

## Book Review

# Aha! ... .. apoptosis: means to an end

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'Means to an end' by DR Green. Published by Cold Spring Harbor Laboratory Press. Cold Spring Harbor Laboratory, New York. 2011, pp 220. Price \$35.

Stuck for ideas over that last-minute present for your partner? Feeling like death after overindulgence at the last party? Do not know what to give your kids? Eureka, buy Doug Green's book on the many ways in which cells can undergo death!

Our bodies contain approximately  $10^{14}$  cells, and each second at least  $10^6$  die by a specific death mechanism. Curiously, although cell proliferation was identified in the 1880's, cell death only really came to the attention of the scientific community in the 1980's. During all this time, scientists never truly posed the question of a child: where are all these proliferating cells going? Were growth not balanced by death, our body would have 2sq km of skin, 2.5 tons of bone marrow, and 16km of guts, including an unpleasant last 500m.<sup>1</sup> Now, however, cell death is an established field, not only as an area of basic research but also one that is beginning to be exploited therapeutically. It is particularly appropriate, therefore, to publish now a general book introducing concepts and mechanisms of cell death, particularly to the expanding audience who wish to manipulate it either positively (as in cancer) or negatively (as in cerebral and myocardial infarction). '*Means to an end*' provides such a resource, aimed at college level and above, and is a life-affirming gallop, which provides a welcome clarity through the complexities of the subject.

The book has the great advantage and disadvantage of being written by a single author. It is composed in a simple and accessible way, with an evenness and homogeneity in style and presentation, and the field is captured in 200 concise pages with informative illustrations. On the other hand, like any committed scientist, Dr. Green, as he freely admits, has his own biases and eccentricities, though these will provoke discussion and controversy (the very life blood of science) rather than confuse the issues.

As a leader in the field of cell death since the late 1980s, Dr. Green's contribution has been pivotal, particularly in defining the process of activation-induced apoptosis in T cells. He was also heavily involved in studies, which led to the understanding of the role of Myc, Bcl-2, death receptors, and lately the mitochondrial pathway in cell death, again with a special emphasis on the immune system. Most importantly, this book proves that he is not only a great writer of formal scientific papers but also a great communicator in general, and his experiences of writing screenplays clearly have subconsciously influenced his pen in this volume. We cannot do better than echo the words of Martin Raff, one of the founders of the cell death field, in his Foreword: '[*This*

*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. Doug Green has achieved all of this admirably.*'

So what is covered in this stocktaking? Chapter 1 is essentially a synopsis, a general view that provides a conceptual background for the reader before getting into the details of the following chapters. Thus, the book starts with the big biological picture, posing the basic questions of why cells die and describing the principal mechanisms of how they do it. Indeed, there would be little point in taxing the readers' brains and patience with the detailed molecular mechanics unless the philosophical necessity for cell death and its long evolutionary pedigree is clearly understood.

Chapters 2 and 3 are focused on caspases, the proteases at the core of the apoptosis machinery, killing by a thousand cuts an enormous number of cellular proteins, which are essential for cellular integrity, and leading indirectly to the ordered cleavage of DNA. From a general view of all caspases and their substrates, including their involvement in processes such as inflammation and differentiation besides cell death (Chapter 2), the author moves on the biochemistry of these enzymes and their inhibitors (Chapter 3).

Chapters 4 and 5 are dedicated to the mitochondrial pathway. Some would argue that the characteristics of mammalian apoptosis have as their origin, the potentially dangerous dialectic between mitochondria and the rest of the cell. Indeed, the level of integration between mitochondrial function and that of the rest of the cell forms one of the switching nodes between death/survival signaling and is an area of very active research (and controversy). Chapter 4 discusses mitochondrial outer membrane permeabilization, and how this leads to caspase activation, whereas Chapter 5 is dedicated to the Bcl-2 family of proteins, whose complex interactions link different signals for cell death to the mitochondria.

The other main initiating pathway of apoptosis, that mediated by cell surface death receptors is described in Chapter 6, together with how these specialized receptors engage a distinct pathway of caspase activation, leading to either death or survival, and in special cases to programmed necrosis (necroptosis). Importantly, the links between this extrinsic and the intrinsic mitochondrial pathway of apoptosis are also discussed here.

Chapter 7 details other caspase activation platforms, including the inflammasome, and therefore reopens the link

between apoptotic regulators and immunity. Indeed, activation can be engaged by signals from infectious organisms as well as by some inert substances, such as asbestos, silica, and possibly nanotubes. This can also trigger inflammatory responses, leading to disease.

Non-apoptotic forms of cell death, such as necrosis and autophagic cell death are discussed in detail in Chapter 8. However, additional forms of cell death such as cornification, the form of cell death of the skin, and erythrocyte maturation are not considered here, presumably because they are thought too specialized—perhaps a pity, as these are physiological rather than pathological cell death.

The next chapter explores the rapid clearance of the apoptotic remains from the body by phagocytosis—the burial phase. Perhaps now is the time to stress that, despite the use of the word ‘death’, it is not death as an instantaneous phenomenon that is being described in the book (indeed, can this really be studied at all?), but rather the processes, in part reversible, which lead to death, and the mechanisms of disposal of the dead remnants. It also introduces the consequences of defective clearance, such as systemic lupus erythematosus, in which apoptotic bodies fail to be cleared, and whose persistence may result in the appearance of a whole variety of anti-self-immune responses.

The deficiency mentioned above in terms of physiological death is in part remedied in Chapter 10, which is dedicated to development. This explores how cell death pathways can be engaged by signals that specify which cells must die in the sculpturing of the embryo.

Chapter 11 focuses on cancer, now considered as much a disease of defective cell death as a proliferative pathology *per se*. It discusses the mechanisms that are in place to prevent cancer and how these are linked to the machinery of apoptosis, as well as the roles cell death may have in promoting cancer, and in cancer therapy.

The final chapter, Chapter 12, explores the future of cell death, and identifies some hard questions that remain in this research field. Here, it is again emphasized how apoptotic pathways are composed of checks and balances, and that, once initiated, death is not an inevitable outcome. One

implication, not fully developed here, is that it is theoretically possible to design two agents, acting on the same molecular target, which either promote death (as cancer therapy) or prevent it (as treatment for cerebral and myocardial ischemia). Nevertheless, the discussion is a stimulating set of ideas for the biological consequences of cell death activation, as well as the practical applications of its manipulation to the treatment of disease.

Who should buy this book—whether for your partner, friends, or kids? Considering the simplicity of figures and its concise text, any student, medic, mature biologist, or even an interested layman would be attracted and inspired by this book, as it provides both a solid basis to those entering the field as well as a fresh and provocative viewpoint for the cognoscenti. Most importantly, it is meant to be read in one go from beginning to end. Even as old deathmen, hopefully with hyperactive IAPs and not yet secreting any eat-me signals, it comes as a stimulating distraction from the passing girls in the Piazzeta in Capri or from the Queens speech in England. In fact, we, having actively been for over 20 years in the field, really enjoyed this reading and had several moments of inspiration and thinking, that are appreciated by the very expert reader too. Indeed, this book contains several ‘Aha! ... ..’ moments.

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