

APOPTOSIS

Apoptosis is critical to tissue homeostasis and serves as a means to delete extraneous or potentially harmful cells (reviewed in ^{1,2}). The dysregulation of apoptosis has been noted as the cause of a variety of developmental and pathological disorders. Resistance to apoptosis can promote tumorigenesis and autoimmunity, while sensitivity can result in neurodegenerative diseases or immune deficiency.

Acquired resistance to apoptosis is central to tumorigenesis. Due to its critical role in cancer formation, the pathways which regulate apoptosis have been intensively studied and found to be executed in a strict and orderly manner. The stages of apoptosis include activation of initiator caspases, mitochondrial release of proapoptotic factors, and the activation of effector caspases. Apoptosis is initiated and executed by two major pathways: the extrinsic (death receptor) pathway and intrinsic (mitochondrial) pathway. Both pathways feature caspases and members of the Bcl-2 family as the central players in initiation and execution of programmed cell death. Execution of the genetic program results in a defined set of morphological changes that culminates in phagocytosis of the dying cell by macrophages and neighboring cells. The morphological hallmarks of apoptosis include cell membrane blebbing, cell shrinkage, chromatin condensation, DNA fragmentation, and the packaging of apoptotic bodies. Due to its central role in disease, the pathways of apoptosis are being targeted to promote the death of unwanted cells or to block cell loss. Strategies that target the mitochondria and caspase cascade are being explored for the development of disease therapies³.

References

1. T. Dragovich, C. M. Rudin, C. B. Thompson, *Oncogene*, 17, 3207-3213 (1998).
2. Z. Jin and W. S. El Deiry, *Cancer Biol Ther.* 4, 139-163 (2005).
3. D. R. Green and G. Kroemer, *J Clin Invest.* 115, 2610-2617 (2005).

Apoptosis is the genetically programmed process of cell death. It is as fundamental as mitosis and is central to development, the immune response, and the protection from DNA damage. Defects in the pathways which regulate apoptosis have been related to a variety of human diseases.

The mechanism of apoptosis can be divided into two major pathways: extrinsic and intrinsic. The extrinsic pathway begins with the triggering of death receptors by death inducing ligands such as Fas-L, TNFalpha, IL-1, and TRAIL. The intrinsic pathway begins with stress signals which originate from DNA damage, growth factor depletion, serum starvation, or exposure to free radicals, radiation, chemicals, or infection. Activation of the intrinsic pathway leads to the inhibition of the protective effects of Bcl-2 in the mitochondrial membrane and release of cytochrome C from the mitochondria.

Release of cytochrome C initiates a cascade of caspase activation which results in cleavage of structural proteins in the cell, fragmentation of chromosomal DNA, and phagocytosis of the cell. Activation of the extrinsic pathway mainly leads to activation of a cascade of caspases and in some cases also engages the mitochondrial pathway. A third apoptotic pathway initiated by DNA damage and p53 signaling can also be considered. The mechanisms of this pathway are not well understood, but appear to engage both the intrinsic and extrinsic pathways. Survival pathways are also critical to the regulation of apoptosis and inhibit programmed cell death via anti-apoptotic factors such as IAP, Bcl-XL and Bcl2. (Figure adapted from the KEGG Pathway Database www.genome.jp/kegg/pathway/hsa/hsa04210.html)

