

Preface

MULTICELLULAR ORGANISMS ELIMINATE infected, damaged, or obsolete cells by activating genetically encoded cell death programs. These self-destruct programs are crucial to normal homeostasis and preservation of the overall health of the organism, but perturbations that enhance or suppress cell death may lead to disease. For example, excessive cell death is associated with neurodegeneration and other chronic inflammatory diseases, whereas too little cell death can promote cancer or susceptibility to infection. Much of this volume is devoted to the cellular signaling that underlies the three most studied cell death programs of apoptosis, pyroptosis, and necroptosis. This knowledge has led to the development of drugs designed to trigger the death of cancer cells and potential therapies for suppressing cell death that would otherwise exacerbate inflammation.

Apoptosis is a death program executed by cysteine proteases called caspases. It can be activated when internal cues alter the balance that exists between proapoptotic and antiapoptotic members of the BCL-2 family of cell death regulators. This volume begins by examining how proapoptotic BCL-2 family members permeabilize mitochondria to release factors that activate caspases and how drugs mimicking proapoptotic BCL-2 proteins have expanded the armamentarium against certain blood cancers. Apoptotic cells are dismantled into membrane-enveloped fragments that are rapidly cleared by phagocytes, so subsequent chapters explore the process of corpse engulfment and how dying cells influence living cells.

Other chapters describe how extracellular death ligands activate caspases to induce apoptosis in a cell-extrinsic manner. Necroptosis and pyroptosis, two death programs that, unlike apoptosis, are lytic in nature are also considered. For example, if caspases are inhibited, death ligands activate the kinase RIPK3 and its pseudokinase substrate MLKL to induce proinflammatory necroptosis. Pyroptosis is also proinflammatory and is driven by caspases that activate pore-forming proteins in the gasdermin family. The nature of these pores is described, as are the most studied triggers of gasdermin pores, the inflammasomes. These intracellular complexes assemble in response to different cellular insults and activate caspases that cleave the inhibitory domain from gasdermin D. Accumulating evidence that these cell death programs contribute to inflammation and various pathologies has sparked much interest in the therapeutic potential of inhibiting key pathway components.

Finally, there are chapters exploring the evolution of the different mammalian cell death programs and the pathogens that seek to subvert them. Cell death signaling mechanisms in plants and lower organisms are also reviewed. An interesting topic is whether these cell death programs arose from a common ancient pathway or by convergent evolution.

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