Preface: Focus on Cell Death

For many centuries, the problems of the two extreme ends of life, birth and death, have been the most exciting and intriguing for humankind. Since the discovery of apoptosis in 1972 by Kerr, Wyllie, and Currie, it has become clear that individual cells can die not only because they are accidentally injured but also because of specific molecular mechanisms. Cell death research is a rapidly evolving field, and more than a dozen nonapoptotic cell death subroutines have been identified so far. Significant efforts have focused on understanding the role of different forms of cell death in health and disease. Most important, cell death research is in the forefront of oncology. Defects in cell death signaling contributing to tumor formation, progression, and resistance to anticancer therapies are well established. This issue attempts to summarize recent developments in the cell death field and how they apply to current and potential therapeutic approaches for cancer treatment.

The issue begins with “Anoikis and EMT: Lethal ‘Liaisons’ during Cancer Progression” by Cao and colleagues, which focuses on current knowledge of the main players involved in anoikis regulation in both normal and malignant epithelial cells. It also considers the potential roles of epithelial-mesenchymal transition (EMT) and actin cytoskeleton remodeling in the acquisition of a migratory and invasive phenotype of malignant cells, and places special emphasis on anoikis resistance in prostate cancer. Of substantial interest is the recent discovery of the functional coupling between phenotypic EMT-MET (mesenchymal-epithelial transition) cycling and anoikis signaling. In addition, the review discusses prospects for the clinical use of anoikis-inducing agents such as quinazoline derivatives, Src inhibitors, Trks inhibitors, c-Met/VEGFR-2 inhibitors, and the antidiabetic agent metformin. Especially useful in this discussion is information on DZ-50, a novel derivative of the quinazoline-based α1-adrenoreceptor antagonist doxazosin.

The second article, “The Role of the Apoptotic Machinery in Ionizing Radiation-Induced Carcinogenesis,” contains important information on the carcinogenic effects of ionizing radiation. Balcer-Kubiczek clearly draws the biological effects of radiation, focusing on DNA damage after irradiation. She then looks at microsatellite and chromosomal instability as initiating lesions of radiation-induced cancers. In my opinion, the choice of papillary thyroid cancer (PTC) in radiation-exposed children and young adults is quite appropriate. Of high importance is the conclusion that only gene rearrangements generating cancer-driving fusion oncogenes are selectively increased in PTC patients with a reported history of radiation exposure. The author also integrates radiation-induced events into the cell death pathways. Considering that this year is the 30th anniversary of the Chernobyl disaster and the 5th anniversary of the Fukushima nuclear accident, it is high time for review on radiation carcinogenesis.

The third article, “The IAP protein family, SMAC Mimetics, and Cancer Treatment,” provides detailed insights into the biology of IAP proteins representing the family of versatile regulators of diverse cellular processes, including prosurvival activity. IAPs are unique in the context of cell death regulation. While they are capable of suppressing both apoptosis and caspase-independent necroptosis, IAPs facilitate activation of NF-κB-mediated prosurvival programs. The emphasis here is given to alterations in IAP proteins detected in a variety of solid tumors and hematologic malignancies. In particular, correlation between expression of individual IAPs and patient outcome or tumor characteristics is taken into account. In the final section, novel anticancer agents aimed at antagonizing IAP proteins are briefly considered. Among them are SMAC mimetics (bircinapant, LCL161, DEBIO1143, etc.), antisense oligonucleotides (AEG35156, LY2181308), and natural compounds along with their derivatives. Evaluation of several IAP antagonists in early clinical trials has provided evidence of their therapeutic benefit.

The next review, “Resistance to Cell Death and its Modulation in Cancer Stem Cells,” is dedicated to
the analysis of molecular mechanisms that regulate the survival, proliferation, and resistance of cancer stem cells (CSCs) to various apoptotic stimuli. Safa introduces key signaling molecules that play critical roles in the formation and maintenance of the minor but crucial population of CSCs. He then describes the molecular pathways that contribute to reduced CSC susceptibility to anticancer treatment. In particular, multidrug resistance transporters, the PI3K/Akt/mTOR signaling pathway, and antiapoptotic proteins are in focus here. Safa also discusses the possible involvement of microRNAs in apoptosis resistance. The agents and approaches that force CSCs to apoptosis are of utmost interest. The development and application of novel agents for eradication of CSCs are analyzed in detail.

The authors of the subsequent article, “Engaging Cell Death Pathways for the Treatment of Rhabdomyosarcoma,” present a comprehensive discussion of multiple aberrations in the apoptotic machinery of rhabdomyosarcoma (RMS) cells. Those defects are believed to play a key role in the pathogenesis of RMS and to contribute to drug resistance. Current facts and ideas concerning the use of IAP antagonists, death-inducing ligands, pannexin channel upregulation and activation, and immunotherapies to circumvent such unresponsiveness and improve patient outcomes are scrupulously reviewed. Moreover, Dobson and coauthors argue that synergistic therapies targeting complementary apoptotic pathways effectively enhance RMS response to widely used chemo- and radiotherapeutic modalities.

Noonan, Zarrer, and Murphy, in “Targeting Autophagy in Glioblastoma,” briefly discuss the function and regulation of autophagy (also known as autophagic cell death). They review the key modulators of autophagy as well as the dual role of autophagy in tumor initiation and progression. Perturbations in autophagy found in glioblastoma have inspired significant interest in autophagy-based therapies. Novel therapeutics that selectively target autophagy are critically analyzed with particular reference to autophagy induction in glioblastoma as a more practical approach. Preclinical or clinical studies presented have demonstrated that the manipulation of autophagy may sensitize glioblastoma cells to standard therapy. Especially useful at this point is information on four molecular subtypes of glioblastoma, which should guide treatment choices.

In the next article, “Cell Death Induction in Cancer Therapy—Past, Present, and Future”, Nonnenmacher and her colleagues nicely lay out distinctions between the reductionist view and Darwinian principles of tumor biology as well as those between the cancer ecosystem and naturally occurring macrobiological ecosystems. They also discuss future strategies in cancer treatment implementing Darwinian principles and ecological considerations. The authors conclude noting that, although “with the advent of the new millennium we have seen a shift in strategy (from maximum tolerated dose to metronomic therapy), as well as an expansion of targets (from mutated cancer cells to the interactions of these cells with their microenvironment or the genetically more stable tumor-associated cells), the induction of apoptosis remains the most promising therapeutic approach.” There is much room for optimism considering such a view of future anticancer therapy.

In the last article, “Strategies to Strike Survival Networks in Cancer,” Pennati and coauthors focus much of their attention on prosurvival pathways that contribute to neoplastic growth and progression. Since signaling mediated by receptor tyrosine kinases (RTKs) is frequently deregulated in cancers, pharmacological inhibition of cell proliferation and survival mediated by RTKs is a powerful tool for anticancer treatment. The authors describe therapeutics (small molecules and humanized antibodies) that selectively target ligand/RTK axes. The mechanisms mediating acquired resistance to RTK inhibitors and the strategies to overcome or prevent this resistance, including combination regimens, are treated in detail. Intriguing are new approaches in combined cancer therapy using compounds that inhibit epigenetic processes, the ubiquitin-proteasome system, or the unfolded protein response, as well as reactivate apoptosis in tumors. The prospects for targeting G-quadruplex structures to strike survival networks in human
malignancies are also discussed.

As mentioned previously, the main idea of this special issue is to highlight recent advances in the study of different forms of cell death—namely, anoikis, autophagy, regulated necrosis, and, of course, apoptosis—in oncogenesis and resistance to anticancer treatment. Undoubtedly, state-of-the-art knowledge in this domain will contribute significantly to our success in combating cancer. The interested reader will find here much useful information.

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