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BOOK REVIEW

Apoptosis in the Light of Targeting Therapy, 2005

(Review on "Application of Apoptosis to Cancer Treatment" (M. Sluyser, ed.), Springer, Dordrecht, The Netherlands, 2005, 370 pp., $139)

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Apoptosis as well other routes of cell death has been one of the most rapidly growing fields in molecular biology and medicine over the last decade, taking into account the involvement of apoptosis in the pathogenesis of human illnesses including atherosclerosis, AIDS, neurodegenerative diseases, ischemic injury, and cancer. The great strides being made in biochemistry and molecular biology of apoptosis have proven that the core components of apoptotic suicide machine may represent exciting targets for therapeutic treatments. Moreover, numerous apoptosis-targeting agents are in clinical development today. It is therefore timely for the book under review to be published.

The monograph "Application of Apoptosis to Cancer Treatment" consists of 15 chapters by 37 contributors from around the globe. M. Sluyser, who incidentally is the Editor-in-Chief of international journals *Apoptosis* and *Anti-Cancer Drugs*, ties together information from different fields pertaining to apoptosis study to provide a fresh perspective of the subject as a whole.

The introductory chapter reviews apoptotic inducers (FasL, TRAIL, TNF-α, p53), effectors (caspases, APAF-1), inhibitors (cFLIP, Bcl-2-like proteins, IAPs), as well as cell-survival regulators (PI3 kinase, Akt, NF-κB). The emphasis here is given to defects of these signaling pathways detected in various malignant cells and cancer tissues. The chapter ends with a short section on apoptosis regulated by hypoxia and extracellular matrix as factors of tumor microenvironment.

The authors of the subsequent chapter present a well-written discussion of apoptosis as a Ca^{2+}-dependent process. In particular, they describe the key regulators of calcium ion homeostasis in prostate cancer cells and their probable significance for apoptosis-related Ca^{2+} signaling. The current facts and ideas concerning the misregulation in Ca^{2+}-dependent signaling pathways in the development of the resistance to apoptotic stimuli are also discussed.

The involvement of recognition signals (phosphatidylserine, CD47, PECAM-1, oxLDL-like sites), phagocytosis receptors (phosphatidylserine receptor, scavenger receptors, lipopolysaccharide receptor, $\alpha_V\beta_3$ and $\alpha_V\beta_5$ integrins), soluble bridging molecules (MGF-E8, Gas-6, protein S, collectins, thrombospondin), and chemotactic factors (lysophosphatidylcholine, S19 ribosomal protein, thrombospondin) in apoptotic cell removal as well as the importance of programmed cell clearance for the resolution of inflammation and the prevention of autoimmune responses are thoroughly covered in chapter 3. The interesting suggestion has been presented that enforced phagocytosis of cancer cells by the compelled expression of "eat-me" signals may serve as an efficient means of deleting these unwanted cells with therapeutic purpose. Although the further clinical investigations have yet to be executed, the so-called "buried alive" hypothesis is nevertheless intriguing.

The innovative concept of delivering human proapoptotic proteins into cancer cells is presented in chapter 4. In particular, novel recombinant fusion protein comprising functionally active serine protease granzyme B and tumor-specific antibody has been proposed for this purpose. Although the results of preclinical studies based on this approach are very promising, the clinical application of these agents remains a distant prospect.

The pair of chapters that follow focuses much attention on oncogenes promoting tumor cell survival (chapter 5) and cell cycle regulators (chapter 6), which may be regarded as suitable molecular targets for the rational design of novel anti-cancer therapeutics. The authors provide detailed insights into the promising approaches aimed at inhibiting Bcl-2, IAPs, Bcr-Abl, receptor tyrosine kinases, Ras, Akt, Hdm2, and NF-κB, as well as proteins essential for cell cycle regulation, chiefly CDKs and cyclins. Certainly, the simultaneous suppression of several related proteins mentioned above seems to be more advantageous. For that reason, the search for bi- or poly-specific inhibitors could be important for designing a future treatment for cancer. Similarly, a cocktail of several selective inhibitors may provide an alternative means of achieving this goal.

The activation of different cell-suicide signaling pathways by toxins fused to the targeting molecules is considered in chapter 7. Although the precise mecha-

nisms of sensitizing action of tumor-targeted toxins to anti-cancer agents are not well understood, these recombinant constructs are efficacious in potentiating the killing of tumor cells.

A beneficial effect of proteasome inhibitors for the treatment of refractory and relapsed multiple myeloma patients is the focus of chapter 8. The strategies to overcome or prevent resistance to proteasome inhibitors are of considerable interest.

The next two chapters (9 and 10) deal with the possible application of several natural products such as cephalostatins, bis-steroidal compounds from a marine worm, and human milk-derived protein–lipid complex HAMLET for induction of apoptosis in cancer cells. Cephalostatin-1 represents an interesting candidate from a pharmacological perspective possessing strong cytotoxic activity in tumor cell lines of diverse origin and several xenograft models. Of special note for chapter 10 is the activation of both caspase-dependent and caspase-independent mechanisms in HAMLET-treated tumor cells.

Chapter 11 discusses various aspects pertaining to the physiological role of TRAIL including regulation of immune tolerance and activation-induced cell death. Besides the selectivity of TRAIL, another clinically relevant advantage of this immunological apoptogen consists in promoting apoptosis in a manner that is independent of cellular p53 status.

Chapter 12 follows with application of histone deacetylase inhibitors (HDIs) in the therapy of TRAIL-non-responsive tumors. It is worth note that HDIs are able to selectively kill malignant cells while sparing healthy cells. Various mechanisms of anti-tumor activity of HDIs are described comprehensively with the emphasis on their role in the regulation of genes that sensitize cells to TRAIL-induced apoptosis.

Chapter 13 focuses on the different cellular responses to ionizing radiation, namely apoptosis, necrosis, mitotic catastrophe, and terminal growth arrest (i.e. senescence) and contains an excellent table of pheno- and genotypic characteristics of those forms of cell killing. The further search for specific biomarkers of radiocurability among death-related genes or gene products seems to be promising in optimizing and/or individualizing radiotherapeutic regimens. Another fruitful aspect of accumulated data on γ-irradiation is the possible clinical use of mediators of radiation-induced apoptosis. These substances are considered to be candidates for improving radiotherapy outcome.

The modern imaging technologies such as positron emission tomography, single photon emission tomography, magnetic resonance imaging, magnetic resonance spectroscopy, optical imaging, and ultrasound imaging are reviewed in chapter 14. The use of proton magnetic resonance spectroscopy for the detection of tumor cell apoptosis *in vivo* is treated more thoroughly since the author of the chapter is one of the pioneers in this approach. The detection of ^{1}H MRS-visible lipids is useful as a technique of noninvasive visualization of apoptotic cells *in vivo*.

In the final chapter, apoptosis inducers currently in clinical trials are considered. Among them are rTRAIL, anti-TRAIL-R1 mAb, antisense oligonucleotides G3139 and LY2181308, proteasome inhibitor PS-341, Hsp90 inhibitor 17-AGG, and replication-incompetent adenovirus Ad5CMV-p53. Unfortunately, some recent developments, for example small-molecule antagonists of Bcl-2-related proteins, caspase activators, and Hdm2 inhibitors are not included at all.

As to a slight critique, the book is very patchy. There is little general discussion on different cell death signaling in normal cells. The overt duplications of the same general subjects related to the concept of extrinsic or intrinsic cell death pathways seem rather unwarranted while such reiterations perhaps cannot be avoided in a multi-authored work. Unfortunately, the list of abbreviations has not been provided. Several criticisms must be addressed directly to the publisher (the misprints including the title of chapter 4 and imperfectly reproduced pictures). These flaws do not detract from the utility of the book, however.

To summarize, I believe this book to be a unique guide for readers who are interested in the present state of the development and application of novel apoptosis-triggered agents for therapeutic intervention. The admirable feature of this treatise is the presentation of unsolved problems stimulating the search for novel approaches in cancer therapy. So, I wish to congratulate the editor and contributors on a professional and well-done job.

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