Systemic Lupus Erythematosus and Apoptosis

A Question of Balance

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Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by the presence of autoantibodies directed against a range of intracellular nucleoprotein targets. SLE patients are believed to develop an autoimmune response triggered by surface-exposed intracellular macromolecules translocated to the cell surface during apoptosis. Apoptosis—or programmed cell death—is a genetically controlled process initiated by two principal pathways. The extrinsic pathway is activated by the ligation of death receptors, and the intrinsic pathway emerges from mitochondria. As shown in fas-deficient mice and humans, the inability of the immune system to eliminate self-reactive lymphocytes by apoptosis can cause persistence of autoreactive cells and autoimmunity. However, as shown in complement deficiencies, increased apoptotic material and altered clearance of apoptotic cells is found in patients with SLE. These results suggest that what is found in rare individuals with genetic deficiencies that develop SLE or SLE-like disease may be found in the larger population of SLE patients as a common end point pattern of unbalanced process of both apoptosis and clearance of apoptotic material.

Index Entries:
SLE; apoptosis; necrosis; dendritic cells; macrophages; autoimmunity.

Programmed Cell Death

Programmed cell death (PCD) plays an important role in development and tissue homeostasis (1,2). Normal and altered PCD were found to be fundamental processes in the pathogenesis of numerous diseases, including cancer, AIDS, neurodegenerative disorders, ischemia, and autoimmune syndromes. The term “apoptosis,” coined in 1972 by Kerr, Wyllie, and Currie (3), is a Greek term that means “falling leaves,” and describes a de-adhesiveness of cells that undergo morphological changes such as cell shrinkage, plasma-membrane blebbing, and chromatin condensation with intact membrane. This is
subsequently followed by cellular fragmentation into apoptotic bodies. Apoptosis is a genetically controlled process initiated by two principal pathways. The extrinsic pathway is activated by the ligation of death receptors, and the intrinsic pathway emerges from mitochondria.

The Extrinsic Pathway: TNF-Superfamily-Mediated Apoptosis

Tumor necrosis factor (TNF)-superfamily members include ligands that regulate specific aspects of cellular or humoral immunity. TNF promote inflammatory responses to microbial infections, LT-β, CD40L, LIGHT, RANKL, and BLYS/BAFF, regulate the formation of lymphoid organs, activate of dendritic cells, and stimulation or survival of T- or B-cells. Yet a subgroup of death ligands and receptors are involved in apoptosis signaling. Death receptors are located on the surface of certain cells, and transmit an extracellular signal for death when they have the cytoplasmatic region known as the death domain. They include: CD95 (Fas, Apo1) and TNFR1 (p55 or CD120a) (4,5), death receptor 3 (DR3; Apo3, WSL-1, TRAMP, LARD) (6–10), DR4 (11), and DR5 (Apo2, TRAIL-R2, TRICK 2, or KILLER) (10,12–17). The ligands that activate these receptors are structurally related molecules that belong to the TNF-gene superfamily (18). TNF-superfamily death ligands exert their biological effects primarily within the immune system, regulating innate as well as adaptive immunity (19,20). FasL (Fas ligand, also known as APO1L or CD95L) regulates activation-induced cell death of peripheral leukocytes (20) and APO2L/TRAIL mediates apoptosis-inducing activities of natural killer (NK) cells and cytotoxic lymphocytes against virus-infected or oncogenically transformed cells (21), as well as primary plasma cells (22). Each member of the TNF superfamily binds at least one receptor from the TNFR superfamily, and some of the ligands bind several receptors. Many of the ligands share some of their receptors with other ligands. CD95 ligand (CD95L) binds to CD95; TNF and lymphotoxin α bind to TNFR1; Apo3 ligand (Apo3L, also known as TWEAK) (23) binds to DR3 (7), and Apo2 ligand (Apo2L, also called TRAIL) (5,24) binds to DR4 (11) and DR5 (10,12–17).

The nonsignaling members of the TNFR superfamily decoy receptor 1 (DcR1), decoy receptor 2 (DcR2), and decoy receptor 3 (DcR3), appear to act as decoys that compete with signaling receptors for ligand binding.

The Intrinsic Pathway: Bcl-2 Family and Mitochondria

The Bcl-2 family gene products include over 15 Bcl-2 family members identified in mammalian cells and several others in viruses (for review, see ref. 25). The Bcl-2 family gene products have survival-promoting (Bcl-2, Bcl-xL, Bag-1, Bik) or death-promoting (Bax, Bak, Bad) capacities. All members possess at least one of four conserved motifs known as Bcl-2 homology domains (BH1–BH4). Most pro-survival members, which can inhibit apoptosis in the face of a wide variety of cytotoxic insults, contain at least BH1 and BH2, and those most similar to Bcl-2 have all four BH domains. The two pro-apoptotic subfamilies differ markedly in their relationship to Bcl-2. Bax, Bak, and Bok (also called Mtd), which contain BH1, BH2, and BH3, resemble Bcl-2 fairly closely. In contrast, the seven other known mammalian “killers” possess only the central short (9–16 residue) BH3 domain; they are otherwise unrelated to any known protein, and only Bik and Blk are similar to each other.

Bcl-2–related proteins control several pro-apoptotic signal-transduction and damage pathways that induce mitochondrial membrane permeabilization (26). The outer mitochondrial membrane becomes completely permeabilized to proteins, resulting in the leakage of intermembrane proteins that orchestrate the degradation phase of apoptosis. These proteins either participate in caspase activation