Resistance to Targeted Anti-Cancer Therapeutics

Volume 6

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For several decades, treatment of cancer consisted of chemotherapeutic drugs, radiation, and hormonal therapies. Those were not tumor-specific and exhibited severe toxicities in many cases. But during the last several years, targeted cancer therapies have been developed. Targeted cancer therapies are drugs or other agents (e.g. antibodies) that block the growth and spread of cancer by interfering with specific gene products that regulate tumor cell growth and progression. Targeted cancer therapies are also sometimes called "molecularly targeted drugs." We have witnessed in the last decade a significant explosion in the development of targeted cancer therapies developed against various specific cancers. These include drugs/antibodies that interfere with cell growth signaling or tumor blood vessel development, promote the cell death of cancer cells, stimulate the immune system to destroy specific cancer cells and to deliver toxic drugs to cancer cells. One of the major problems that arises following treatment with both conventional therapies and targeted cancer therapies is the development of resistance, preexisting in a subset of cancer cells or cancer stem cells and/or induced by the treatments. Tumor cell resistance to therapies remains a major problem and several strategies are being considered to reverse the resistance to various manipulations.

Resistance to Targeted Anti-Cancer Therapeutics will focus on the basic and translational research behind the molecular mechanisms of resistance found in many kinds of anti-cancer therapeutics.

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Resistance to Immunotoxins in Cancer Therapy

Springer

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Preface

Cancer includes a large class of diseases of abnormal cell growth and is the most life-threatening disease mankind has ever seen; it accounted for an astonishing 14.6% of all human deaths globally, according to the world cancer report in 2014. In the United States, 18,860 projected new cases and 10,460 deaths were reported in 2014 for acute myeloid leukemia—the most common form of leukemia. Although most of the global research is focused on developing therapeutics for cancers and cancer-related diseases, the successful treatment of cancer has been limited—due primarily to the emergence of resistance that leads to recurrence of a more aggressive form of the disease. As a result, there is an urgent need to reconsider current strategies of treatment and investigate the mechanisms of resistance.

This volume focuses on mechanisms of resistance and strategies to improve targeted therapy using immunotoxins and related therapies. The development of recombinant immunotoxins, using toxins as killing moieties conjugated with antibodies or ligands against cancer cell surface proteins, met the criteria of improving specificity and the cytotoxicity. Immunotoxin therapy, due to its specificity, is one of the major strategies used in targeted therapy that has shown promise in clinical trials. The toxins used are usually derived from bacterial or plant toxins, which are highly immunogenic. To reduce immunogenicity, genetically engineered versions were made by either silencing immunogenic epitopes or developing humanized versions of immunotoxins. However, the emergence of resistance and failure of the immunotoxins in many clinical trials have raised concerns about their utility, although immunotoxin is still the most promising approach used so far. The targeted therapeutic approach has been an attractive alternative in contrast to conventional treatment modalities. The development of monoclonal antibodies to specific surface targets on cancer cells led to the exponential growth of targeted therapy for better efficacy; this is evident from the fact that several monoclonal antibody-based therapies have been approved by the FDA. (These antibodies were later modified into single chain and recombinant versions.) Further, to minimize immunogenicity, humanized monoclonal antibodies were developed and, to improve activity, antibodies were conjugated with drugs or protein toxins. However, the problems of immunogenicity, specificity, and toxicity have yet to be completely eliminated.

Chapter 1 describes the history, construction, and types of immunotoxins developed to date. Chapter 2 presents a comprehensive view of resistance to cancers, different mechanisms involved in immunotoxin resistance, the role of cancer stem cells in resistance, and underlying mechanisms; it also presents future perspectives about strategies that could be used to target resistant cancer stem cells. Chapter 3 describes the factors associated with sensitivity and potential resistance of cancer cells to pseudomonas exotoxin-derived immunotoxins. Chapter 4 provides an overview of signaling pathways involved in resistance. Chapter 5 focuses on the treatment of hematologic neoplasms using antibody-drug conjugates, and immunotoxins. Chapter 6 discusses the challenges involved in pseudomonas exotoxin-based immunotoxins. Chapter 7 deals with resistance to the antibody-drug conjugate gentuzumab ozogamicin, while Chapter 8 discusses overcoming resistance to apoptosis using engineered human Granzyme B and Angiogenin. Chapter 9 presents immune responses in cancer and their therapeutic impact.

Resistance to Immunotoxins in Cancer Therapy, which includes reports about and reviews of cancer resistance, molecular and cellular mechanisms involved in resistance to targeted therapy, and methods to overcome resistance, is a comprehensive guide to the complete understanding of resistance to immunotoxins.

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About the Editor

Rama Shanker Verma is Professor, Indian Institute of Technology, Department of Biotechnology, Chennai, India. He is also Visiting Professor, Pondicherry University, Department of Biochemistry and Molecular Biology, and Visiting Professor, University of Madras. His awards and fellowships include a UNESCO fellowship and the Genomic Pioneer Recognition Award from HUGO. Professor Verma was recently elected Fellow, AMI, and is Fellow, Indian Academy of Science, India.

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