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APOPTOSIS

The cells of a multicellular organism are members of a highly organized community. The number of cells in this community is tightly regulated—not simply by controlling the rate of cell division, but also by controlling the rate of cell death. If cells are no longer needed, they commit suicide by activating an intracellular death program. This process is therefore called **programmed cell death**, although it is more commonly called apoptosis (from a Greek word meaning "falling off," as leaves from a tree).

The amount of apoptosis that occurs in developing and adult animal tissues can be astonishing. In the developing vertebrate nervous system, for example, up to half or more of the nerve cells normally die soon after they are formed. In a healthy adult human, billions of cells die in the bone marrow and intestine every hour. It seems remarkably wasteful for so many cells to die, especially as the vast majority are perfectly healthy at the time they kill themselves.

In adult tissues, cell death exactly balances cell division. If this were not so, the tissue would grow or shrink. If part of the liver is removed in an adult rat, for example, liver cell proliferation increases to make up the loss. Conversely, if a rat is treated with the drug phenobarbital—which stimulates liver cell division (and thereby liver enlargement)—and then the phenobarbital treatment is stopped, apoptosis in the liver greatly increases until the liver has returned to its original size, usually within a week or so. Thus, the liver is kept at a constant size through the regulation of both the cell death rate and the cell birth rate.

Cells that die as a result of acute injury typically swell and burst. They spill their contents all over their neighbors—a process called *cell necrosis*—causing a potentially damaging inflammatory response. By contrast, a cell that undergoes apoptosis dies neatly, without damaging its neighbors. The cell shrinks and condenses. The cytoskeleton collapses, the nuclear envelope disassembles, and

the nuclear DNA breaks up into fragments. Most importantly, the cell surface is altered, displaying properties that cause the dying cell to be rapidly phagocytosed, either by a neighboring cell or by a macrophage , before any leakage of its contents occurs. This not only avoids the damaging consequences of cell necrosis but also allows the organic components of the dead cell to be recycled by the cell that ingests it. The intracellular machinery responsible for apoptosis seems to be similar in all animal cells. This machinery depends on a family of proteases that have a cysteine at their active site and cleave their target proteins at specific aspartic acids. They are therefore called caspases. Caspases are synthesized in the cell as inactive precursors, or *procaspases,* which are usually activated by cleavage at aspartic acids by other caspases .Once activated, caspases cleave, and thereby activate, other procaspases, resulting in an amplifying proteolytic cascade . Some of the activated caspases then cleave other key proteins in the cell. Some cleave the nuclear lamins, for example, causing the irreversible breakdown of the nuclear lamina; another cleaves a protein that normally holds a DNA-degrading enzyme (a DNAse) in an inactive form, freeing the DNAse to cut up the DNA in the cell nucleus. In this way, the cell dismantles itself quickly and neatly, and its corpse is rapidly taken up and digested by another celProcaspases Are Activated by Binding to Adaptor Proteins.

All nucleated animal cells contain the seeds of their own destruction, in the form of various inactive procaspases that lie waiting for a signal to destroy the cell. It is therefore not surprising that caspase activity is tightly regulated inside the cell to ensure that the death program is held in check until needed

How are procaspases activated to initiate the caspase cascade? A general principle is that the activation is triggered by adaptor proteins that bring multiple copies of specific procaspases, known as *initiator procaspases,* close together in a complex or aggregate. In some cases, the initiator_procaspases have a small amount of protease activity, and forcing them together into a complex causes them to cleave each other, triggering their mutual activation. In other cases, the aggregation is thought to cause a conformational change that activates the procaspase. Within moments, the activated caspase at the top of the cascade

cleaves downstream procaspases to amplify the death signal and spread it throughout the cell.

Procaspase activation can be triggered from outside the cell by the activation of *death receptors* on the cell surface. Killer lymphocytes ,for example, can induce apoptosis by producing a protein called Fas ligand, which binds to the death receptor protein Fas on the surface of the target cell. The clustered Fas proteins then recruit intracellular adaptor proteins that bind and aggregate procaspase-8 molecules, which cleave and activate one another. The activated caspase-8 molecules then activate downstream procaspases to induce apoptosis . Some stressed or damaged cells kill themselves by producing both the Fas ligand and the Fas protein, thereby triggering an intracellular caspase cascade.

When cells are damaged or stressed, they can also kill themselves by triggering procaspase aggregation and activation from within the cell. In the best understood pathway, mitochondria are induced to release the electron carrier protein *cytochrome* , into the cytosol, where it binds and activates an adaptor protein called Apaf-1 . This mitochondrial pathway of procaspase activation is recruited in most forms of apoptosis to initiate or to accelerate and amplify the caspase cascade. DNA damage, for example, as discussed earlier, can trigger apoptosis. This response usually requires p53, which can activate the transcription of genes that encode proteins that promote the release of cytochrome *c* from mitochondria. These proteins belong to the Bcl-2 family. The **Bcl-2 family** of intracellular proteins helps regulate the activation of procaspases. Some members of this family, like *Bcl-2* itself or *Bcl-*X_L, inhibit apoptosis, at least partly by blocking the release of cytochrome *c* from mitochondria. Other members of the Bcl-2 family are not death inhibitors, but instead promote procaspase activation and cell death. Some of these apoptosis promoters, such as *Bad*, function by binding to and inactivating the death-inhibiting members of the family, whereas others, like *Bax* and *Bak,* stimulate the release of cytochrome *c* from mitochondria. If the genes encoding Bax and Bak are both inactivated, cells are remarkably resistant to most apoptosis-inducing stimuli, indicating the crucial importance of these proteins in apoptosis induction. Bax and Bak are themselves activated by other apoptosis-promoting members of the Bcl-2 family such as Bid.

Another important family of intracellular apoptosis regulators is the **IAP (inhibitor of apoptosis) family**. These proteins are thought to inhibit apoptosis in two ways: they bind to some procaspases to prevent their activation, and they bind to caspases to inhibit their activity. IAP proteins were originally discovered as proteins produced by certain insect viruses, which use them to prevent the infected cell from killing itself before the virus has had time to replicate. When mitochondria release cytochrome *c* to activate Apaf-1, they also release a protein that blocks IAPs, thereby greatly increasing the efficiency of the death activation process.

The intracellular cell death program is also regulated by extracellular signals, which can either activate apoptosis or inhibit it. These signal molecules mainly act by regulating the levels or activity of members of the Bcl-2 and IAP families. We see in the next section how these signal molecules help multicellular organisms regulate their cell numbers.

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