PREFACE

Metastasis is the main cause of cancer-related deaths. In simple terms, metastasis is the spread and colonization of neoplastic cells from the place where they originate to another body part. The spread, or dissemination, of metastatic cells can be hematogenous, lymphogenous, or simple seeding into body cavities. The process of metastasis is orchestrated by a complex network of biological events, and our understanding of the processes that regulate metastasis has significantly improved. Consequently, the clinical management of metastatic cancer has also improved. The 13 chapters of this book provide an in-depth analysis of our understanding of the molecular mechanisms, and clinical management of metastatic cancer.

In *Chapter 1,* Schroeder and Hall from the Department of Radiology and Imaging Sciences, Emory University, Atlanta, GA, USA, discuss the advantages of molecular imaging of brain metastases with positron emission tomography. Brain metastases are becoming a more frequent occurrence in the clinical setting. The chapter focuses on the usefulness of positron emission tomography to detect brain metastases while imaging for other sites of metastatic disease, discriminate treatment related changes from tumor recurrence, and identify patients for targeted radiotherapy from theranostic molecular imaging and targeted radiotherapy agents. In *Chapter 2,* Lumbreras and colleagues from the Miguel Hernandez University Alicante, Spain, describe the use of imaging tests for the diagnosis and management of lung nodules. With the implementation of screening programs and the increasing sensitivity of imaging tests, pulmonary nodules are more frequently detected. The authors discuss the role of imaging for surveillance, management of pulmonary nodules for the early diagnosis of lung cancer, and treatment decisions.

In *Chapter 3,* Mangiameli et al. from the IRCCS Humanitas Research Hospital, Milan, Italy, discuss the state of art of thoracic surgery for surgical management of lung cancer. Various techniques such as open lobectomy, lymphadenectomy, video-assisted thoracoscopic surgery, and robotic-assisted thoracoscopic surgery are covered. A description of the traditional and innovative approaches along with an overview of the innovation and future perspective in thoracic surgery are presented. In *Chapter 4,* the same group complete the picture by focusing on the surgical principles, indications, and innovations in the management of pulmonary metastasis. The principles of pulmonary metastasectomy, a comparison between thoracotomy and mini-invasive surgery, different surgical indications, and oncological outcomes are presented. In *Chapter 5,* Hoivik from the University of Bergen, Norway, provides an elegant description of the genomic landscapes and tumor evolution in metastatic gynecological cancers. Recent tumor evolutionary studies have provided a phylogenetic interpretation of gynecological cancer metastasis. This chapter provides an overview of the characterization of cancer genomes, from primary tumors to metastatic lesions of the major gynecological cancers, and how such data are interpreted in an evolutionary context.

In *Chapter 6,* Aviles et al. from the MD Anderson Cancer Center at Cooper, Camden, New Jersey, USA, focus on metastatic ovarian cancer. Epigenetic changes

to gene expression in neoplastic cells are crucial factors that may contribute to the high rates of chemoresistance and metastasis. The role of aberrant epigenetic changes in metastasis and chemoresistance of ovarian cancer, and the reversal of these aberrant epigenetic changes as potential therapeutic targets are discussed. In *Chapter 7,* Wiggins et al. from Burlington, Massachusetts, USA, provide an overview of MetastamiRs, i.e., miRNAs that are implicated in metastasis, specifically in the metastatic genomic arena of prostate cancer. The chapter focuses on the biological processes and molecular targets through which miRNAs act and that may serve as therapeutic targets. In *Chapter 8,* Vazquez and Arnaud from the Institute du Cancer Avignon-Provence, France, highlight the hematological toxicity induced by radiation therapy targeting metastases of the skeletal system. Radiotherapy is frequently used in patients with bone metastasis. However, radiotherapy for bone metastasis cause clinically significant hematological toxicity both by depleting the blood cells and by damaging the proliferating bone marrow. The chapter provides an overview of radiotoxicity.

In *Chapter 9,* Yin et al. from the Ohio State University Comprehensive Cancer Center, Columbus, USA, describe the role of DNA damage response in cancer metastasis. The DNA damage response system is critical to maintain genomic integrity and guard against DNA damages. There is increasing evidence of an important role of DDR in regulating multiple facets of cancer metastasis. The chapter summarizes the current knowledge of the role of DNA damage response in cancer metastasis, its clinical implications, and therapeutic opportunities. In *Chapter 10,* Hida and colleagues from Hokkaido University Graduate School of Dental Medicine, Sapporo, Japan, discuss the roles of tumor endothelial cells in cancer metastasis. Tumor angiogenesis is essential for tumor progression. Without tumor angiogenesis, most solid tumors remain dormant. Apart from supplying tumors with nutrients and oxygen, tumor blood vessels provide a route for metastasis. Endothelial cells are key players in the formation of neovessels. This chapter highlights the role of endothelial cells in the initial steps of tumor metastasis.

In *Chapter 11,* Moreno-Celis et al. from Facultad de Ciencias Naturales, Universidad Autónoma de Querétaro, México, discuss the concept of apoptosis-induced compensatory proliferation in cancer. Apoptosis is a biological process that allows adequate cellular turnover and the elimination of damaged or infected cells. Emerging evidence show that there are compensatory molecular mechanisms that promote cell proliferation after increased apoptotic events. The chapter provides a snapshot of apoptosis-induced compensatory proliferation, and its importance in cancer development, progression, and therapy resistance. In *Chapter 12,* Dogan and colleagues from the Ege University Faculty of Medicine, Department of Medical Biology, Izmir/Turkey, analyze the potential of targeting apoptosis to overcome chemotherapy resistance. Chemotherapy resistance is a major limiting factor for the extensive use of chemotherapeutic drugs in cancer treatment. Dysregulation of apoptosis-regulatory mediators, particularly high levels of anti-apoptotic proteins, is one of the main mechanisms by which tumor cells acquire resistance to chemo- and radiotherapy. This chapter summarizes mechanisms of chemotherapy resistance, discuss the role of extrinsic and intrinsic apoptotic pathways in chemoresistance, and review the current experimental strategies to overcome chemotherapy resistance targeting the apoptotic pathways.

In *Chapter 13,* Zetouni and Sergi from the University of Alberta and Ottawa, Canada, highlight the features of metastatic Ewing sarcoma or primitive neuroectodermal tumor. A better understanding of the molecular basis of the development of Ewing sarcoma is needed to help improve survival, especially in metastatic/resistance cases. Light an electron microscopic features, oncogenetic origins, cell signaling, patterns of metastatic spread, and therapeutic challenges of metastatic Ewing sarcoma are discussed.

I thank the authors for their dedication and professionalism in contributing to this book. We have a lot to learn about metastasis, and I believe this book will encourage readers to delve deeper into this field and take up the critical challenge of working toward effective treatments for metastatic cancers.

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