# Preface

Over the last ten years, the field of Programmed Cell Death (PCD/apoptosis) has changed from a relatively obscure speciality within specific areas of developmental biology, immunology and pathology, to a mainstream subject of fundamental importance to biology and medicine as a whole. Capturing on the printed page relevant and lasting ideas in any rapidly evolving field is never an easy task. Nonetheless, this is what we hope we have achieved, even if many of the details have changed as new stories have emerged. Luckily, the fundamental framework for understanding the mechanisms by which cells are programmed to die has not changed significantly over the last few years in which this book has been in production. Overall, therefore, we have included most of the important stories that have shaped our conceptual understanding of PCD through primarily focusing on the molecular mechanisms and pathways central to its regulation.

The remit of this book is to introduce the fundamentals of PCD to researchers new to this field, whether they are scientists, clinicians or undergraduates. In order to achieve this we have concentrated on the fundamental molecular processes of PCD at the expense of the more disease-associated research. The (re) discovery and background of PCD (apoptosis) is covered in chapter 1, with chapters 2-7 expanding upon individual areas of study that have aided greatly our understanding of PCD. As will be apparent throughout the book, the overall picture of PCD is gathered from many research disciplines. Arguably, much of the insight into the regulation of PCD has come from the study of less complex organisms such as the nematode worm *Caenorhabditis Elegans* (chapter 2) and the fruit fly *Drosophila* (chapter 3). The foundations laid by genetic studies in these two organisms have provided guidance for and complemented the biochemical, cellular and molecular studies conducted in mammalian cells as discussed in subsequent chapters.

The core of the death programme in animals consists of a proteolytic cascade involving a family of cysteine proteases called caspases (chapter 4). This protein family includes both the executioner caspases that target multiple cellular proteins for destruction, acting to carry out the apoptotic death of the cell, as well as death-signalling caspases that target caspases and other proteins in cell death pathways, serving to propagate or amplify the caspase death program. Two protein families play a major role in regulating this caspase cascade: the Bcl-2 family (chapter 5) and a group of proteins related to the baculovirus IAPs (Inhibitor of Apoptosis Proteins, discussed in chapters 3-5 and 8-10). The major known site of action for most of the Bcl-2 family proteins is the mitochondrion (Chapter 6), where Bcl-2 proteins regulate the release of factors from the mitochondrial inner membrane into the cytoplasm. These factors (cytochrome c, AIF, and Smac/Diablo) then activate caspases, either directly or via intermediate caspase-binding adapter/regulator proteins, and

thereby trigger the death program. Crucial in both the discovery and elucidation of the biochemical function of these mitochondrial factors and their targets has been the use of cell-free systems (chapter 7).

The remainder of the book (chapters 8-11) covers the most important and best-understood pathways that regulate the intracellular death program, relaying the extracellular survival and death signals that ultimately control cell survival and death. Nearly all animal cells are programmed to die by default and are continually instructed to survive by a plethora of molecular signals (1). Recent evidence suggests that there are key proteins involved in integrating many of these signals. One such protein is the serine/threonine kinase Akt (chapter 9). Akt, a downstream target of PI-3 kinase, is implicated in the survival of many cell types and as a result any loss of function may have many repercussions in mammalian biology. In addition to these survival signals, there are also molecular signals that can specifically trigger cells to die. A particularly well-studied mechanism that has received much attention over recent years is that of the 'death receptor' pathway (chapter 8), mainly because this pathway represents a direct mechanism for activating the downstream death machinery and has been pivotal in identifying many of the key proteins that regulate PCD.

There are some disciplines in biology and medicine in which the study of PCD has been particularly important and has been so even before the decade of the 1990's that saw the emergence of apoptosis as a mainstream field of cell and molecular biology. Unfortunately, as it is not possible to cover all of these areas in just one book, we have chosen just two of the fields in which the study of PCD has made a major contribution. The first of these is virology (chapter 10). PCD is one of the cell-intrinsic mechanisms by which organisms attempt to prevent viral propagation. Essentially by committing suicide, an infected cell can prevent a virus from spreading to infect neighbouring cells and compromising the whole organism. Of course, viruses have evolved the means to counter this primitive defence, by evolving or picking up from their hosts genes that encode proteins that inhibit PCD. By understanding these viral proteins and how they work, we have been able to gain a deeper understanding of the mechanisms by which PCD operates in cells.

The second field in which PCD has had a major impact is Neurobiology. Its importance has been recognised very early on by developmental neurobiologists, and for several decades it was the main focus (although not generally recognised as such) of studies of the first described growth and survival factor, Nerve Growth Factor. Chapter 11 reviews PCD in the nervous system as an example of how PCD functions in the development of complex multicellular organisms. This chapter also reviews what we know about the role of PCD in diseases of the central nervous system, including stroke as well as more chronic degenerative diseases such as Alzheimer's disease.

There are many other areas where the discovery of PCD has revolutionised the understanding of biological function, not least in immunology, cancer and developmental biology. Regretfully, it has not been possible to cover these subjects here; however, they have been extensively reviewed in a number of books and reviews (2-7).

In closing, we would like to thank all of the contributing authors for their hard work and patience during the production of this book. This book was commissioned at a time when key researchers in PCD were being asked to contribute to books, journals and reviews on the subject every other day and many were suffering from repetitive strain injury and a lack of new plots! Our authors have managed to produce both informative and novel reviews of their specialist subjects and we are indebted to them. We would also like to thank the production team at Oxford University Press for all their help, encouragement and perseverance with this project. Finally, we hope that this book achieves its aims; to be informative, concise and clear in a subject that is forever revealing new aspects of cellular regulation that are applicable to many areas of biological research.

*January 2002*

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