ognize the deep connections between retrotransposon transcription and integration on the one hand and components of the transcriptional control, chromatin formatting, and signal transduction systems on the other hand in budding yeast (D. Voytas and J. Boeke; S. Sandmeyer et al.) and in *Drosophila* (M. Labrador and V. Corces). We need to learn more about how these connections form the molecular basis for the regulated timing and specificity of retrotransposition insertions in these organisms. A second new direction reflects our growing knowledge about the direct involvement of nucleic acid sequences and structure in guiding the non-random targeting of mobile DNA. Specific instances are the RNA-guided insertion of retrohoming introns (M. Belfort et al.), guidance of micronuclear DNA processing by injected macronuclear sequences in ciliated protozoa (M.-C. Yao et al.), and Tn7 hotspotting at the ends of triplex DNA targets (N. Craig). Just as we are rapidly learning about RNAi and other RNA-directed regulatory processes, we are certainly destined to discover further examples of sequence-directed DNA rearrangements.

Although *Mobile DNA II* has a wide coverage, there are some gaps. It is disappointing that some important topics were not included. There is no chapter on T-DNA transfer from *Agrobacterium* to plant genomes, and the only aspect of immune system rearrangements covered is V(D)J joining (M. Gellert). The absence of a chapter on immunoglobulin class switching (constant region rearrangements) is particularly unfortunate because that process is where we have the most direct evidence that regulated promoter activation guides the cellular choice of DNA rearrangement targets. Regrettably, none of the chapters provides a detailed account of how much McClintock's molecular followers have learned about the relationship between epigenetic modification of maize MGEs and the amazing variety of developmental controls she documented in the earliest days of mobile DNA. Many chapters do hint at how profoundly our knowledge of MGEs and natural genetic engineering activities has revolutionized our thinking about evolution (notably M. Kidwell and D. Lisch), but no chapter deals specifically with the mounting sequence evidence for DNA mobility systems at work during genome evolution.

Mobile DNA II is not for the faint of heart. At 50 chapters and 1158 pages of text, this is an imposing volume. The authors have written in the telegraphic style used in reviews directed at their colleagues, not in a didactic style aimed at a wider audience. So no one who does not have to review the book is likely to read it from cover to cover, even though the experience is highly educational. This caveat notwithstanding, I have to say that the chapters are of high quality, and the entire volume is an exceptional compendium of information about MGEs and molecular systems that rearrange phosphodiester linkages in cellular genomes. There are also two useful chapters on how to take advantage of MGEs for high-tech in vivo genetic manipulations (J. Boeke; R. Sauer). Undoubtedly, this book will serve as the major reference work on mobile DNA until ASM assembles the next group of editors about ten years from now to produce the third volume in this invaluable series. The editors are to be congratulated on the results of their labors.

To sum up, *Mobile DNA II* shows us the nuts and bolts of non-random natural genetic engineering processes. It will become increasingly evident in the years to come that these regulated cellular functions constitute the mechanistic backbone for genetic changes underlying the evolutionary patterns we are learning to discern in whole genome sequences. When *Mobile DNA III* comes out in the next decade of this century, we can look forward not only to learning more about the mechanics of mobile DNA but also about its regulation, its specificity, its biological utility, and even its own unique brand of molecular informatics. Mobile DNA is the key to a 21st Century view of evolution.

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Apoptosis: More than Meets the Eye

Apoptosis: The Molecular Biology of Programmed Cell Death
Edited by Michael D. Jacobson and Nicola McCarthy
Oxford: Oxford University Press (2002).
321 pp. $60.00

Apoptosis or programmed cell death is an essential building block for the normal development of any multicellular organism. Although Karl Vogt first described the occurrence of "physiological cell death" during vertebrate development in 1842, it took almost 150 years to identify the first molecular component of the apoptosis machinery. Ever since, a bewildering number of pro- and antiapoptotic molecules dedicated to implementing this cellular suicide process have been discovered. In *Apoptosis: The Molecular Biology of Programmed Cell Death*, Jacobson and McCarthy undertake the enormous challenge of presenting a comprehensive and up-to-date view of the fundamental molecular processes governing programmed cell death. This book gives an excellent introduction into the basic molecular interplay of the numerous components of the cell death machinery that are evolutionarily conserved from worms to humans. The multiauthor book reviews the last ten years of apoptosis research, which has seen significant advances in the identification of the machinery that executes apoptosis and the mechanisms that regulate this potentially catastrophic process.

Despite substantial progress and the identification of numerous key players of the innate cell death machinery, surprisingly little is known about the pathways that regulate developmental cell death. For instance, the answer to how, in the same tissue, one cell dies and its sibling survives remains largely open.

A general principle of animal development is the massive overproduction of many more cells than are required to build the mature organ. Cellular overproduction followed by an apoptotic cull during later stages of development ensures that the correct number of different cells types are matched to achieve proper organ function and provides developmental systems with the

astonishing ability to correct for developmental errors. Both the nervous system and the immune system arise through overproduction of excess cells followed by deleting those cells that fail to make functional synaptic connections or productive T cell antigen receptors. During the epigenetic self-organization of the brain, for instance, apoptosis matches the number of neurons to the number of target cells they innervate. Similarly, the immune system generates an enormous amount of immature thymocytes. But from the 20–40 million new T cells that are produced daily by the murine immune system, only about 2%–3% finally leave the thymus and enter the T cell pool (Chen et al., Thymus *5*, 179–185, 1983). Thus, in the thymus and in the nervous system, apoptosis serves as a quality control mechanism and morphogenetic tool to achieve proper organ size and function. Formation of the *Drosophila* head is another recent example where apoptosis is directly used as a morphogenetic tool. Thus, the *Drosophila* homeobox-containing transcription factor Deformed sculpts segment boundaries of the head by directly engaging the cell death machinery through promoting expression of the proapoptotic gene *reaper* (Lohmann et al., Cell *110*, 457–466, 2002). The ability to activate the suicide program in supernumerary or nonfunctional cells forms the basis for the high level of plasticity during animal development. Accordingly, no two brains are ever identical and even the number of neurons in the hippocampus of monozygotic human twins varies as much as 20%. Furthermore, misshaped embryos often develop into surprisingly normal adults despite severe developmental errors earlier on. In such embryos cell death compensates for tissue overgrowth and mispatterning, acting as part of a general repair mechanism safeguarding normal development. Failure to implement this repair mechanism through mutations dysregulating the cell death machinery dramatically impairs animal development and has been proposed to significantly contribute to the pathology of many human diseases. Aberrant cell survival may cause cancer, autoimmune disease, or sustained viral infection while excessive cell death is implicated in neurodegenerative disorders, stroke, and AIDS.

All cells appear to activate the same basic elements of the death-inducing program whether they are instructed to die as a consequence of developmental and immune-mediated signals ("extrinsic" or death by social control) or injuries ("intrinsic" or cell-autonomous death) inflicted by DNA damaging agents, oxidative stress, or viral infections. At the core of this suicide program lies a set of highly specific cysteine proteases called caspases. These proteins form the key destructive engines of the cell death machinery and their activation is an essential step in apoptotic signaling. Once activated, caspases cleave a wide range of structural and regulatory proteins, a process culminating in the disassembly of the cell. Given the irreversible nature of caspase-mediated proteolysis, caspase activation and activity is, not surprisingly, subject to complex regulation. The pathways that signal and control caspase activation are biochemically conserved throughout evolution. This was first demonstrated by experiments with human *bcl-2* in 1992, which showed that the cell death inhibitor Bcl-2 efficiently blocked developmental cell death in the worm and substituted, at least in part, for its *C. elegans* ortholog CED-9 (Vaux et al., Science *258*, 1955–1957, 1992). However, the first evidence for a genetic basis of apoptosis came from studies in *C. elegans* (Horvitz et al., Neurosci. Comment *1*, 56–65, 1982). The invariable, lineage-restricted form of development has made *C. elegans* particularly useful to study apoptosis. Genetic screens for mutations in the apoptotic program led to the identification of the core elements that regulate and execute apoptosis.

Accordingly, the book dedicates two chapters to the genetically amenable invertebrate model systems that have provided an important conceptual framework for elucidating the mechanisms and control of apoptosis in vertebrates. These chapters include aerial views of developmental patterns of cell death in the nematode *C. elegans* and the fruit fly *D. melanogaster*. The authors refreshingly link biology with the basic molecular components of the cell death machinery and review recent insights into how this machinery is regulated to create and destroy organs and to generate sex-specific differences. Xue et al. (for *C. elegans*) as well as Bergmann and Steller (for *Drosophila*) not only comprehensively summarize the field of invertebrate apoptosis, but also present potential models and resurrect long-forgotten conundrums.

A significant portion of the book is dedicated to the basic molecular events surrounding caspase activation. Thus, the key death regulators such as death receptors, Bcl-2s, caspase-activating adaptor molecules, IAPs, and caspases are discussed from various angles in numerous chapters. Cellular and molecular apoptotic focal points are broken down into separate chapters, working backwards from the terminal event of cell corpse removal to caspase-mediated substrate cleavage, mitochondrial membrane permeabilization, and extracellular stimulation of death receptors. Furthermore, the book provides an integrated and detailed overview of the molecular components of cell death and disease in the nervous system and a fascinating perspective on apoptosis from a viral point of view.

To date, eleven human, ten murine, four avian, four fish, eight amphibian, seven insect, and three nematode caspases have been identified that can be grouped into "initiator" and "effector" caspases. Caspase activation represents the ultimate target of most, if not all, apoptotic intent, whether socially or cell-autonomously initiated. The substrate specificities of caspases reinforces the idea of apoptosis as a refined and coordinated mode of action, rather than one of unrestricted carnage. Roy and Cardone cover caspase classification, structure, and substrate specificities as well as the functional significance of caspase-mediated proteolysis on cellular function. Unfortunately, details of the mechanisms of caspase activation and inhibition are only briefly covered, even though relevant sections are often present in greater detail in other chapters, but are not referred to. For example, the mechanistic roles of Inhibitor of Apoptosis proteins (IAPs) in caspase inhibition and their interplay with a growing number of IAP-antagonizing proteins, harboring an evolutionary conserved IAP binding motif, are covered with far greater detail, albeit from an invertebrate point of view, in the preceding chapter. However, as a general introduction it serves its purpose, describing the ultimate function of the core effectors of

apoptosis and preparing the reader for some of the chapters to come.

David Vaux reveals that the ongoing evolutionary arms race between the virus and the host's antiviral defense has created a number of ingenious strategies to either promote or counter viral proliferation and survival. Apoptosis of a virally infected host cell represents the most effective, but also drastic, mechanism to prevent viral replication and expansion. Nevertheless, through diverse modes of actions, virally encoded cell death inhibitor proteins are able to negate apoptosis. Their discovery, in addition to the virally encoded proliferative proteins, pointed to the viral need for complimentary, but functionally distinctive, cooperating oncogenes and the uncoupling of the growth-promoting from the apoptotic pathways. Through direct association, a number of viral proteins target the downstream apoptotic effectors, namely the caspases, either emulating cellular IAPs or acting as inhibitory, decoy substrates. Other viral proteins interfere with the signaling pathways upstream of caspase activation, blocking the release of mitochondrially sequestered proapoptotic factors such as cytochrome c and IAP-antagonists.

A diverse number of stress and survival signals act upon the mitochondria and thus this organelle denotes a site of apoptotic judgement, the outcome being determined through a struggle between pro- and antiapoptotic proteins—a battle that viruses have subverted through viral-mediated reinforcement of the antiapoptotic proteins. Two chapters focus on the importance of the mitochondria as a major integration site of apoptotic signaling. Tsujimoto extensively covers the central regulatory role of the Bcl-2 protein family members in controlling mitochondrial integrity, as well as their controversial direct role in pore formation. In the following chapter, Zamzami, Susin, and Kroemer describe the events downstream of the loss of mitochondrial integrity due to the subsequent release of a variety of proapoptotic factors—a situation they envisage as opening "Pandora's Box." Dominating the text are the caspase-associated apoptotic factors cytochrome c and mitochondrial caspases, as well as the caspase-independent apoptotic factor AIF. Unfortunately, it does not include the recently discovered group of IAP-antagonists, such as Smac/DIABLO and HtrA2/Omi.

Much like the struggle between pro- and antiapoptotic Bcl-2 molecules at the mitochondrial membrane, McCarthy and Bennett extensively describe another battle occurring at the plasma membrane. In response to ligand binding, pro- and antiapoptotic adaptor proteins are recruited to cytoplasmic tails of plasma membrane-associated death receptors, where they form complex multimers. Their relative composition can influence apoptotic and survival pathways, potentially simultaneously, but interactions both at and downstream from the receptor can determine the predominance of one outcome over the other. Again, viruses have evolved proteins that act on these complexes that are able to block apoptotic but allow survival signaling.

Due to the frantic pace of discoveries in apoptosis signaling, any coverage of the subject in form of a book requires the almost immediate need for updating. For instance, recent data suggests that Bcl-2 regulates a caspase activation program independent of mitochondrial permeabilization and the release of cytochrome c (Marsden et al., Nature *419*, 634–637, 2002). Stress-induced apoptosis resulting in caspase-2 activation also appears to occur prior to mitochondrial permeabilization (Lassus et al., Science *297*, 1352–1354, 2002). Nevertheless, the book functions well and will be useful to researchers both in and outside the field of apoptosis. It provides a reasonably contemporary biological and molecular overview of the field, as well as introducing some of the tools and models used to study apoptosis. However, there is a lack of a comprehensive crossspecies comparison between *C. elegans*, *Drosophila*, and mammals, which would have highlighted some of the conceptual differences that exist and frustrate the central apoptotic dogma. Regrettably, the majority of the chapters function in isolation of each other and fail to provide a coherent flow—a common problem of multiauthor works. Frequent overlaps and repetition further reinforces the segregation of one chapter from another. Nevertheless, with the same outlook the book does provide autonomous, stand-alone chapters, which independently function well, although such construction fails to harness the true potential and enhance the scope of the amassed apoptotic knowledge within.

The complexity of apoptotic regulation reinforces the need for a more inclusive, global vision of both the survival and apoptotic pathways, rather than examining them in isolation. As, in fact, they are both sides of the same coin. Ideally, a series of cellular snapshots are required to understand the complex interplay and interdependency of these signaling pathways. Such a universal approach could perhaps explain how such an enormous amount of diverse and sometimes conflicting information, generated from both internal and external events, is integrated into a qualitative answer of life or death. What tips the balance and determines the ultimate outcome, as cells are capable of proliferation or dying and are not held in a permanent state of indecision, remains to be resolved, and is really one of the major questions of apoptotic research. The answer almost certainly lies within the realm of integration of multiple signals from a diverse range of sensors—a truly awesome task in understanding.

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