

PREFACE

Programmed cell death (PCD) plays important roles in animal development, and its original discovery dates back to 1842 when Karl Vogt reported that cell death is associated with the removal of the notochord during amphibian metamorphosis. During the past two decades, dramatic progress has been made in understanding the biochemical basis of the most prominent form of naturally occurring PCD, termed apoptosis. At the same time, much remains to be learned about the physiological roles and regulation of apoptosis *in vivo*, and how diverse signaling pathways are integrated to select specific cells fated to die during organismal development. Work primarily from three major model systems, the nematode *Caenorhabditis elegans*, the fruit fly *Drosophila melanogaster*, and the mouse *Mus musculus*, has revealed a remarkable complexity in how apoptotic cells interact with their cellular environment during normal development. These interactions play critical roles in the decision of cells to die, and in the recognition and clearance of apoptotic cells by phagocytes. Surprisingly, apoptotic cells were also found to be the source of diverse signals that profoundly influence the fate of surviving neighbors and can affect tissue growth and morphogenesis. This issue of *Current Topics in Developmental Biology* reviews some of the exciting recent advances in this field. The first two chapters focus on the nematode *C. elegans*, where the conserved core pathway for apoptosis was originally discovered. Zuckerman Malin and Shai Shaham review both the classic work and also discuss new findings indicating that the interaction between dying and engulfing cells is more complex than originally thought, and that PCD, at least in some cells, requires more than one death program. The next chapter by Seervi and Xue details the roles of mitochondrial proteins in the execution of cell death in *C. elegans*, including chromosome fragmentation, phosphatidylserine externalization, and elimination of mitochondria. We then have a series of chapters devoted to work on *Drosophila*. Anding and Baehrecke review the complex roles of macroautophagy in cell survival and death, and what is known about autophagic cell death *in vivo*. Peterson *et al.* highlight advances in our understanding of cell death in the germline, focusing on the *Drosophila* ovary. This is followed by a review from Domsch *et al.* on the regulation of apoptosis by HOX genes, covering work from worms, flies, and mice. Miura and Yamaguchi discuss the role of caspases during neural development, both in the context of apoptosis and the

nonlethal action of caspases for the pruning of axons and dendrites. This is followed by two chapters on the regulation of apoptosis by the ubiquitin-proteasome system. Vasudevan and Ryoo review regulation of cell death by Inhibitor of Apoptosis Proteins, a conserved family of E3 ubiquitin ligases that includes the major known direct negative regulators of caspases. Meier et al. expand on the roles of the ubiquitin system in the regulation of cell death, inflammation, and immunity. The next chapter by Fogarty and Bergmann summarizes our current knowledge about signaling by apoptotic cells, an unexpected and rapidly expanding field. The following two chapters are devoted to the final step in the execution of apoptosis, the engulfment, and clearance of apoptotic cells. The chapter by Nagata and colleagues provides a comprehensive review on the clearance of apoptotic cells by macrophages, with an emphasis on mammals and human disease. Shklover et al. discuss advances from different genetic model organisms, such as *C. elegans*, *Drosophila*, zebrafish, and mouse. Despite a wealth of information on these pathways, many fundamental questions regarding apoptotic cell clearance during development still remain unclear. The final chapter by Monier and Suzanne discusses the morphogenetic role of apoptosis and the crucial role of live imaging for these studies. One of the unexpected new concepts emerging here is the idea that apoptosis may be a source of mechanical force for morphogenetic movements.

Collectively, this series of reviews illustrates both the remarkable advances that have been made in elucidating pathways and detailed biochemical mechanisms to explain key events during apoptosis, but they also reveal the many unresolved questions and unexpected new opportunities that we still face for understanding the physiological regulation and function of PCD.

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