Apoptosis

Printed from https://www.cancerquest.org/cancer-biology/apoptosis on 11/22/2026

In normal tissues there is a balance between the generation of new cells via cell division and the loss of cells via cell death. Old cells become damaged over time and are eliminated. This is an essential form of renewal. Examples include shedding of skin cells and the replacement of the cells lining our digestive tract. Like cell division, cell death is also tightly controlled. Cells frequently die by a process termed programmed cell death or apoptosis. 1 Apoptosis is the cellular equivalent of a “self destruct” button.

Apoptosis is a very orderly process during which the genome of the cell is broken down, the cell is fragmented into smaller pieces and the debris is consumed by nearby cells (phagocytes) that clean up the cell fragments. Besides getting rid of damaged, potentially dangerous cells, apoptosis is crucial for embryological development and neurologic pruning. The term “apoptosis” comes from the Greek words apo (from) and ptosis (falling) and it was used to describe leaves falling from a tree.2

There are two distinct phases in apoptosis, the initiation phase and the execution phase. The initiation phase involves many different proteins and it is quite complex. It is started by various “stresses” from either outside the cell (extracellular) or inside the cell (intracellular).3 Some examples of extracellular signals that trigger apoptosis include loss of growth factors, low oxygen levels (hypoxia), and radiation. Intracellular signals include DNA damage, the damage caused by chemotherapy drugs, telomere malfunction, and infection with viruses. The initiation phase triggers the execution phase. The execution phase involves the activation of specialized enzymes (caspases and others) that directly result in cell death.3 Further information on the topics on this page can also be found in most introductory Biology textbooks, we recommend Campbell Biology, 11th edition.4

Normal cells will trigger their own death (apoptosis) when they become damaged.

Cancer cells can defend themselves and survive even when they're damaged. They can produce protein shields.

Some cancer cells are no longer able to make death signals that work like they should.

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Apoptosis Pathways

Initiation Phase

Extrinsic or Receptor-Mediated Pathway

Members of the **t**umor **n**ecrosis **f**actor (TNF) receptor superfamily of transmembrane proteins control the extrinsic pathway. All TNF receptors, also known as death receptors, share a region of 80 amino acids called the “death domain”. 5 This region plays a critical role in transmitting death signals across the cell membrane. Inside the cell

a cascade of proteins is turned on. At the end of these pathways, initiator caspase-8 is activated and the execution phase of apoptosis is triggered. 2, 2

Intrinsic or Mitochondrial Pathway

The Bcl-2 family of proteins controls the intrinsic pathway. There are 25 known proteins in the Bcl-2 family. The different members function to either stimulate apoptosis (pro-apoptotic) or block apoptosis (anti-apoptotic). 6 There is a delicate balance between pro-apoptotic and anti-apoptotic proteins within a cell. BH3-only proteins sense intrinsic signals to undergo apoptosis, such as DNA damage. They travel to the mitochondrial membrane and activate the pro-apoptotic proteins Bax or Bak or inhibit anti-apoptotic proteins. When activated, Bax and Bak bind, and cause mitochondrial outer membrane permeabilization (MOMP). 3 This perforates the mitochondrial membrane, and induces the release of a crucial pro-apoptotic factor, cytochrome c, into the cytosol. Cytochrome c joins another pro-apoptotic factor, APAF1, to form the “apoptosome” complex, which in turn activates a series of caspases, leading to cell destruction. The cell death proteins are closely regulated by the tumor suppressor protein p53. 2

Perforin/Granzyme

In some cases, immune cells called cytotoxic T lymphocytes can start apoptosis. This happens when the lymphocytes secrete a protein called perforin and small particles containing specialized enzymes. Perforin creates holes in plasma membrane of the target cell. The additional particles use the holes to enter the cell. After entering the cell, they release their enzymes (granzymes A and B) that start the execution pathway and wreak havoc on cell structure and function. 7

Execution Phase

The extrinsic and intrinsic pathways both stimulate the execution phase. During this phase a group of protein-cutting enzymes called caspases lead directly to cell death. The main execution caspases are caspases-3, 6 and 7. 2 Caspases are present in lethal doses within each cell, but they only become active via the initiation process. Caspase-3 is considered the most important of all the caspases. It can cause DNA and chromatin damage, re-arrange the cytoskeleton, and disrupt intracellular transport, cell division, and signal transduction. Once activated the execution caspases cannot be stopped, cell death is certain. Cell fragments produced during the final stage of apoptosis are quickly recognized, engulfed, and digested by macrophages or surrounding epithelial cells. 2

Cancer and Apoptosis

Apoptosis is one of the checks and balances built into the cell cycle. Normally when something goes wrong in a cell, it is quickly destroyed via apoptosis. 3 This safeguard helps prevent the development of cancer. For example, when skin cells are damaged by ultraviolet radiation (i.e. sun, tanning beds) apoptosis is normally triggered. This helps eliminate any badly damaged cells. If apoptosis does not occur, these damaged cells may survive and develop into cancerous cells. Apoptosis also plays a role in cancer progression. For a cancer cell to move to another part of the body (metastasize) it must be able to survive in the blood or lymphatic systems and invade foreign tissue. Normally apoptosis would prevent these things. Cells typically “self destruct” when they are not touching other cells or the extracellular matrix. 8

Cancer cells are able to evade apoptosis and continuously divide despite their abnormalities. The loss of the p53 tumor suppressor is a common cause; inactivation of the p53 protein renders the cell unable to sense DNA damage that spurs apoptosis. 8 Anti-apoptotic Bcl-2 family members and IAPs (inhibitor of apoptosis proteins that disable caspases) are upregulated, and counteract the anti-apoptotic actions of BH3 only proteins. 1 Bcl-2 is able to bind to Bax and Bak, preventing pore formation. It can also inhibit BH3 proteins, preventing responses to DNA damage. Avoidance of cell death despite damage, coupled with continued cell division leads to the growth of the tumor. 8

Apoptosis and Cancer Treatment

Chemotherapy drugs and radiation work by forcing the cancer cells to undergo apoptosis, triggering death signals by causing DNA damage or cellular distress. In addition, many apoptosis-inducing drugs are currently being researched, and some are in clinical trials. 2 In cancer cells, pro-death BH3 proteins accumulate but do not exert strong enough effects to overcome the excess of Bcl-2 antiapoptotic proteins. Drugs that mimic BH3 proteins can give an extra push to strengthen the pro-death signals, driving the intrinsic pathway forward and causing apoptosis. Some agents currently being tested directly target the anti-apoptosis Bcl-2 family proteins and IAPs, and some restore pro-apoptotic factors that have been knocked out, such as caspases or p53 function. 2

Clearly, there are many ways a cancer cell can avoid apoptosis. While drugs can target and restore the apoptotic pathway, cancer cells can acquire new mutations and become resistant. For example, if a drug inhibits Bcl-2 family proteins, it will initiate apoptosis in cancer cells. But, if the cancer cells then acquire a mutation that upregulates caspase inhibitors, the drug will no longer be effective. 2

Apoptosis Summary

Background

- Apoptosis is a form of programmed cell death
- It is a very orderly process during which the genome of the cell is broken down, the cell is fragmented into smaller pieces and the debris is consumed by nearby cells (phagocytes) that clean up the cell fragments
- The initiation phase of apoptosis is started by extracellular or intracellular stress, such as low oxygen levels or DNA damage
- The execution phase of apoptosis is carried out by enzymes called caspases that cause DNA damage, re-arrange the cytoskeleton, and disrupt intracellular transport, cell division, and signal transduction.

Pathways

- The extrinsic pathway is mediated by membrane receptors that respond to death signals by activating caspases
- The intrinsic pathway or mitochondrial pathway is controlled by members of the Bcl-2 family, which can exhibit pro-apoptotic or anti-apoptotic activity. Holes are punched in the mitochondrial membrane and pro-apoptotic factors are released.
- Sometimes, cytotoxic T cells of the immune system can start apoptosis by secreting perforin and making holes in the cell membrane.

Cancer and Apoptosis

- Cancer cells often have the ability to evade apoptosis, despite damage. This is often because of a nonfunctional p53 protein or an upregulation of anti-apoptotic members of the Bcl-2 family.

Treatment

- Chemotherapy drugs and radiation work by forcing the cancer cells to undergo apoptosis, triggering death signals by causing DNA damage or cellular distress.

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