Preface

Diagnosis of cancer can be devastating and often creates fear in the heart of the patient. Part of this fear may stem from the known toxic and debilitating effects of current cancer treatments. Chemotherapy drugs have been a mainstay of anticancer treatments for several decades. In certain forms of cancer, chemotherapy drugs are highly effective, whereas in other malignancies, only modest or partially effective chemotherapy regimens have been identified. Unfortunately, treatment with chemotherapy, as well as radiation, is inevitably associated with adverse effects on normal cells, leading to undesirable toxicities and side effects for the patient. Even molecular targeting agents, which hold the promise of more precise targeting of tumor cells, are limited by nonspecific activities and adverse toxicities. The limitations of chemotherapy, radiation, and molecular targeting agents are exacerbated by the inherent resistance of many cancer cells to these agents and by the development of acquired resistance. These resistance mechanisms directly contribute to reduced anticancer efficacy and increased side effects in patients. Thus, a key goal in cancer research is the development of new agents and strategies that can be used to overcome either inherent or acquired resistance to standard of care therapies.

Efforts to rationally devise approaches for overcoming resistance to chemotherapy, radiation, and molecular targeting agents will benefit from a thorough understanding of the mechanisms responsible for resistance. In recent years, a great deal has been learned about the proteins, pathways, and processes that contribute to resistance to anticancer agents. This book will highlight current knowledge of the cell-survival pathways that are integral to drug resistance in cancer. Particular emphasis is placed on preclinical and clinical studies that have examined the impact of targeting these pathways as a means of overcoming either inherent or acquired resistance. The book begins by describing cell-survival pathways mediated by growth factor receptors and how these pathways promote drug resistance. Signaling emanating from members of the epidermal growth factor receptor and fibroblast growth factor receptor families, as well as hepatocyte growth factor receptor and AXL and MERTK will be discussed. The impact of targeting these cell-surface receptors in preclinical models and in clinical trials using recently described inhibitors will be described. The role of intracellular signaling molecules, including JNKs, PI3K, STAT3, and the Hippo pathway, and the benefit of targeting these molecules and pathways to promote sensitization to chemotherapy are then discussed. Lastly, recent breakthroughs in our understanding of the cellular processes of DNA repair, genome methylation, autophagy, and necroptosis are reviewed. Aberrant alteration or activation of these processes can play important roles in the development of drug resistance. Successes in restoring tumor sensitivity to chemotherapy in preclinical models and cancer patients using epigenetic modulators or therapies targeting DNA repair, autophagy, or necroptosis are summarized in these final chapters.

Targeting Cell Survival Pathways to Enhance Response to Chemotherapy will be of particular interest to cancer biologists, biochemists, and molecular biologists interested in the mechanisms and pathways that regulate the sensitivity and resistance of cancer cells and tumors to standard of care therapies. Translational researchers and physician scientists will benefit from the emphasis placed in each chapter on findings from clinical trials and analysis of primary patient specimens. Pharmaceutical industry and academic scientists focused on anticancer drug discovery will gain deeper understanding of current opportunities, as well as challenges, in the development of new molecular targeting agents aimed at combating chemotherapy resistance.

This book summarizes work from a broad array of dedicated scientists. I am thankful for their excellence. I also wish to gratefully acknowledge those whose work was not presented, or whose research area did not fit within the specific focus of this book. Special thanks go to my scientific mentors, Mark A. Bothwell and Lewis T. Williams, for guiding me in my early scientific studies and introducing me to cell-survival signaling. I am particularly grateful for the encouragement and inspiration of fellow scientists and friends Jennifer Grandis, Bob Redner, and Richard Steinman. Finally, I wish to express much appreciation to my wife Sylvia and my children, Rachel, Josiah, and Matthew, for the care and delight they bring to myself and to others.

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