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Book Review

Apoptosis, cancer therapy, and beyond

Alex Philchenkov

RE Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology, 45 Vasilkovskaya Street, Kyiv 03022, Ukraine
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Application of Apoptosis to Cancer Treatment. By M Sluyser (Ed.). Springer, Dordrecht, Netherlands: 2005. 378 pp. ISBN: 1-4020-3303-6. $139, hardcover

Apoptosis as a primary cause or a secondary effect in various diseases seems to represent a very attractive 'target' for the development of new therapeutics. The book under review is not only a collection of surveys on apoptosis-targeted therapies but also a coherent account of the 'achievements of research made in … a completely novel way of cancer therapy… using drugs that directly switch on the cell death machinery in tumors'.

The book starts with a review of the core components in cell-death and survival pathways by Yang. The next chapter is devoted to the analysis of molecules and channels that modulate Ca^{2+} entry into cells (especially prostate cancer cells), and their role in apoptosis-related Ca^{2+} signaling as well as in development of apoptotic resistance. Fadeel then summarizes the mechanisms of programmed cell clearance mediated by recognition (or so-called 'eat me') signals, phagocytosis receptors, soluble bridging molecules, and chemotactic factors. Of particular interest is a provocative 'buried alive' hypothesis, proposing that 'enforced phagocytosis in the absence of a death signal may serve as an efficient means of deleting cancer cells without the associated bystander effects observed during conventional treatment'.

Liu, Cheung, and Rosenblum put forward the innovative concept of delivering human proapoptotic proteins into tumor cells. They designed a novel recombinant fusion protein Grb/scFvMEL comprising a single-chain antibody that targets gp240-bearing tumor (melanoma, lobular breast carcinoma) cells. This granzyme B-containing construct has *in vitro* and *in vivo* cytotoxic activity against human tumor cells primarily through direct activation of the apoptotic machine and may sensitize tumor cells to conventional chemotherapeutics.

The next chapters provide valuable insights into oncogenes promoting tumor cell survival (Phillips) and cell cycle regulators (Mazumder, Plesca, and Almasan) as suitable molecular targets. Much of the attention is focused on the therapeutic promise of 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 (however, it should be cautioned that according to the newest findings Akt itself can block cancer cell migration and invasion). Undoubtedly, the use of bi- or polyspecific inhibitors could be more advantageous for cancer treatment.

Recent advances in targeting tumor cells, using toxins attached to the recombinant proteins, are briefly presented by Thornburn. Intriguingly, the author shows that combination of targeted toxin with another anticancer agent may shift the patterns of tumor cell death. Chauhan and Andersen examine the feasibility of targeting the cell-death pathways in multiple myeloma focusing on proteasome inhibition as a novel approach to treating refractory and relapsed multiple myeloma. Mechanisms mediating drug resistance and strategies to overcome or prevent drug resistance are treated in detail.

A pair of chapters on the tumoricidal activity of natural products (marine bis-steroidal compounds, cephalostatins by Dirsch and Vollmar, and human milk-derived protein-lipid complex HAMLET by Duringer and associates) prove their true utility for tumor-specific induction of apoptosis. The convincing evidence is given that caspase-dependent apoptosis of Jurkat cells mediated by selective induction of Smac/DIABLO release is triggered by cephalostatin-1. Although cephalostatin-1 displays strong cytotoxic activity in both the NCI-60 panel and several xenograft models, it is still too early to extrapolate these findings to clinical benefit.

The subsequent chapter analyzes the attempts to use TNF-related apoptosis-inducing ligand (TRAIL) as an approach to cancer immunotherapy. Griffith and co-authors discuss the various aspects pertaining to the physiological role of TRAIL/TRAIL receptor pathway as well as antitumor activity of TRAIL. The most interesting is the section devoted to the mechanisms regulating sensitivity or resistance of tumor cells to TRAIL. The chapter by Neuzil, Andera, and Gabrielli sheds light on the application of histone deacetylase inhibitors (HDIs) in the therapy of TRAIL-nonresponsive tumors. As most oncologists are not well aware of the ability of HDIs and TRAIL to synergize, this chapter may stimulate studying the sensitization of cancer cells by HDIs to other biologic or pharmacologic agents.

Faulhaber and Bristow nicely review recent advances in research on tumor cell loss following radiotherapy. Interestingly, the cells of most epithelial tumors respond to radiotherapy by mitotic catastrophe or permanent growth arrest, whereas apoptosis induction is preferential for more sensitive tumors (e.g., germ cell tumors or lymphomas). The compounds targeting apoptotic, cell cycle, and DNA repair machines may be profitably used as radiosensitizers.

The Hakumaki's survey on noninvasive real-time measurement of apoptosis *in vivo* is appropriate, as accurate visualization and quantification of apoptotic cells may be

promising for clinical applications including precise evaluation of response to therapeutic intervention. The advantages and drawbacks of modern imaging technologies are presented. The information on ^{1}H MRS-detectable lipids will be extremely useful to medical practitioners interested in the recent developments in noninvasive visualization of apoptosis in the clinics.

Hu and Kavanagh produce a condensed analysis of the current status and prospects for the clinical use of apoptosis inducers including agents that have already entered the clinical trials (e.g. rTRAIL, anti-TRAIL-R1 mAb, G3139, PS-341, INGN201, etc.). The data presented suggest that most novel apoptosis-triggering compounds are active not only as single agents but also in combination with widely used chemo- and radiotherapeutic modalities. Personally, I was disappointed, however, that some fairly recent developments, such as small-molecule antagonists of Bcl-2-related proteins, Smac mimetics, caspase activators, and Mdm2 inhibitors, are not mentioned.

I do not wish to criticize the editor's selection of subjects, but only to comment that the book is very patchy. Several chapters are relatively short and lack illustrations. Many of the figures are sloppily executed and the style of the bibliography through the book is inconsistent. However, these are minor flaws compared to the merits of the book. I also think that at least several specialists representing the pharmaceutical or biotech companies should have been recruited as the contributors to such a book.

In sum, I am confident that *Application of Apoptosis to Cancer Treatment* is an important source of information for anyone interested in the design and discovery of novel apoptosis-triggered agents, full of stimulating ideas, which may be advantageous for improving the outcome of cancer treatment for years to come.