

Programmed Cell Death

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Programmed cell death (PCD) is cellular death that is deliberately induced via an intracellular program. There are two main mechanisms of PCD, apoptosis and autophagic cell death. The most common form of PCD in multicellular organisms, including humans, is apoptosis.

A cell undergoing apoptosis dies via an organized and minimally inflammatory process that relies on an intracellular proteolytic cascade. Caspases are cysteine proteases that cleave nuclear and cytosolic proteins, triggering cell death. Caspases are synthesized intracellularly as inactive procaspases that are activated by cleavage at specific aspartic acid residues by fellow caspases. Once a caspase is activated, it cleaves and activates other procaspases, which results in a proteolytic cascade that is irreversible and self-amplified. Some caspases can also cleave nuclear lamins, resulting in loss of integrity of the nuclear lamina. Others can cleave proteins that maintain the inactive form of DNAses, allowing DNA degradation. During apoptosis, the cell shrinks, chromatin condenses, nuclear DNA fragments, the cell membrane blebs, and apoptotic bodies form. Finally, the remnants of the apoptotic cell are phagocytosed before its contents can leak into the extracellular space and cause inflammation.

Apoptosis is highly regulated. Its activation can be triggered by intrinsic (mitochondrial) and extrinsic (extracellular) signals. For example, as a result of DNA damage protein p53 induces mitochondria to release cytochrome *c*. Cytochrome *c* binds to a protein called Apaf-1 that then activates procaspase-9, which in turn activates effector procaspases such as procaspase-3 to induce apoptosis via the intrinsic pathway. The Bcl-2 proteins regulate apoptosis. Some Bcl-2 proteins, including Bcl-2, inhibit apoptosis by blocking cytochrome *c* release from mitochondria. Conversely, Bad, Bax, and Bak are members of the Bcl-2 protein family that promote apoptosis by inactivating apoptosis inhibitors or by stimulating mitochondrial cytochrome *c* release. The IAP (inhibitor of apoptosis) family also regulates apoptosis, likely by inhibiting both procaspase activation as well as caspase activity.

Extracellular killer lymphocytes carrying the Fas ligand can activate Fas receptor proteins on the surface of the target cell. These receptors then cluster and initiate an intracellular cascade that ultimately activates procaspase-8 molecules, inducing apoptosis. Cells can also self-initiate apoptosis by producing their own Fas ligands and receptors.

Apoptosis plays an essential role in guiding morphological changes throughout embryogenesis and facilitates the formation of various organs and structures during development. For example, apoptosis transforms the spade-like predecessors of hands into more functional and refined structures by eliminating cells between digits to form fingers. It also serves to control cell quality throughout development by eliminating cells with DNA damage and harmful mutations. Finally, apoptosis regulates the number of cells in many tissues, including the developing nervous system.

Aberrant apoptosis is an influential contributor to teratogen-induced congenital defects. The effects of many teratogens are associated with inappropriate induction or disruption of the

normal apoptotic process that occurs during development in certain embryonic tissues. These teratogens can be physical or chemical, and many substances necessary for normal fetal development (such as retinoic acid) can be teratogenic when the developing fetus is exposed to toxic levels. Alterations in apoptosis have been noted in cases of retinoic acid excess as well as in vitamin A deficiency.

Neurons demonstrate a variety of mechanisms of cellular death, including apoptosis, autophagic cell death, excitotoxicity, and necrosis. Aberrant neuronal cell death is implicated in many neurodegenerative diseases, such as Alzheimer's (AD) and Parkinson's (PD), as well as in damage caused by cerebral ischemia. AD is modern society's most common neurodegenerative disease. Its classical clinical presentation involves progressive memory loss and cognitive dysfunction. AD pathogenesis involves hippocampal pyramidal neuronal loss and the presence of amyloid plaques and neurofibrillary tangles. Mutations in amyloid precursor protein, presenilin-1, or presenilin-2 are found in familial form of AD. Some post-mortem studies of the brain tissue of AD-affected patients reveal the presence of active caspases, suggesting that neuronal apoptosis occurs in the course of AD. Other models suggest the role of presenilin mutations in sensitization to cell death, as well as amyloid-induced apoptosis. However, the exact mechanism for the progressive neurodegeneration found in AD is unknown.

PD pathogenesis involves the atrophy of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies within the remaining neurons. The resulting dopamine depletion within the striatum causes the motor dysfunction characteristic of PD. The exact molecular mechanisms that initiate dopaminergic neuron loss in PD are unknown and disease pathogenesis is likely due to a complex interaction of genetic predisposition, environmental toxicity, and aging. However, there is evidence that PCD may contribute to neuronal loss in PD.

Cerebral ischemia can be characterized by both acute and delayed neuronal cell death as a result of deficient cerebral perfusion that leads to brain hypoxia. The acute phase of cell death in the ischemic core is primarily necrotic, and delayed cell death occurring in the surrounding penumbra region is primarily apoptotic. Neuroprotective mechanisms have been identified in ischemic tissue. The recruitment of certain heat shock proteins has shown protective effects in models of ischemia as well as in neurodegenerative disease. Many of these heat shock proteins modify the apoptotic response, reducing cell death.

Further Reading:

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