

Book Review

The Siren's Song: a new book on the perils and benefits of (cell) death

Cell Death and Disease (2010) 1, e39; doi:10.1038/cddis.2010.13; published online 6 May 2010

Subject Category: Experimental Medicine

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

This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits distribution and reproduction in any medium, provided the original author and source are credited. This license does not permit commercial exploitation without specific permission.

The book edited by Gerry Melino and David Vaux functions as a compendium of cell death research, a journey that takes us back to the origins, while at the same time offers a glimpse into the future of research in this area. Cell demise is a crucial 'event' in the regulation of development, tissue homeostasis and immune response. Dysregulation of cell death is known to contribute to human diseases, from cancer to autoimmune disorders. Although this book provides a useful source for experts in the field, it will also serve as a textbook for students at the undergraduate or postgraduate level who wish to explore the dynamics and regulation of cell death, from *Caenorhabditis elegans* to humans. As often the case with review books of this nature, there is a certain degree of repetition between chapters. This could have been avoided if the book was structured to follow a more defined line of thought. Nevertheless, each chapter contains novel information ensuring that this book stands out among the numerous others centred on cell death and constitutes an extremely useful addition.

The Philosophy of (Cell) Death

The first chapter serves as an introduction to not just the history of the study of cell death but also to the philosophy of studying cell death. Appropriately, the stage is set with the question of suicide proffered by the existential writer Camus and the over-arching theme of the Siren's Song from Homer's *Odyssey* (Figure 1). Even for those of a less philosophical bent, this chapter provides a thorough history of the study of cell death and serves as a reminder to even the most ardent student that cell death was recognised in the nineteenth century and that morphology was well described in the 1950s and 1960s. Besides the subsequent recent history of a more mechanistic elucidation of cell death, the authors also discuss cell death from an evolutionary angle and consider the therapeutic implications of many decades of research in this area.

All in all, an effective and illuminating introduction that leads to an interesting chapter is written by Jean-Claude Ameisen.

This is a thematic continuation of the first one in that it discusses the origin and evolution of programmed cell death. Besides being a primer on cell death in evolutionary older 'simpler' organisms, this chapter also asks the central question of when and why cell death arose and why this question is not just a function of 'complexity'. Using *C. elegans* as a model but not forgetting unicellular organisms and higher animals, the author comes to the conclusion that the molecular effectors of most essential functions, such as metabolism, differentiation, cell cycle, etc., will induce cell death if not regulated properly, whether for self-organisation of the tissue in mammals or for host-pathogen interactions in bacteria. Quite strikingly, Ameisen refers to this as the 'Original Sin' hypothesis, that the cell's ability to commit suicide is a direct consequence of its capacity to self-organise, flourish and reproduce. Perhaps a little anthropocentric but nevertheless, food for thought!

Mechanisms: from *C. elegans* to Mammals

The following chapter comes from another leading scientist in the field of *C. elegans*, Michael Hengartner. In particular, the authors propose the idea that cell death is a 'terminal' cell fate during development. An interesting question raised by the authors is why blocking death results in a fixed number of undead cells, although its activation does not have equally 'precise' effects. Germline cell death is nicely written and clear to non-experts, whereas the idea of oocytes acting as nurse cells is very intriguing and requires further validation. It remains to be established whether cell death in the *C. elegans* germ line is a stochastic phenomenon or whether nurse cells are indeed more prone to cell death than fully functional oocytes.

Mechanisms: Digestion by Caspases

The book then moves on to analysing the execution phase of cell death, and in particular focuses on the involvement of caspases. The chapter by Nicholson *et al.* provides an

overview of the history and classification of caspases. A useful summary of the structure and active sites of caspases is provided, detailing how these domains interact with each other or with their adaptors and more than 1000 substrates. Clear diagrams are used to introduce the three classes of caspases on the basis of their function and structure. The important features of regulatory and executioner caspases, as well as their role in regulating the different stages of apoptosis are described. This chapter then goes on to show how understanding of the molecular mechanisms of catalysis and identification of functional domains of caspases, as well as their effectors and inhibitors, has led to the development of pharmacological caspase inhibitors. As highlighted and discussed by the authors, the therapeutic outlook of a new class of low-molecular-weight non-peptide caspase inhibitors is promising for the development of future therapeutics, but issues with efficacy and toxicity need to be resolved.

Upstream to caspase activation lies the apoptosome, the subject of the chapter by Ceconi and Ferraro. A detailed description of the structure of Apaf1, Cyt *c* and caspase 9 illustrates the complex conformational changes resulting from various interactions of the domains or modifications of Cyt *c* that are necessary for the formation of an active apoptosome. Importantly, the review describes the different levels of Apaf1 regulation by transcriptional regulation, gene hypermethylation or interaction with other cellular proteins. Rightly so, this chapter also underlines the importance of the apoptosome not only in cancer but also in neurodegenerative and human congenital brain malformations, stressing the biomedical importance of this complex.

Two chapters, by Walsh/Martin and Deming/Kornbluth, are well written and raise a number of interesting questions. However, both of these chapters recapitulate many of the aspects of caspase classification, function and regulation that have been extensively discussed already in the previous two chapters. Nonetheless, they both add further clarification to different aspects of the execution phase of apoptosis. In particular, Walsh and Martin discuss the role of caspases in controlling the clearance of apoptotic debris, whereas Deming and Kornbluth draw five simple illustrations explaining the processes leading to the dismantling of the cell during programmed cell death.

Mechanisms: Intrinsically Mitochondria

As mentioned above, the main drawback of this book is the lack of a clear rational ordering of the different chapters, as chapters on the execution phase somewhat counter intuitively precede those dedicated to the initiation phase. A 'grande presentation' is given by David Vaux on the role of BCL2 family in cell-death regulation. This chapter is very useful for anyone approaching this subject. A subclass of BCL2 family members, the BH3-only proteins are key regulators of the initiation phase of cell death. This is the subject of a well-written chapter by Strasser *et al.*, which provides useful insights into the role of the individual BH3 family members in the initiation of appropriate cell type and stimulus-specific apoptosis. The exact mechanism of how BH3-only proteins activate the pro-apoptotic members of the family such as Bax/Bak to unleash the effector phases of apoptosis is

currently unclear. It is therefore particularly helpful to be provided with clear explanation of the competing models of either direct or indirect interaction of BH3-only proteins with Bax, Bak and Bcl-2. This chapter reviews new insights into the regulatory pathways controlling their expression and function, such as microRNA-mediated control. Finally, it discusses the involvement of BH3-only proteins in cancer and the development of the BH3-mimetic drugs, providing a very useful table on current and ongoing clinical trials with two such small molecule BH3-mimetics, ABT-263 and its close relatives.

Most BCL2 family members display either a constitutive or transient association with the mitochondria. These organelles have a crucial role in the transduction of apoptotic signals through the intrinsic pathway and work as gatekeepers of cell demise. Parsons and Green, two leading researchers in this field, describe the defining feature of the intrinsic pathway, that is, the mitochondrial outer membrane permeabilisation (MOMP). Importantly, the authors also explain how the non-apoptotic function of the mitochondria, that of generating energy for the cell (bioenergetics) is central to MOMP and subsequent cell death. This is consistent with Ameisen's hypothesis in Chapter 2. Furthermore, it is not only factors extrinsic to the mitochondria but the organelle's inner workings that regulate MOMP and cell death. These checkpoints function in concert to control the mitochondrion's and thus the cell's proper function. The mitochondria do not exist as single entities but rather form long chains of fused organelles. These chains undergo rounds of fusion/fission events, which have been proposed to have a role during programmed cell death. A chapter by Benard *et al.* on this subject clearly outlines the regulation of mitochondrial network dynamics in cellular physiology, and its key role in cell death. Addition of a few important references should be helpful to the readers, including the role of OPA1 in cristae remodelling (Scorrano's group) and the link between fusion and neurodegeneration (Chan's group).

Mechanisms: Death Threats from the Outside

Programmed cell death can be induced through the extrinsic pathway, which has an important role in the immune system. Death receptors (DRs) are central in this context. Kramer and Lavrik's short review on DRs is a short article that highlights signalling through the different DRs and their corresponding ligands. Discussion of DISC formation and downstream regulation of caspase activity illuminates the differences between various DR pathways. This chapter is complex and lacks a conclusions/perspective section and a number of important studies are not discussed, such as those on TWEAK and its receptor Fn14 are missing. The potential of therapeutic agents targeting DRs in cancer cells is discussed in the following chapter by MacFarlane, which focuses on TNF-related apoptosis-inducing ligand (TRAIL) and its receptors TRAIL-R1 and TRAIL-R2. Understanding of the structure and molecular mechanisms of these proteins has already led to the development of therapeutic compounds. The determination of the structure of TRAIL and TRAIL-R has clearly aided the development of TRAIL-targeted therapeutics, several of which are currently in phase I and II clinical trials. Further knowledge into the mechanisms underpinning

tumour selectivity and resistance is likely to result in the development of further improved TRAIL-based anticancer drugs.

DRs induce not only apoptosis but also other forms of cell death, such as necroptosis. This is reviewed in the chapter by Declercq and colleagues, who are experts in this field. In contrast to necrosis, this type of cellular demise is not accidental and is dependent crucially on whether caspases are active or not. DR-induced necroptosis signalling complexes and necroptosis stimuli are nicely illustrated in a figure and a table. The physiological role of necroptosis in conditions such as neurodegenerative diseases and viral infection highlights the importance of this type of cell death in the whole animal and the value of targeting this pathway for therapeutic purposes.

How to Escape Death

In addition to BCL2-family members, apoptosis can be inhibited by BIR domain-containing proteins. Another comprehensive chapter by David Vaux on this subject focuses on the individual members of this family. This section further highlights the domain structures and organisation of this family, as well as their pathological roles as determined in knockout mice or mutations in humans. The *IAP* genes have been implicated in cancer and are amplified, translocated or deleted in different malignancies. The structural basis of the interaction between BIR-containing proteins and BCL2 family members is discussed in the following chapters, authored by Hinds *et al.* These structural studies have led to the development of several peptide mimetic drugs that are in clinical trials at present. Another chapter is dedicated to a more detailed analysis of structural features of protein interactions in cell-death regulation (by Wu and Lo). This chapter is very well organised and informative to the non-experts.

Dead Corpses and Scavengers

Once cell death has occurred, the remains of the cell are often engulfed by specialised cells. Alterations of this process can lead to pathological states. This topic is extensively reviewed by Nagata and colleagues who introduced us first to the 'find-me' signals that dying cells secrete to attract professional phagocytes. On binding to these signals, phagocytes upregulate the expression of specific genes involved in phagocytosis, such as *MFG-E8*, a bridging molecule that recognises phosphatidyl serine (an 'eat-me' signal) on the apoptotic cell and integrins on the phagocyte. An interesting comparison is made between engulfment genes in *C. elegans* and mammalian cells as the worm uses neighbouring sister cells, whereas mammals use specialised professional phagocytes.

Self-Digestion: to Die or to Live?

Self-digestion can be achieved not only through induction of apoptosis but also through a different intracellular degradation pathway known as autophagy. This chapter is timely due to a recent explosion in interest and published reports on autophagy. Autophagy has a Janus-type function in development,

tissue homeostasis and cancer, as it can serve as either a pro- or anti-cell death mechanism. Two very chapters expand on this subject, the first authored by Colombo/Simon, who provide a detailed outline of the molecular mechanisms of autophagy and examine its role in a number of pathologies, including neurodegenerative disease, cardiac disease, cancer, infection and inflammation. Interestingly, they conclude with a discussion on how autophagy interplays with cell death to spare cells from death or actually promote apoptosis. The subject of the following chapter written by two leading researchers in the field, Eric Baehrecke and Jahda Hill, introduces the genetics of autophagy. This chapter is well written and understandable to the non-expert. Very helpful insights are also given into the role of autophagy in disease pathogenesis. For instance, the authors discuss a number of studies suggesting that autophagy can compensate for proteasome impairment and degrade intracellular aggregates in models of neurodegeneration. In this regard, autophagy has an anti-ageing effect in worms and flies potentially through its capacity to degrade intracellular, toxic aggregates. Lipton and colleagues extensively discuss the available literature on the effect of ROS and NO on protein misfolding and synaptic damage. The exciting possibility that S-nitrosylation of the ubiquitin ligase parkin and protein disulphide isomerase can contribute to neurodegeneration is presented. The authors also discuss the potential use of drugs that protect neurons from oxidative stress in treating neurodegenerative conditions.

Immune System, Pathogens and Cell Death

Alterations of programmed cell death have implications for immunity and inflammatory diseases, as discussed in the chapter by LeBlanc and Saleh. The introduction to this chapter is very useful and sums up the history of immunity/inflammation research, by highlighting all the key findings in the last half-century or so. Given the intricacy of the pathogen recognition machinery, the authors have tried to summarise and critically discuss the currently available literature. To this end, they have chosen an evolutionary angle, supported by helpful cartoons, which guides the reader through the different mechanisms regulating the response to pathogens from insects to mammals. Finally, chapters on the involvement of caspases in inflammatory disorders, and on caspases and the immune response are well written, comprehensive and very informative. This is definitely one of the better chapters.

Cell death has a major role in developing the immune system and in modulating its response to pathogens. A well-written chapter by Georg Haeker is dedicated to microbial infections and their ability to influence cell death. This chapter extensively reviews the mechanisms by which viruses, intracellular/extracellular bacteria and parasites interact with intracellular cell death pathways.

A further chapter focuses on immunity and cell killing. This is the result of a combined effort by Nigel Waterhouse's group and Joseph Trapani, two leading experts in the field of granzymes. Importantly, the authors stress up front that lysis-mediated cell death after formation of the synapse has not been formally demonstrated *in vivo*, and that instead forms of non-lytic cell death are more plausible. Furthermore, the

authors raise the relevant question of how lymphocytes escape the toxic effects of the perforin/granzyme system they actually enable.

Too Much or Too Little (Death) is Equally Bad for You

The book then takes a turn and switches to alterations of the apoptosis machinery in disease, a chapter authored by Vince and Silke. Using two clear illustrations, they review the components of the intrinsic and extrinsic pathways of cell death, which are nicely illustrated in two figures. The remainder of the article is devoted to a discussion of the role of apoptotic genes in human disease. Discussion of mutations in patients is particularly informative. This is a very appealing and generally well-constructed chapter.

A number of hereditary disorders are characterised by alterations of the cell death machinery, as Su and Lenardo nicely illustrate. In particular, the roles of DRs and their ligands in autoimmune diseases are detailed with specific emphasis on Fas, a major mediator of extrinsic apoptosis in lymphocytes. Selective ablation of the *Fas/FasL* gene or loss of Fas signalling in dendritic, B or T cells has established that in any of these cell subsets, Fas defects promote disease by perturbing the normal cellular control mechanisms. The human genetic autoimmune lymphoproliferative syndrome is indeed due to defects in apoptosis. This chapter provides a useful insight into how mutations in the components of the apoptotic pathway can induce autoimmunity and unbalanced lymphocyte homeostasis in humans.

What about cell death and cancer? A book on apoptosis would not be complete without a chapter on the tumour suppressor p53. This responsibility fell on Wolyniec *et al.* As befitting its status as the most studied tumour suppressor, the authors concentrate on p53 function in cancer, as opposed to development or other pathologies. They then outline how these stresses activate and regulate p53 and how p53 signals apoptosis. After a (too brief from the point of view of those of who study p63/p73) section on the other p53 family members, the authors delineate how and what we have learned about p53 function and regulation, which is now being translated for therapy, with a number of small molecules and peptide-derived candidates being developed as drugs.

When Corpses are Useful

Sometimes the presence of a 'dead cell' has a key physiological role. This is the case of cornification of the skin, a process discussed and reviewed by Candi *et al.* Cornification of the skin is a highly regulated temporal and spatial process of terminal differentiation of keratinocytes in which the resultant dead cells form a barrier in the uppermost layer of the skin. The authors provide a thorough description of the various classes of proteins and their enzymology as it relates to cornification and the detailed coordination of their interactions. In conclusion, a very informative comparison

of the similarities and differences in cell death in keratinocyte apoptosis in the skin basal layer, and the keratinocyte terminal differentiation that constitutes cornification, is elucidated.

And to Finish...

Fittingly, the last chapter in this textbook is entitled 'Drug Discovery in Apoptosis', by O'Brien and Dixit. The authors directly address the dichotomy between the benefits and harms of death effector molecules, specifically caspases, in inflammatory diseases, infection, neurodegenerative diseases and cancer. What is necessary is to realise that for some pathologies, the clinician wishes to promote cell death, whereas for others, prevention of cell death is of therapeutic value. Focusing on caspase active site inhibitors, the authors take us on an informative if more than sobering journey through candidate drug discovery and clinical development. Not all is doom and gloom as we are shown that alternative approaches to caspase inhibition, based on allosteric inhibition, may be more fruitful. Gratifyingly, at least in this reviewer's opinion, the authors discuss non-caspase targets for drug discovery, such as pro-survival Bcl-2 family inhibitors (but why not pro-apoptotic family member agonists?), IAP inhibitors and SMAC-mimetics. With the number of possible targets, greater modifications, and experience of past failures, there is hope that the mechanistic knowledge gained in the past two decades of cell death research will soon translate to success in the clinic for a wide range of diseases.

Conflict of interest

The authors declare no conflict of interest.

P Salomoni^{*1}, S Basu², M Tavassoli³ and CJ Watson⁴

¹ Samantha Dickson Brain Cancer Unit, UCL Cancer Institute, 72 Huntley Street, London WC1E 6BT, UK;

² Cell Survival Signalling Laboratory, Centre for Molecular Oncology and Imaging, Institute of Cancer, Barts and the London School of Medicine, Queen Mary University of London, John Vane Science Centre, Charterhouse Square, London EC1M 6BQ, UK;

³ Head and Neck Oncology Group, Floor 28 Guy's Hospital, Dental Institute, King's College London, London SE1 9RT, UK and

⁴ Department of Pathology, University of Cambridge, Tennis Court Road, Cambridge CB2 1QP, UK

* Corresponding author: P Salomoni, UCL Cancer Institute, Paul O'Gorman Building, Samantha Dickson Brain Cancer Unit, 72 Huntley Street, London WC1E 6DD, UK.

Tel: +44 0207 679 0728; Fax: +44 0207 679 6643;

E-mail: p.salomoni@cancer.ucl.ac.uk



Cell Death and Disease is an open-access journal published by **Nature Publishing Group**. This article is licensed under a **Creative Commons Attribution-NonCommercial-No Derivative Works 3.0 License**. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/3.0/>