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BOOK REVIEW

Programmed Cell Death in Cancer Progression and Therapy, in Advances in Experimental Medicine and Biology, Vol. 615

(R. Khosravi-Far and E. White, eds., Springer, 2008, 356 p, 119.95 Euro)

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Programmed cell death (PCD) is an intriguing term that was introduced by Richard Lockshin nearly 45 years ago. As we know now, several alternative genetic programs of cell death exist and their basic mechanisms are largely different although partially interconnecting. Generally speaking, this book is about PCD with intense focus on apoptosis and the exploitation of PCD for treating cancer.

The volume commences with a short but important chapter coauthored by R. Lockshin. The ideas and developments in our knowledge of different PCD forms are presented here in historical perspective. Separate chapters provide comprehensive reviews of extrinsic (death receptor) and intrinsic (mitochondrial) death pathways with the emphasis on proteases from the caspase family as the key effectors of apoptosis. It is a pity that the alternative intrinsic pathway triggered by endoplasmic reticulum stress is not discussed in the book. The major apoptotic alterations contributing to neoplastic transformation and progression of cancer are highlighted. Special attention is given to the multiple mechanisms of radiation and drug resistance, including the activation of prosurvival pathways, the loss of p53 function, and the defects in apoptosis signaling. A number of approaches for overcoming drug resistance are also analyzed.

Great progress in the understanding of how the apoptotic signaling pathways are dysregulated in cancer progression and resistance to therapy is advantageous for developing the new strategies for cancer treatment. Three main types of proapoptotic therapeutics are summarized in the volume. These are the compounds directly targeting the apoptotic machinery; agents that affect components of other regulatory systems; and sensitizers of conventional chemo- and radiotherapy. Among the compounds of the first group are recombinant TRAIL (APO2L/TRAIL-PRO1762), agonistic antibodies against TRAILR1 or TRAILR2 (HGS-ETR1, -ETR2, -TR2J), antisense oligonucleotides against Bcl-2 (oblimersen sodium), survivin (ISIS 2181308) or X-linked inhibitor of apoptosis protein (AG35156), non-peptidic small-molecule inhibitors of antiapoptotic Bcl-2 proteins (GX15-070, AT101). The second group includes agents that suppress selectively cell survival signaling. The examples of the most promising of them are monoclonal antibodies against growth factor receptors (IMC-C225, rhuMAb 2C4), small-molecule inhibitors of such kinases as Raf (BAY43-9006), MEK (CI-1040, PD 0325901), PI3K (PX-866), Akt (API-59-OME), and mTOR (CCI-779, RAD001, AP23573), as well as NF-κB inhibitors (BAY-7085, PS-341). Most of the compounds listed, with the exception of BAY-7085 and API-59-OME, are currently entering clinical trials for treating solid and hematological malignancies. Of note, the antagonists that might target the group of related proteins may be highly advantageous from a therapeutic perspective.

An entire chapter deals with autophagy as one of the caspase-independent cell-suicide programs. The authors describe mTOR, DAP-kinase, beclin 1, smARF, and p53 as the key regulators of the autophagosome machinery. Although basic mechanisms of autophagy are well established, its role in tumorogenesis is currently the subject of some controversy. In particular, it is still under discussion whether inhibitors or inducers of autophagy should be used for combating cancer. The detection of new markers allowing one to accurately assess the autophagic cell death *in vivo* will be helpful to clarify this problem. Anyway, autophagy as well as other forms of non-apoptotic cell death may represent attractive targets for novel anti-cancer agents.

Then the recent advances in research on the role of NF-κB in apoptosis, autophagy, and necrosis are nicely reviewed. The reader will find here the latest data on the involvement of NF-κB in inflammation-associated tumor promotion, progression, and metastasis. Interestingly, the persistent activation of NF-κB in the tumor microenvironment is prominent in promoting tumor cell growth. In addition, the compounds targeting NF-κB signaling are briefly discussed.

A pair of chapters on therapeutic potential of proteasome inhibitors and histone deacetylase inhibitors proves their true utility for induction of apoptosis. Here it is important to emphasize that both types of inhibitors are

more cytotoxic to malignant cells than normal ones. The authors also describe in detail how to combine the proteasome or histone deacetylase inhibitors with chemotherapeutic drugs, irradiation, and biologically-based modalities to improve the outcome of cancer treatment.

One chapter is devoted to the current status of microRNAs (small noncoding hairpin RNAs) research. Although the findings suggesting the involvement of microRNAs in apoptosis and carcinogenesis are presently few, the subject in general is thoroughly discussed. The book closes with a chapter on cancer stem cells representing the minor but crucial population sustaining the tumors. Such cells have been identified not only for leukemias but also for such solid tumors as breast, prostate, brain, ovary, colon, and pancreatic cancers, melanoma and, possibly, retinoblastoma. The novel therapeutic strategies aimed at eliminating the malignant stem cells are of utmost interest. Unfortunately, no information on the drugs affecting them specifically has been presented, although the potential application of parthenolide and TDZD-8 as apoptosis inducers for leukemic stem cells is now under intensive study.

All chapters are well edited and thoroughly referenced. The nicety of the book is the use of numerous color figures.

In my opinion, both scientists and clinicians, experienced or beginning, will profit from a thoughtful reading of *Programmed Cell Death in Cancer Progression and Therapy*.

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