

Preface

Our effort to edit this book is aimed to present readers who sincerely endeavor to examine the role of the PI3K-AKT-mTOR signaling pathway in the context of the emerging challenges of oncology, including energy metabolism, genomic instability, signaling-driven combination therapies, drug response, and drug resistance. Through our effort, we seek to engage translational researchers, clinicians, and clinical researchers who aspire to develop therapies for the management of cancer patients. The book is a reference textbook intended for readers who are actively perusing basic, translational and clinical studies in the course of their graduate classes and fellowship trainings as well as researchers from academia, hospitals, and pharmaceutical industries.

We were fortunate to have Prof. Lewis C. Cantley, who had kindly agreed to author the opening chapter of the book. It is any editor's dream to have an introductory chapter of a book entitled "*PI3K-mTOR in Cancer and Cancer Therapy*" to be written by none other than Prof. Lewis C. Cantley. We feel privileged and grateful to Prof. Lewis C. Cantley. The topic of "*PI3K-mTOR in Cancer and Cancer Therapy*" is too diverse and extensive to be covered in one book with less than ten chapters. We decided to present the book in two parts, Part I entitled "PI3K-mTOR Pathway in Cancers" containing four Chapters (2–5) and Part II entitled "PI3K-mTOR Pathway in Cancer Medicine" containing four Chapters (6–9). The first part comprises of four basic and translational topics emerging in the field of PI3K-mTOR signals, including cancer cell metabolism, DNA damage repair, drug response prediction and prognostic signatures and resistance to anti PI3K-mTOR pathway related drugs.

Keeping in mind the central role of the PI3K-mTOR pathway in sensing tumor cells' nutrient and energy need and rewiring it with the growth signals, the Chap. 2 of the first part of the book is written by Prof. Estela Jacinto and his colleagues. The review focuses on the role of mTOR complex 1 and mTOR complex 2 in different metabolic and biosynthetic processes with special emphasis on the role of mTORCs in the reprogramming of cancer metabolism. The chapter also discusses the role of mTOR in the metabolic processes of tumor cells and how oncogenic mutations can

trigger metabolic reprogramming. The chapter encourages readers to study the clinical relevance of targeting mTOR and metabolic pathways for cancer therapy. In reading this chapter, a reader will get the basic knowledge to understand how mTORCs reprogram metabolic and biosynthetic pathways under specific oncogenic mutations and how mTORCs signal will influence the sensitivity to chemotherapeutic agents especially towards the development of resistance to mTOR/PI3K inhibition due to induction of alternative pathways. As wisely pointed out by Prof. Estela Jacinto that *“identifying synthetic lethal interactions and drug resistance mechanisms inherent to metabolic or growth signaling pathways upon mTOR inhibition will be important to develop more effective cancer therapy”*.

The PI3K-AKT-mTOR pathway interacts with the DNA damage repair pathway in solid tumors. In Chap. 3 of the first part of the book, we have tried to review how the PI3K-AKT-mTOR pathway cooperates with the DNA damage repair pathway toward oncogenesis of Triple Negative Breast Cancers in the light of the translational relevance of a combination of PARP inhibitors with PI3K-AKT-mTOR inhibitors. Delving into this chapter, a reader will learn that alteration(s) of the PI3K-AKT-mTOR pathway in breast cancers and its subtypes are contextual and DNA damage response is one of such important contexts in Triple Negative Breast Cancers. We intended to focus on the recent development in the field of a combination of PARP inhibitor(s) and PI3K-AKT-mTOR pathway inhibitor(s) in the light of drug-sensitivity and development of resistance.

Chapter 4 of the first part of the book is written by Prof. Mariaelena Pierobon and his colleagues on *“The AKT-mTOR signaling pathway for drug response prediction and prognostic signatures”*. This chapter provides *“an overview of the role of the PI3K-AKT-mTOR signaling network as a predictive and prognostic biomarker across different tumors along with a panel of high throughput and multiplex technologies used to broadly investigate functional changes”*.

Chapter 5 of the first part of the book is written by Prof. Sarat Chandarlapaty and his colleagues on *“Resistance to PI3K pathway inhibition”*. The chapter describes the basic circuitry of the PI3K-AKT-mTOR pathway and its mechanism of reaction to inhibitors in bringing the *“drug-induced relief-of-feedback results in pathway reactivation”* and *“drug-induced adaptive/compensatory activation of parallel signaling pathways in the network”*. Built on this, the chapter then elegantly introduces the concept of development of resistance to the PI3K-AKT-mTOR pathway inhibitors and discusses the *“coordinated activation of RAS/RAF signaling in resistance,” “feedback regulation of nuclear hormone signaling,” “Wnt- β -catenin cooperation with PI3K signaling,” “Myc amplification,” and “JAK2/STAT5 inhibition.”* We are convinced that in reading this chapter, a reader will comprehend *“mechanisms of resistance common to cellular signaling pathways”*.

In the second part of the book, we have compiled four chapters describing the state-of-art of the PI3K-mTOR pathway based cancer therapies in selected solid and liquid tumors. Keeping in mind that the PI3K-mTOR pathway is one of the most genetically altered pathways in cancers and a vast intellectual wealth that is vested on exploiting this pathway towards the development of therapies to manage cancers, Chap. 6 is written by Prof. Funda Meric-Bernstam and Prof. Gordon Mills. In this

chapter authors have eloquently described the signaling basis of “*combination therapies targeting the PI3K/AKT/mTOR pathways*” including “chemotherapy,” “hormonal agents,” “immunotherapy,” “biological therapy,” “proximal/distal inhibition,” “parallel signaling,” “biomarkers,” and “pharmacodynamic markers of response.”

Inhibitors targeting the pathway are entering clinical trials at a rapid pace. Recently isoform specific (p110 delta) inhibitor has been approved by FDA in hematological malignancies. Chapter 7, the second chapter of the second part of the book is written by Dr. Chan and her colleague on “*phospho-inositol-3-kinase activity and dysregulation in pediatric leukemia and lymphoma*” highlighting the studies that have defined the role of PI3K regulatory and catalytic subunits in childhood hematologic malignancies, and addressing how these findings are now being translated into murine preclinical and human clinical trials.

In Chap. 8, the third chapter of the second part of the book we have reviewed the “*HER2 signaling network in advanced breast cancers as a basis for combination therapies*.” A reader of this chapter will have an opportunity to learn in-depth signaling of the pathway and how the response to HER2/HER-family inhibitors in combination with isoform-specific/pan PI3K/dual inhibitors has shaped the current status of the clinical practice of oncology.

Chapter 9, the fourth chapter of the second part of the book is written by Prof. Leland W.K. Chung and his colleague on “biological significance and therapeutic opportunities” of the PI3K/AKT/mTOR pathway inhibitors in prostate cancers. The chapter discusses the development as well as the use of pathway inhibitors as single or combined therapies highlighting ongoing clinical trials for the treatment of prostate cancers.

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