Apoptosis, Senescence, and Cancer
Cancer Drug Discovery and Development

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The goals of chemotherapy (and radiotherapy) are to eliminate tumor cell targets by promoting cell death. In recent years, a major focus has been placed on programmed cell death or apoptosis as the primary mechanism of cell killing. However, tumor cells may respond to various forms of treatment in diverse ways, only some of which culminate in cell death and loss of clonogenic survival. In addition to apoptosis, cell death may occur through mitotic catastrophe, autophagy (a subtype of apoptosis), or anoikis. Alternatively, cells may undergo either transient or prolonged growth arrest; in addition, senescence arrest or accelerated senescence is now recognized as a response to various treatments, which may also play a role in preventing cell transformation. Consequently, “permanent” growth arrest, possibly mediated through senescence, could contribute to loss of self-renewal capacity, particularly in solid tumors. The question of why some tumor cells within a population ultimately recover proliferative capacity (whether in cell culture, in xenograft models as a component of tumor growth delay, or in patients in relation to disease recurrence) remains an unresolved question in the fields of experimental chemotherapy and radiotherapy and a critical problem in the clinical treatment of malignancies. The possibility that surviving and recovering cells represent a resistant stem cell population has recently gained credence, although evidence in support of this hypothesis is far from conclusive.

The purpose of this book is to contribute to an understanding of the growth arrest and cell death pathways mediating the response to chemotherapy in tumor cells. The book is divided into six sections. The first reviews the major cell death pathways. The second develops the themes of telomeres, telomerase, and senescence in genetic stability and tumorigenesis. The third provides an in-depth dissection of the critical DNA damage and response signaling pathways. The fourth deals with the fundamental limitations on therapy conferred by drug resistance, as well as current approaches to circumvent or attenuate drug resistance. The fifth and sixth sections provide an analysis of our understanding of the responses to both conventional strategies and newly developed therapies against cancer.

It is our hope that this book will provide basic scientists and clinicians with a deeper and more thorough understanding of the cellular responses of malignant cells to common therapeutic modalities, which may determine the effectiveness of treatment, both in the initial phase of the disease and the latter stages, including recurrence and metastatic disease.

David A. Gewirtz
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The title of this book might suggest that one mode of cell death (apoptosis) and one mode of growth arrest (senescence) represent the critical elements of tumor cell responses to various forms of cancer therapy. However, a quick glance through the section and chapter headings will readily convey the range of possible responses to both conventional therapies, such as standard cytotoxic drugs and radiation, to more recent therapies, such as monoclonal antibodies and targeting of specific receptor and signaling pathways, to developing modalities, such as photodynamic therapy and approaches targeting the vascular system. With regard to senescence, in addition to the relatively recent realization that senescence is likely to mediate the growth arrest response to many therapeutic treatments and could potentially act as a rational drug response, a considerable section of this book has been devoted to the role of senescence in genomic instability and tumor development. In addition, the reader will find that the theme of genomic instability runs through other sections, such as the consideration of mitotic catastrophe, as well as regulatory functions of ataxia telangiectasia mutated (ATM)/ATM-related (ATR) and DNA-dependent protein kinase. Likewise, the relationship between c-myc and cyclin-dependent kinase inhibitors is considered in terms of tumor progression, as well as their relevance for cancer therapy and the promotion of apoptosis.

**CELL DEATH PATHWAYS**

For almost two decades, the cell death response to chemotherapy and radiation has focused almost exclusively on apoptosis. In view of the importance of apoptotic cell death, two introductory chapters in this section provide a detailed and learned overview of both the intrinsic and the extrinsic pathways of apoptosis. However, there is extensive evidence that apoptosis is not the only mode of cell death or possibly the primary mode of cell death in solid tumors. It is therefore of particular importance to review the approaches utilized to conclude that a particular mode of cell death is relevant to drug or radiation treatment.

It has been well established for many years that at least one other mode of cell death, that of mitotic catastrophe, is quite common, particularly in tumors that have been exposed to ionizing radiation. However, the basis for the cell “choosing” or preferring a particular mode of cell death is not understood, even at the most fundamental level. Relatively recently, at least one additional mode of cell death has been recognized, known as autophagy. Autophagy is a complex response because, unlike apoptosis or mitotic catastrophe, autophagy can function as a cytoprotective mechanism when initiated under certain modes of cell stress, such as nutrient deprivation. Finally, an area that is appropriately receiving renewed attention is a subspecies of apoptosis that is termed “anoikis,” or cell death subsequent to loss of adhesion to substratum. The ability of tumor cells to resist anoikis may provide the necessary survival advantage that permits a tumor cell to metastasize.
SENESCENCE GROWTH ARREST

Within the same time frame that autophagy has been recognized as a mode of cell death, stress-induced senescence (also known as premature or accelerated senescence) has been recognized as a unique mode of growth arrest. The uniqueness and signaling elements of this pathway has resisted facile dissection as the genetic elements that appear to be involved overlap quite closely with those involved in the G1 arrest pathway, specifically induction of p53 (although it is clear that p53-independent senescence also exists), p21^{wafl/cipl}, dephosphorylation of pRb- or Rb-related proteins such as p130 and p107, and suppression of E2F-mediated transcription. Analysis of the molecular elements involved in stress-induced senescence has also been hampered by reliance on a limited number of senescence markers, specifically senescence-associated $\beta$-galactosidase staining, cell morphology (flattening, enlargement, and granulation), and telomere dysfunction, which is in dramatic contrast to the multiple signaling and regulatory elements events that have been identified for death-related pathways. Of particular interest, the specific therapeutic targeting of telomeres to induce senescence may provide an under-explored, if not novel, targeted approach for cancer therapy.

DRUGS, MECHANISMS, AND RESISTANCE

Although a great deal of information has been published on the mechanism of action of different classes of antitumor drugs, the chapters in this book attempt to focus, in part, on the importance of different modes of cell death. We have attempted to cover major classical chemotherapeutic agents including the antimetabolites, platinum-based compounds and alkylating agents, topoisomerase I and topoisomerase II inhibitors, and microtubule poisons. In addition to these classical and conventional therapies, relatively new approaches such as antibody therapy, tyrosine kinase, and epithelial growth factor receptor (EGFR) inhibitors are described in detail in this book. Many “cutting edge” therapies are at various stages of development, including antiangiogenic agents and photodynamic therapy. Finally, the possibility of TRAIL as a therapeutic target has been considered, in particular because of its potential to be a highly selective target that is limited to tumor cells.

It is likely that any reader of this book will already be familiar with the difficulties encountered in cancer therapy, many of which are associated with various forms of resistance, including intrinsic mechanisms or those that develop in response to the treatment challenge. To address this issue, specific signaling pathways are considered both in the context of conferring resistance and for converting these pathways into potential targets for drug development and sensitization to existing therapies.

DNA DAMAGE RESPONSE

Although not all cancer therapies involve DNA damage, many of the traditional and conventional treatments do promote cellular stress, either directly through damage to DNA or indirectly through interference with the function of alternative targets. It was therefore considered to be of particular relevance to address specific components of the DNA damage response and signaling pathways, focusing on ATM/ATR, H2AX/53BP1, and DNA PK.
UNANSWERED QUESTIONS

What we still do not understand, despite our best efforts, is precisely how tumor cells “decide” on the nature of their response to these treatment modalities, especially related to recovery and/or resistance. It is generally thought that less severe “lesions” result in a transient growth arrest, and once such lesions are repaired (or the cell determines that the lesion is not “life-threatening”), growth will resume. Although without solid experimental evidence, it is possible to speculate that disease recurrence at the site of the primary tumor could be related to recovery after transient growth arrest; that is, one can consider this transient growth arrest to be analogous to tumor cell dormancy. A closely related question, one which we have not attempted to address in this book, is the nature of the signaling response that is required for proliferative recovery in “dormant” tumors. Finally, the basis for the therapeutic selectivity of many if not most of current conventional or more novel treatment modalities is still far from being fully elucidated.

The editors express their deep appreciation to all the contributors to this text, scientists, researchers, and clinicians who somehow managed to take the time and effort to provide the benefits of their expertise in specific fields of research to contribute chapters to this book. We also credit the editors at Humana Press for their endless patience with the process of developing this book.

We would like to dedicate this book to all those who have suffered and continue to suffer from the ravages of cancer in the hope that the information gathered in this text might provide some small element of guidance in the efforts of our scientific colleagues to defeat this disease.

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