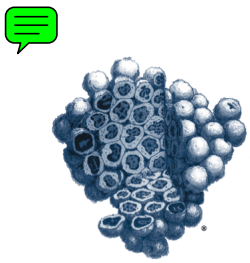

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The Molecular Perspective: Caspases

David S. Goodsell

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STEM CELLS
Fundamentals of Cancer Medicine

The Molecular Perspective: Caspases

DAVID S. GOODSELL

Cells die in two different ways. When they die through accidental injury, they undergo a traumatic death, swelling and bursting and flooding their surroundings with their internal components. The area then becomes inflamed as the body cleans up this necrotic mess. But cells may also undergo a controlled, antiseptic death termed "apoptosis" or "programmed cell death." When given the signal, a cell will shut down its major regulatory and homeostatic systems, it will disassemble its internal infrastructure, and it will fragment itself into neat, bite-size pieces ready to be consumed by neighboring cells. All cells are primed with this "cyanide pill," ready to commit suicide at a moment's notice. Apoptosis is used throughout development of higher animals, as cells are patterned within the embryo. In adults, obsolete cells are given the signal to die, and rogue cells damaged by radiation or viral infection are destroyed cleanly by apoptosis.

Caspases (Fig. 1) are the executioners of apoptosis. Caspases are cysteine proteases, using the sulfur atom in cysteine to cleave polypeptide chains. Caspases are not indiscriminant proteases, however. They search for a specific sequence in their target proteins, typically cleaving solely next to aspartate amino acids (thus the name "caspase": "c" for cysteine protease and "asp" for the strong aspartate preference).

The targets of caspases are carefully planned, like charges planted during a building demolition, to allow the ordered destruction of the cell. Regulatory proteins such as Rb (retinoblastoma protein) are cleaved, halting cell-cycle progression, and nucleic acid synthesis is halted by destruction of polymerases. Major homeostatic and repair mechanisms are disabled by cleavage of key enzymes. Structural proteins, such as cytoplasmic actin and nuclear lamins (Fig. 2), are specifically disassembled. DFF (DNA fragmentation factor) is activated, leading to fragmentation and condensation of the cell's genetic material. And finally, to facilitate rapid recycling, adhesion proteins are cleaved, releasing the cell from the surrounding tissue, and the lipids in the cell membrane are subtly changed, signaling to neighboring cells that the apoptotic cell is fair game.

Tumor growth is the result of a deadly combination: a mutation in cyclin or another gene controlling the cell cycle, which removes the normal restraints on growth, combined with a mutation in apoptosis, which disables the system that normally catches these abnormally growing cells. As well as removing the means to destroy rapidly growing tumor cells, faulty apoptosis also confers resistance against many major medical treatments. Chemotherapy and radiation therapy kill cancer cells not by producing necrotic

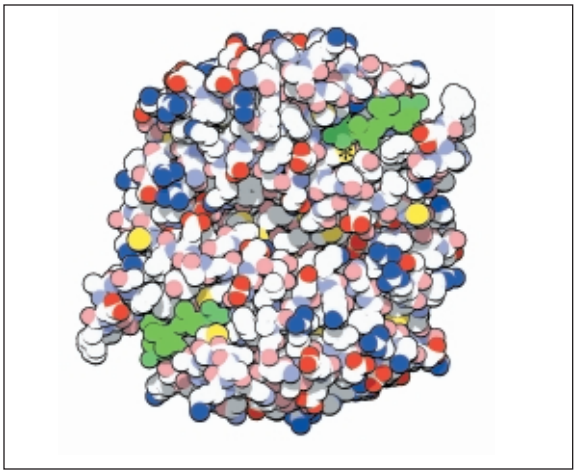

Figure 1. Caspase-3. *The active form of caspase-3 has two active sites, occupied in this illustration by small inhibitory peptides (green). The cysteine sulfur atom that performs the cleavage reaction is marked in the upper active site with an asterisk. Coordinates are taken from entry 1cp3 at the Protein Data Bank (http://www.rcsb.org/pdb).*

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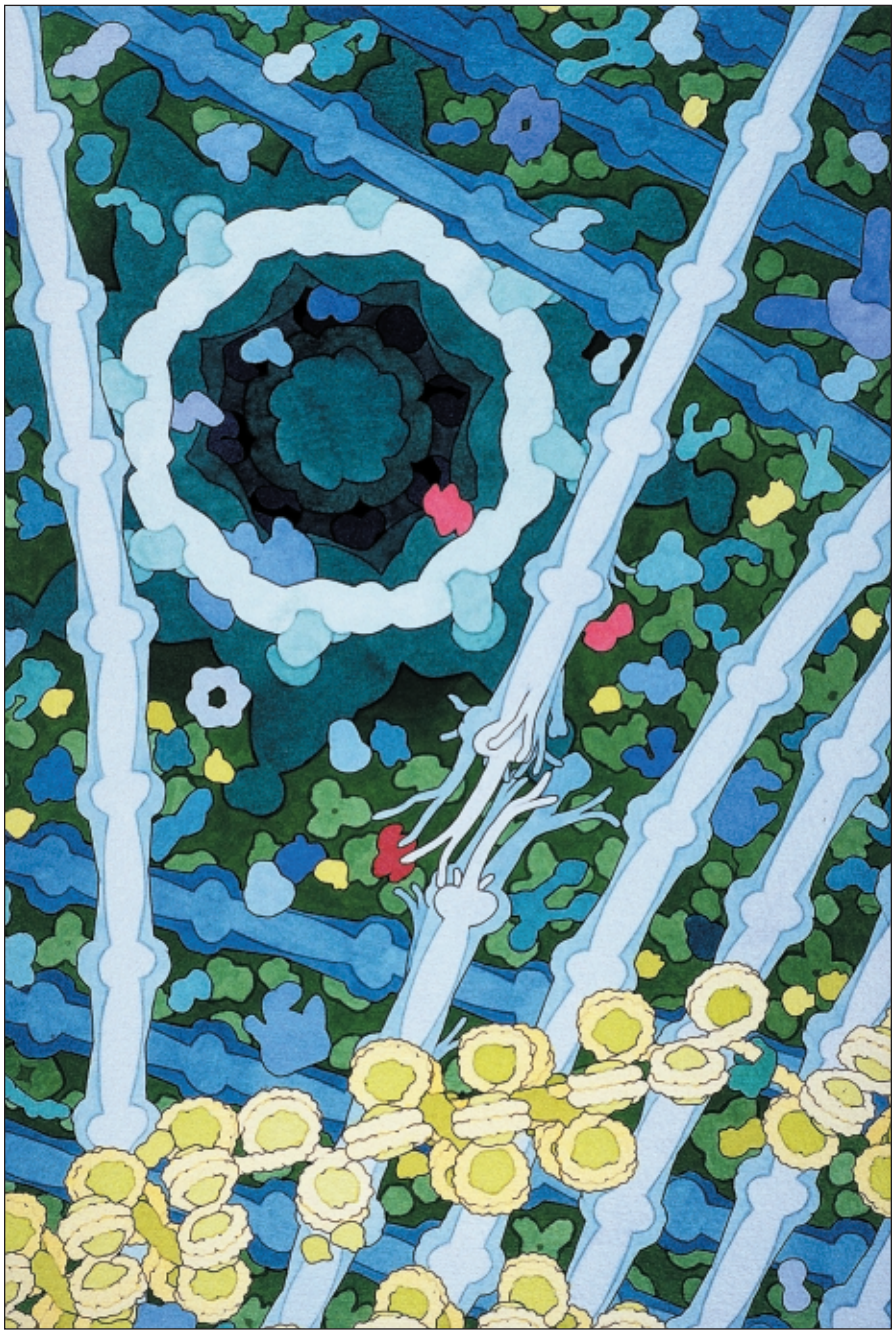

Figure 2. Caspases in action. *The illustration shows the inner face of the nuclear membrane, which is supported by a lattice of lamin filaments (long, knobbed strands) termed the "nuclear lamina." Chromatin (yellow) binds to regions of the nuclear lamina with densely packed filaments, as shown along the bottom. Caspases (in red) cleave lamins at a specific point in the center of each polypeptide chain, fragmenting the filaments, as shown at the center. A large nuclear pore complex is shown at upper left.*

damage to cells, but instead by creating enough genetic or metabolic trouble that apoptosis is induced. If apoptosis is blocked, these therapies are ineffective. Mutations in apoptosis are doubly dangerous, compromising both our natural and our medical defenses against cancer.

Additional Reading

Cryns V, Yuan J. Proteases to die for. Genes Dev 1998;12:1551-1570.

Hetts SW. To die or not to die: an overview of apoptosis and its role in disease. JAMA 1998;279:300-307.

Nicholson DW, Thornberry NA. Caspases: killer proteases. Trends Biochem Sci 1997;22:299-306.

Thompson CB. Apoptosis in the pathogenesis and treatment of disease. Science 1995;267:1456-1462.

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