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BOOK REVIEW

Apoptosis in the Light of Targeting Therapy, 2006

(Review on "Apoptosis and Cancer Therapy: from Cutting-Edge Science to Novel Therapeutic Concepts" (K.-M. Debatin and S. Fulda (eds.), Vols. 1/2, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2006, 1129 pp., $565)

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In 2005-2006, several monographs devoted to apoptosis-related topics appeared in different countries. Among this bouquet are such books as "Apoptosis in Health and Disease: Clinical and Therapeutic Aspects" (M. Holcik, E. LasCasse, A. MacKenzie, and R. Korneluk (eds.)), "Apoptotic Pathways as Targets for Novel Therapies in Cancer and Other Diseases" (M. Los and S. Gibson (eds.)), "Application of Apoptosis to Cancer Treatment" (M. Sluyser (ed.)), "Apoptosis and Cancer: Moving from Laboratory to Clinics" (A. Philchenkov and R. Stoika), "Apoptosis, Genomic Integrity and Cancer: An Introduction to Interacting Molecules" (J. van Lancker), and finally the currently reviewed book. While all the works in the list cover much of the same area, "Apoptosis and Cancer Therapy" occupies a unique place as the most comprehensive monograph on the biology of apoptosis and the approaches for developing the apoptosis-based therapeutics.

All 113 contributors to the book are leading experts in the corresponding fields. The substantive chapters are arranged in 14 parts comprising two volumes devoted to theoretical and applied aspects, respectively.

Part I gives a summary of receptor-mediated cell signaling initiated by death ligands such as TRAIL, FasL, and TNF or by absence of ligands for dependence receptors such as $p75^{NTR}$, DCC, UNCSH, RET, and integrins. One of the chapters provides valuable insight into apoptosis-related and nonapoptotic functions of the cellular FLICE-inhibitory protein, presenting several useful and comprehensive tables on the subject.

Part II is dedicated to the analysis of the intrinsic apoptotic pathway, with particular reference to the contribution of cytochrome *c*, Smac/DIABLO, HtrA2/Omi, ARTS, AIF, and endonuclease G to caspase-dependent and -independent cell death. The message from studies on apoptogens liberated from mitochondrial intermembrane space upon apoptosis is clear—these key effectors of cell death are exceptionally suitable for drug discovery.

Recent progress in studying cell death effector systems, including the various caspase-activating platforms, is the focus of Part III. Of special importance are the new data on involvement of deregulated caspase activity and aberrant Apaf-1 expression in oncogenesis or resistance to chemotherapy.

In Part IV, the interplay between pro- and anti-death members of the Bcl-2 family controlling cell death/survival is considered. For those readers who are interested in the development of novel approaches to inhibit prosurvival Bcl-2 family proteins, it should be mentioned that these regulators could also act in a proapoptotic manner in certain contexts.

The inhibitors of apoptosis proteins (IAPs) are in focus of the next Part V. By comparison with Bcl-2-related proteins, IAPs are more universal apoptotic regulators since they directly bind to and inhibit both the initiator and effector caspases. Survivin as one of IAPs members may serve as a prime target for therapeutic purposes because of its predominant expression in tumors and dual functionality (regulation of cell division and cell survival).

The chapters of Part VI concentrate almost exclusively on inactivation of components of cell death machinery by cell survival signaling with an emphasis on recently discovered facts, which give the evidence of the utmost complexity of the hierarchy in apoptosis suppression. Certainly, inhibitors of the various components of anti-death cell machinery, especially protein kinases, might prove useful for cancer therapy (see below).

Part VII concerns the involvement of several protooncogenes and tumor suppressor genes in regulation of cell cycle progression and apoptosis. The crucial roles of p53, Rb, and p73 isoforms lacking N-terminal transactivation domain in malignant transformation and tumor growth are thoroughly discussed.

In the section on calcium ion as apoptotic messenger (Part VIII), the mechanisms of Ca^{2+}-mediated endoplasmic reticulum stress response and permeabilization of the outer mitochondrial membrane are treated. Of particular relevance is the discussion on potential targets for Ca^{2+} signaling in apoptosis. Special attention is paid to the role of calcium ion in the phagocytosis of dead and dying cells.

Part IX summarizes recent advances in understanding the mechanisms of lysosomal cell death pathway with an emphasis on the role of the cathepsins. In addition to their involvement in caspase-independent cell death, these lysosomal proteases may participate in cancer cell invasion and angiogenesis upon being released into extracellular milieu. These data may lead to novel therapeutic strategies implying lysosome-targeting compounds.

Two final chapters of Volume 1 (Part X) represent deep analysis of the terminal stages of apoptosis resulting in cell clearance. It is becoming increasingly clear that the formation of so-called phagocytic synapse between the dying cell and phagocyte or neighboring cell is required for silent cleanup of the apoptotic corpse. The hypothesis on apoptosis as a primary oncogenic event is intriguing.

The second volume contains four parts covering a broad spectrum of applied topics. There are the chapters on model systems, molecular diagnosis, cellular stress, DNA damage and repair, molecular targets, and therapeutic problems.

The use of animal models in cancer research is the focus of Part XI. In particular, genetically engineered mice as an alternative to classic models and a powerful tool to dissect the various aspects of cancer biology are discussed. It is important to note that several findings on the roles of specific genes in origin and development of tumors or treatment sensitivity obtained from *in vivo* experimental models have been confirmed in humans.

Imaging modalities and probes used for real-time assessment of specific molecules related to tumor growth, invasion, and metastasis are shown in Part XII. The authors analyze the advantages and disadvantages of bioluminescence, fluorescence, magnetic resonance, or nuclear imaging for the study of cancer. Innovative techniques for noninvasive visualization and quantification of apoptosis *in vivo* are briefly described. There is an excellent review of the microarray technology designed for cancer diagnosis and prognosis. The discussion includes a variety of microarray formats, such as PCR fragment, oligonucleotide, and antibody microarrays. The microarray-assisted identification of molecular signatures of metastasizing or chemoresistant tumors may represent effective and beneficial strategy.

One chapter of the following section (XIII) serves to present current knowledge on the activation of BH3-only proteins and stress-activated kinases in response to diverse stress stimuli. The subject of death-provoking cellular stress continues in a chapter entitled "Hypoxia in cancer". The remainder of the part is devoted to the analysis of the major mechanisms of DNA damage-triggered apoptosis and DNA repair. The reader may find recent data on the noncanonical pathways of DNA repair mediated by topoisomerase I or polymerase η.

The closing part of the book (XIV), which is the longest section (258 pages), starts with the reviewing chapter written by the editors of the book. They provide a concise but comprehensive coverage of modern strategies for the development and application of novel apoptosis-triggered agents in cancer therapy. Then the useful chapter on caspase- and IAPs-based therapeutics follows. While the promising small-molecule caspase activators are still in the preclinical assay phase, XIAP or survivin antisense oligonucleotides has recently entered the early clinical trials.

The authors of the following chapter consider in detail a number of Hdm2/p53-based small molecules, such as sulfonamide, HLI98 compounds, nutlins, RITA, sanvigamycin, CDB3, CP-31398, WR1065, PRIMA1, and ellipticines that can be used to reactivate the p53-dependent apoptosis pathway. It would be of interest to learn whether some of these compounds become attractive candidates for combination cancer therapy. The next chapter deals with the rationale of IAPs as anticancer targets and the structural basis for designing small molecules targeting BIR domains within several IAP family members. The drug-oriented reader who is interested in the present state of the development of peptidic or nonpeptidic antagonists directed toward BIR domains can find many useful ideas from the practical point of view for designing new agents.

Another chapter dwells on such problems as involvement of Hsp90, the key member of the chaperone family, in cell death/survival machineries with particular focus on recently discovered Hsp90 inhibitors. The PI3K/Akt/mTOR pathway is among the key signaling cascades involved in the survival of tumor cells and their resistance to anticancer therapies. Therefore, many of these signaling components are the potential targets for treating a wide array of human malignancies. In particular, the powerful pharmacological inhibitors of PI3K, Akt, PDK-1, and mTOR have been developed and some of them (perifosine, CCI-779, RAD001) are currently undergoing the clinical evaluation. In the chapter on those agents, the interested clinician may be acquainted with the valuable recommendations for designing appropriate trials in cancer clinics.

One of the following chapters is devoted to the identification of molecular mechanisms of ceramide-mediated apoptosis, including the formation of so-called ceramide-enriched membrane platforms. It is a pity, however, that some hopeful proapoptotic compounds that may increase the intracellular levels of ceramide have escaped the authors' attention. Another chapter deals with the development of histone deacetylase (HDAC) inhibitors capable of inducing apoptosis or autophagy in tumor cells. The author suggests that these compounds look very promising as molecularly targeted drugs. Some hydroxamates, cyclic peptides, aliphatic acids, and benzamides representing several structural classes of HDAC inhibitors are under clinical trials now. Of interest, several HDAC inhibitors may have potential to block angiogenesis. Also briefly treated are hopeful treatment strate-

gies to trigger apoptosis selectively in malignant glioma cells by targeting p53, IAPs, Bcl-2 family proteins, modulators of growth factor-dependent signal transduction, and death ligands.

Several alternative radiation-induced cell demise—apoptosis, micronucleation, mitotic catastrophe, and necrosis—are then described. Much emphasis is placed on the direct inducers of apoptosis and modulators of the apoptotic threshold that proved to be of high potential value for reinforcement of the radiation response. Five excellent tables summarizing the recent preclinical and clinical investigations on antitumor efficiency of combined treatment with TRAIL, synthetic phospholipid analogs, antibody-based therapeutics like cetuximab, inhibitors of different kinases like gefitinib, or nonsteroid anti-inflammatory drugs (NSAIDs), and ionizing radiation may be highly advantageous from a therapeutic standpoint. The discussion of γ-irradiation toxicity for normal tissues is extremely useful. The most significant contribution here is the idea that "negative modulation of the apoptotic signal transduction may also be an additional useful strategy in order to increase the therapeutic gain".

The closing chapter of Volume 2 is "Tumor angiogenesis". Here, the reader is introduced to such topics as the genesis of blood and lymphatic vessels, the regulatory mechanisms of hemangiogenesis (in physiological conditions and cancer) and tumor lymphangiogenesis. The authors briefly discuss the basic anti-angiogenic strategies to combat tumor growth and metastasis that have been elaborated over several recent years. It is a pity that the apoptosis-related aspects claimed in the title of the book are not covered here.

All chapters in this book are well edited, and I did notice only a very small number of factual errors or misprints. For example, the opinions of the authors such as "Common treatments for cancer include UV, radiation, and chemotherapy" (p. 299) or "... this pathway can be modulated by Hsp70 and Hsp27 by inhibitory interactions with DAXX and ASK-1, respectively" (p. 767) are incorrect. Figure 29.3 is mentioned in the text instead of Fig. 29.2 (p. 766) and Fig. 30.2 in place of Fig. 30.3 (p. 779). Such errors are not terribly serious.

The book is profusely illustrated with line diagrams and half-tone and color plates. The numerous tables are consistently pointed and readable. Many up-to-date references that greatly increase usefulness of the book are included. Especially valuable is a 23-page index.

Several remarks are worthwhile noting for re-editions of the book. The data on the prognostic/predictive value of apoptosis markers, which are scattered throughout the book, are worth more detailed analysis. The abbreviation list is highly desirable as well as the list of biotech companies and research groups developing and assaying apoptotic drugs. Finally, owing to its high price, the book in its present edition is not available to the majority of potential and really interested readers.

To sum up, this is one of the best books of its kind available. I am sure that no experimental pathologist, biochemist, cell biologist, pharmacologist, or radiologist working in the field of cancer research and cancer therapy can afford to be without this superb two-volume set.

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