The Extrinsic (Death Receptor-Initiated) Pathway of Apoptosis

This pathway is initiated by engagement of plasma membrane death receptors on a variety of cells. Death receptors are members of the TNF receptor family that contain a cytoplasmic domain involved in protein-protein interactions that is called the *death domain* because it is essential for delivering apoptotic signals. (Some TNF receptor family members do not contain cytoplasmic death domains; their function is to activate inflammatory cascades [Chapter 3], and their role in triggering apoptosis is much less established.) The best known death receptors are the type 1 TNF receptor (TNFR1) and a related protein called Fas (CD95), but several others have been described. The mechanism of apoptosis induced by these death receptors is well illustrated by Fas, a death receptor expressed on many cell types (Fig. 2-25). The ligand for Fas is called Fas ligand (FasL). FasL is expressed on T cells that recognize self antigens (and functions to eliminate self-reactive lymphocytes), and on some cytotoxic T lymphocytes (which kill virus-infected and tumor cells). When FasL binds to Fas, three or more molecules of Fas are brought together, and their cytoplasmic death domains form a binding site for an adaptor protein that also contains a death domain and is called FADD (*F*as-*a*ssociated *d*eath *d*omain). FADD that is attached to the death receptors in turn binds an inactive form of caspase-8 (and, in humans, caspase-10), again via a death domain. Multiple pro-caspase-8 molecules are thus brought into proximity, and they cleave one another to generate active caspase-8. The subsequent events are the same as in the mitochondrial pathway, and culminate in the activation of multiple executioner caspases. This pathway of apoptosis can be inhibited by a protein called FLIP, which binds to pro-caspase-8 but cannot cleave and activate the caspase because it lacks a protease domain. Some viruses and normal cells produce FLIP and use this inhibitor to protect themselves from Fas-mediated apoptosis.

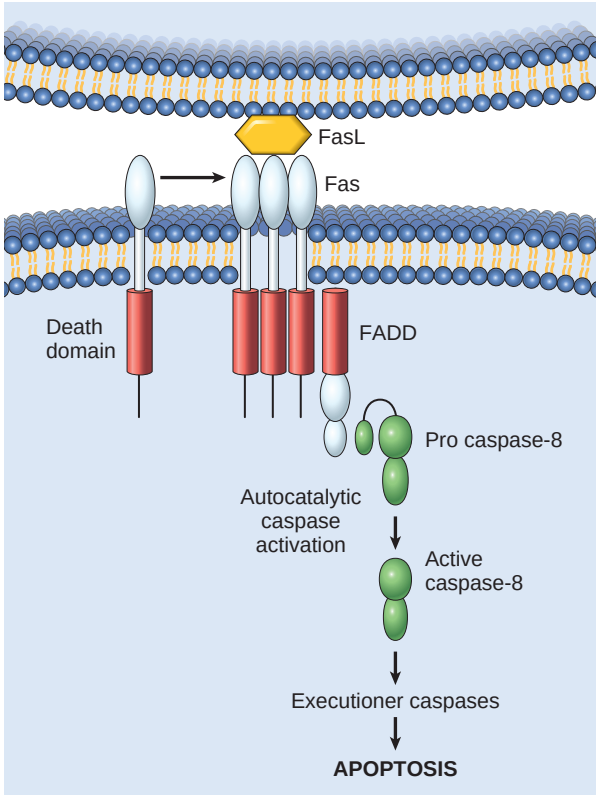

Figure 2-25 The extrinsic (death receptor initiated) pathway of apoptosis, illustrated by the events following Fas engagement. FAAD, Fas-associated death domain; FasL, Fas ligand.

The extrinsic and intrinsic pathways of apoptosis involve fundamentally different molecules for their initiation, but there may be interconnections between them. For instance, in hepatocytes and pancreatic β cells, caspase-8 produced by Fas signaling cleaves and activates the BH3-only protein BID, which then feeds into the mitochondrial pathway. The combined activation of both pathways delivers a fatal blow to the cells.

The Execution Phase of Apoptosis

The two initiating pathways converge to a cascade of caspase activation, which mediates the final phase of apoptosis. The mitochondrial pathway leads to activation of the initiator caspase-9, and the death receptor pathway to the initiator caspases-8 and -10. After an initiator caspase is cleaved to generate its active form, the enzymatic death program is set in motion by rapid and sequential activation of the executioner caspases. Executioner caspases, such as caspase-3 and -6, act on many cellular components. For instance, these caspases, once activated, cleave an inhibitor of a cytoplasmic DNase and thus make the DNase enzymatically active; this enzyme induces cleavage of DNA. Caspases also degrade structural components of the nuclear matrix and thus promote fragmentation of nuclei. Some of the steps in apoptosis are not fully defined. For instance, we do not know how the structure of the plasma membrane is changed in apoptotic cells, or how membrane blebs and apoptotic bodies are formed.

Removal of Dead Cells

The formation of apoptotic bodies breaks cells up into "bite-sized" fragments that are edible for phagocytes. Apoptotic cells and their fragments also undergo several changes in their membranes that actively promote their phagocytosis so they are most often cleared before they undergo secondary necrosis and release their cellular contents (which can result in injurious inflammation). In healthy cells, phosphatidylserine is present on the inner leaflet of the plasma membrane, but in apoptotic cells this phospholipid "flips" out and is expressed on the outer layer of the membrane, where it is recognized by several macrophage receptors. Cells that are dying by apoptosis secrete soluble factors that recruit phagocytes. Some apoptotic bodies are coated by thrombospondin, an adhesive glycoprotein that is recognized by phagocytes, and macrophages themselves may produce proteins that bind to apoptotic cells (but not to live cells) and thus target the dead cells for engulfment. Apoptotic bodies may also become coated with natural antibodies and proteins of the complement system, notably C1q, which are recognized by phagocytes. Thus, numerous receptors on phagocytes and ligands induced on apoptotic cells serve as "eat me" signals and are involved in the binding and engulfment of these cells. This process of phagocytosis of apoptotic cells is so