Ending it all in style

‘Means to an End: Apoptosis and Other Cell Death Mechanisms,’ by Douglas R. Green
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I recently took ‘Means to an End: Apoptosis and Other Cell Death Mechanisms’ by Douglas Green along on a summer vacation trip. Although it’s not quite a beach read, its entertaining style, easy flow of information and informative sidebars made it just as fun. This beautifully produced book, with its highly informative illustrations and carefully selected coverage of highlights in the cell death field, comes in at less than 200 pages of paperback text, but is deceptive in its apparent simplicity. In reality, the book provides a neat package of the background needed to read the cell death literature, offering a molecular and functional framework in which to understand the history of the field and to appreciate recent novel findings. Without getting bogged down in the details found in the hundreds of thousands of papers published on cell death, this book is an outstanding entrée into the field for trainees or more senior investigators who are unfamiliar with cell death pathways. Green also offers gems for the experts, including observations that many might not have known or may have forgotten. Green’s own well-informed opinions on some still-controversial areas also make this book a treat to read.

Green introduces his topics in an order that is the reverse of what others might have done: after a very brief introduction to the different forms of cell death, he begins by describing the molecular underpinnings of the death process and then, later in the book, places cell death in more physiological and pathological contexts. This is pleasing, as one can more easily appreciate contextual nuances having first gained an understanding of the molecules that drive the observed phenotypes.

Although the book focuses on multiple types of cell death, Green begins with apoptosis, which is probably the most well understood in molecular terms and is also the area of the field in which he has made a number of seminal contributions. The foundation for understanding apoptotic cell death is an appreciation of the mechanisms underlying the activation of caspases, which are the cell death proteases that cleave key cellular proteins to package the dying cell. In the first few chapters, the book nicely lays out the distinctions between initiator and executioner caspases, their mechanisms of action and their distinct but related substrate specificities. A table that summarizes a subset of known caspase substrates, their cleavage sites and consequences of cleavage is a handy reference. It also points out that caspase cleavage can destroy protein function or dismantle cellular structures, result in gain of protein function or new enzymatic activities, and in some cases even appears to do nothing. Green nicely puts the notion that an individual cleavage event might be inconsequential in perspective, saying ‘even if an event seems likely to be important, upon reflection, its importance may pale in the context of death. For example, the activation of an important transcription factor by an executioner caspase is unlikely to result in the production of a protein if at the same time the genome has been dismantled by DNA fragmentation’.

In the third chapter, Green clearly draws the distinction between executioner caspases, which exist in cells as inert but pre-formed dimers, and initiator caspases, which exist as monomeric proteins and are juxtaposed and thereby activated by adaptors to form activated dimers. Once active, the initiator caspases then cleave and activate the executioner caspases. The illustrations are especially helpful in this section, including diagrams of the key structural motifs that guide interactions between caspases, their adaptors and other caspase regulators [e.g. proteins containing death domains (DDs), caspase activation and recruitment domains (CARDs), pyrin domains (PYDs), and death effector domain (DEDs)]. The evolutionarily mysterious but indisputable importance of homotypic interactions between like domains of apoptotic signaling proteins is clearly explained using relevant examples. Green does not shy away from debunking commonly held misbeliefs or past errors in the field. For years, it was believed (incorrectly) that initiator caspases were activated by cleavage, rather than dimerization. Commenting on the use of caspase cleavage as an indicator of enzymatic activation, Green says, “as with many areas of science, the fact that a conclusion is published does not make it true”. This point alone makes this book of value to student readers.

Throughout the book, important findings are placed in evolutionary context, by comparing cell death pathways in nematodes, flies and vertebrates. For example, inhibitor of apoptosis proteins (IAPs) play a central role in regulating apoptosis in the fly, but they play more ancillary or situation-dependent roles in vertebrates. Furthermore, in introducing the intrinsic pathway of apoptosis [whereby cell-damaging stimuli (or other internal cellular cues) promote apoptosis by triggering mitochondrial outer membrane permeabilization (MOMP), release of mitochondrial cytochrome c and consequent caspase activation], Green draws the reader in with evolutionary conjecture, invoking an
analogies to Rudyard Kipling’s ‘Just So Stories’ that explain biological phenomena through whimsical fables. In doing so, he offers the plausible idea that the endosymbiotic bacteria that evolved into the mitochondria of modern-day cells were, at first, triggers for cell death, but later succeeded as endosymbionts by responding selectively to death cues, so as not to kill the ‘host’ cell indiscriminately.

There is no shortage of published findings with which to pack a book on cell death, but Green is selective in his choices, offering well-placed scientific clues to keep the reader engaged in learning the full story. The section on the governors of mitochondrial permeabilization – the Bcl-2 family proteins – could easily have degenerated into a confusing melee of three-letter acronyms. Instead, Green paints a satisfying picture by describing the ability of anti-apoptotic Bcl-2 family proteins to bind and neutralize the key pro-apoptotic family members, Bak and Bax, and by explaining that these players alone cannot be the whole story given that some anti-apoptotic family members (e.g. Mcl-1) can block Bax-mediated apoptosis despite having poor Bax-binding ability. This sets the stage for the introduction of what Green terms the ‘something’s missing’ – i.e. the BH3-only proteins, which can neutralize anti-apoptotic Bcl-2 family members and/or, in some cases, activate Bax and/or Bak. The different BH3 proteins are then placed in physiological contexts with, for example, evidence supporting a role for proteins such as Bim and Bad as sensors of various stressors, and Bim and Bmf in mediating death that occurs upon detachment of cells from the substratum in a process known as anoikis. The book also provides a hint of the broader literature on Bcl-2 family members, alluding to their ‘day jobs’ in controlling mitochondrial dynamics, as well as their participation in mitophagy (the autophagic removal of mitochondria). For the interested reader who wants to follow up on these areas, Green also provides a list of additional resources at the end of the text.

The sections on the core apoptotic machinery are rounded out by a description of extrinsic (or cell-surface-receptor-mediated) apoptosis, including mechanisms by which this class of receptors signal. This section builds on the earlier section in which DDs, DEDs etc. and the importance of homotypic interactions were introduced, in explaining how engagement of the CD95 receptor by its ligand leads to cell death. Again, Green uses structural illustrations and clear explanations to describe how the assembly of the death-inducing signaling complex (DISC) occurs upon ligand binding to CD95, promoting interaction of the DD in CD95 to the DD in an adaptor protein known as FADD. This produces a conformational change in FADD to expose its DED, leading to the binding of FADD’s DED to a similar domain on caspase-8 to induce caspase-8 dimerization and activation. I must admit that I had never considered that caspase-8, an initiator caspase, had a second DED until reading Green’s mention of the speculation that ‘the second DED in the initiator caspase helps to hold the first in check to prevent spontaneous interactions’.

Although the first half of the book focuses on apoptotic mechanisms, the book is true to its title, as Green then makes a foray into non-apoptotic death pathways. However, he first takes a brief detour into other platforms of caspase activation, including, for example, a description of recent studies detailing how caspase-1 is activated in signaling complexes known as inflammasomes. Although this work is not central to understanding cell death, similarities between how these signaling pathways are organized, and the fact that the same principles govern the underlying molecular interactions, makes this segue easy to understand and informative.

Green then turns his attention to the non-apoptotic pathways, surveying the growing number of emerging cell death paradigms. The literature on this is confusing, perhaps because authors so often attempt to explain their findings about cell death in black and white, when the biological reality is rarely so clear cut. In this regard, I appreciated Green’s comments on accidental versus intentional cell death, where he notes that such distinctions can be “too artificial to be useful.” He then walks through a few detailed molecular pathways, including programmed necrosis, and autophagic pathways that generally favor survival but can be responsible for cell death in certain contexts. He also mentions cell death pathways, such as mitotic catastrophe, that are still not well defined at the molecular level.

In moving on to discuss cell death in physiological and pathological contexts, I suspect that Green was faced with a dilemma, because topics such as cell death in development or cell death in cancer could fill entire volumes. He wisely sticks with the regulatory themes highlighted in the preceding sections, using specific contextual examples, rather than providing a catalog of scenarios in which programmed cell death of one type or another occurs. No book on cell death would be complete without a picture of webbed feet (or paws) and an accompanying explanation that failure of cells to die during separation of the digits during development results in the lingering web. Green nicely ties this back to earlier explanations on BH3-only proteins and their regulation of Bax and Bak.

In the section on cancer, Green introduces key signaling molecules that every student should be familiar with, such as Myc and p53, and neatly ties them into the cell death pathways described in earlier sections. The notion that these pathways might be exploited for therapeutic advantage is introduced, together with the idea that antagonists of anti-apoptotic Bcl-2 family members might more effectively kill cancer cells that are ‘primed’ to die, without affecting normal cells in which Bax and Bak are not activated to induce MOMP.

In telling these tales of cellular suicide and murder, Green leaves few stones unturned in the field of cell death research. He manages to introduce and define a wide range of topics concisely, yet without being superficial, so as to whet the appetite of the reader. Overall, it is an entertaining and educational read that promises plenty of exciting twists and turns for scientists at all levels.