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Foreword

Biologists have been relatively slow to recognize and study the degradation processes that operate in cells, compared with the generative processes. Our understanding of protein degradation, for example, lagged well behind our comprehension of protein synthesis. And so has it been for cell death, where understanding followed many years behind the comprehension of cell division. Although it had long been recognized that cell death can be an important part of normal animal development and tissue homeostasis, it was only in 1972 that Kerr, Wyllie, and Currie drew a clear distinction between the conserved cytological features of these normal cell deaths and the very different features of acute pathological cell deaths. They coined the term apoptosis for the former type of cell death and, importantly, suggested that it might reflect the operation of a conserved intracellular death program, by which animal cells can actively kill themselves in a tidy and controlled way.

This important idea remained largely dormant for almost 20 years, and the study of apoptosis remained confined to a small group of aficionados working on diverse organisms. The big bang in the cell death field came from Horvitz and colleagues at the end of the 1980s and early 1990s with the genetic identification of the intracellular proteins that mediate and regulate apoptosis in the nematode *Caenorhabditis elegans* and, soon thereafter, the demonstration that related proteins operate in similar ways in other animals, including humans. In this way, it rapidly emerged that a family of cysteine proteases—the caspases—mediate the apoptotic death program and that a family of regulatory proteins—the BCL-2 proteins—either activate or repress the program. These spectacular findings indicated that apoptosis is a fundamental property of animal cells and that the proteins that mediate and regulate it have been largely conserved in evolution from worms to humans. The findings launched the subject into the cell biological stratosphere, where it remains to this day, having gone from neglect to hysteria in only a few years.

As the cell death field matured, it became increasingly clear that there are multiple ways of activating and repressing the apoptotic program from both inside and outside the cell. It also emerged that the molecular details can vary from organism to organism

and that other nonapoptotic death programs can operate in animal cells. This added complexity has created a pressing need for a comprehensive stock taking—a cool, clear, overview of cell death that cuts through the detail in a logical and engaging way while making it clear where controversy and mystery remain. The author of *Means to an End*, a highly respected leader in the field, has achieved all of this admirably. The writing is remarkably clear and is bolstered by simple, informative figures.

Whether you are a cell death expert or a neophyte, or even a retired cell biologist like me, you are likely to find the book informative, clarifying, and enjoyable. If you are a scientist just starting your career in the cell death field, it is unlikely that you will find a better place to identify important unsolved problems on which to work. If you are a drug developer, you will find an enlightened discussion of how one might design drugs to either encourage dangerous cells to kill themselves or discourage transiently injured cells from doing so. All you need to know about cell death is covered here, with panache, and all in fewer than 250 pages—a remarkable achievement.

MARTIN RAFF

London, July 2010

Introduction

Like all living things, cells die. Indeed, a great many cells in our bodies die throughout our lives, and their deaths are essential for our survival. They die by highly conserved mechanisms that may have their evolutionary origins more than 1 billion years ago. This book is about how that death happens and how it contributes to physiological homeostasis and disease. The focus is on cell death in animals and predominantly on only one form of cell death, called *apoptosis*, for two reasons. First, most cells that die in humans die by apoptosis. Second, it is the type of cell death about which we currently know most. So, although other types of cell death are covered in some detail, most of our discussion concerns apoptosis.

The underlying mechanisms of apoptotic cell death are found throughout the animal kingdom, but probably nowhere else.¹ In all animals studied (including many of the phyla), the features of this type of cell death are the same: The dying cell effectively “packages” itself to be eaten by healthy cells and digested. Furthermore, many of the specific molecules involved in this process are conserved in animals. However, the specific molecular pathways, although similar, can have fundamental differences. Throughout most of this book, we focus on the molecular pathways of apoptosis (and cell death in general) that function in humans. This unabashedly anthropocentric (or, at least, “backbonecentric”) view is our goal, with apologies in advance to those readers who consider themselves “fly people” or “worm people” and those with interests in other organisms.²

¹ There is a literature that explores cell death in other types of organisms, including plants and yeast, and it remains possible that within the cell death mechanisms in such organisms is a vestige of a far more ancient process than we currently suspect. However, the molecules involved in the process are, at best, very distantly related to those in animals, and the actual pathways remain to be elucidated.

² In fact, it is largely owing to those who study such organisms (especially nematodes and insects) that we know so much about the molecular mechanisms of apoptosis, and hence the apology (however flippant it may appear) is meant with sincerity. Robert Horvitz was awarded a Nobel Prize in Medicine and Physiology in 2002 for his pioneering studies of cell death in nematodes.

We will quickly step off into the deep end of the molecular pool with the biochemical mechanisms of cell death. For reasons that will become clear, a “bottom-up” view of cell death by apoptosis comprises the first several chapters. But before we dive in, it may be useful to say a word about how the chapters that follow are organized.

- Chapter 1 is essentially a synopsis, a quick take on the rest of the book. It is a chance to get our bearings and take a stab at the big picture, starting with why cells die and the three major types of cell death. It goes on to outline the molecular mechanisms covered in subsequent chapters.
- Chapters 2 and 3 concern caspases, the proteases that orchestrate apoptosis by cleaving substrates in the cell. Chapter 2 introduces the caspases and explores those substrates that have known roles in apoptosis. We also discuss caspases that are not involved in apoptosis, *per se*. Chapter 3 considers the biochemistry of activation of different types of caspases, as well as inhibitors of caspases and their roles.
- Chapters 4 and 5 cover the mitochondrial pathway of apoptosis, the major way in which apoptosis occurs, at least in vertebrates. Chapter 4 discusses the events that occur once the mitochondrial pathway is engaged and how this leads to caspase activation. It also introduces the caspase activation pathways of flies and nematode worms, together with ideas on how apoptosis may have evolved. Chapter 5 introduces the BCL-2 family of proteins, whose complex interactions link different signals for cell death to the mitochondria.
- Chapter 6 considers another way apoptosis is engaged in vertebrates—by cell surface death receptors—and how these specialized receptors engage a distinct pathway of caspase activation. This pathway can also link to the mitochondrial pathway to cause apoptosis.
- Chapter 7 looks at additional pathways for caspase activation. One is engaged by signals from infectious organisms and some inert substances and can result in a form of apoptosis but also triggers inflammatory responses. Another pathway involves the most highly conserved of the caspases and how it is activated, but its role in cell death is obscure.
- Chapter 8 explores the other major forms of cell death, necrosis, and autophagic cell death. Chapter 9 covers what happens after a cell dies. Regardless of how it died, a dead cell is rapidly cleared from the body by phagocytosis. But once the cell is gone, there are additional consequences, including effects on the immune system and proliferation of healthy cells.
- Chapter 10 provides examples of cell death in development, exploring how the cell death pathways can be engaged by signals that specify which cells must die. Chapter 11 introduces the idea that cancer is, in part, a disease of defective cell death. It discusses the mechanisms that are in place to prevent cancer and how

these link to the machinery of apoptosis, as well as the roles that cell death may have in promoting cancer and in cancer therapy.

- Chapter 12 explores the mechanisms of cell death as we understand them and how these are tested. These include formal models and their consequences for biology, as well as the practical applications of these mechanisms to the treatment of disease.

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