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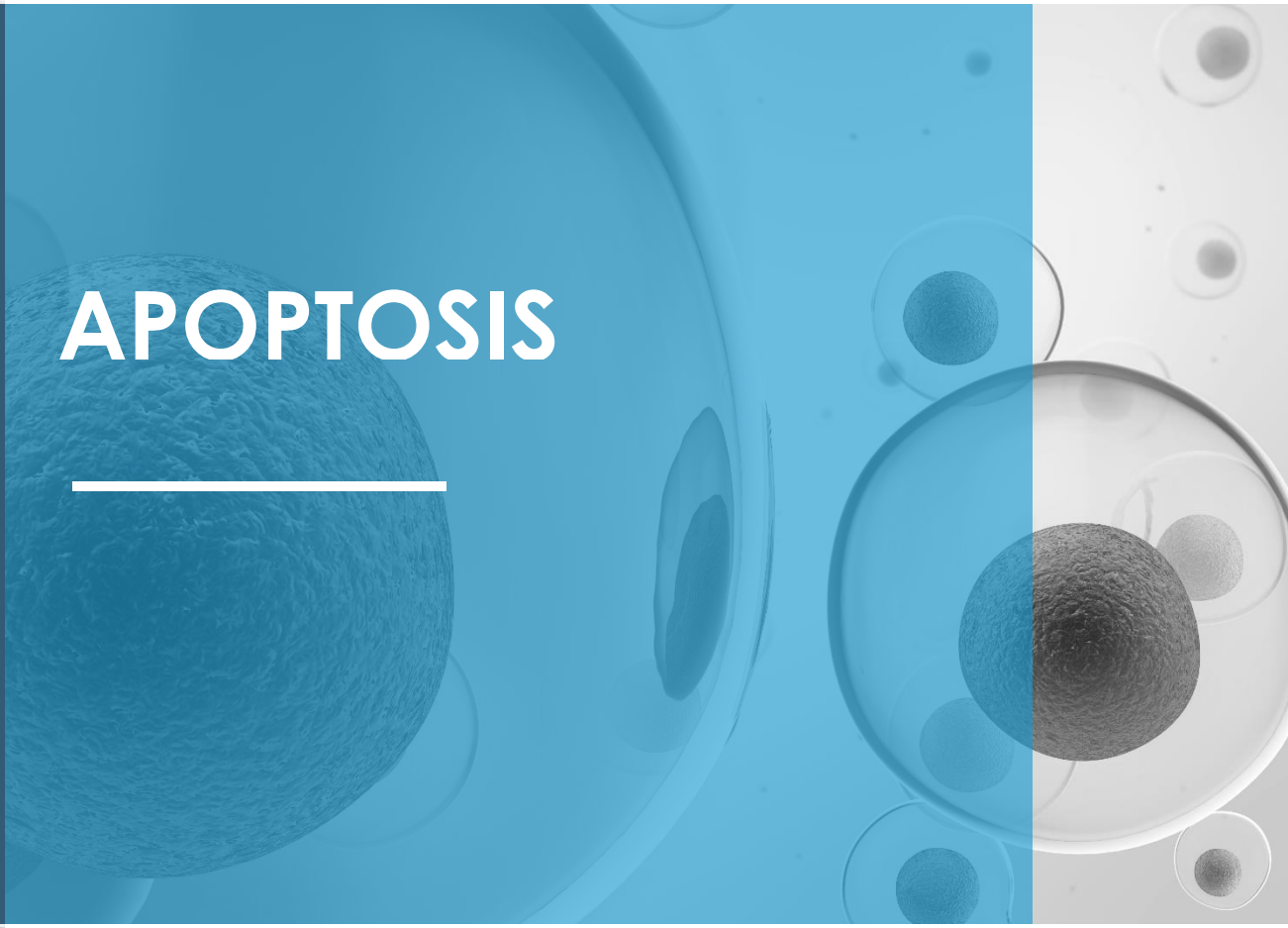
APOPTOSIS



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Apoptosis

Apoptosis is a form of programmed cell death that occurs in multicellular organisms. It causes characteristic changes (morphology) and death in cells. These changes include blistering, cell shrinkage, nuclear fragmentation, chromatin condensation, chromosomal DNA fragmentation, and global mRNA decay. Due to apoptosis, averages of 5 to 70 billion cells are lost per adult per day. Apoptosis is a highly regulated and controlled process that plays an important role in the life cycle of an organism. For example, the separation of fingers and toes in a developing human embryo occurs because the cells between the fingers undergo apoptosis. Unlike necrosis, apoptosis produces cell debris called apoptotic bodies that can be swallowed and removed before the contents of the cells spill onto and damage the surrounding cells. Apoptosis can be initiated by two ways, internal pathway and external pathway. The cell self-destruction in the internal pathway is because it senses the pressure of the cell; while in the external pathway, the cell self-destruct is due to signals from other cells. A weak external signal may also activate the intrinsic pathway of apoptosis. Both pathways kill cells by activating caspase and indiscriminately degrading the protein.

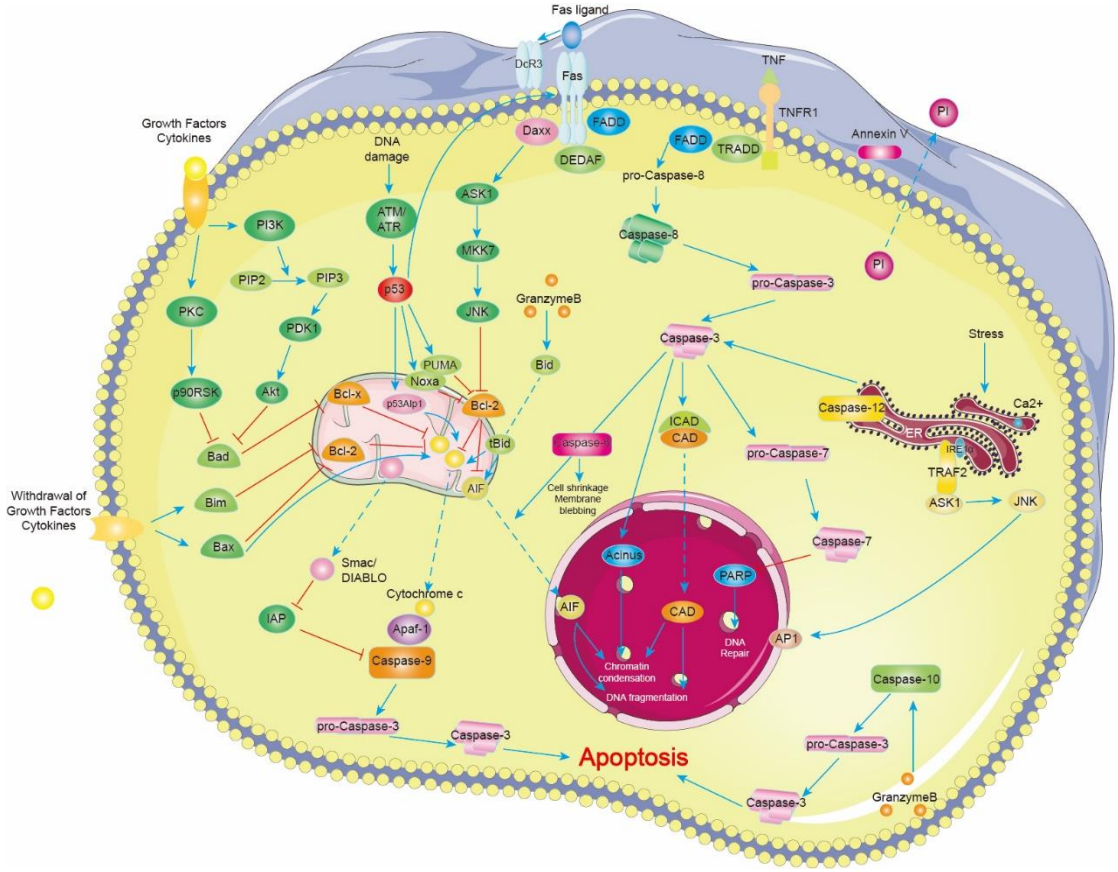

Figure 1. Overview of the apoptosis process.

Intrinsic pathway

Mitochondria are vital organelles in cells. If mitochondria are damaged, cellular respiration is affected and rapidly dies. This fact constitutes the basis of some apoptotic pathways. Apoptotic proteins that target mitochondria affect mitochondrial function in different ways. For example, apoptotic proteins cause mitochondrial swelling by forming a membrane pore, or increase the permeability of the mitochondrial membrane and cause the leak of apoptosis effector. Studies have shown that nitric oxide can induce apoptosis by helping to dissipate the membrane potential of mitochondria and make apoptosis effector more permeable from mitochondria during the induction of apoptosis through the intrinsic pathway. The mitochondrial protein (second mitochondria-derived caspase activator), then called SMAC, is released into the cytoplasm of the cell as the mitochondrial membrane permeability increases. SMAC binds to proteins that inhibit apoptosis (IAP), the processes is inactivating IAP and releasing the inhibition of apoptosis by IAP, and thus allowing apoptosis to proceed. Moreover, IAP also typically inhibits the activity of a group of cysteine proteases called caspase which can be used for cell degradation. Therefore, it can be seen that apoptosis of cells is indirectly regulated by mitochondrial permeability.

In addition to changes in the permeability of the mitochondrial membrane, some apoptotic proteins can also form channels in the mitochondrial outer membrane. The formation of channel on the outer membrane of the mitochondria also causes the release of mitochondrial cytochrome c from mitochondria, which is closely related to oxidative respiration, act to induce apoptosis before morphological changes related to apoptosis in mitochondria. Upon release of cytochrome c, it binds to apoptotic protease activator-1 (Apaf-1) and ATP, and then ATP binds to pre-caspase-9 to form a protein complex called apoptosome. Apoptosome cleave caspase into their active form of caspase-9, which in turn activates effector caspase-3. And then, caspase-3 induces cell apoptosis.

External pathway

At present, two mechanisms for directly initiating apoptosis in mammalian cells have been proposed for the extrinsic pathway of apoptosis: TNF-induced (tumor necrosis factor) model and Fas-Fas ligand-mediated model, both of which involve TNF receptor (TNFR) family is coupled to an external signal.

- TNF pathway

  TNF-a is a kind cytokine which produced by activated macrophages. It is a major extrinsic mediator of apoptosis. Most cells in the human body have two TNF-a receptors: TNFR1 and TNFR2. The binding of TNF-a and TNFR1 can initiate a pathway which leading to caspase activation via the intermediate membrane protein TNF receptor associated death domain (TRADD) and Fas-associated death domain protein (FADD).

- Fas pathway

  Fas receptors (also known as Apo-1 levels or CD95) are members of the transmembrane protein TNF family. The interaction between Fas and FasL results in the formation of a death-inducing signaling complex (DISC) comprising FADD, caspase-8 and caspase-10. In certain types of cells (type I), processed caspase-8 directly activates other members of the caspase family and triggers the execution of apoptosis. In other cell types (type II), Fas-DISC initiates a feedback loop, increased release of mitochondrial pro-apoptotic factors and activation of caspase-8 amplification.

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