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Current Topics in Microbiology and Immunology

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Apoptosis is a regulated, energy-dependent process by which a cell self-destructs. This mechanism of programmed cell death plays an important role in normal development and control of cell numbers in mature animals. Apoptosis was initially defined by morphological criteria to describe the distinctive appearance of dying cells that developed nuclear condensation, cell shrinkage, and cytoplasmic blebbing. Initiation of the apoptotic process can come from external or internal stimuli and is highly regulated both by molecules that facilitate and by molecules that inhibit the process. Common features of apoptosis include activation of proteases and nucleases, mitochondrial membrane permeabilization, chromatin disruption, and translocation of phosphatidylserine from the inner to the outer surface of the plasma membrane. Apoptotic cells attract phagocytes that engulf the apoptotic bodies and prevent tissue damage in the region. Intense investigation of the cell death process has defined many molecular features of the pathway by which regulation and execution can be exploited by pathogens.

It can be envisioned that apoptosis as a response to an intracellular pathogen is a useful way for the host to eliminate infected cells, decreasing the likelihood of spread of the infection to neighboring cells and preventing pathogen persistence. Alternatively, the apoptotic response may be a major mechanism by which the host is harmed by a pathogen. Apoptosis can also play an important role in regulation of the immune response both by allowing cross-presentation of antigens and enhancing the T cell response and also by inducing death of inflammatory cells and suppressing the immune response.

Apoptosis can be initiated directly by contact of the pathogen with a target cell (e.g., Yersinia, Entamoeba histolytica), by delivery of proteases into a target cell (e.g., natural killer cells, cytotoxic T lymphocytes), or by triggering intracellular cell death signaling pathways (e.g., Sindbis virus, Salmonella). Apoptosis can also be initiated indirectly by induction of the expression of ligands that interact with death receptors on the cell surface (e.g., reovirus) or activating intracellular stress pathways (e.g., herpes simplex virus). For some slowly replicating intracellular pathogens inhibition of apoptosis is necessary for life cycle completion (e.g., baculovirus, Toxoplasma gondii). For rapidly replicating pathogens (e.g., Sindbis virus, poliovirus) delay of cell death is not necessary and pathogen growth may
actually be facilitated by the apoptotic intracellular environment. Interestingly, for malaria, apoptosis of both the *Plasmodium* parasite and cells in the mosquito vector work together to enhance the likelihood of subsequent pathogen transmission by the mosquito.

The immune response to a pathogen can also be regulated to the host’s or the pathogen’s advantage by apoptosis. If the infected cell expresses a ligand that induces the death of macrophages, activated lymphocytes or other leukocytes (e.g., rabies virus, *Yersinia, Salmonella, T. gondii*), there will be suppression of the immune response and clearance mechanisms may be impaired. If the apoptotic bodies are engulfed by antigen-presenting cells, then the immune response will be enhanced and cross-presentation of antigens to CD8 T cells facilitated.

This volume provides examples and reviews of this wide variety of contributions of apoptosis to the pathogenesis of infectious diseases.

*Diane E. Griffin*
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