Preface

Wilms' tumor (WT), also called nephroblastoma, is a rare kidney cancer that is usually diagnosed in children under the age of 6. WT arises from nephrogenic rests, which are undifferentiated embryonic tissues retained after birth. At molecular level, in a proportion of patients, WT has been shown to be the result of aberrations in *WT1* gene, located on chromosome 11p13. In addition to being a risk factor for WT, germ line *WT1* aberrations can cause renal and extrarenal developmental abnormalities and predispose to other malignancies. In the past two decades, there has been a considerable improvement in our understanding of WT and *WT1*. This book brings together recently uncovered basic and clinical aspects of the burgeoning WT and *WT1* research under three sections: epidemiology and clinical aspects, biology, and *WT1* gene aberrations in other malignancies.

Section I provides a comprehensive guide to the epidemiology, diagnosis, management, and treatment of WT. Chapter 1 describes the morphology and differential diagnosis of WT. It presents a clear view of the common histological components of WT. While stage and histological subtypes are well-known prognostic factors for WT, age at diagnosis is also an independent risk factor for recurrence. Chapter 2 elegantly summarizes the clinical relevance of age at presentation in WT management. Chapter 3 provides a comprehensive review of the histopathology, genetics, and molecular biology of WT. Also, this chapter discusses how these changes influence the prognosis and differential diagnosis. The clinical features and surgical management of WT is discussed in chapter 4. Especially, this chapter emphasizes the necessity of a multidisciplinary approach for the effective surgical management of WT.

Bilateral WT represents 4–7% of all WT, typically presenting at a younger age than unilateral WT. The major challenge in the treatment of bilateral WT is the preservation of renal function. Chapter 5 gives an overview of the current status of management of bilateral WT. Extrarenal WT is a rare entity, which usually occurs in the retroperitoneum or inguinal region. Chapter 6 presents a comprehensive review of the challenges in diagnosis, histopathology, staging, treatment, and prognosis of extrarenal WT. In chapter 7, the authors share their experience on the use of preoperative transcatheter arterial chemoembolization combined with systemic chemotherapy for the management of unilateral advanced WT. Treatment of advanced cancers that have metastasized to distant parts, irrespective of the cancer type, continues to be a challenge. Dendritic cell-based immunotherapy has been presented as a viable treatment option in many cancers. In chapter 8, the authors present autologous dendritic cell vaccines for the treatment of WT

as a possible future option. Chapter 9 addresses the problem of chronic kidney disease and renal function in WT survivors.

Section II covers the biological aspects of WT and *WT1* under three headings. WT displays morphological and molecular characteristics that resemble early stages of kidney development. Therefore, a study of molecular pathways relevant to normal kidney development may provide insights into the events that drive WT. Based on this rationale, chapter 10 gives an overview of the link between Wnt signaling, microRNA biogenesis, and β-catenin in regulating kidney differentiation. Chapter 11 focuses on the transcriptional regulation of the human thromboxane A2 receptor gene by WT1. The prostanoid thromboxane A2 is implicated in neoplastic diseases. In humans, TXA2 signals through the T-prostanoid (TP)α and TPβ isoforms of the TP receptor, two structurally related receptors transcriptionally regulated by distinct promoters, Prm1 and Prm3, respectively, within the TP gene (*TBXA2R*). A particular focus is placed on the role of WT1 in the regulation of TPα expression through Prm1 in megakaryoblastic and endothelial cells of vascular origin and in prostate and breast carcinoma cells. Chapter 12 gives a comprehensive review of the inflammatory microenvironment of human WT with a comprehensive picture of various immune cells and inflammatory markers.

Section III focuses on the role of *WT1* in cardiac development, prostate cancer, glioblastoma, and minimal residual disease. *WT1* has been identified as a crucial player in cardiac development. Absence of *WT1* leads to major cardiac malformations, including incomplete formation of coronary vasculature, resulting in embryonic lethality. Chapter 13 describes the diverse and unique roles of *WT1* during heart development and disease. *WT1* is expressed in prostate cancer (PC) epithelial cells and regulates PC critical genes. *WT1* promotes metastatic disease by enhancing motility of PC cells with low-migratory and metastatic potential. While the mechanisms are multifactorial, chapter 14 focuses on how *WT1* interacts with vascular endothelial growth factor (*VEGF*) and androgen receptor to promote prostate cancer progression and metastasis. While WT1 is widely considered as a tumor suppressor, it can also act as an oncogene in some cancers. For example, WT1 is overexpressed in most glioblastoma. Chapter 15 describes the functional role of WT1 in glioblastoma and how it regulates proliferation and apoptosis of glioblastoma cells. Finally, chapter 16 focuses on the role of *WT1* in minimal residual disease in acute myeloid leukemia (AML). *WT1* is overexpressed at mRNA level in 80–90% of AML cases, and there are reports of poor outcome for patients having *WT1* levels above reference thresholds at specific time points. This chapter gives a comprehensive review of the role of WT1 in AML, molecular markers to stratify high-risk AML patients, and interventional therapy based on *WT1* expression.

The intended audience of this book is students, basic scientists, and clinicians who are interested in the basic and/or clinical aspects of WT and *WT1*. It is our wish that this book would serve as an authoritative source for readers who want a comprehensive understanding of the development, progression, management, and treatment of WT.

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