Apoptosis and Autophagy Pathways

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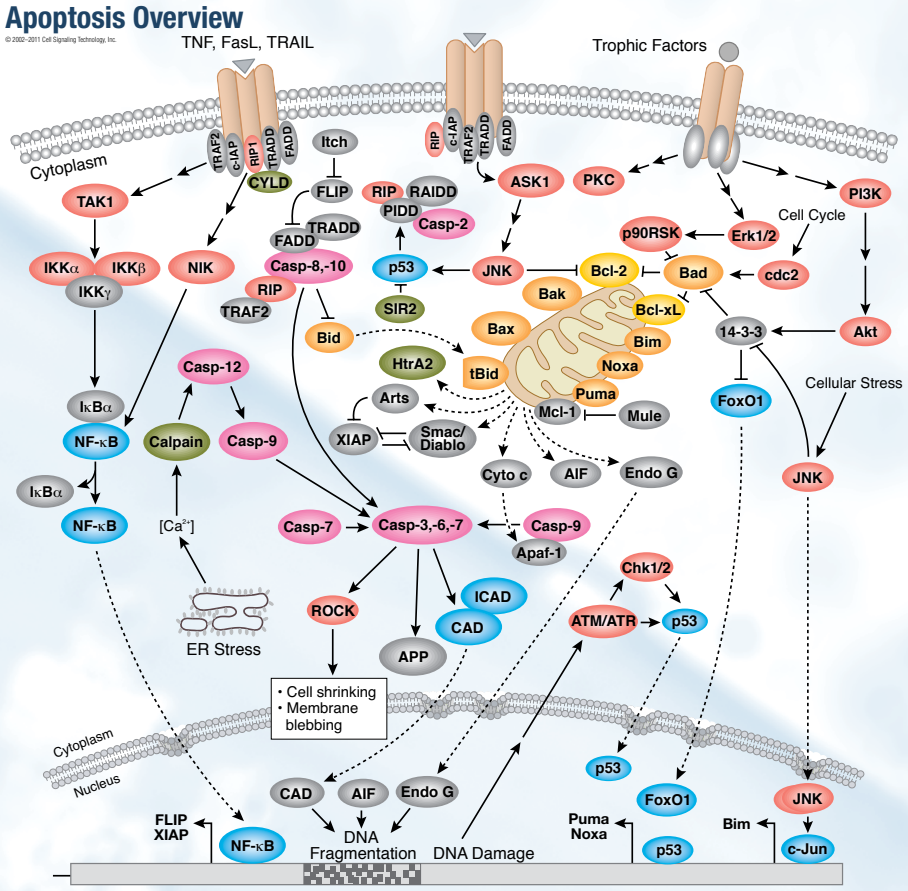
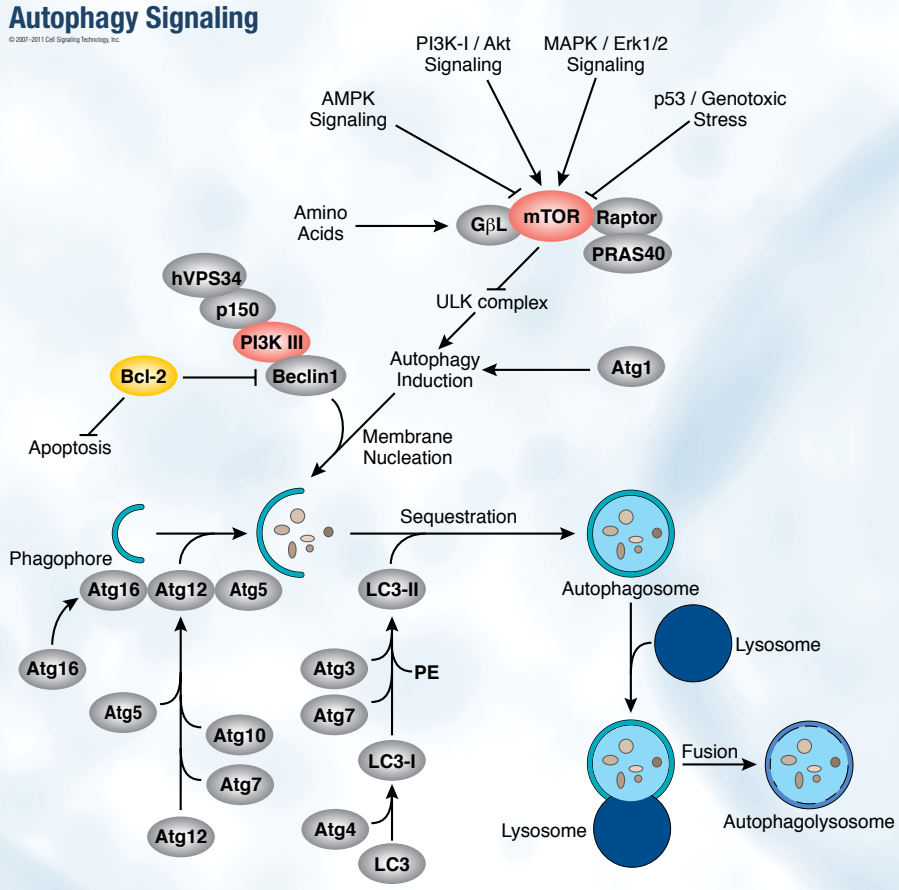
All pathways were created by research scientists at Cell Signaling Technology and reviewed by leading scientists in the field. Visit www.cellsignal.com for additional reference materials and comprehensive validation data for over 3,000 antibodies and related reagents.

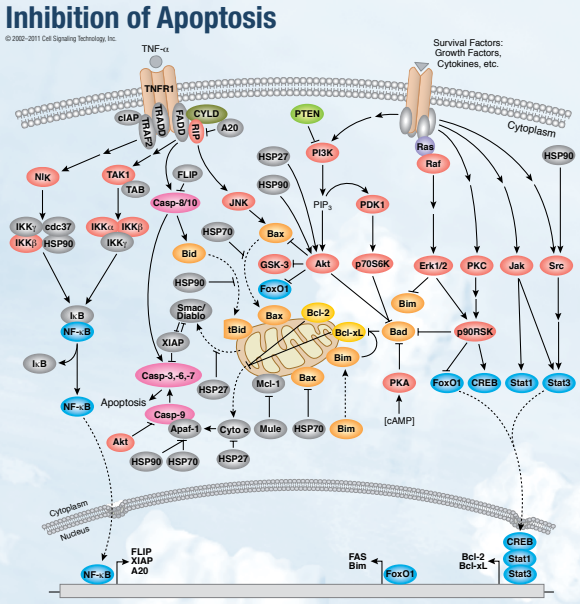
Apoptosis Overview



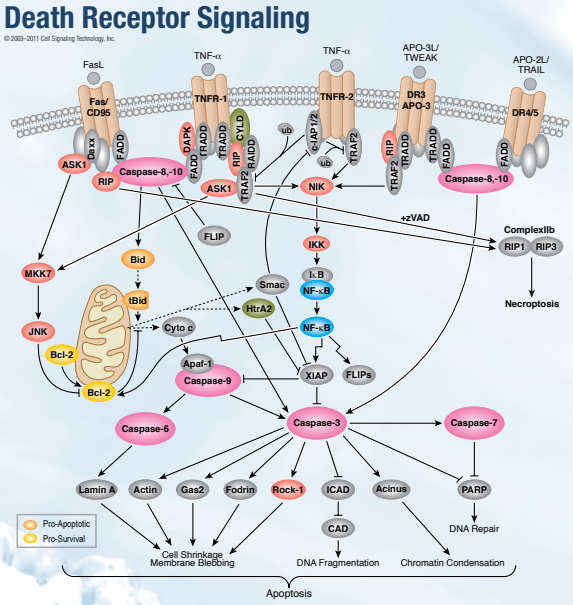
Autophagy Signaling



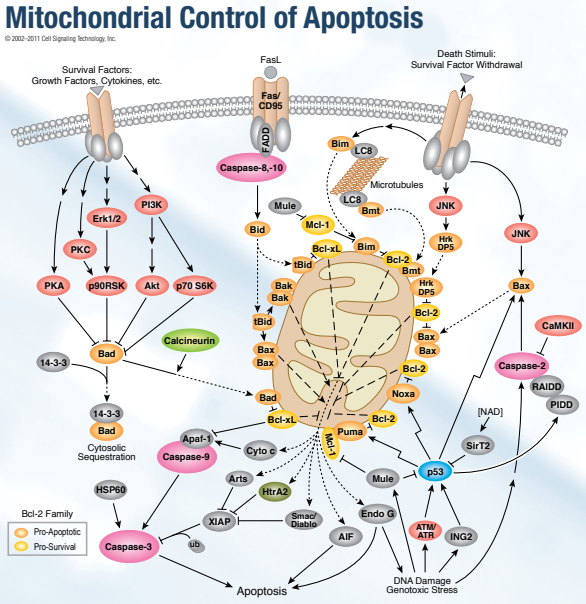
Inhibition of Apoptosis



Death Receptor Signaling



Mitochondrial Control of Apoptosis



→ Direct Stimulatory Modification
⊣ Direct Inhibitory Modification
→ → Multistep Stimulatory Modification
→ ⊣ Multistep Inhibitory Modification
– – → Tentative Stimulatory Modification
– – ⊣ Tentative Inhibitory Modification
Transcriptional Stimulatory Modification
Transcriptional Inhibitory Modification
Separation of Subunits or Cleavage Products
Joining of Subunits
- - - → Translocation
Kinase
Phosphatase
Transcription Factor
Caspase
Receptor
Enzyme
Pro-apoptotic
Anti-apoptotic
GAP
GEF
GTPase
G-protein, ribosomal subunit

Apoptosis Overview Pathway Description:

Apoptosis is a regulated cellular suicide mechanism characterized by nuclear condensation, cell shrinkage, membrane blebbing, and DNA fragmentation. Caspases, a family of cysteine proteases, are the central regulators of apoptosis. Initiator caspases (including caspase-2, -8, -9, -10, -11, and -12) are closely coupled to pro-apoptotic signals. Once activated, these caspases cleave and activate downstream effector caspases (including caspase-3, -6, and -7), which in turn execute apoptosis by cleaving cellular proteins following specific Asp residues. Activation of Fas and TNFR by FasL and TNF, respectively, leads to the activation of caspase-8 and -10. DNA damage induces the expression of PIDD which binds to RAIDD and caspase-2 and leads to the activation of caspase-2. Cytochrome c released from damaged mitochondria is coupled to the activation of caspase-9. XIAP inhibits caspase-3, -7, and -9. Mitochondria release multiple pro-apoptotic molecules, such as Smac/Diablo, AIF, HtrA2 and EndoG, in addition to cytochrome c. Smac/Diablo binds to XIAP which prevents it from inhibiting caspases. Caspase-11 is induced and activated by pathological proinflammatory and pro-apoptotic stimuli and leads to the activation of caspase-1 to promote inflammatory response and apoptosis by directly processing caspase-3. Caspase-12 and caspase-7 are activated under ER stress conditions. Anti-apoptotic ligands including growth factors and cytokines activate Akt and p90RSK. Akt inhibits Bad by direct phosphorylation and prevents the expression of Bim by phosphorylating and inhibiting the Forkhead family of transcription factors (FoxO). FoxO promotes apoptosis by upregulating pro-apoptotic molecules such as FasL and Bim.

Autophagy Signaling Pathway Description:

Macroautophagy, often referred to as autophagy, is a catabolic process that results in the autophagosomic-lysosomal degradation of bulk cytoplasmic contents, abnormal protein aggregates, and excess or damaged organelles. Autophagy is generally activated by conditions of nutrient deprivation but has also been associated with physiological as well as pathological processes such as development, differentiation, neurodegenerative diseases, stress, infection and cancer. The kinase mTOR is a critical regulator of autophagy induction, with activated mTOR (Akt and MAPK signaling) suppressing autophagy, and negative regulation of mTOR (AMPK and p53 signaling) promoting it. Three related serine/threonine kinases, UNC-51-like kinase -1, -2, and -3 (ULK1, ULK2, ULK3), which play a similar role as the yeast Atg1, act downstream of the mTOR complex. ULK1 and ULK2 form a large complex with the mammalian homolog of an autophagy-related (Atg) gene product (mAtg13) and the scaffold protein FIP200 (an ortholog of yeast Atg17). Class III PI3K complex, containing hVps34, Beclin 1 (a mammalian homolog of yeast Atg6), p150 (a mammalian homolog of yeast Vps15), and Atg14-like protein (Atg14L or Barkor) or ultraviolet irradiation resistance-associated gene (UVRAG), is required for the induction of autophagy. The Atg genes control the autophagosome formation through Atg12-Atg5 and LC3-II (Atg8-II) complexes. Atg12 is conjugated to Atg5 in a ubiquitin-like reaction that requires Atg7 and Atg10 (E1 and E2-like enzymes, respectively). The Atg12–Atg5 conjugate then interacts noncovalently with Atg16 to form a large complex. LC3/Atg8 is cleaved at its C terminus by Atg4 protease to generate the cytosolic LC3-I. LC3-I is conjugated to phosphatidylethanolamine (PE) also in a ubiquitin-like reaction that requires Atg7 and Atg3 (E1 and E2-like enzymes, respectively). The lipidated form of LC3, known as LC3-II, is attached to the autophagosome membrane. Autophagy and apoptosis are connected both positively and negatively, and extensive cross-talk exists between the two. During nutrient deficiency, autophagy functions as a pro-survival mechanism; however, excessive autophagy may lead to cell death, a process morphologically distinct from apoptosis. Several pro-apoptotic signals, such as TNF, TRAIL, and FADD, also induce autophagy. Additionally, Bcl-2 inhibits Beclin-1-dependent autophagy, thereby functioning both as a pro-survival and as an anti-autophagic regulator.

Inhibition of Apoptosis Pathway Description:

Cell survival requires the active inhibition of apoptosis, which is accomplished by inhibiting the expression of pro-apoptotic factors as well as promoting the expression of anti-apoptotic factors. The PI3K pathway, activated by many survival factors, leads to the activation of Akt, an important player in survival signaling. PTEN negatively regulates the PI3K/Akt pathway. Activated Akt inhibits the pro-apoptotic Bcl-2 family member Bad, Bax, caspase-9, GSK-3 and FoxO1 by phosphorylation. Many growth factors and cytokines induce anti-apoptotic Bcl-2 family members. The Jaks and Src phosphorylate and activate Stat3, which in turn induces the expression of Bcl-xL and Bcl-2. Erk1/2 and PKC activate p90RSK, which activates CREB and induces the expression of Bcl-xL and Bcl-2. These Bcl-2 family members protect the integrity of mitochondria, preventing cytochrome c release and the subsequent activation of caspase-9. TNF-α may activate both pro-apoptotic and anti-apoptotic pathways; TNF-α can induce apoptosis by activating caspase-8 and -10, but can also inhibit apoptosis signaling via NF-κB, which induces the expression of anti-apoptotic genes such as Bcl-2. cIAP1/2 inhibit TNF-α signaling by binding to TRAF2. FLIP inhibits the activation of caspase-8.

Death Receptor Signaling Pathway Description:

Apoptosis can be induced through the activation of death receptors including Fas, TNFαR, DR3, DR4, and DR5 by their respective ligands. Death receptor ligands characteristically initiate signaling via receptor oligomerization, which in turn results in the recruitment of specialized adaptor proteins and activation of caspase cascades. Binding of FasL induces Fas trimerization, which recruits initiator caspase-8 via the adaptor protein FADD. Caspase-8 then oligomerizes and is activated via autocatalysis. Activated caspase-8 stimulates apoptosis via two parallel cascades: it can directly cleave and activate caspase-3, or alternatively, it can cleave Bid, a pro-apoptotic Bcl-2 family protein. Truncated Bid (tBid) translocates to mitochondria, inducing cytochrome c release, which sequentially activates caspase-9 and -3. TNF-α and DR-3L can deliver pro- or anti-apoptotic signals. TNFαR and DR3 promote apoptosis via the adaptor proteins TRADD/FADD and the activation of caspase-8. Interaction of TNF-α with TNFαR may activate the NF-κB pathway via NIK/IKK. The activation of NF-κB induces the expression of pro-survival genes including Bcl-2 and FLIP, the latter can directly inhibit the activation of caspase-8. FasL and TNF-α may also activate JNK via ASK1/MKK7. Activation of JNK may lead to the inhibition of Bcl-2 by phosphorylation. In the absence of caspase activation, stimulation of death receptors can lead to the activation of an alternative programmed cell death pathway termed necroptosis by forming complex IIb.

Mitochondrial Control of Apoptosis Pathway Description:

The Bcl-2 family of proteins regulate apoptosis by controlling mitochondrial permeability. The anti-apoptotic proteins Bcl-2 and Bcl-xL reside in the outer mitochondrial wall and inhibit cytochrome c release. The proapoptotic Bcl-2 proteins Bad, Bid, Bax, and Bim may reside in the cytosol but translocate to mitochondria following death signaling, where they promote the release of cytochrome c. Bad translocates to mitochondria and forms a pro-apoptotic complex with Bcl-xL. This translocation is inhibited by survival factors that induce the phosphorylation of Bad, leading to its cytosolic sequestration. Cytosolic Bid is cleaved by caspase-8 following signaling through Fas; its active fragment (tBid) translocates to mitochondria. Bax and Bim translocate to mitochondria in response to death stimuli, including survival factor withdrawal. Activated following DNA damage, p53 induces the transcription of Bax, Noxa, and PUMA. Upon release from mitochondria, cytochrome c binds to Apaf-1 and forms an activation complex with caspase-9. Although the mechanism(s) regulating mitochondrial permeability and the release of cytochrome c during apoptosis are not fully understood, Bcl-xL, Bcl-2, and Bax may influence the voltage-dependent anion channel (VDAC), which may play a role in regulating cytochrome c release. Mule/ARF-BP1 is a DNA damage activated E3 ubiquitin ligase for p53, and Mcl-1, an anti-apoptotic member of Bcl-2.

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