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Book Review

Cell Death

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Cell Death. By Gerry Melino and David Vaux. Publisher: Wiley-Blackwell (an imprint of John Wiley & Sons Ltd). ISBN-10: 0470715731. ISBN-13: 978-0470715734. Price £85.00

'A hero is someone who rebels or seems to rebel against the facts of existence and seems to conquer them. Obviously that can only work at moments. It can't be a lasting thing. That's not saying that people shouldn't keep trying to rebel against the facts of existence. Someday, who knows, we might conquer death, disease…'. This quote of the late Doors front man Jim Morrison would have been a befitting addition to the first chapter of the book on Cell Death, edited by Melino and Vaux. In this well-versed chapter, the editors entertain the reader with a philosophical and mythological view on cell death research to explain the late onset, yet quick ascent, of this area of biomedical research. In our view, their justified conclusion is that a life-oriented society was not ready for research on the essence of death and therefore rather focused on the biology of life. Despite the long lag phase, cell death now has a firm position in research, but whether this is out of biological interest or more due to our desire to 'conquer death', as Jim Morrison puts it, is not clear. Nevertheless, this is why we believe a book summarizing the different aspects of cell death is a welcome addition to the broad pallet of scientific literature. The book of Melino and Vaux is definitively a tremendous effort to summarize the vast amount of knowledge. It is divided into 29 chapters, which are all written by the leading experts in the field. Chapters range from basic biochemical mechanisms to therapy, from apoptosis to autophagy and from lower organisms to humans, and as such give a great overview of the research area.

Evolution and Lower Organisms

In his chapter, Jean Claude Ameisen explores the evolutionary origin of cell death trying to explain how Darwin's view of evolution can be applied to cell death. He also describes the potential function of programmed death in unicellular organisms and puts forward interesting theories that imply that all molecules involved in cell death also share a different function in cells.

Cell death pathways in *Caenorhabditis elegans* are summarized by Sendoel and Hengartner in the third chapter. The organism that pointed towards molecular players involved in cell death has proven to be a powerful genetic model, and this chapter gives a comprehensive overview.

Caspases, Dismantling and Phagocytosis

Chapters 4, 6 and 7, dedicated to explain the role of caspases in cell death (by Hernandez/Houde/Hoek/Butts/Mehmet/Nicholson, Walsh/Martin and Deming/Kornbluth, respectively), are all a pleasure to read and highly recommendable, in particular for newcomers in the area. They describe the initial identification of the caspase protein family, the structure and classification, modes of activation and execution, cellular consequences of caspase activation, caspase-deficient mice and more. It is somewhat disturbing that these chapters sometimes provide overlapping or confusing information. For example, the numbers of caspase substrates given vary from 'over 400' to 'over 1000'. The caspase chapters are accompanied by a thorough overview of the apoptosome platform by Ferraro and Cecconi. In this chapter, the authors characterize not only the components of the complex released under cell death stimuli but also the implication of apoptosome-like complexes in evolution.

Once cells undergo caspase-dependent death, their fate *in vivo* is normally engulfment and disposal through phagocytosis. This process is nicely reviewed by the group of Nagata, the leading expert in this field. They discuss the mechanistic aspects, the important players and also the fundamental role of regulated phagocytosis in preventing inflammation. As such, this chapter elegantly bridges the gap between the two chapters on immunity. The first chapter by Waterhouse, Susanto, Sedelies and Trapani describes the role of granzymes, which are enzymes released by so-called killer cells, in the induction of cell death. The main focus is on granzyme B, for which the induction of cell death is best clarified and mimics caspases. The other granzymes are reviewed as well and appear to induce less typical forms of cell death. Finally, the clearly death-oriented chapters mentioned above are complemented by a chapter on inflammation and immunity by

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LeBlanc and Saleh, who eloquently describe the role of caspases in non-death processes.

Mitochondria, the Bcl-2 Family and IAP Regulators

Clearly, a large part of the book is dedicated to the role of the mitochondria in cell death induction. Although the energy-producing factories of cells were long regarded as essential for life, they have proven over the last several decades to be as essential for the induction of death. Bernard, Peng and Karbowski give a splendid overview of the structure and dynamics of the mitochondria and describe what they believe is the role of fission and fusion of the mitochondria in apoptosis induction. Parsons and Green complement this with a discussion on the mechanism of mitochondrial outer membrane permeabilization and its role in the release of critical molecules, such as cytochrome *c*. They highlight the regulation of this event by the Bcl-2 family and discuss the relationship with mitochondrial fission and mitochondrial permeability transition.

Vaux in his chapter on Bcl-2 family members and Happo, Strasser and Scott in their chapter on BH3-only Bcl-2 family members extend the mitochondrial discussion towards all stress signals and regulatory mechanisms that are in place to manage the induction of mitochondrial outer membrane permeability. The different members, the knockout mice available and the development of therapeutics targeting this family are all excellently described.

Death Receptors and Death

Besides the intracellular induction of cell death, death receptor-induced cell death is an important aspect discussed in the several chapters of the book. Lavrik and Krammer present the current view on how CD95 (APO-1/Fas) stimulation by CD95L is translated into an apoptotic signal inside the cell by formation of the CD95 death-inducing signaling complex. They also provide a comparison of this molecular machine to those triggered by other apoptosis-inducing stimuli, such as TNF and TRAIL.

Marion MacFarlane then takes a detailed look at the molecular interactions of TRAIL (Apo2L) with its different apoptosis- and non-apoptosis-inducing receptors and how minor natural differences – or indeed targeted alterations – in these interactions, can cause major differences in applicability of different TRAIL receptor agonists for clinical use in cancer treatment. Declerq and colleagues leave apoptosis behind and return to the origins of TNF research by contemplating a form of cell death recently termed 'necroptosis' due to its regulated, non-accidental, yet still necrosis-like presentation. They review recent data on RIP1 and RIP3 in this form of cell death and discuss how this may link back to energy metabolism and production of ROS.

Structures and Cell Death Inhibitors

David Vaux first provides a precise historical account of the discovery of the inhibitor of apoptosis proteins (IAPs) before he explains how they achieve their eponymous function, how physiological IAP antagonists work and how this led to the development of a novel class of cancer drugs, namely the IAP antagonists or Smac mimetics. Hinds *et al*. then provide further molecular insight into the ubiquitin E3 ligase activity of certain IAPs and how this activity contributes to the proapoptotic function of Smac mimetics. These authors also take a close look at the structure–function relationship of the various subclasses of Bcl-2 family members, i.e., how they interact to induce or inhibit apoptosis at the level of mitochondria.

Wu and Lo embark on a central topic of structural research in the apoptosis field, as they explain the structure–function relationship for proteins belonging to the different subfamilies of the death domain (DD) superfamily, i.e., the DD-, DED-, the CARD- and the PYD-containing proteins. This analysis reveals partly surprising stoichiometries for protein complexes that are central to the apoptotic process. Georg Häcker examines the fascinating and often mechanistically revealing strategies used by infectious microbial agents to halt the apoptotic process either permanently or transiently to complete their life cycle or to provide for the required niche inside the infected cell or organism.

Other Forms of Cell Death

Although non-apoptotic forms of cell death are mentioned and discussed throughout the book, several chapters are also dedicated to this topic. Two chapters deal with autophagy, a form of death that has gained importance in recent years. The first chapter by Colombo and Simon describes autophagy in mammalian systems, whereas the second chapter by Hill and Baehrecke gives a detailed view on what is known in non-mammalian organisms. The basic mechanisms and components involved are clearly presented. Of course, the role in cell death is also extensively described, as well as the potential physiological functions of this form of death. Finally both chapters describe the involvement of autophagy in disease and the potential role of some animal models for their study.

A more peculiar form of death, which is normally described as differentiation, is described by Candi, Knight and Melino. Keratinocyte differentiation is in the strict sense rather a cell death fate, forming a highly specialized barrier essential to protect mammals from the environment. The insightful description of this form of death exemplifies how cell death is not only essential for renewal of tissues, but also for direct protection from the outside world of pathogens.

Death in Disease

A book on cell death would not be complete without a discussion of multiple disease implications. Both, too much and too little cell death, are detrimental to an organism and many dreadful diseases, such as cancer or neurodegenerative disorders, are characterized by such an imbalance. It is therefore not surprising that several very well-written and informative chapters discuss the association between apoptosis and disease. Vince and Silke take a view from the proteins involved in apoptosis and describe what is known about mutations in these players, both from human diseases and from mouse models. A separate chapter by Wolyniec, Haupt and Haupt is dedicated to summarizing the enormous

bulk of literature on cell death and p53, a gene that is mutated in ~50% of human cancers. Su and Lenardo in turn zoom in on inherited autoimmune disorders, especially in ALPS patients, who suffer from lymphoproliferative disorders. The capacity of certain proteins to execute either apoptotic or non-apoptotic functions, depending on the biological context is well discussed. The book ends with a chapter on drug development targeting dysfunctional genes implicated in apoptosis. The development of caspase inhibitors is broadly illustrated and several examples are given. Drugs targeting other proteins such as Bcl-2 and IAP, however, are only briefly discussed providing just one example for each type of inhibitor.

Therefore, is this book just a pleasure to read? Yes it is, but of course similar to every overview on a particular topic, editors have to make choices. Owing to the vast amount of information and different type of chapters, the reader may at times have some difficulties to find his/her way through the chosen assembly of the different topics and be struck by a certain amount of overlap. However, the careful reader will appreciate that the presented variations on the theme give an account of a very active and evolving research field with different views on important aspects of cell death. Nevertheless, we would have loved to see a more extensive review on different model organisms such as *Drosophila melanogaster* or on other 'differentiation/death programs', such as erythrocyte or platelet maturation. In addition, a more extensive coverage on other cell death pathways, such as necrosis, mitotic catastrophe and caspase-independent death could have been presented as well. On the other hand, these processes are far less well understood and would have been a more speculative addition to the book.

However, this should not keep any *aficionado* of cell death research – or anybody who wants to become one – from reading this book. We believe that this is an impressive compilation on Cell Death from the field's leading scientists that will undoubtedly inspire newcomers to this booming area of research. We hope it may induce more scientists to accomplish the dream of Jim Morrison to conquer death and consequently fight diseases. We wish you a pleasant time reading this book.

Conflict of interest

The authors declare no conflict of interest.