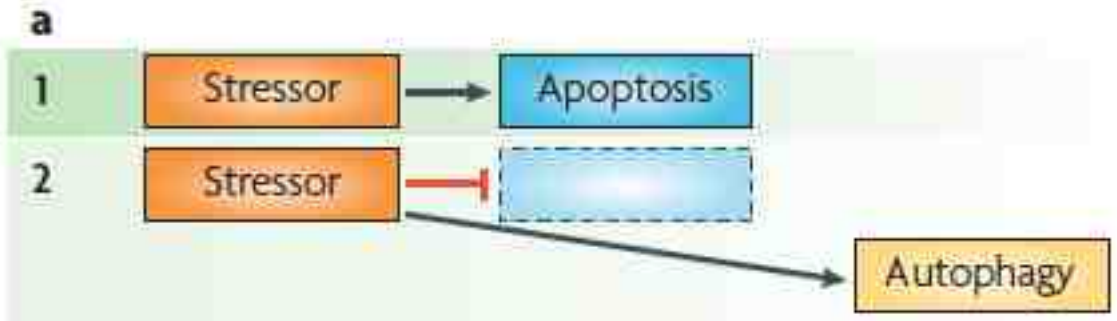
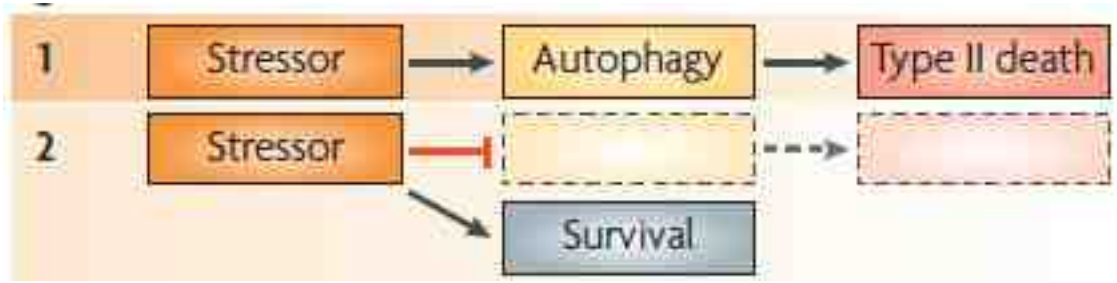
A particular set of insults induces apoptosis (part 1), which, if inhibited, can switch to autophagy. At least in some cellular settings, autophagy serves as a defence mechanism that prevents or retards necrosis (parts 2,3).



b | Some conditions can trigger a lethal autophagic response that is responsible for cell death, for example, in naïve cells (parts 1,2) or in cells in which the apoptotic pathways have been interrupted.



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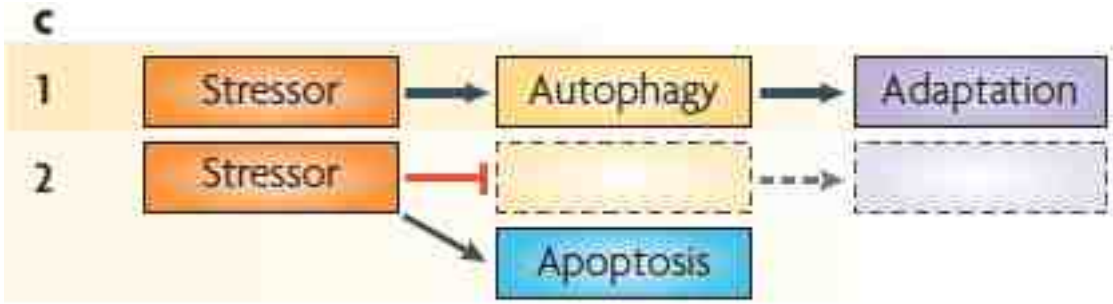
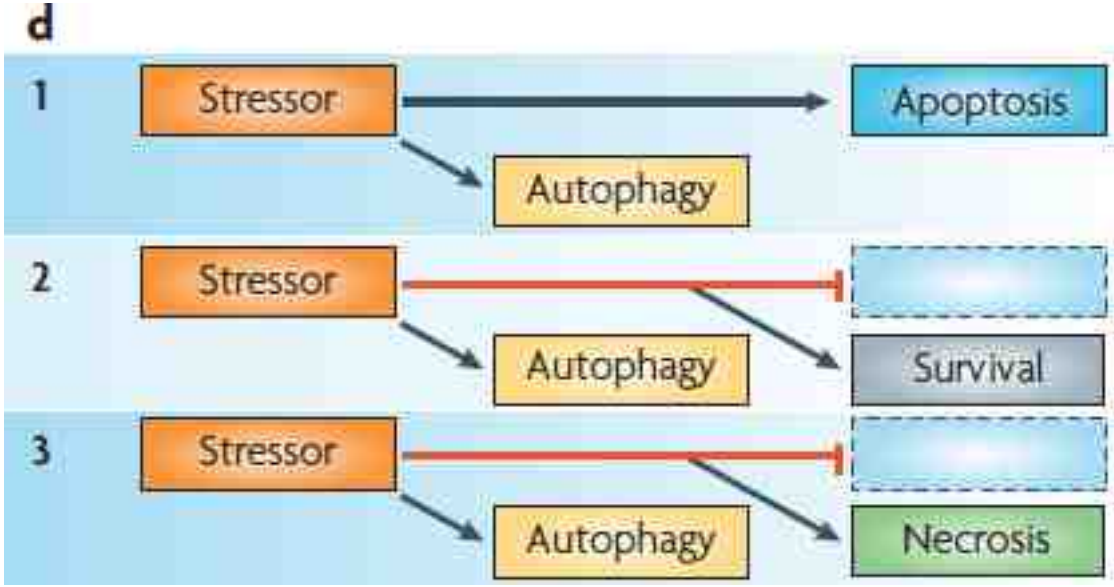
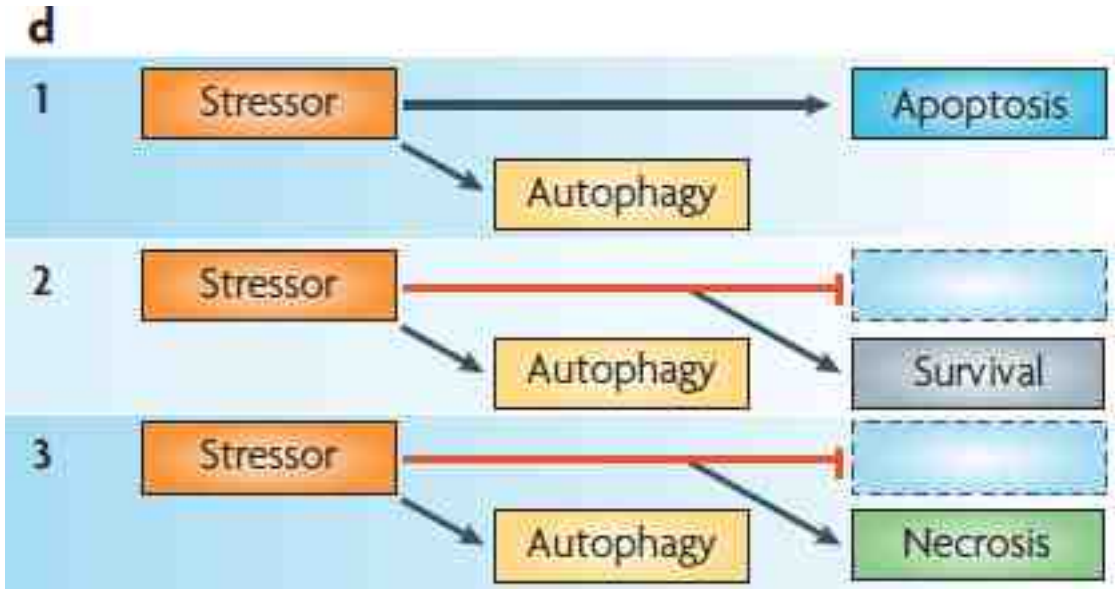


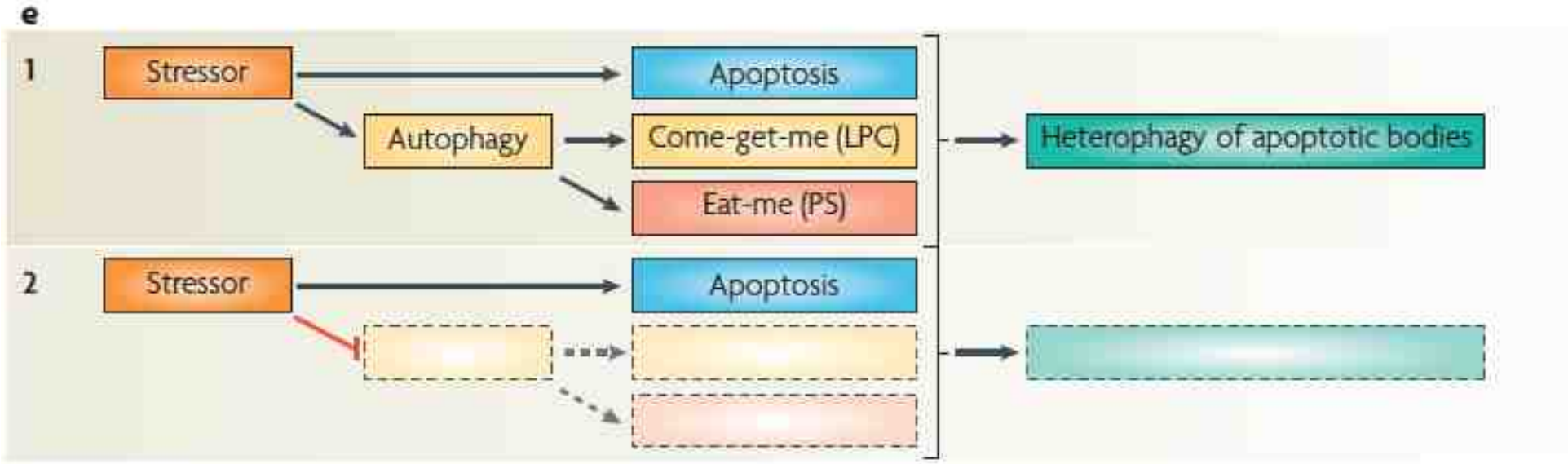
c | Another set of stimuli (or perhaps simply a lower dose of insults) provokes a protective autophagic response (part 1), which is required for adaptation of the cell and the avoidance of apoptosis (part 2).



d | Frequently, lethal conditions trigger an autophagic response that, independently of the autophagic response, is followed by apoptosis (part 1). In this case, inhibition of apoptosis causes either cell survival (part 2) or necrosis (part 3).
In this scenario, the order of events (autophagy, then apoptosis) is chronological, not hierarchical, meaning that inhibition of autophagy does not prevent apoptosis.



d | Frequently, lethal conditions trigger an autophagic response that, independently of the autophagic response, is followed by apoptosis (part 1). In this case, inhibition of apoptosis causes either cell survival (part 2) or necrosis (part 3). In this scenario, the order of events (autophagy, then apoptosis) is chronological, not hierarchical, meaning that inhibition of autophagy does not prevent apoptosis.



e | Autophagy can be indispensable for sustaining the high ATP levels that are required for cells to emit signals to phagocytic cells that engulf the apoptotic bodies (part 1). Inhibition of autophagy does not affect apoptotic cell death, yet it abolishes the heterophagic removal of apoptotic material (part 2). LPC, lysophosphatidylcholine; PS, phosphatidylserine.

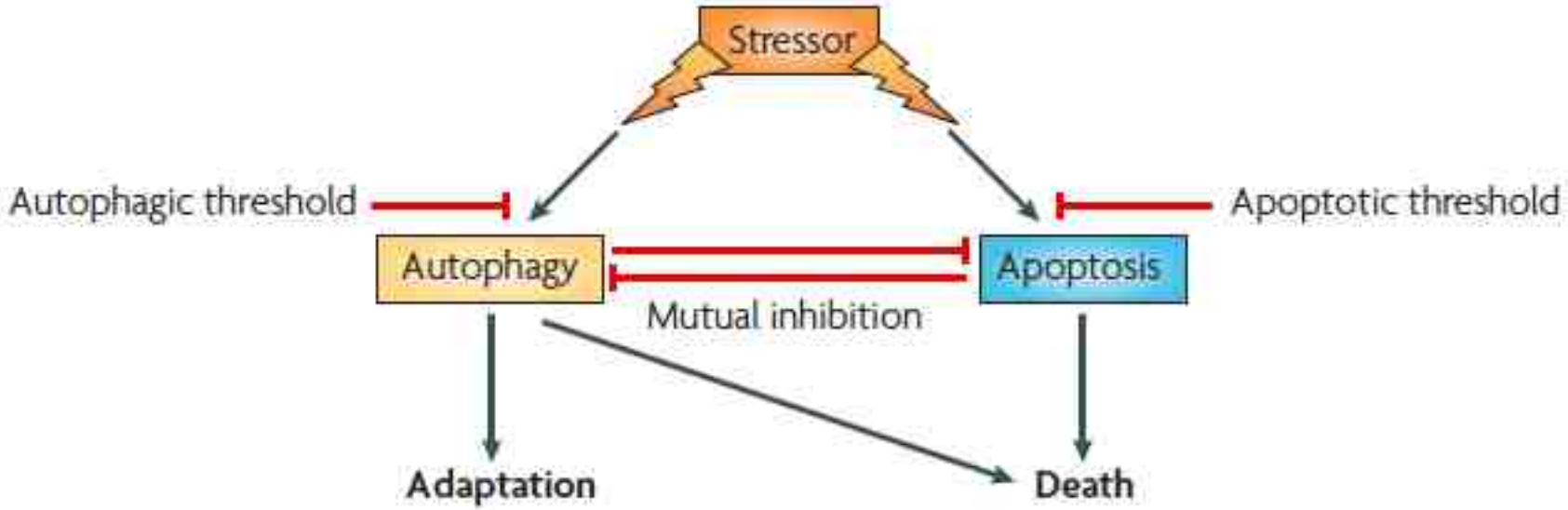


Figure 1 | **The relationship between apoptosis and autophagy.** Similar stressors can induce either apoptosis or autophagy in a context-dependent fashion. It is possible that different sensitivity thresholds, the exact nature of which remain to be determined, can dictate whether autophagy or apoptosis will develop. Alternatively, the choice between apoptosis and autophagy is influenced by the fact that the two catabolic processes exhibit some degree of mutual inhibition. In some cases, a mixed phenotype of apoptosis and autophagy can be detected at the single-cell level. Although autophagy mostly allows cells to adapt to stress, massive autophagy can also kill cells.

Pathway to autophagy

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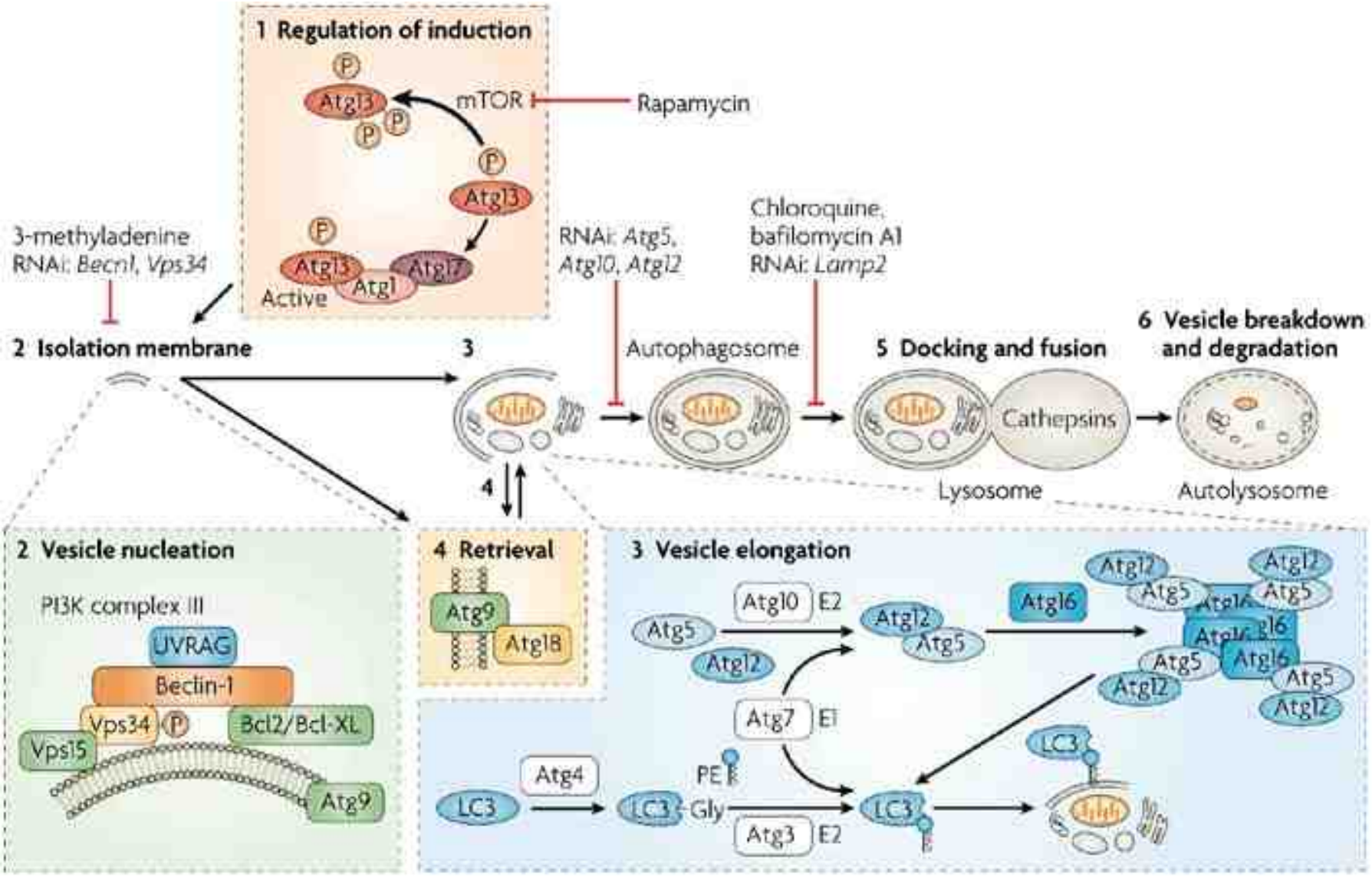

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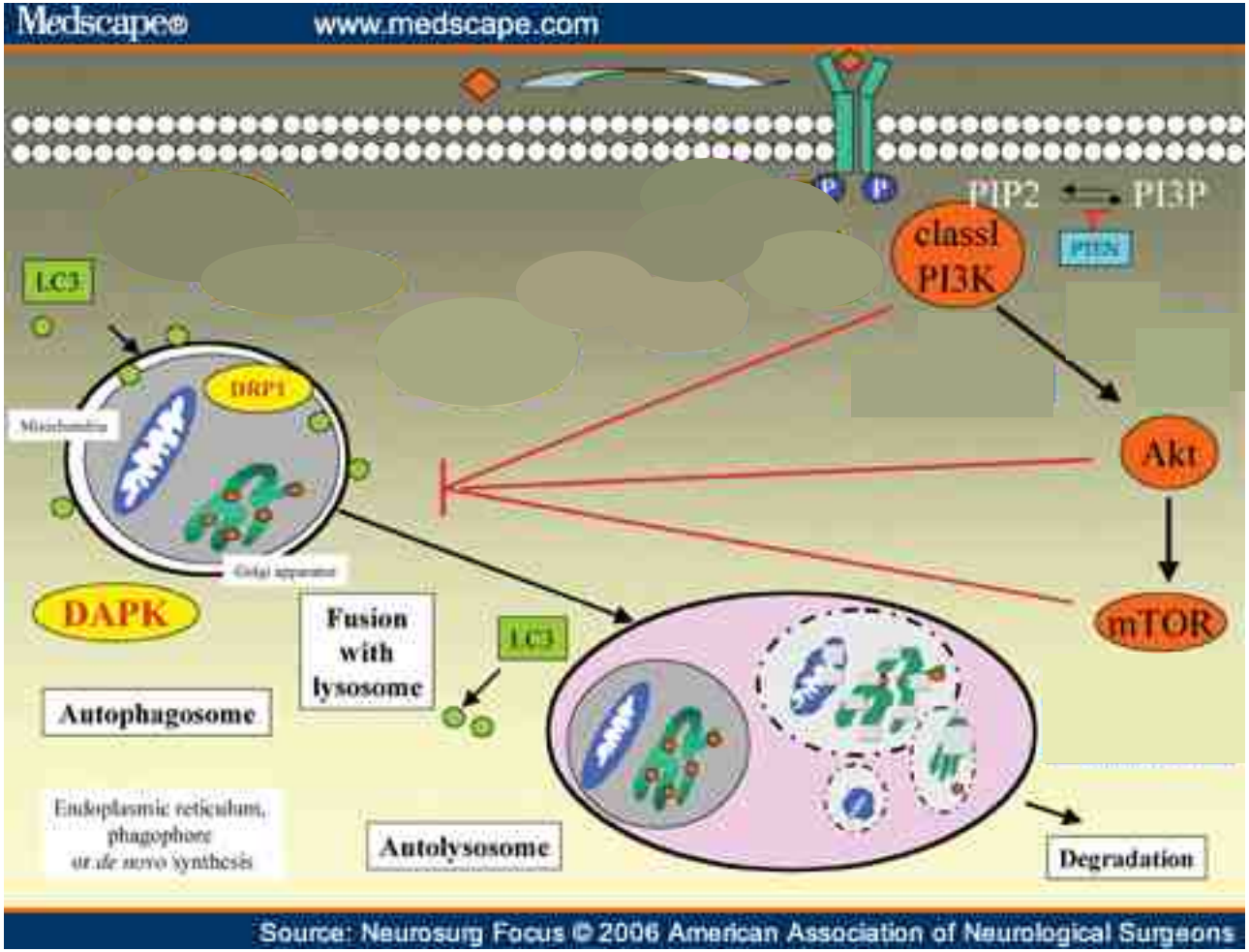
In the presence of growth factors, growth factor receptor signaling activates: Class I PI3K, which activates the downstream targets Akt and mTOR, resulting in inhibition of autophagy. The PTEN gene mutation promotes Akt activation.



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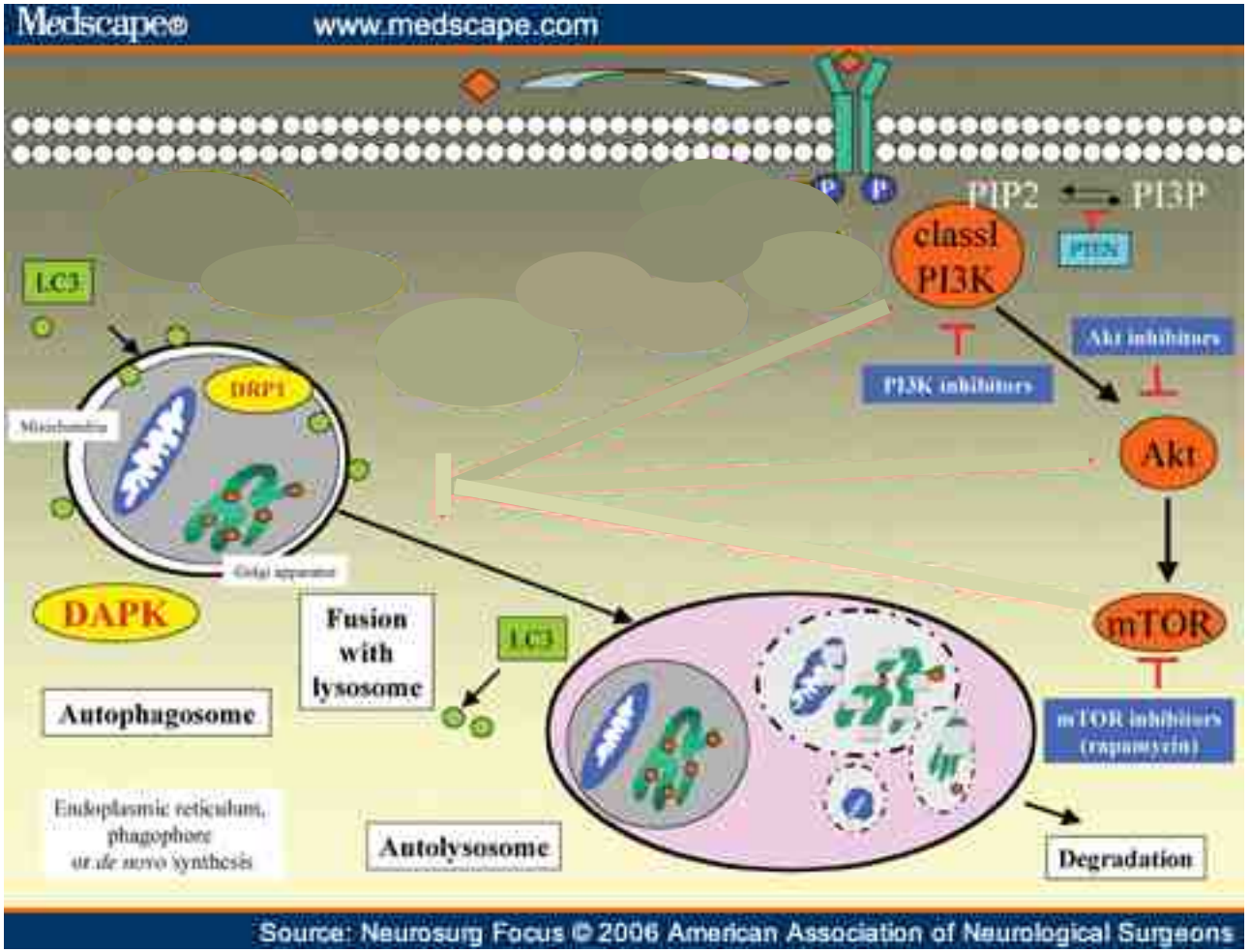
Rapamycin, an inhibitor of mTOR, induces autophagy.



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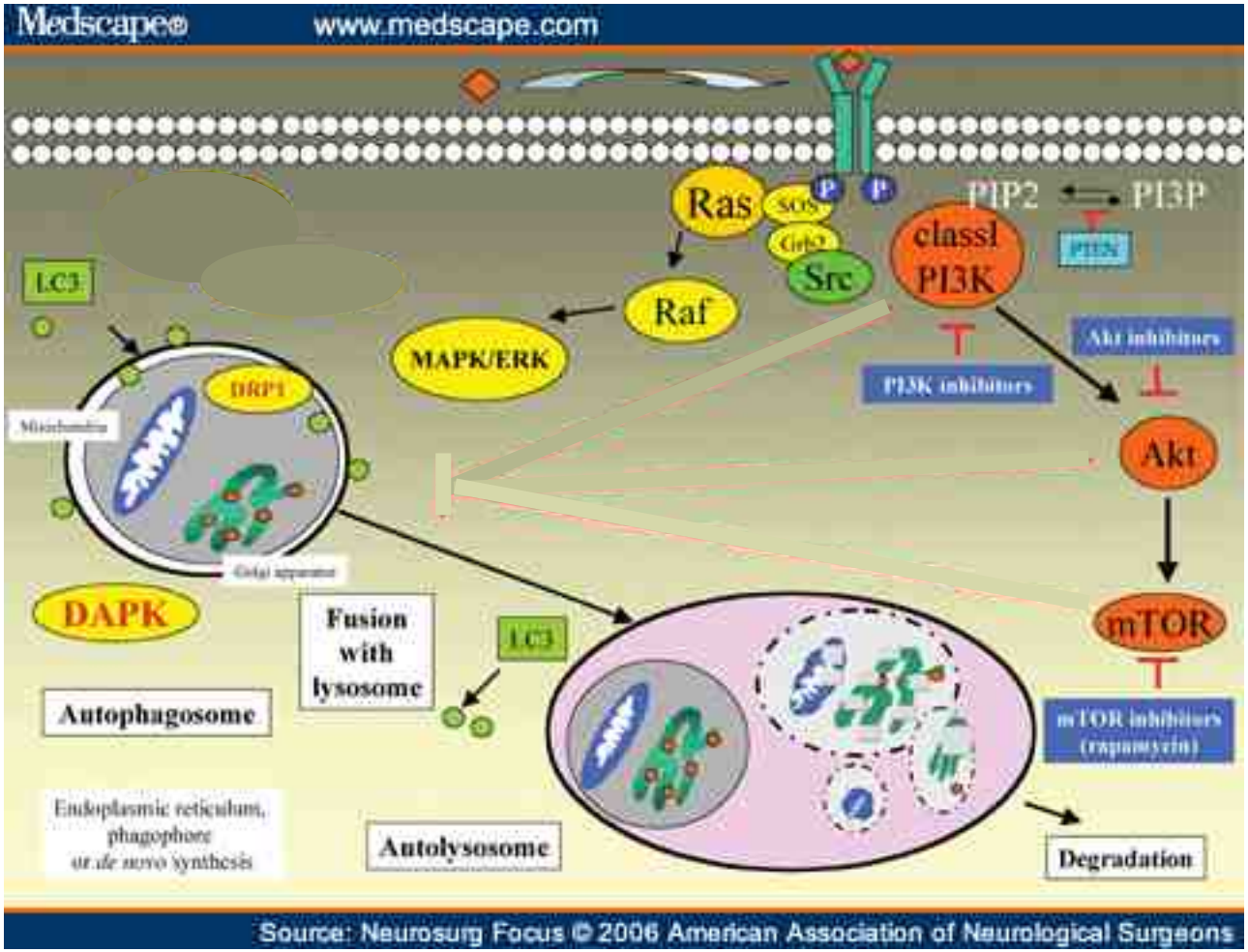
Ras has a dual effect on autophagy; when it activates Class I PI3K, autophagy is inhibited, but when it activates the MAPK cascade, autophagy is stimulated.



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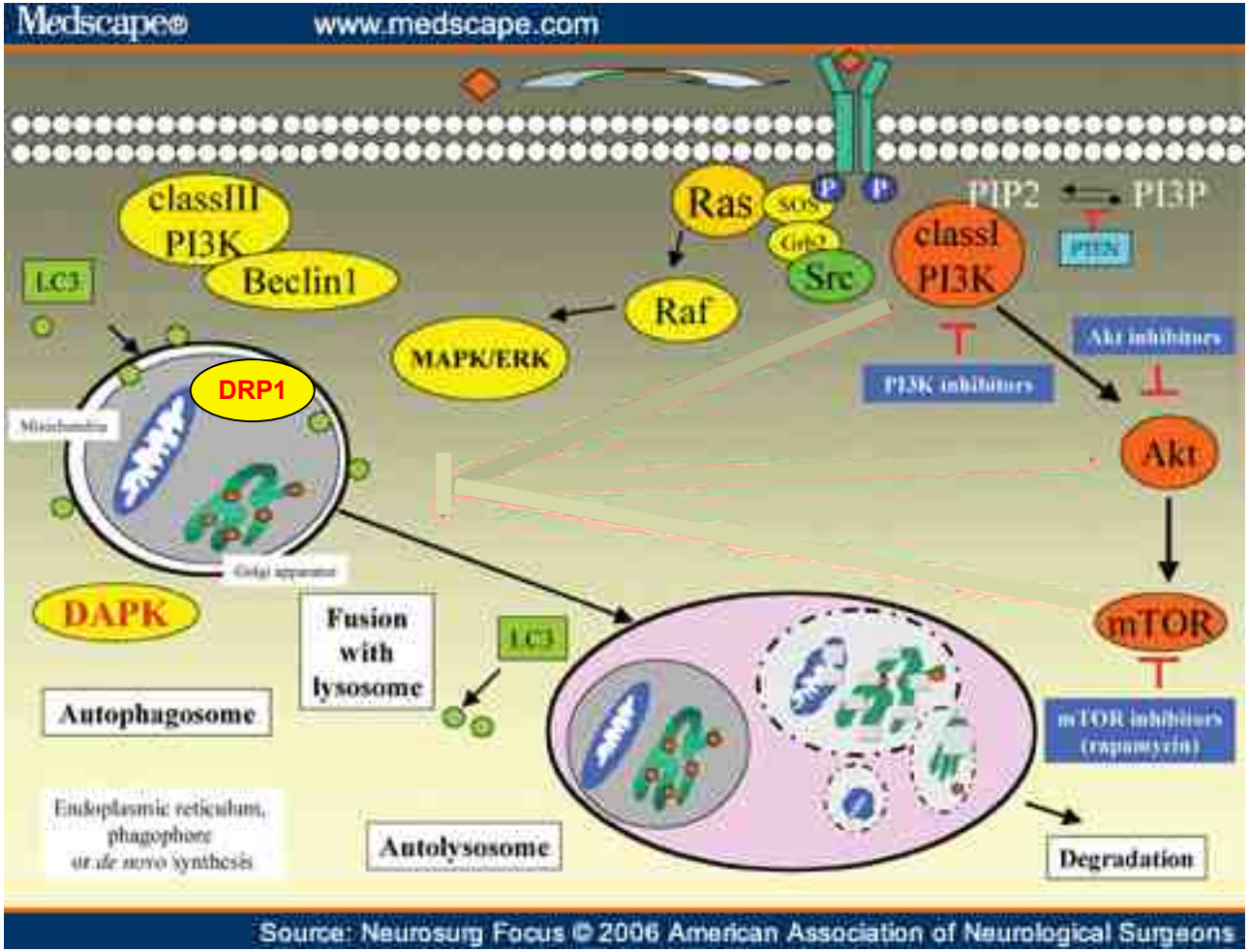
A complex of Class III PI3K and beclin1 (a tumor suppressor gene) is required for a proximal step in autophagy. Autophagy is also induced by the cell death-associated protein kinase (DAPK) and the death-associated related protein kinase 1 (DRP1). Class III PI3K has been shown to be required for both autophagic vesicle formation and vesicular transport to the lysosome. LC3 = microtubule-associated protein light-chain 3.



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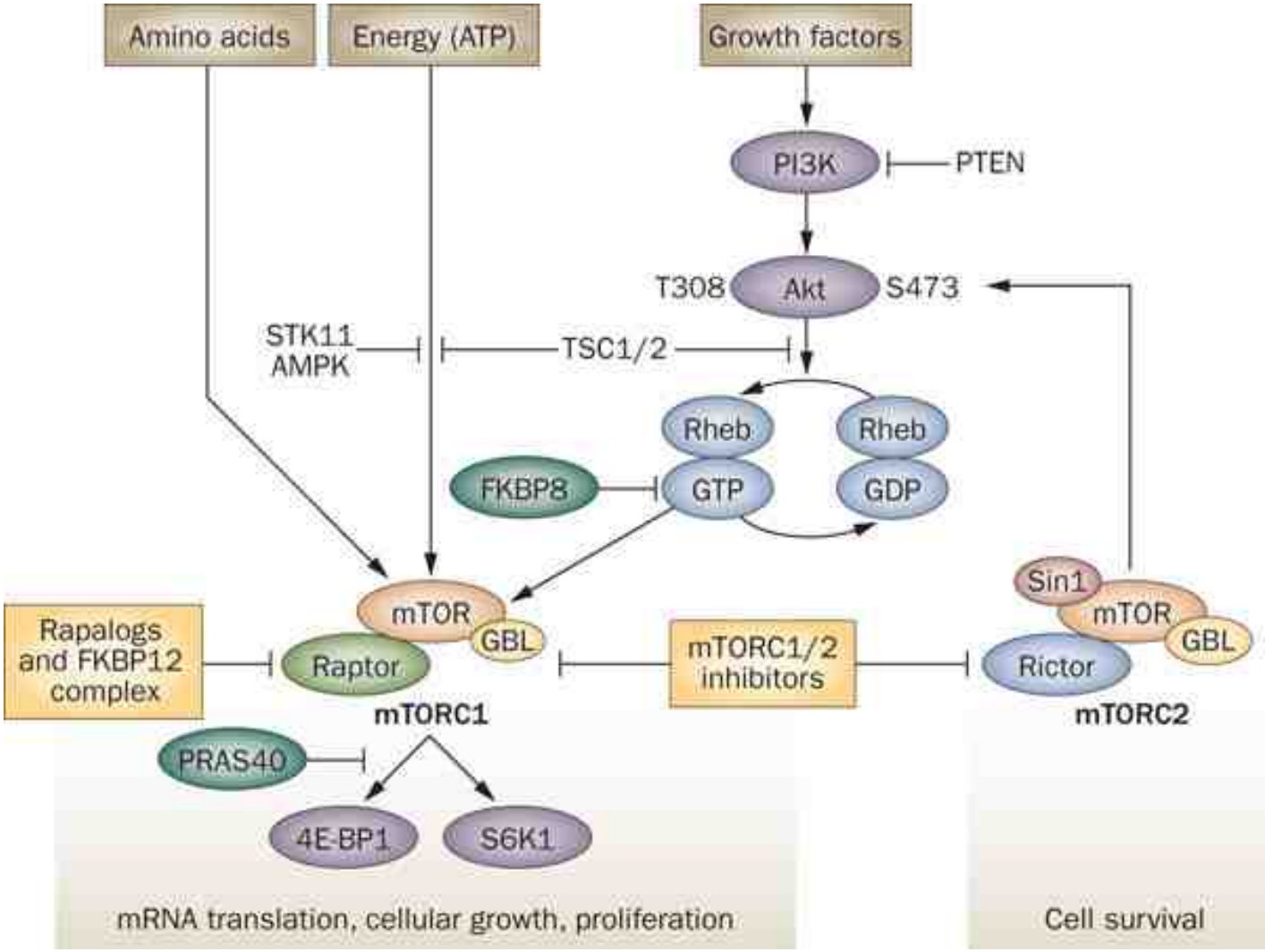
mTOR forms complexes with other proteins, including Raptor (forming mTORC1) or Rictor (forming mTORC2).

ATP, amino acids and signals from the PI3K/Akt pathway modulate mTOR function. Activation of PI3K and Akt inhibits hamartin and tuberin repression of Rheb, which leads to mTORC1 activation and phosphorylation of S6K1 and 4E-BP1. Akt is pivotal in mTOR signaling, as it is both an upstream activator of mTORC1 and downstream effector of mTORC2. Negative regulators of mTOR include FKBP8, which prevents Rheb from activating mTORC1, and PRAS40, which competes with Raptor for binding to S6K1 and 4E-BP1. When intracellular ATP is depleted relative to AMP, AMPK and its upstream regulator STK11 phosphorylate tuberin, which inactivates Rheb and mTORC1 signaling.

Hypoxia and low amino acid levels also negatively regulate mTOR. Rapalogs associate with FKBP12 and preferentially disrupt mTORC1 whereas small-molecule mTOR kinase inhibitors target both mTOR complexes. Abbreviations: AMPK, AMP-activated kinase; 4E-BP1, eIF4E-binding protein 1; FKBP12, FK506 binding protein 12; GBL, G protein beta subunit-like; mTORC, mammalian target of rapamycin complex; PI3K, phosphatidylinositol 3-kinase; PRAS40, proline-rich Akt1 substrate 1; PTEN, phosphatase and tensin homolog deleted on chromosome 10; S6K1, p70 S6 kinase 1; Sin1, stress-activated protein kinase interaction protein 1; STK11, serine/threonine-protein kinase 11; TSC, tuberous sclerosis complex.

Nature Reviews Clinical Oncology **7**, 209-219 (April 2010)

Amino acids, energy, growth factors postively activate mTOR
Starvation, hypoxia and low amino acid levels negatively regulate mTOR



Nature Reviews Clinical Oncology **7**, 209-219 (April 2010)

Activation of growth factor receptors stimulates the class I PtdIns3K complex and small GTPase Ras, which leads to activation of the PtdIns3K–PKB–mTORC1 pathway and the Raf-1–MEK1/2–ERK1/2 pathway, respectively. mTORC2 inhibits autophagy through the phosphorylation and activation of PKB. Metabolic stress, such as high AMP/ATP ratios resulting from energy depletion, or an increase in the cytosolic free Ca2+ concentration or cytokines, cause the AMP-activated protein kinase (AMPK) to be phosphorylated and activated by LKB1, CaMKKb, and TAK1, respectively. AMPK phosphorylates and activates TSC1/TSC2, leading to inactivation of mTORC1 and autophagy induction. Genotoxic and oncogenic stresses result in nuclear p53 stabilization and activation, which stimulates autophagy through activation of AMPK or upregulation of DRAM. In contrast, cytosolic p53 has an inhibitory effect on autophagy. Antiapoptotic proteins, Bcl-2 or Bcl-XL, associate with Beclin 1 and inhibit the Beclin 1-associated class III PtdIns3K complex, causing inhibition of autophagy.

GFs

↓

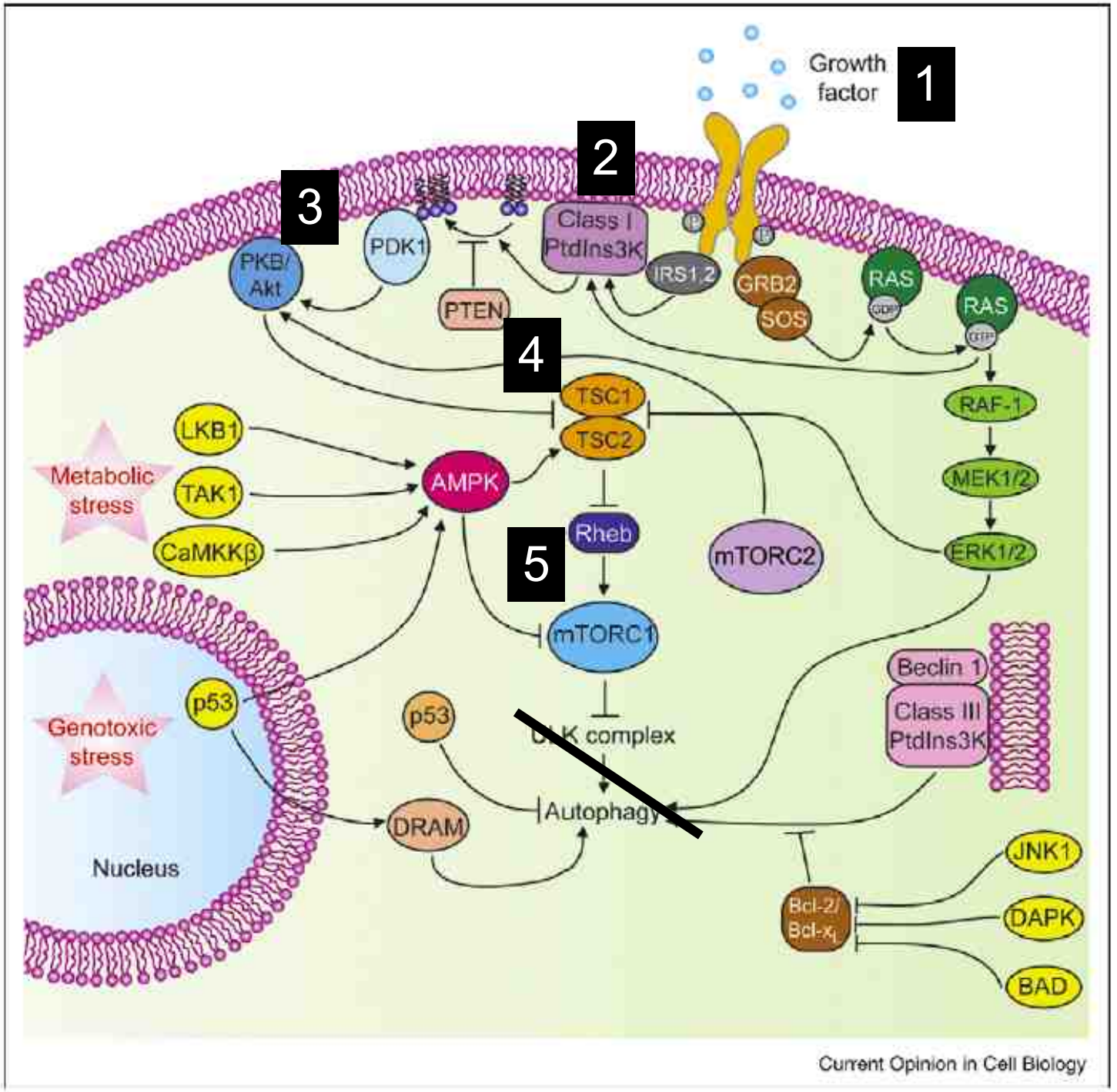
PI3K

↓

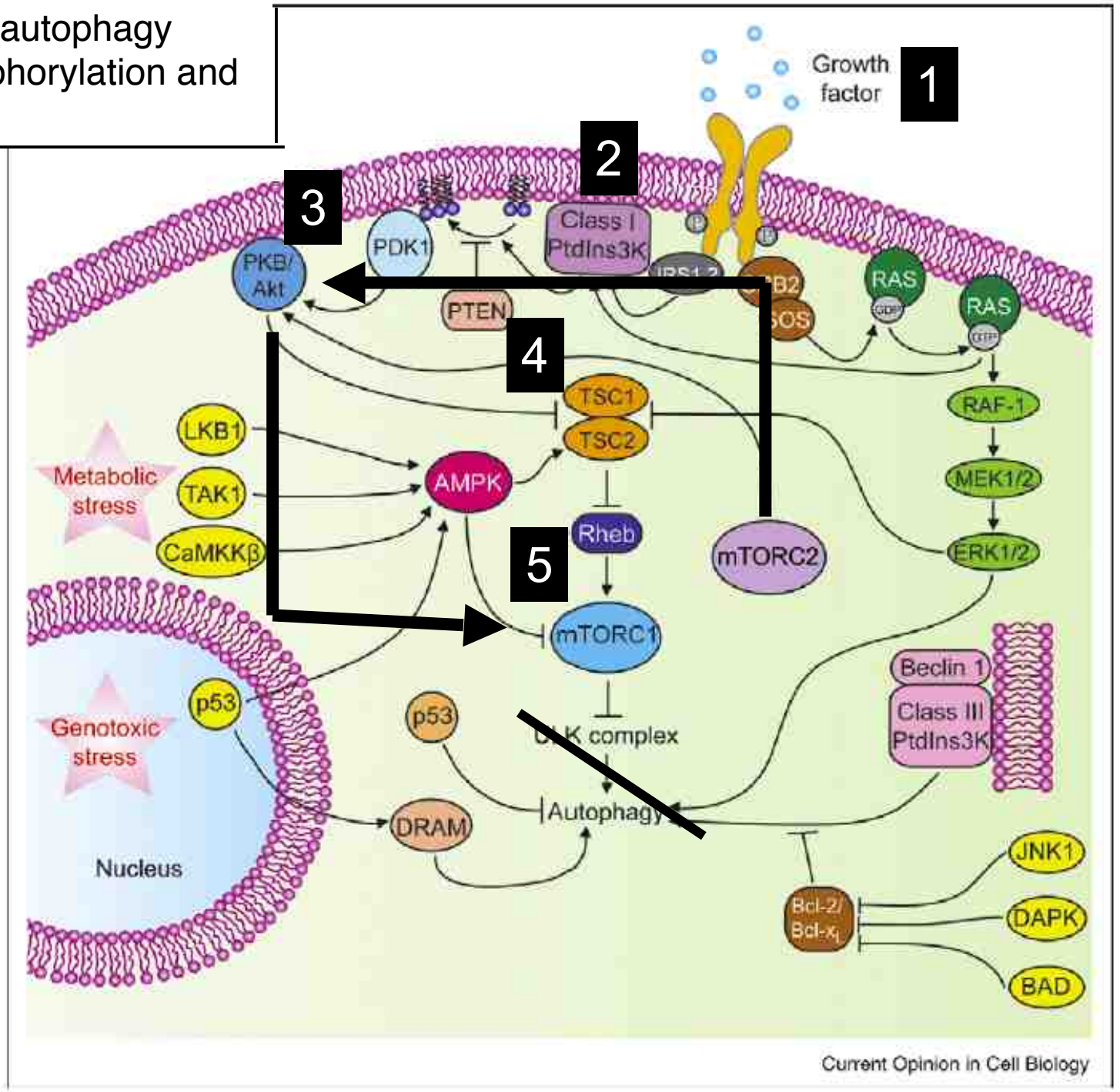
mTORC1 activation

↓

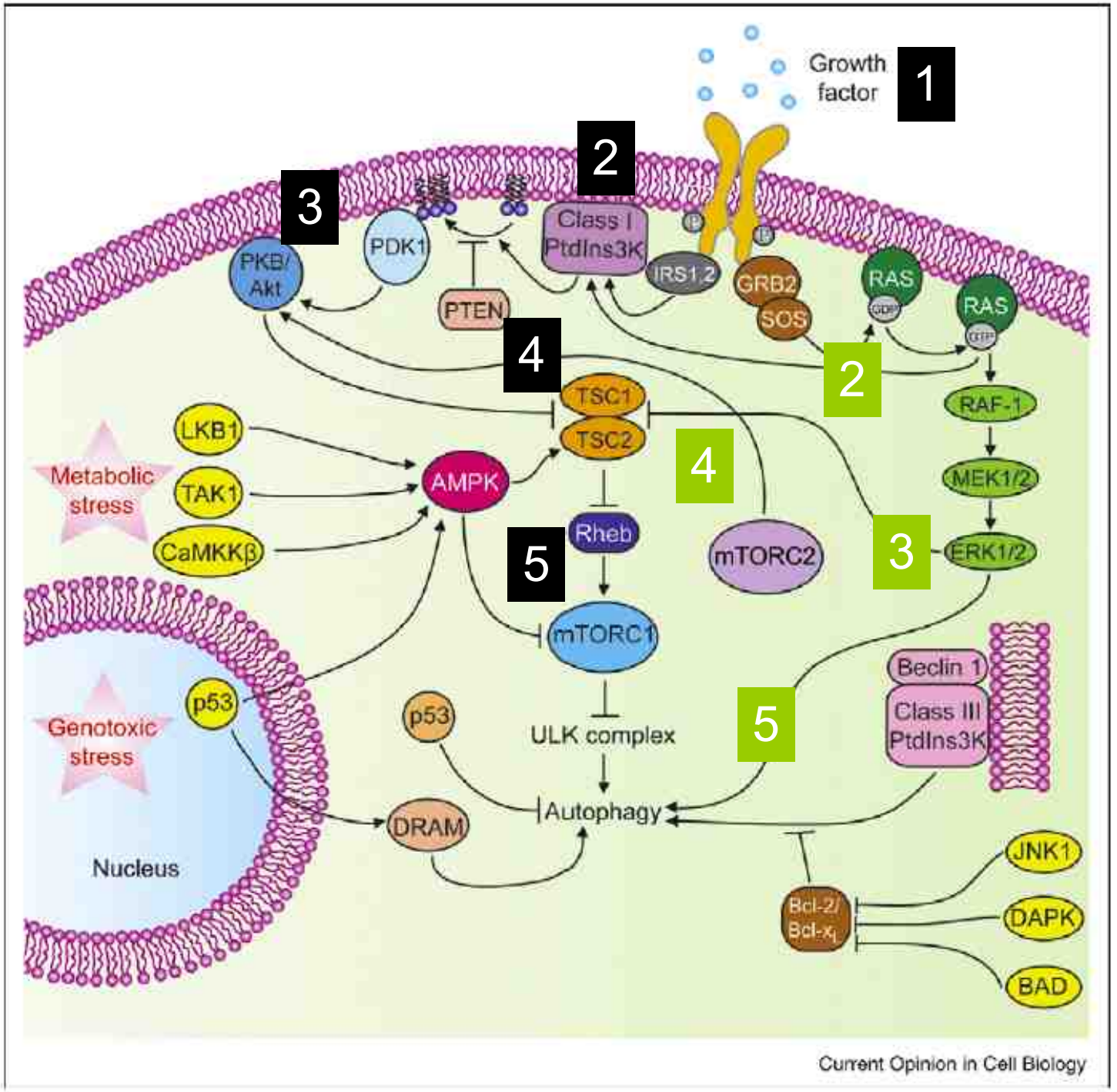
No autophagy



mTORC2 inhibits autophagy through the phosphorylation and activation of PKB



Dual effect of MAPK pathway



Metabolic Stress

↓

AMPK

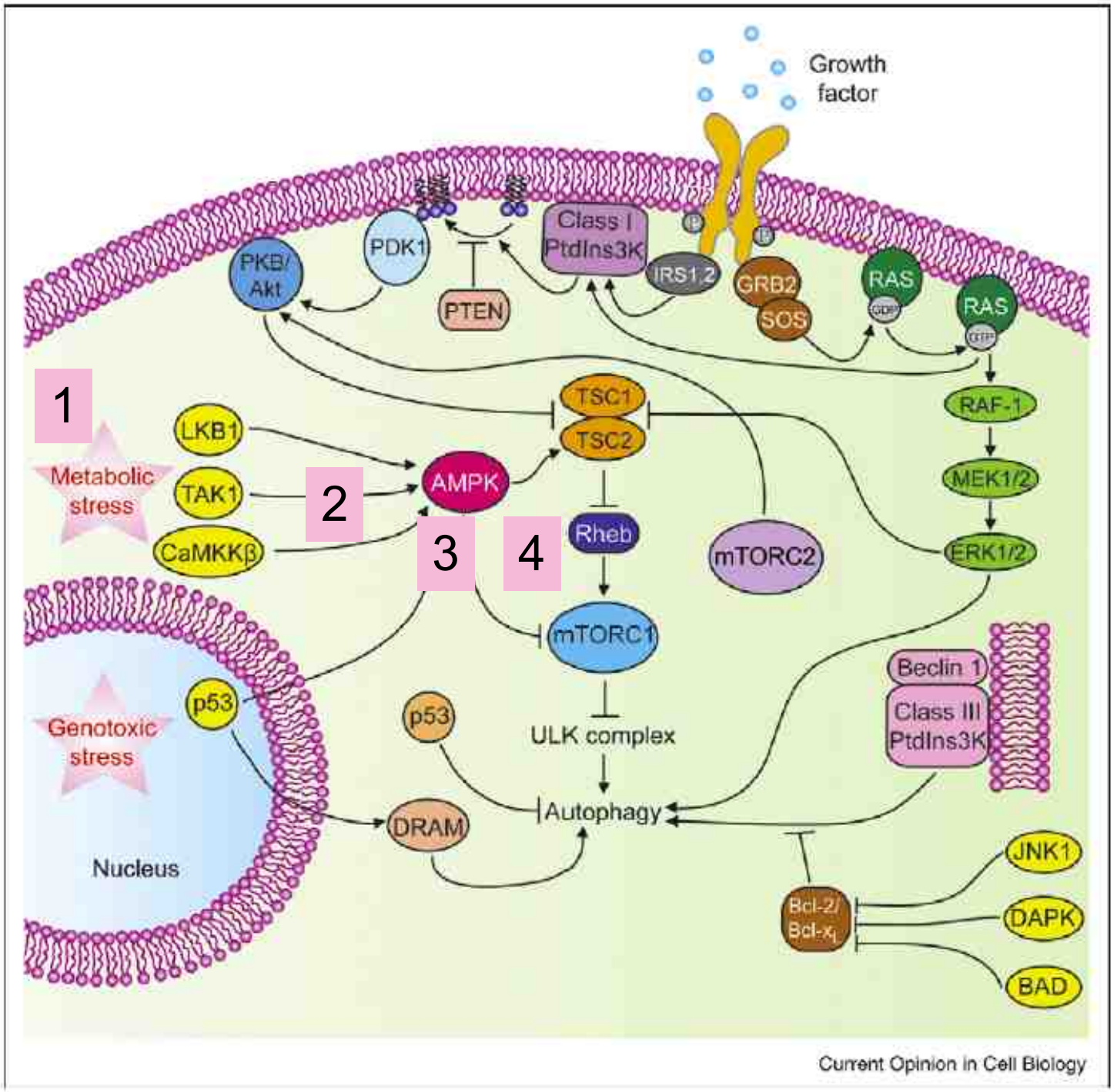
AMP-activated protein kinase

↓

mTORC1 inhibition

↓

autophagy induction



Genotoxic and oncogenic stresses

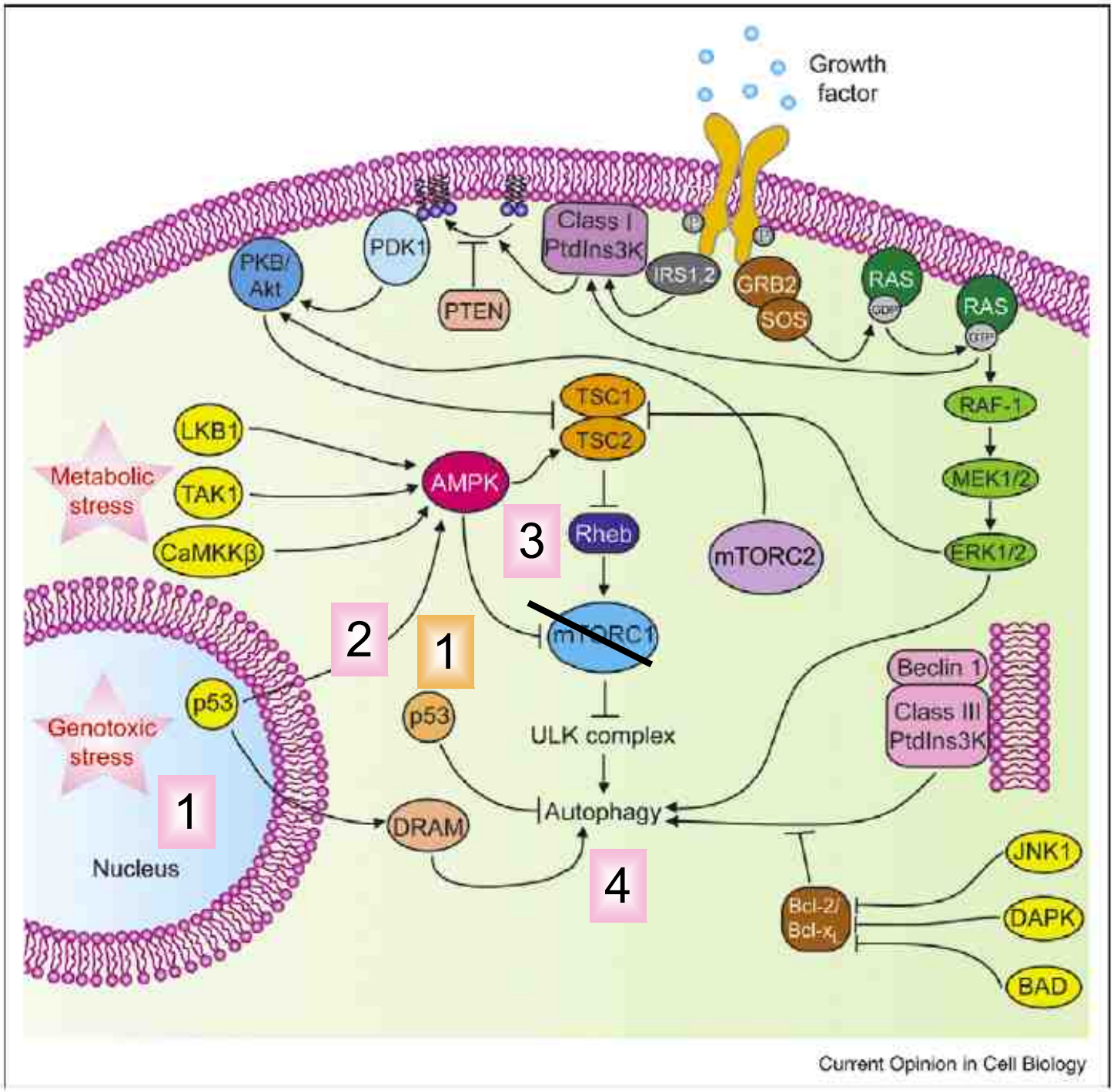
P53

nuclear

cytosol

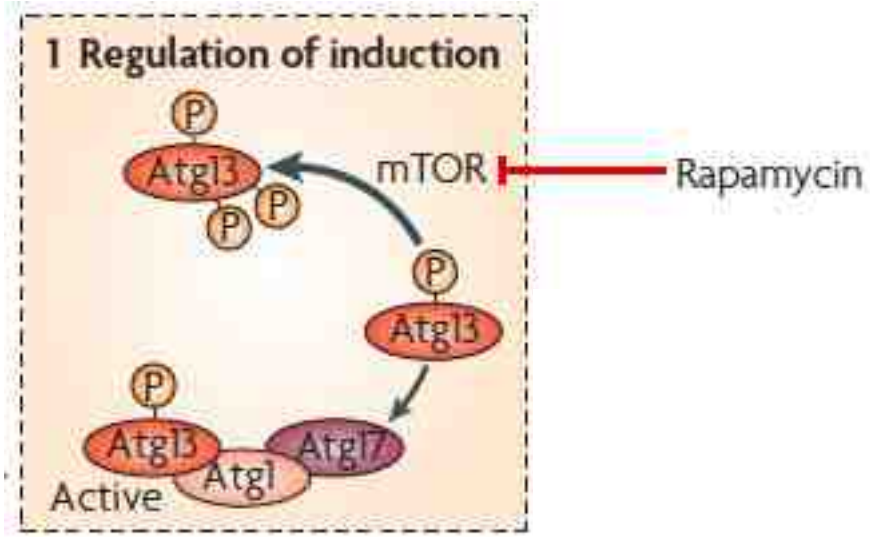
autophagy induction

autophagy inhibition

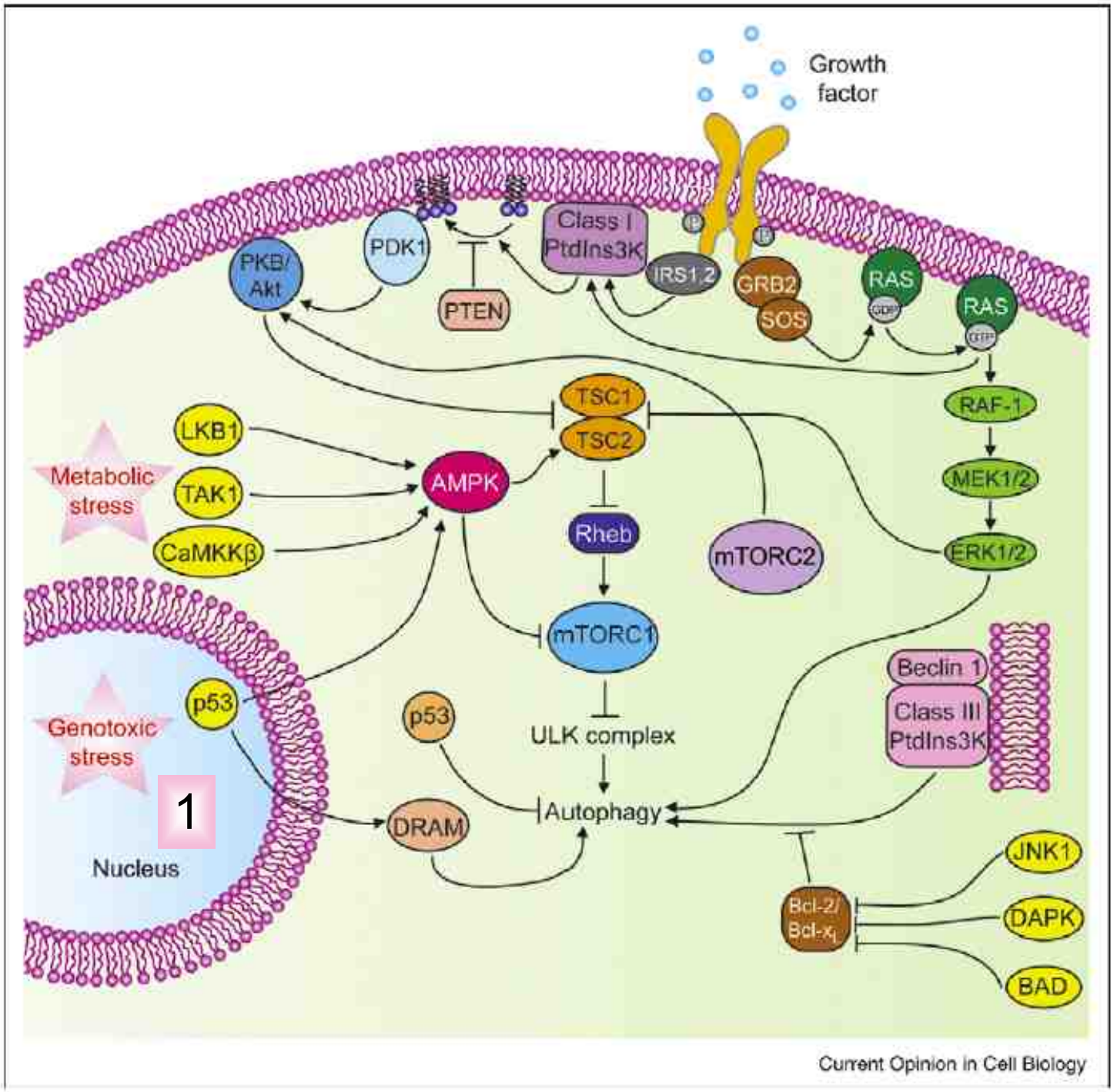


In many cellular settings, the first regulatory process involves the de-repression of the mTOR Ser/Thr kinase, which inhibits autophagy by phosphorylating autophagy protein-13 (Atg13). This phosphorylation leads to the dissociation of Atg13 from a protein complex that contains Atg1 kinase (and Atg17), and thus attenuates the Atg1 kinase activity.

When mTOR is inhibited, re-association of dephosphorylated Atg13 with Atg1 stimulates its catalytic activity and induces autophagy.



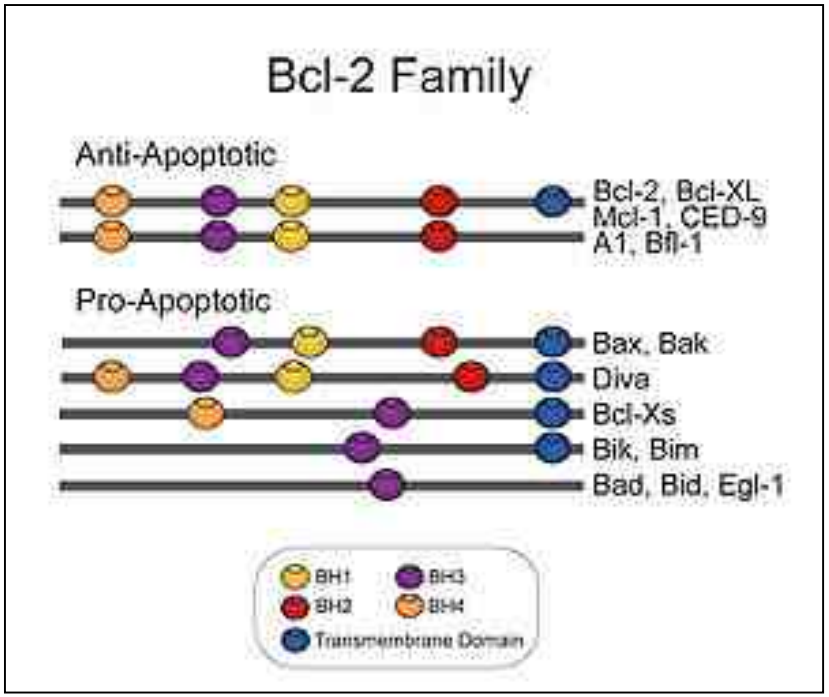
Antiapoptotic proteins, Bcl-2 or Bcl-XL, associate with Beclin 1 and inhibit the Beclin 1-associated class III PtdIns3K complex, causing inhibition of autophagy.

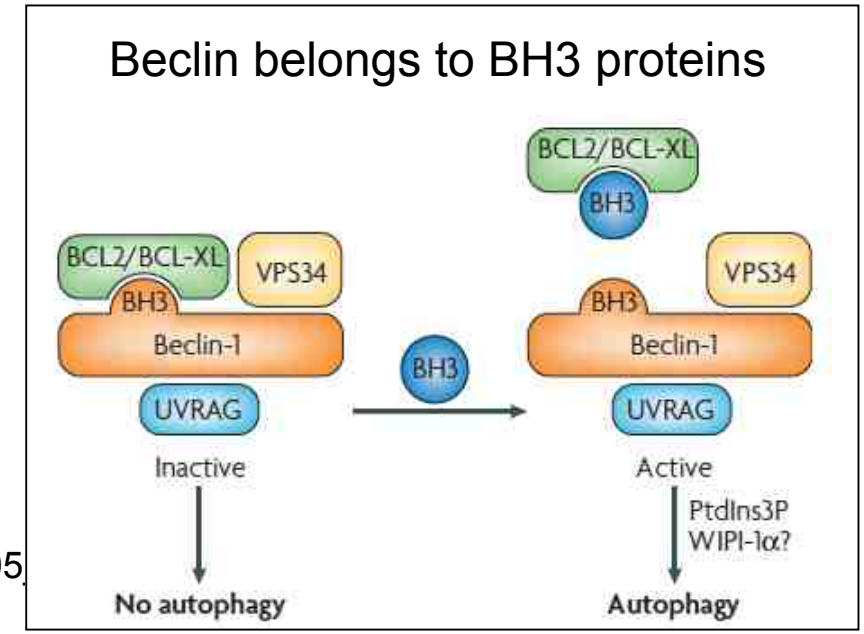


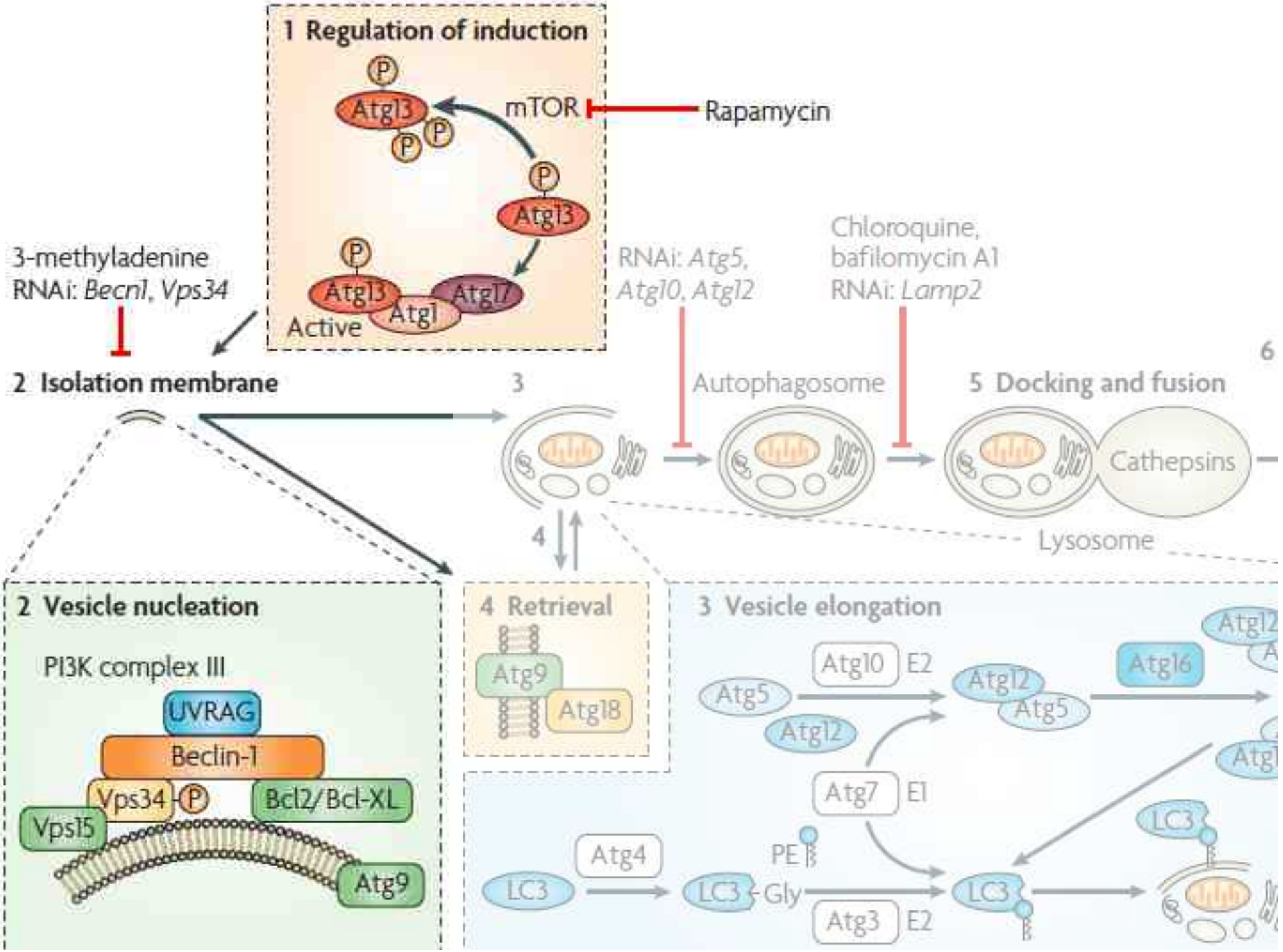
Beclin-1–BCL 2 interaction

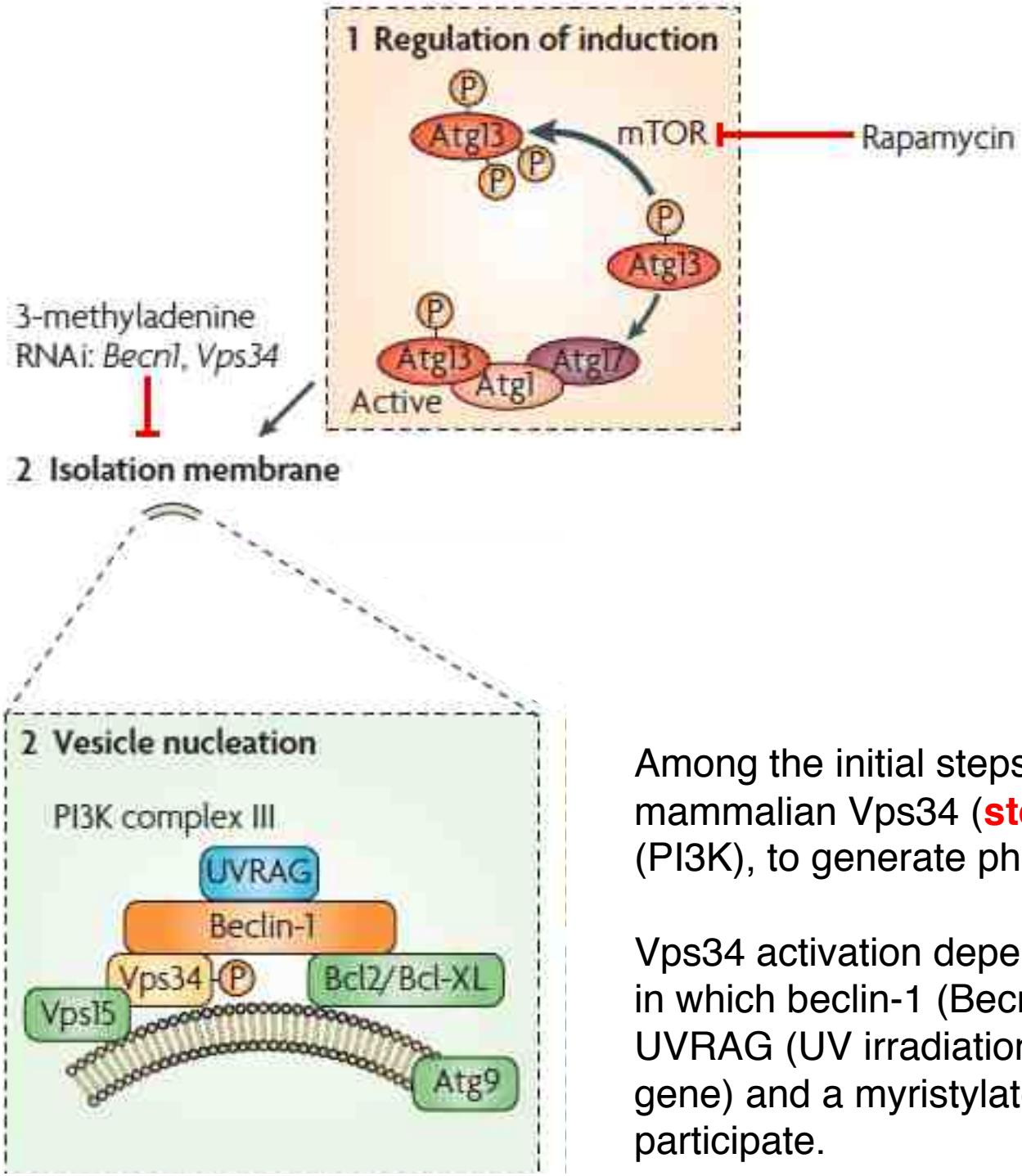
Proteins that contain BCL2 homology-3 (BH3) domains or small molecules that mimic BH3 domains can bind to the BH3-receptor domain of BCL2 or BCL-XL and, hence, competitively disrupt the interaction between BCL2 or BCL-XL and beclin-1.

This probably leads to the activation of the lipid kinase activity of the class III phosphatidylinositol 3-kinase VPS34 (which depends on the interaction with UVRAG (UV irradiation resistance associated tumour suppressor gene), thereby provoking the production of phosphatidylinositol-3-phosphate (PtdIns3P). In turn, this leads to vesicle nucleation in a manner that probably involves WIPI-1a (WD-repeat protein interacting with phosphoinositides).






1 Regulation of induction
P
Atg13
mTOR
Rapamycin
P
P
P
Atg13
P
Atg13
Atg17
Atg1
Active
3-methyladenine
RNAi: Becn1, Vps34
RNAi: Atg5, Atg10, Atg12
Chloroquine, bafilomycin A1
RNAi: Lamp2
2 Isolation membrane
3
Autophagosome
5 Docking and fusion
6
Cathepsins
Lysosome
4
2 Vesicle nucleation
PI3K complex III
UVRAG
Beclin-1
Vps34
P
Bcl2/Bcl-XL
Vps15
Atg9
4 Retrieval
Atg9
Atg18
3 Vesicle elongation
Atg10
E2
Atg5
Atg12
Atg12
Atg5
Atg16
Atg12
Atg7
E1
Atg4
LC3
PE
LC3
Gly
Atg3
E2
LC3
LC3



In many cellular setting regulatory process (**step 1** de-repression of the m kinase, which inhibits a phosphorylating autophag (Atg13).
When mTOR is inhibited, of dephosphorylated Atg1 stimulates its catalytic induces autophagy.
Notably, the mammalian the yeast Atg13 has not bee date.

Among the initial steps of vesicle nucleation is the acti mammalian Vps34 (**step 2)**, a class III phosphatidylinc (PI3K), to generate phosphatidylinositol-3-phosphate (

Vps34 activation depends on the formation of a multip in which beclin-1 (Becn1; the mammalian orthologue c UVRAG (UV irradiation resistance-associated tumour gene) and a myristylated kinase (Vps15, or p150 in hu participate.