are able to counteract volume perturbations following a shift in extra- or intracellular osmolarity.
- Osmotically swollen cells release KCl, nonessential organic osmolytes, and cell water, thereby reducing the cell volume towards the original value, the process of regulatory volume decrease (RVD).

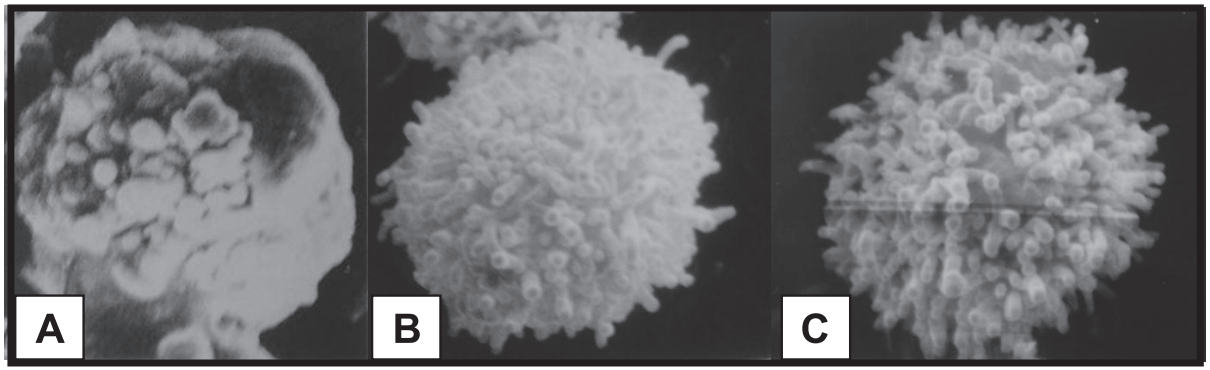


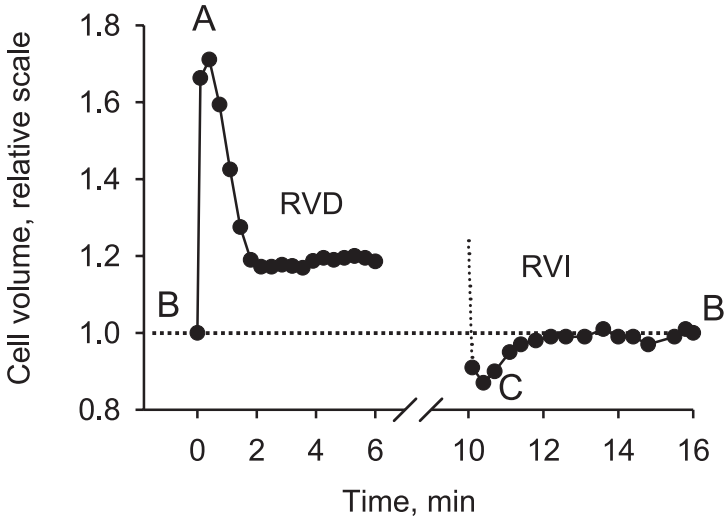
CELL VOLUME REGULATION

- Osmotically shrunken cells generally initiate a net gain of KCl and cell water, thereby increasing cell volume towards the original value, the process of regulatory volume increase (RVI).
- RVD is dependent on increases in the net efflux of Cl, K, and organic osmolytes, whereas RVI involves the activation of Na-K-2Cl cotransport, Na/H exchange, and nonselective cation channels.



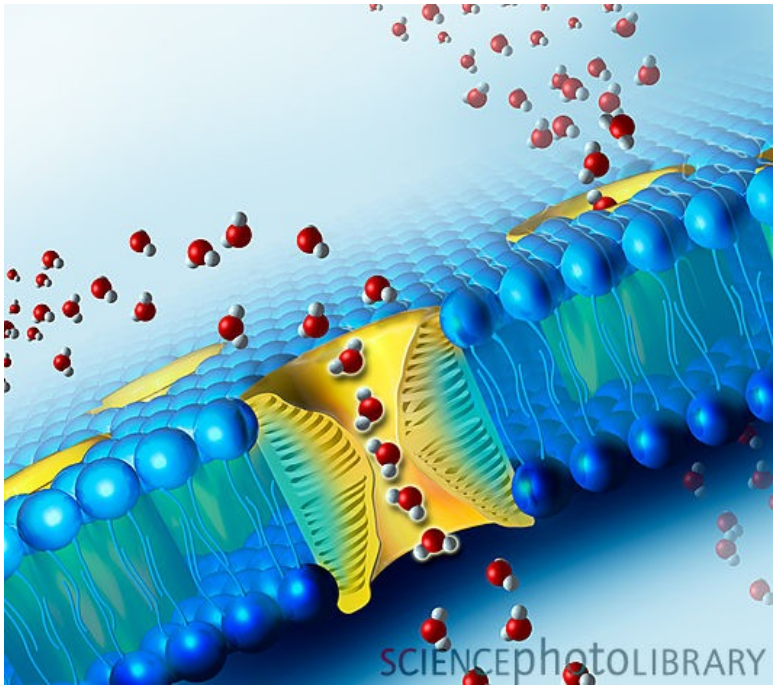
CELL VOLUME REGULATION





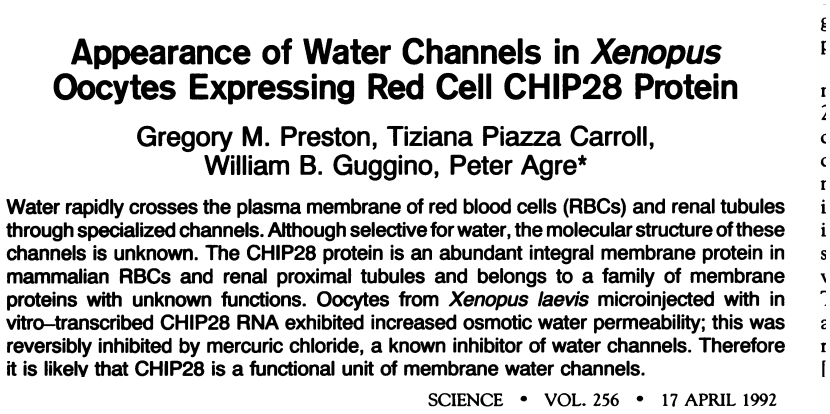
AQUAPORINS (AQP)

- Our understanding of the movement of water through cell membranes has been greatly advanced by the discovery of a family of water-specific, membrane-channel proteins —the aquaporins.



AQUAPORINS (AQP)

- The existence of proteins that form water-specific membrane channels was postulated for several decades, largely on the basis of biophysical measurements of membrane permeability in red blood cells and in epithelial cells of the renal proximal tubule.
- However, the identity of such channels remained unknown until approximately 26 years ago, when the serendipitous discovery of a red-blood-cell protein led to the description of aquaporin-1 (AQP1) as the first molecular water channel



Appearance of Water Channels in *Xenopus* Oocytes Expressing Red Cell CHIP28 Protein

Gregory M. Preston, Tiziana Piazza Carroll, William B. Guggino, Peter Agre*

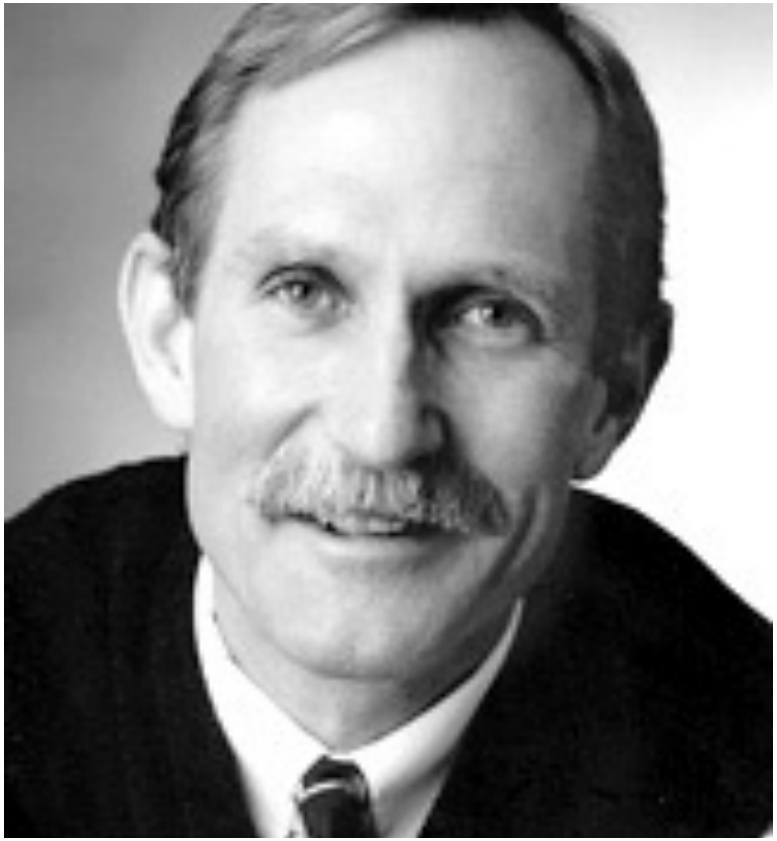
Water rapidly crosses the plasma membrane of red blood cells (RBCs) and renal tubules through specialized channels. Although selective for water, the molecular structure of these channels is unknown. The CHIP28 protein is an abundant integral membrane protein in mammalian RBCs and renal proximal tubules and belongs to a family of membrane proteins with unknown functions. Oocytes from *Xenopus laevis* microinjected with in vitro–transcribed CHIP28 RNA exhibited increased osmotic water permeability; this was reversibly inhibited by mercuric chloride, a known inhibitor of water channels. Therefore it is likely that CHIP28 is a functional unit of membrane water channels.

SCIENCE • VOL. 256 • 17 APRIL 1992

AQUAPORINS (AQP)

- The 2003 Nobel Prize in Chemistry was awarded jointly to Peter Agre for the discovery of aquaporins and Roderick MacKinnon for his work on the structure and mechanism of potassium channels

- http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2003/agre-lecture.html



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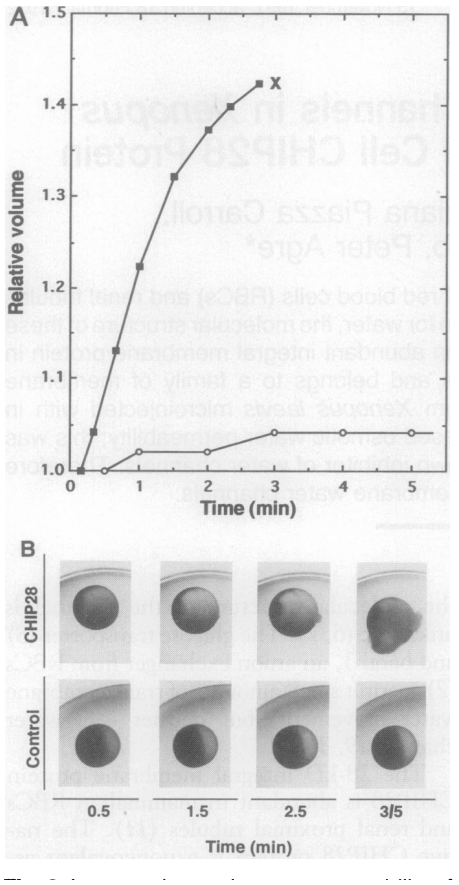


Fig. 2. Increased osmotic water permeability of CHIP28 RNA–injected *Xenopus* oocytes. After 72 hours, control-injected and CHIP28 RNA–injected (10 ng) oocytes were transferred from 200 mosM to 70 mosM modified Barth's buffer, and changes in size were observed by videomicroscopy (*19*). (**A**) Osmotic swelling of representative control-injected (open circles) and CHIP28 RNA–injected (filled squares) oocytes. Time of rupture is denoted (X). (**B**) Photos of injected oocytes at indicated times. Oocytes injected with CHIP28 RNA (3 min) or control (5 min) are denoted 3/5.

Water can be transported to varying degrees by other membrane proteins, for example, ion channels or the Na+/glucose co-transporter.

However, recognition of the unique properties of the aquaporins led to a paradigm shift in our consideration of membrane permeability: it is now known that **water transport across the membrane can be regulated independently of solute transport**.

The aquaporin protein family

- Eleven mammalian aquaporins have been reported so far (TABLE 1). Each has a unique cellular and subcellular distribution, with little overlap between homologues.

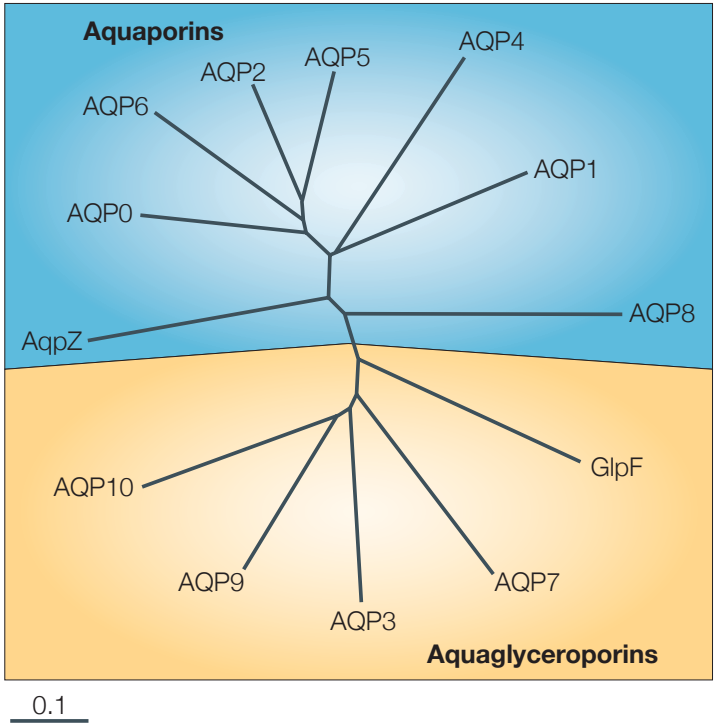
Table 1 | **Permeability characteristics and predominant distribution for the known mammalian aquaporin homologues**

Aquaporin	Permeability	Tissue distribution	Subcellular distribution*
AQP0	Water (low)	Lens	Plasma membrane
AQP1	Water (high)	Red blood cell, kidney, lung, vascular endothelium, brain, eye	Plasma membrane
AQP2	Water (high)	Kidney, vas deferens	Apical plasma membrane, intracellular vesicles
AQP3	Water (high), glycerol (high), urea (moderate)	Kidney, skin, lung, eye, colon	Basolateral plasma membrane
AQP4	Water (high)	Brain, muscle, kidney, lung, stomach, small intestine	Basolateral plasma membrane
AQP5	Water (high)	Salivary gland, lacrimal gland, sweat gland, lung, cornea	Apical plasma membrane
AQP6	Water (low), anions (NO_3^- > Cl^-)	Kidney	Intracellular vesicles
AQP7	Water (high), glycerol (high), urea (high), arsenite	Adipose tissue, kidney, testis	Plasma membrane
AQP8‡	Water (high)	Testis, kidney, liver, pancreas, small intestine, colon	Plasma membrane, intracellular vesicles
AQP9	Water (low), glycerol (high), urea (high), arsenite	Liver, leukocytes, brain, testis	Plasma membrane
AQP10	Water (low), glycerol (high), urea (high)	Small intestine	Intracellular vesicles

*Homologues that are present primarily in either the apical or basolateral membrane are noted as residing in one of these membranes, whereas homologues that are present in both of these membranes are described as having a plasma-membrane distribution. ‡AQP8 might be permeated by water and urea. AQP, aquaporin.

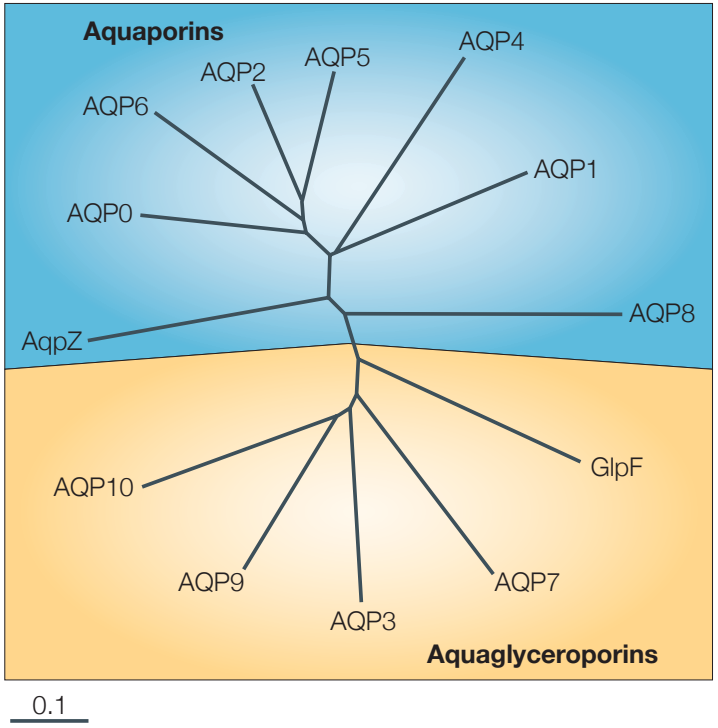
The aquaporin protein family

- The aquaporin family can be divided into two groups on the basis of their permeability characteristics, which generally coincide with specific amino-acid-sequence patterns.



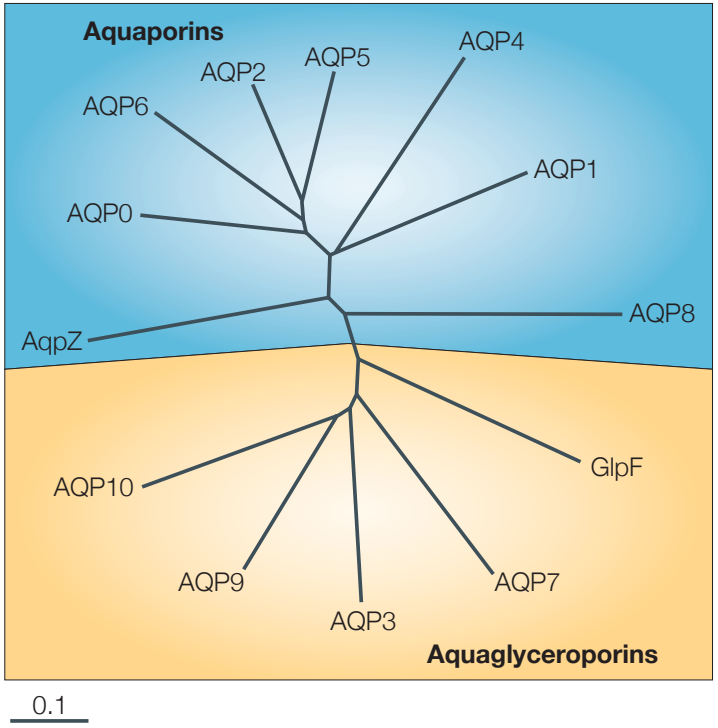
The aquaporin protein family

- Most members of the first group (aquaporins) are only permeated by water, and this group includes AQP0, AQP1, AQP2, AQP4, AQP5,AQP6 and AQP8.
- AQP6 and AQP8 are in this group on the basis of sequence analysis, although AQP6 is permeated by anions and AQP8 might be permeated by water and urea.



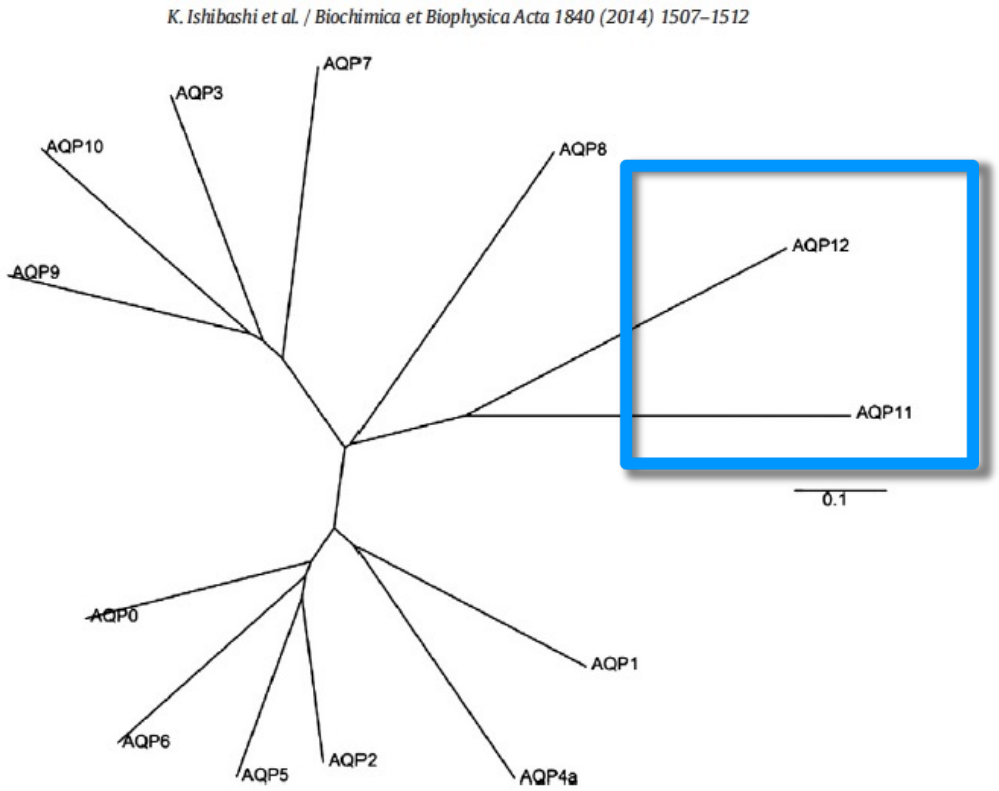
The aquaporin protein family

- Members of the second group (aquaglyceroporins), which includes AQP3, AQP7,AQP9 and AQP10, are permeated by water to varying degrees, but are also permeated by other small solutes, in particular, glycerol.
- The bacterium *Escherichia coli provides a model for this categorization*, as it contains two aquaporin homologues — AqpZ, which is a water-permeable channel, and GlpF, which is a glycerol transporter



The aquaporin protein family: superaquaporins

- The structural basis for this dichotomy of AQPs was challenged by the discovery of a new group of AQPs highly deviated from the previous AQPs especially around the AQP signature sequence, NPA box.
- This third subfamily was named superaquaporin after super-gene family of AQP family to indicate its very low homology with the previous two subfamilies. Interestingly, this subfamily is absent in single cell organisms and the plant.
- AQP11 and AQP12 localization is exclusively intracellular. plants.
- They may may function as glyceroporin,aquaporin and peroxiporin, H_2O_2 transporter.

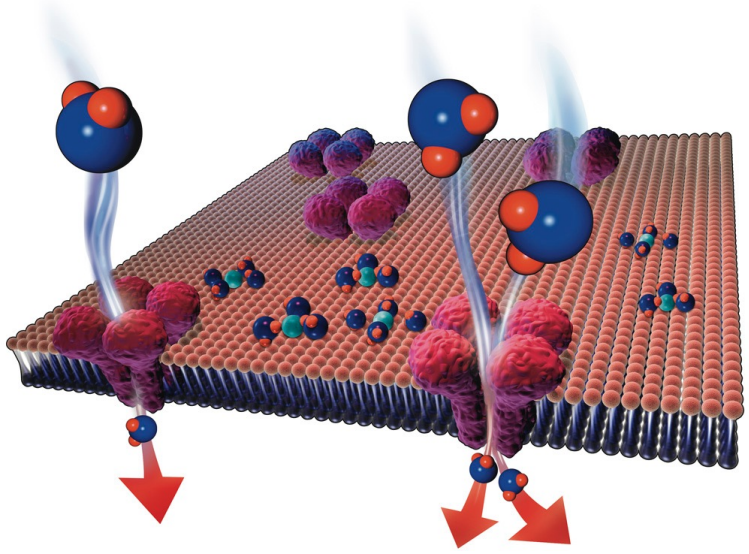


The aquaporin protein family

- Why do we need so many aquaporins? The answer probably derives from the diverse requirements in different cells and organs for the regulation of water homeostasis.
- Aquaporins in the collecting duct of the kidney, capillaries in the lung and secretory cells in salivary glands are all capable of high rates of water transport. However, across the aquaporin family, differences have been identified in the transcriptional regulation of the genes, as well as in the post-translational modification, stability and polarized distribution of the proteins.
- The complexity in the regulation of expression, membrane targeting and permeability necessitates the existence of more than just a single water-channel gene.

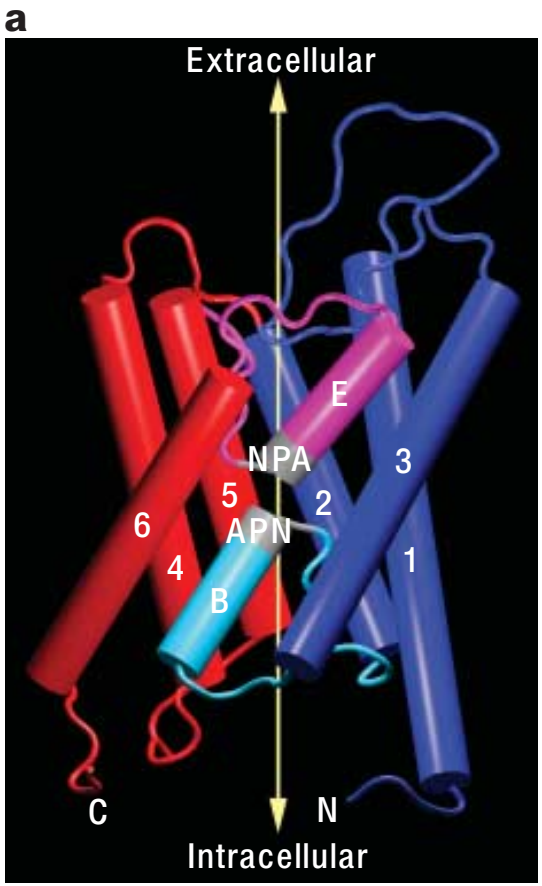
The unique aquaporin structure

- Biochemical analyses of AQP1 revealed that the 28-kDa polypeptide that was evident on immunoblots represented the monomeric form of the protein, but that AQP1 (as well as other aquaporins) is present as a tetramer in the cell membrane.



Monomer structure

The signature sequence motif of the aquaporins is the three-amino-acid sequence NPA (Asn-Pro-Ala). One NPA motif is found in the aminoterminal half of each monomer, and a second NPA motif is found in the carboxy-terminal half. When their amino termini are aligned, the overall percentage sequence identity among the aquaporin-family members is ~25–40%. However, it is much higher for the sequences that flank each of the NPA motifs. In addition to the similarity between the different aquaporins, the amino- and carboxy-terminal halves of AQP1 are related by their sequence, although these halves are oriented in opposite directions across the membrane bilayer.

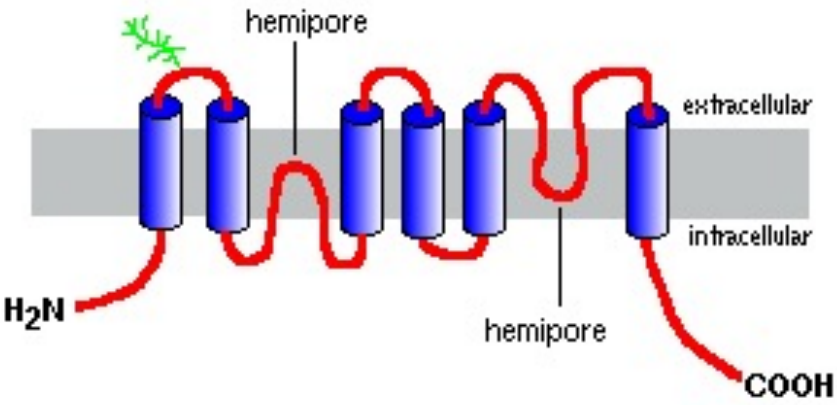


Monomer structure

Although **superaquaporins** are not much similar with each other, they have a perfectly conserved cystein residue downstream of the second NPA box (arrowed) which is critical for function.

Monomer structure

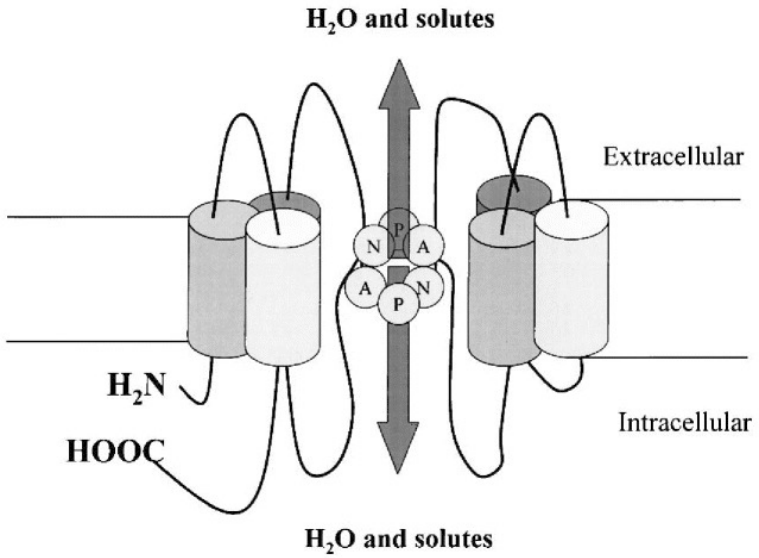
- Hydropathy analysis of AQP1 indicated the presence of six transmembrane helices in each monomer.



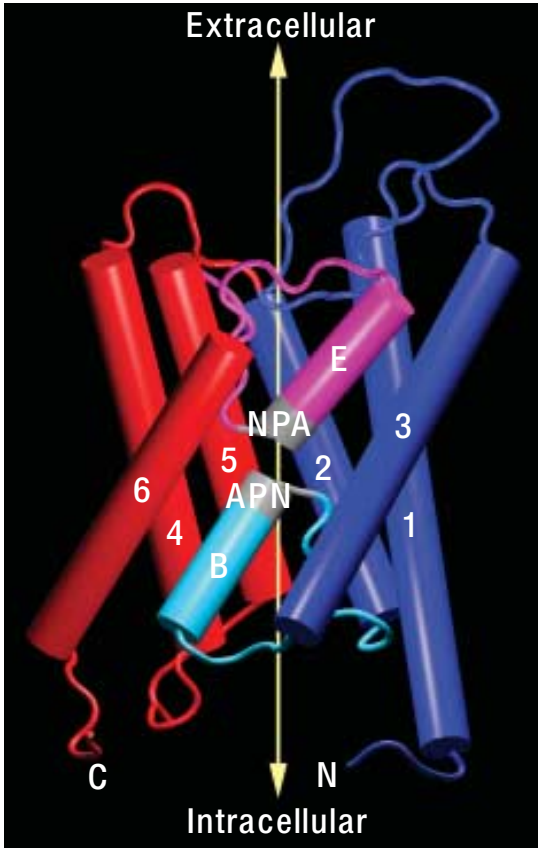
Adapted from King and Agre, 1998

Monomer structure

Mutational anayses of residues around the conserved NPA motifs led to predictions of an 'hourglass' structure, with two loops — the intracellular loop B and the extracellular loop E — folding into the membrane to form the pore.



a

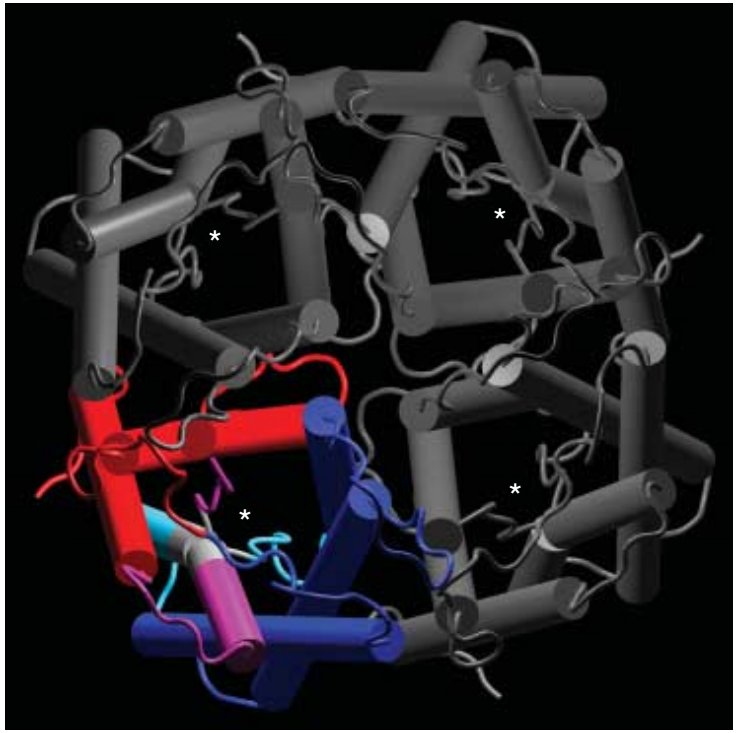


Tetramer formation

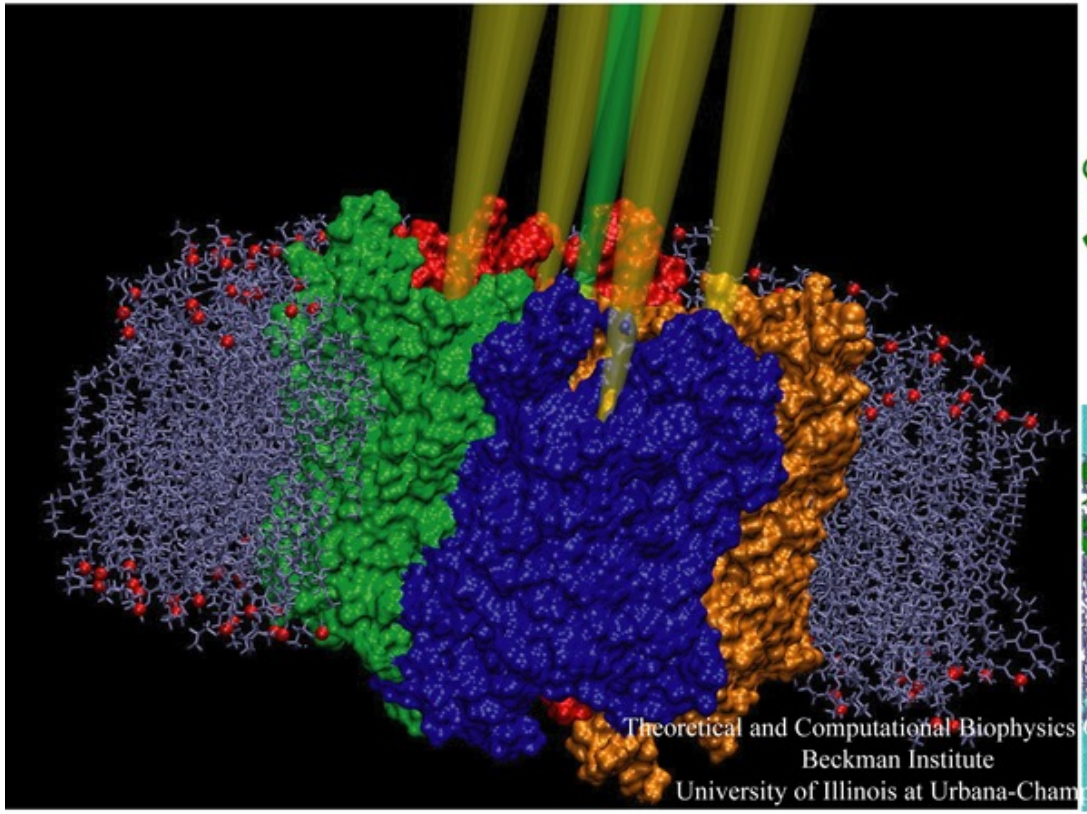
- Aquaporins are present in the membrane as tetramers, but, unlike ion channels, the channel for water permeability does not reside at the fourfold axis (the centre of the tetramer). Instead, each monomer contains a channel (FIG. 2b).

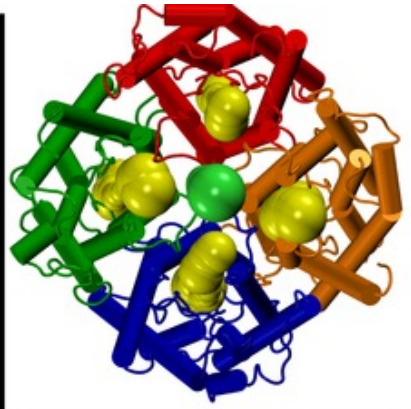
- Structural studies have provided insights into the apparent requirement for tetramer formation. The helices of each AQP1 monomer that are positioned on the outside face of the tetramer are hydrophobic, whereas those that are placed towards the center of the tetramer are hydrophilic

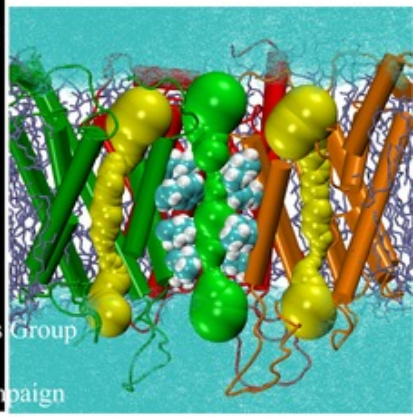
b



Tetramer formation

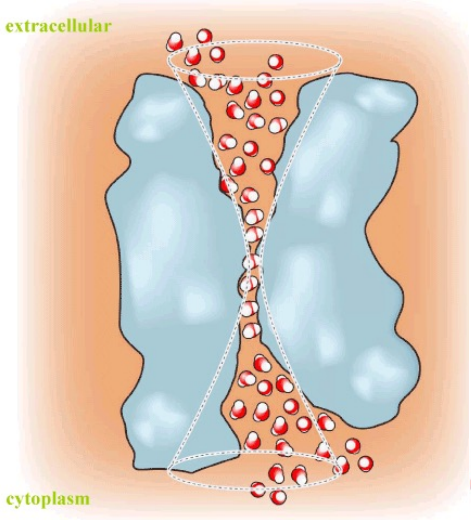


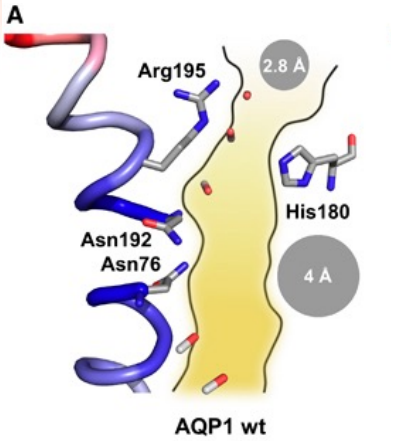




Channel selectivity and gating

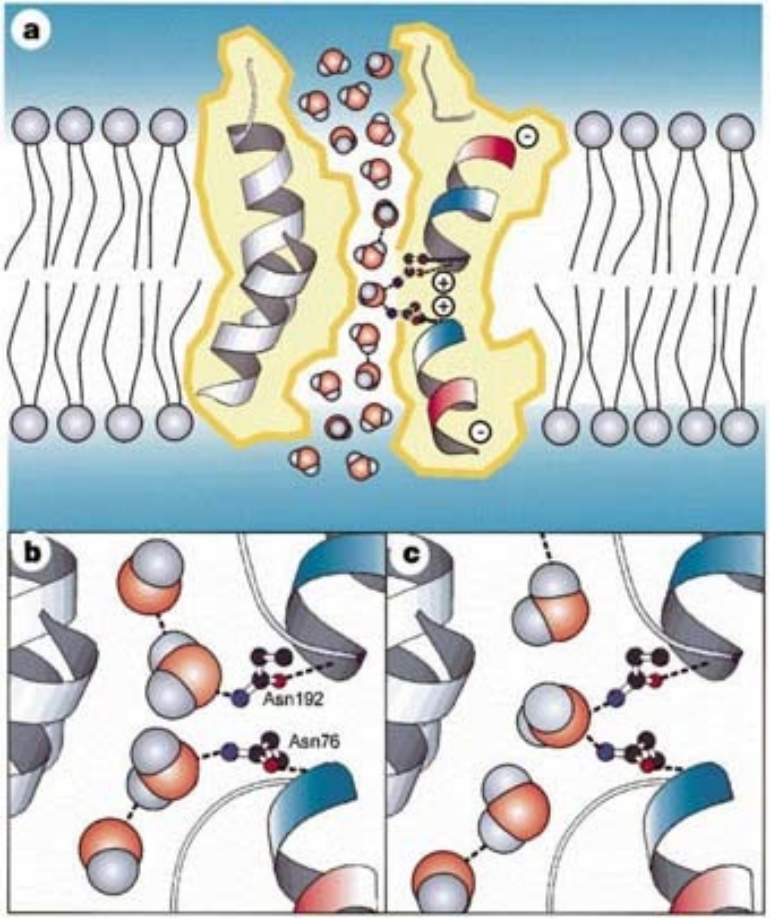
- Structural studies also revealed that the restriction of AQP1 permeability to water — excluding even hydronium (H_3O^+) ions — arises from two principal mechanisms.
- First, the channels narrow to a diameter of 2.8 Å approximately 8Å above the centre of the bilayer, which physically limits the size of molecules that can pass through them. A highly conserved **arginine** residue provides a fixed positive charge at this constriction site in each channel.
- The narrowest part of an *E. coli GlpF channel is ~1 Å wider* than in AQP1, and this increased diameter is sufficient to allow glycerol to pass through GlpF channels.





Channel selectivity and gating

- The second mechanism involves the orientation of a pair of DIPOLES at the NPA motifs. These dipoles interact with individual water molecules and prevent them from hydrogen bonding to adjacent water molecules. The functional separation of water molecules eliminates the possibility of H+ transfer through a channel. The combination of size and charge restrictions provides the basis for the unique permeability characteristics of the aquaporins.



Channel selectivity and gating

- For several members of the aquaporin family, channel gating might have an important role in regulating permeability.
- In contrast to other aquaporins, **AQPo** might also fulfil a structural role at the membrane junction between fiber cells in the lens. In double-layer AQPo crystals, which are representative of the arrangement of AQPo in the membrane junction, all of the subunits of a tetramer in one layer interact with two subunits of a tetramer in the adjacent layer. In this conformation, the pores were noted to be too narrow even for the passage of water, which indicates that membrane-junction formation stabilizes AQPo in a closed conformation

Aquaporin-0 membrane junctions reveal the structure of a closed water pore

Tamir Gonen[1], Piotr Sliz[2], Joerg Kistler[3], Yifan Cheng[1] & Thomas Walz[1]

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[2]*Howard Hughes Medical Institute and Children's Hospital Laboratory of Molecular Medicine, 320 Longwood Avenue, and Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, 240 Longwood Avenue, Boston, Massachusetts 02115, USA*
[3]*School of Biological Sciences, University of Auckland, Auckland PO Box 92019, New Zealand*

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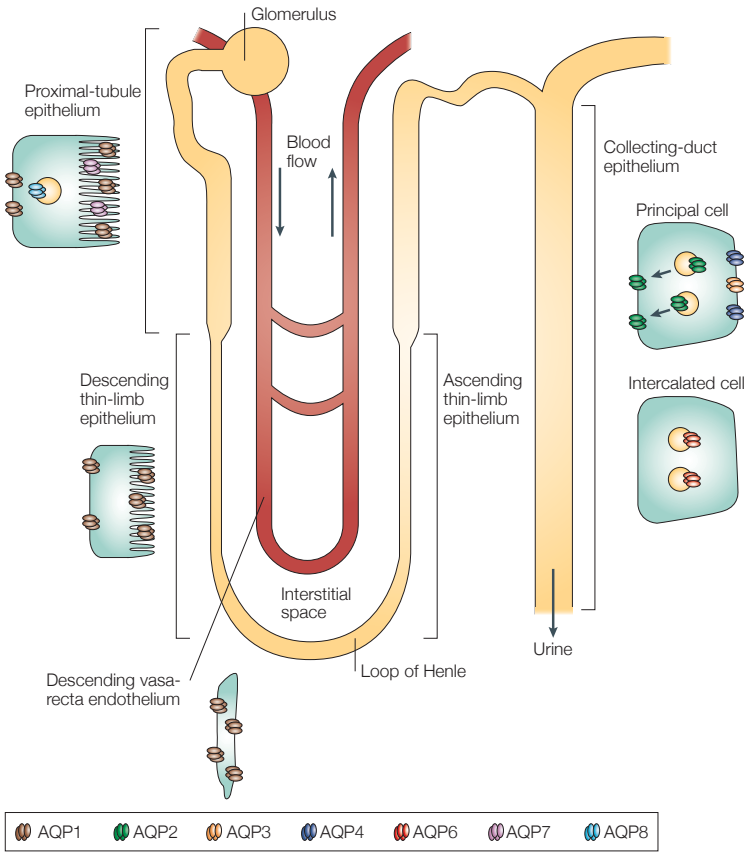
Channel selectivity and gating

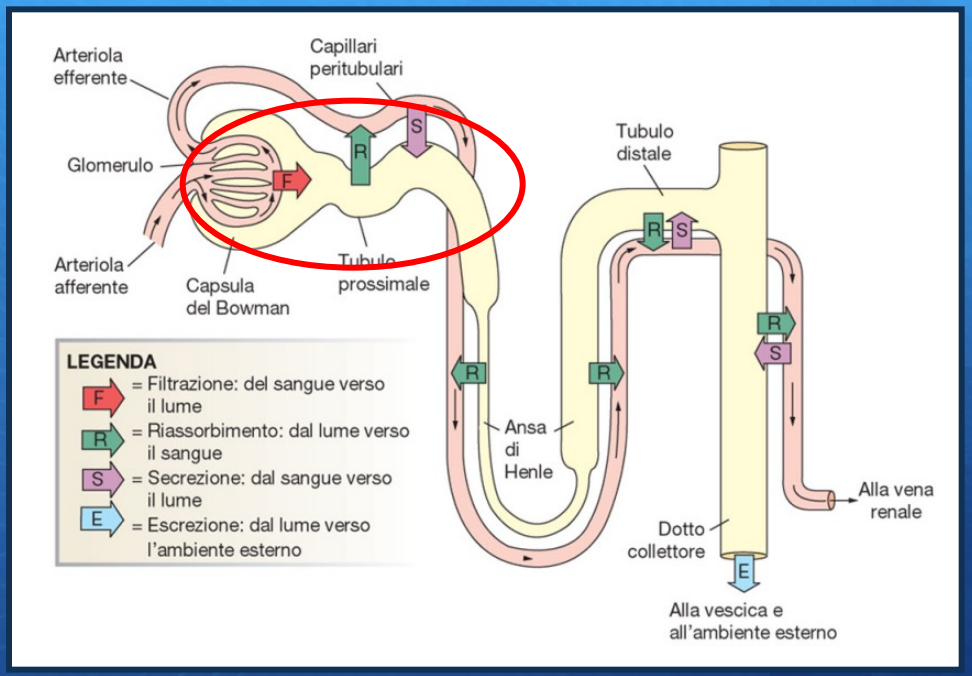
- AQP3 permeability is reduced by low pH in oocytes, and by low pH and nickel in cultured lung epithelial cells.
- The water and ion permeability of AQP6 is activated by low pH and nitrate in oocytes and cultured cells.
- Yool and colleagues reported that the ion permeability of AQP1 that had been expressed in oocytes was gated by cyclic GMP. However, the number of channels that are activated by cGMP could be as low as one AQP1 molecule per million, so the physiological implications of this result remain undefined.

Aquaporin physiology in health and disease: Aquaporins in the kidney.



- The mammalian kidney is the primary organ that regulates total body-water balance, and aquaporin-related physiology is most well understood in this organ.
- In the proximal nephron, AQP1 is abundant in both the apical and basolateral membranes of the proximal tubule and the descending thin-limb epithelium, as well as in the endothelium of the descending vasa recta. AQP7 and AQP8 are also present in the proximal-tubule epithelium.

Tubulo Prossimale



+ La funzione principale del tubulo prossimale e' il riassorbimento di un elevato volume di liquido isoosmotico

- **180L/die plasma filtra nella caps. Di Bowman (300mOsM)**
- **Nel tubulo prossimale il 70% è riassorbito (54L – 300mOsM)**
- Nell' ansa di Henle transitano 18L/die – 100mOsM (90%)
- Nel tubulo distale e dotto collettore 1.5L – 50-1200mOsM (99%)

Aquaporin physiology in health and disease: Aquaporins in the kidney.

- **Recent investigations in both mice and humans confirmed a functional role for AQP1 in the kidney**.
- ***Ma, T. et al. Severely impaired urinary concentrating ability in transgenic mice lacking aquaporin-1 water channels. J. Biol. Chem. 273, 4296–4299 (1998).***
- Mice with a targeted knockout of *Aqp1 had increased* urine output (polyuria) and a decreased urine-concentrating ability, as well as a decreased water permeability of the proximal tubule and the descending vasa recta. When deprived of water for 36 hours, *Aqp1-null mice became profoundly* dehydrated as a result of the urine-concentrating defect, and the SERUM OSMOLALITY increased from the normal value of approximately 310 mosmol kg–1 to nearly 500 mosmol kg–1

Aquaporin physiology in health and disease: Aquaporins in the kidney.

- An extracellular epitope on AQP1 encodes the minor blood-group-antigen Colton, and seven Colton-null families have been identified worldwide.
- Individuals in three of the Colton-null families were found to be homozygous for distinct mutations in the *AQP1 gene* and had a complete absence or marked deficiency of the AQP1 protein. Surprisingly, these individuals **suffered no obvious clinical consequences**
- So, what does this mean?

Aquaporin physiology in health and disease: Aquaporins in the kidney.

- To examine the hypothesis that the absence of AQP1 would produce defects in water homeostasis under stress conditions, renal function was evaluated in two *AQP1-null humans.*
- ***King, L. S., Choi, M., Fernandez, P. C., Cartron, J. P. & Agre, P. Defective urinary-concentrating ability due to a complete deficiency of aquaporin-1. N. Engl. J. Med. 345, 175–179 (2001).***
- *Both individuals had normal* urine volumes, and normal indices of baseline renal function.
- When deprived of water, the *AQP1-null individuals* had normal increases in serum osmolality and vasopressin levels.
- However, both had a limited ability to concentrate urine, with the maximal urine osmolality being less than half as concentrated as in normal individuals following overnight water deprivation. Measurements of proximal-tubule fluid reabsorption and the glomerular filtration rate were normal.
- This indicates that, in contrast to the *Aqp1-null mice, the primary defect in these rare AQP1-null humans is not in the proximal tubule, but* rather is in the descending thin limb and/or the descending vasa recta.

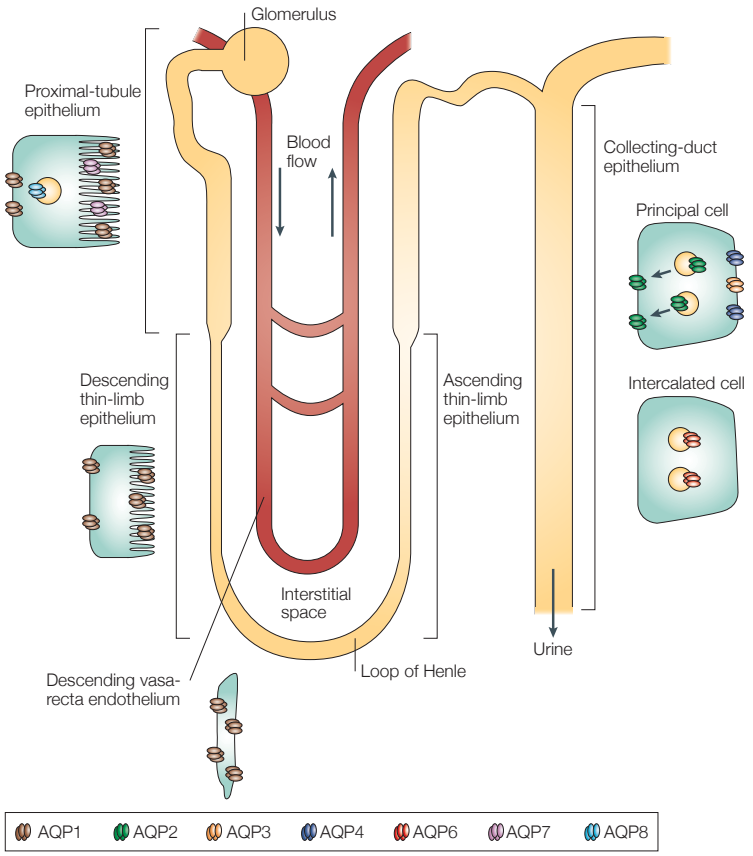
Aquaporin physiology in health and disease: Aquaporins in the kidney.

- Intrinsic differences between mice and humans with regard to maximal urine-concentrating ability are well established — mice can concentrate urine to greater than 3,000 mosmol kg–1, whereas humans can maximally concentrate urine to ~1,200 mosmol kg–1.

- Nonetheless, the manifestations of an AQP1 deficiency in mice are more severe than in *AQP1-null humans, which indicates significant* species-specific differences in the mechanisms of proximal- tubule water reabsorption.

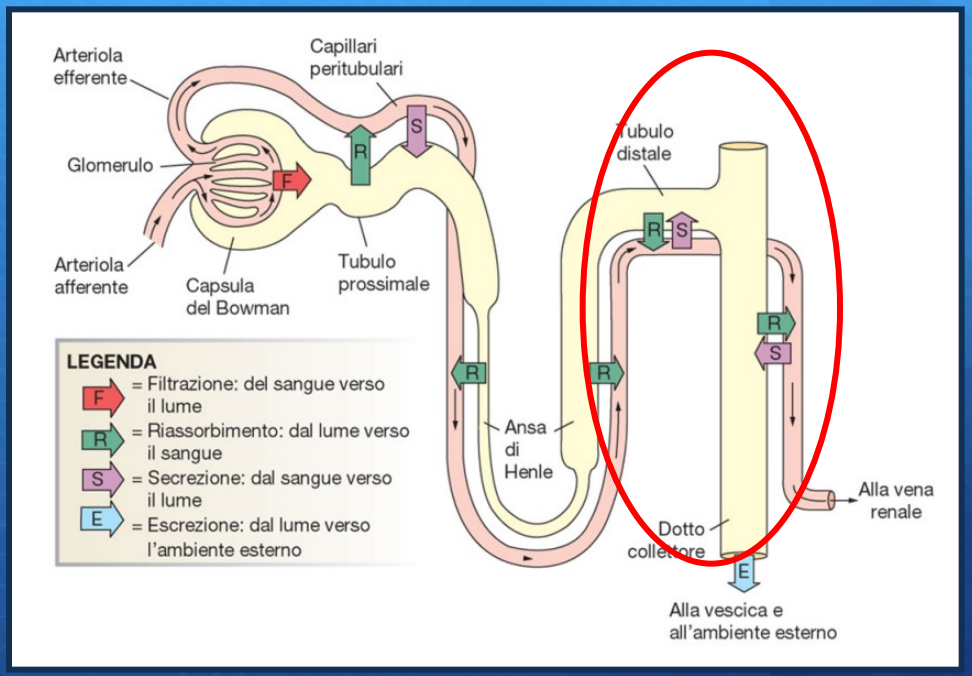
- Alternatively, the extremely low frequency of this AQP1 deficiency in humans might indicate that these individuals have some, still unidentified, form of compensation.

Aquaporin physiology in health and disease: Aquaporins in the kidney.



+ Several water-channel proteins are expressed in the renal collecting duct . For example, AQP2 is present in the water-absorbing principal cells of the renal collecting duct. Vasopressin is the anti-diuretic hormone that is released from the pituitary gland and that stimulates urine concentration by increasing the water permeability of the collecting duct. After vasopressin binds to its receptor on collecting-duct epithelial cells, intracellular vesicles that contain AQP2 translocate to the apical membrane, which markedly increases collecting-duct water permeability.

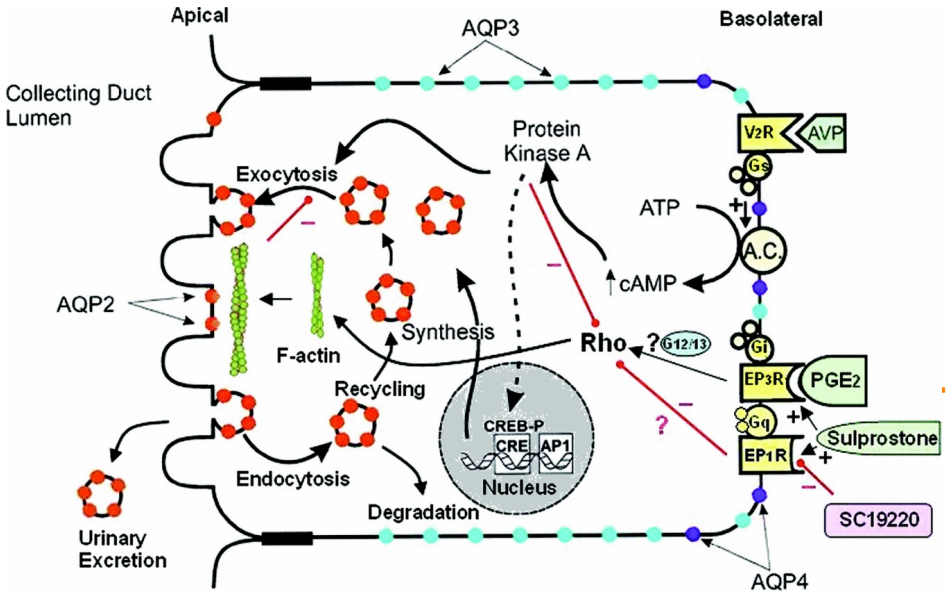
Tubulo distale e dotto collettore



- Regolazione fine del bilancio idrosalino sotto il controllo ormonale.
- Il riassorbimento e la secrezione nel tubulo collettore determinano la funzione finale e la concentrazione delle urine.

- **180L/die plasma filtra nella caps. Di Bowman (300mOsM)**
- Nel tubulo prossimale il 70% è riassorbito (54L – 300mOsM)
- Nell' ansa di Henle transitano 18L/die – 100mOsM
- **Nel tubulo distale e dotto collettore 1.5L – 50-1200mOsM**

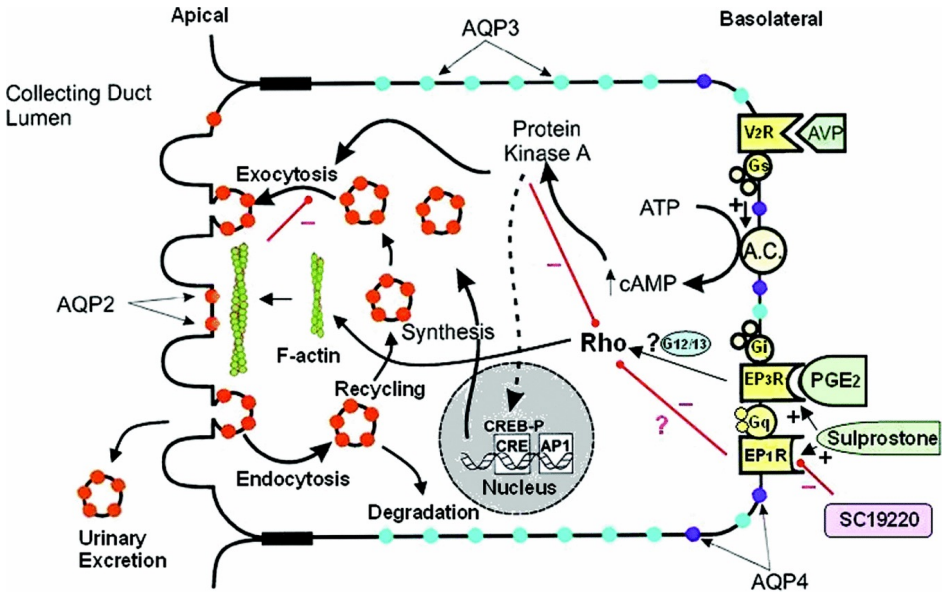
Aquaporin physiology in health and disease: Aquaporins in the kidney.



Following the binding of vasopressin to its receptor, cyclic AMP levels increase and AQP2 is phosphorylated on Ser256 by protein kinase A. AQP2-containing vesicles then undergo microtubule-mediated translocation to the apical membrane, where specific vesicle-docking proteins participate in membrane fusion.

Inhibiting Rho kinase led to AQP2 being targeted to the apical membrane even in the absence of vasopressin, which indicates that a combination of positive and negative signals might dictate vesicle trafficking.

Aquaporin physiology in health and disease: Aquaporins in the kidney.



- The cGMP-mediated targeting of AQP2 to the plasma membrane has also been described.
- As was observed for the cAMP stimulated trafficking of AQP2, phosphorylation of Ser256 was required for this cGMP-stimulated apical membrane targeting.

Aquaporin physiology in health and disease: Aquaporins in the kidney.

- The first example of a clinically important water channel defect that altered the water permeability of an organ was provided in 1994.

- They identified *AQP2 mutations in individuals with hereditary* nephrogenic diabetes insipidus (NDI) — a rare disorder that results in the excretion of large volumes of dilute urine. Mutations that produce both autosomal-dominant and autosomal-recessive inheritance patterns have been identified. In general, the autosomal-dominant mutations in *AQP2 produce trafficking* defects — heterotetramers, which are composed of mutant and normal AQP2 monomers, are not transported to the plasma membrane. By contrast, the autosomal-recessive mutations lead to the misfolding of the mutant monomers, which are presumably degraded and therefore cannot oligomerize with the normal monomers. As a result, normal function is retained in heterozygotes.

Aquaporin physiology in health and disease: Aquaporins in the kidney.

- At the other end of the water-imbalance spectrum, excessively high levels of AQP2 have been described in conditions of fluid retention, which include congestive heart failure, cirrhosis and pregnancy. These observations confirm that **AQP2** has a fundamental role in various pathological disorders of water homeostasis

Aquaporin physiology in health and disease: Aquaporins in the kidney.

- AQP6 is an intracellular water channel that resides in the intracellular vesicles of acid-secreting intercalated cells of the collecting duct. In these vesicles, AQP6 colocalizes with the H+-ATPase, a protein that participates in the secretion of acid into the urine. In contrast to other aquaporins, AQP6 is permeated by anions as well as by water, and channel function is activated by low pH6 and nitrate. AQP6 probably participates in acid–base homeostasis by regulating the content of intercalated-cell vesicles.

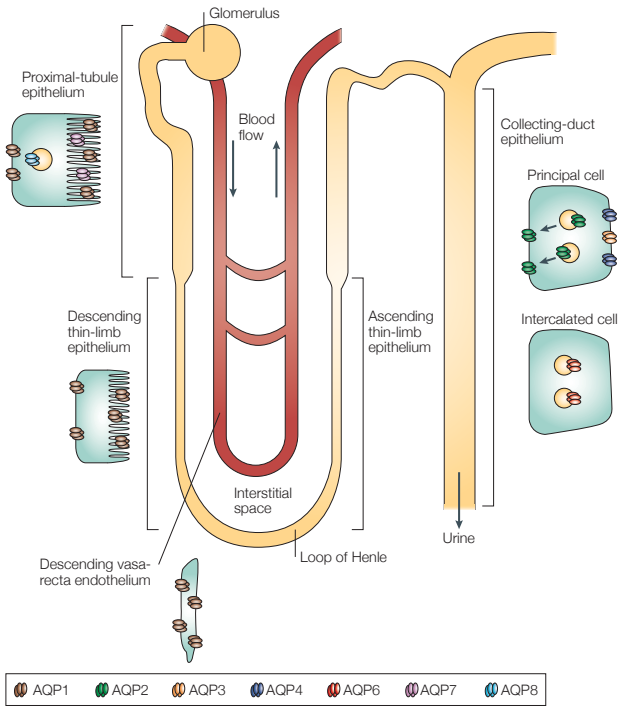
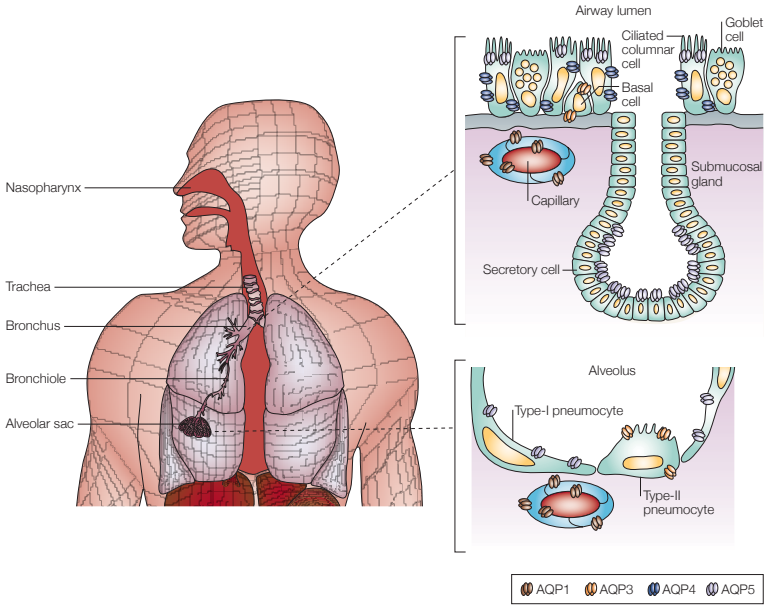


Figure 3 | **Aquaporin distribution in the human kidney.** A schematic of a nephron showing the

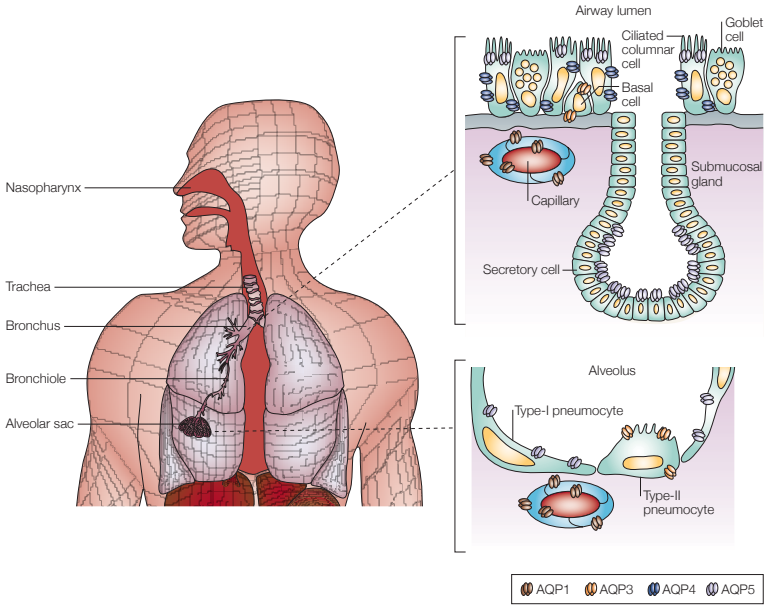
Aquaporin physiology in health and disease: Aquaporins in the lung.

- Water homeostasis is a crucial element of numerous pathophysiological processes that occur in the respiratory tract, and a network of aquaporins is present in this tract



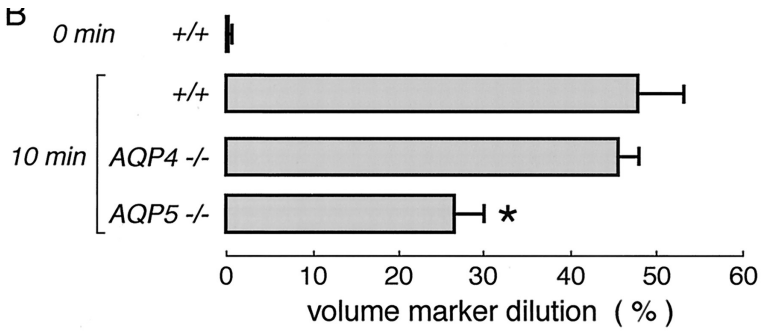
Aquaporin physiology in health and disease: Aquaporins in the lung.

- Several lines of evidence indicate functional roles for aquaporins in the airways of the lung. Submucosal glands in the airways contribute significantly to the generation of a liquid film that lines the airways. This film — an aqueous phase that underlies a layer of mucous — helps to trap inhaled particulate matter and microorganisms, so that they can be swept out of the lung by cilia on the surface of cells.



Aquaporin physiology in health and disease: Aquaporins in the lung.

- the apical membrane of secretory cells in these glands and, compared to wild-type mice, *Aqp5-null mice have* reduced secretion from their airway submucosal glands. Furthermore, Krane and colleagues observed that, compared to wild-type mice, *Aqp5-null mice show* a greater constriction of the airways in response to pharmacological stimulation with methacholine or acetylcholine — that is, they are hyperresponsive to such agents

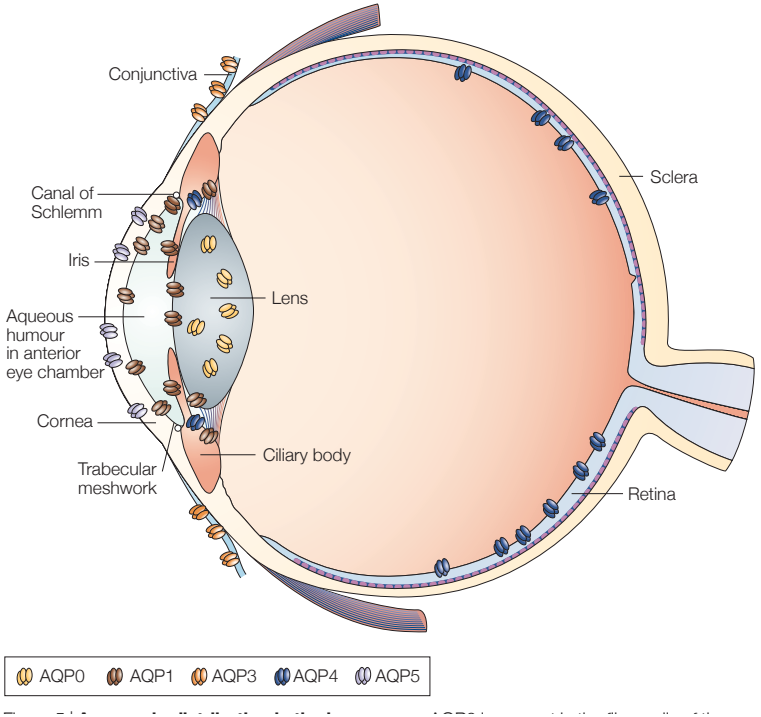


Song Y , Verkman A S J. Biol. Chem. 2001;276:41288-41292

Aquaporin physiology in health and disease: Aquaporins in the eye.

- Water homeostasis is crucial for the normal functioning of the eye — for example, for protecting the epithelium, for regulating intra-ocular fluid levels and pressure, and for maintaining the transparency of the pathway for light. A network of aquaporins in the eye carry out these functions.

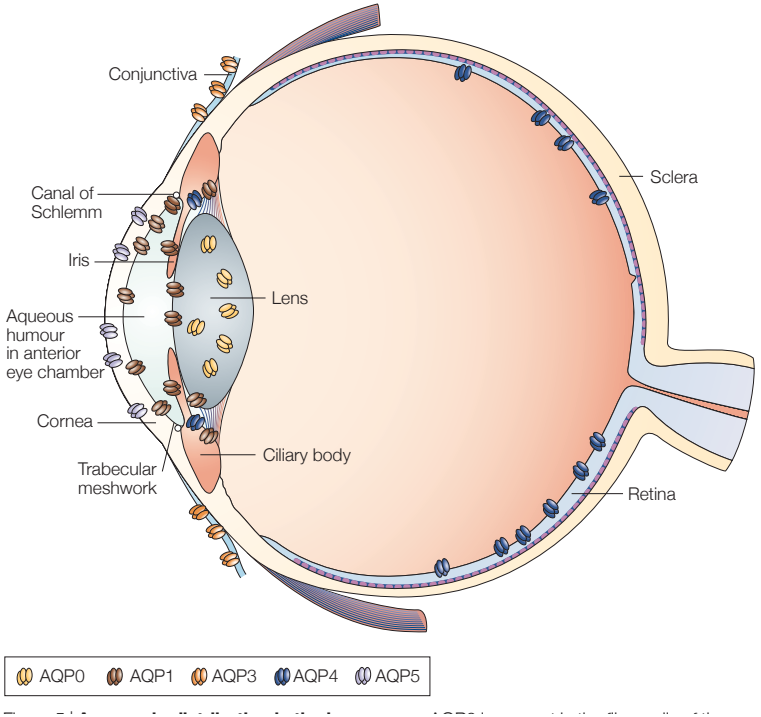
- AQP0 constitutes 50% of the total membrane protein in the fiber cells of the lens. Here, it is believed to have a structural role as a cell–cell adhesion molecule, in addition to functioning as a low-capacity water channel.



Aquaporin physiology in health and disease: Aquaporins in the eye.

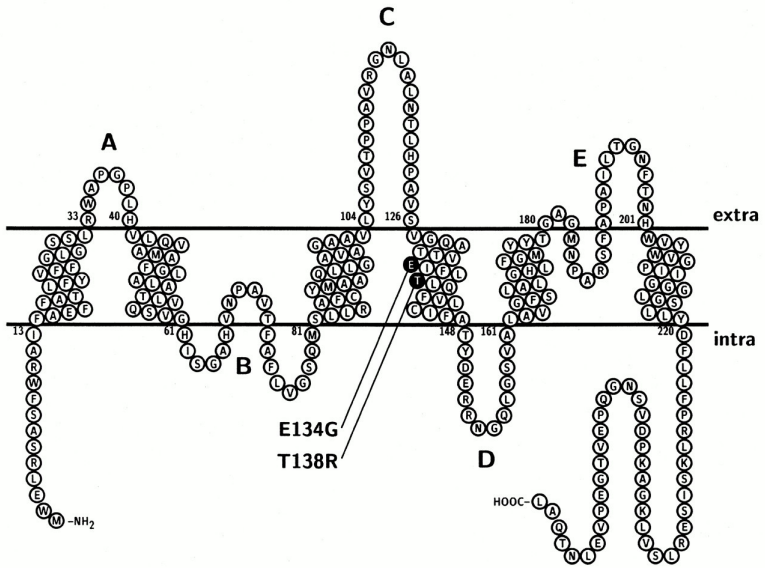
- The gene that encodes AQPo has been identified as the site of two naturally occurring mutations in mice that produce congenital bilateral CATARACTS.

- Two families with dominantly-inherited cataracts have been found to contain different missense mutations in *AQPo. These mutations* — *Glu134Gly or* Thr138Arg — produced surprisingly distinct phenotypes in heterozygotes, despite their close proximity in the protein



Aquaporin physiology in health and disease: Aquaporins in the eye.

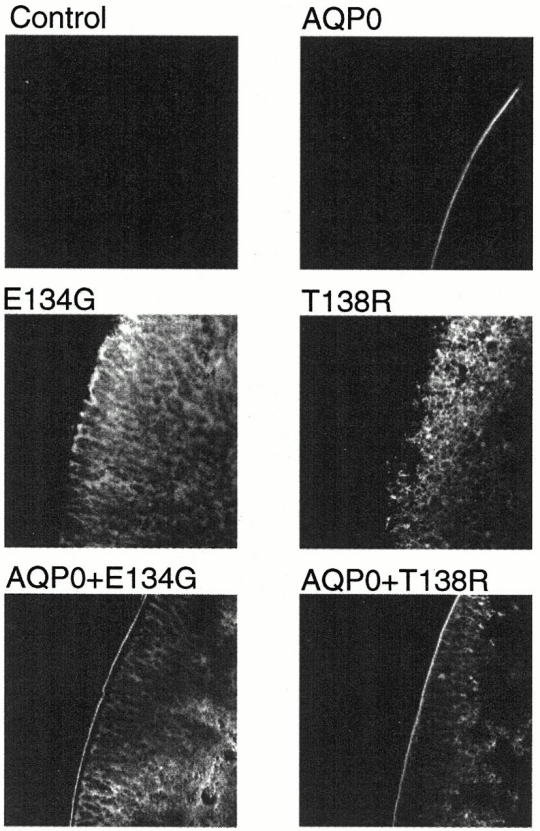
- The Glu134 and Thr138 residues are highly conserved among aquaporins. On the basis of the three-dimensional structure of AQP0, both residues are located in the fourth transmembrane helix on the structurally important face inside each aqueous pore.



Francis P et al. Hum. Mol. Genet. 2000;9:2329-2334

Aquaporin physiology in health and disease: Aquaporins in the eye.

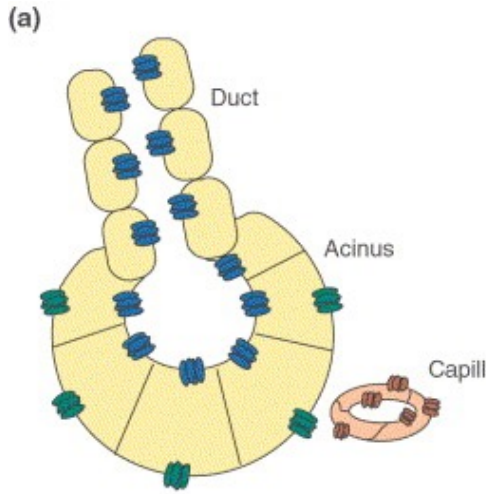
- When expressed in *X. laevis* oocytes, both substitutions impair AQPo transport to the plasma membrane. The development of cataracts in heterozygotes for each mutation indicates that AQPo might have a structural role (for example, it might contribute to cell–cell adhesion)



Francis P et al. Hum. Mol. Genet. 2000;9:2329-2334

Aquaporin physiology in health and disease: Aquaporins in secretory glands.

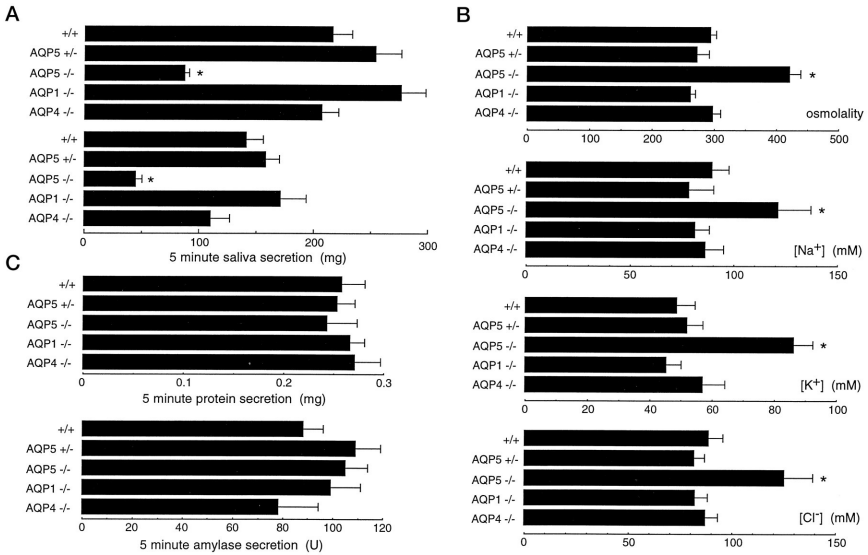
- Secretion from salivary glands, lacrimal (tear) glands and sweat glands is differentially regulated. However, in each gland, secretions are generated by coupling active electrolyte transport to water flow, and AQP5 can be found at the apical membrane of secretory cells in each of these glands



Schematic of AQP expression in human salivary gland, showing expression of AQP1 (red) in the capillary endothelium, AQP3 (green) in the basolateral membrane of acinar cells and AQP5 (blue) in the apical membrane of acinar cells and portions of the duct.

Aquaporin physiology in health and disease: Aquaporins in secretory glands.

- Ma and colleagues showed that mice with an *Aqp5* deletion have decreased salivation following stimulation with pilocarpine and that the saliva from these mice was hypertonic (~450 mosmol kg–1). Krane and colleagues also observed a decreased salivation in *Aqp5*-null mice following stimulation using pilocarpine.



Ma T et al. J. Biol. Chem. 1999;274:20071-20074

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Thank you