

Preface

Multicellular organisms have evolved complex cellular communication pathways that enable cells to function and communicate in specific ways. These processes are mediated through a diverse group of cell surface receptors, including a group called receptor tyrosine kinases (RTKs). Receptor tyrosine kinases have intrinsic ability to transfer the gamma phosphate group from adenosine triphosphate to a tyrosine residue on a substrate protein, serving as an important signal for maintenance of cellular homeostasis or changes in cellular function. Accordingly, RTKs regulate a diverse array of cellular functions including cellular proliferation, survival, differentiation, migration, and metabolism.

The human genome encodes 58 RTKs that fall into 20 subfamilies based on the ligands they bind, their sequence homology, and structure. The architecture of all RTKs is highly conserved from the nematode *Caenorhabditis elegans*, with an extracellular ligand-binding domain, a single transmembrane α helix, an intracellular tyrosine kinase domain, and a tyrosine-rich C-terminal tail. Receptor tyrosine kinases are activated upon binding to cognate ligands present in the extracellular milieu, leading to receptor homo- or hetero-dimerization, kinase domain activation, and subsequent phosphorylation of tyrosine residues located within the cytoplasmic tail. Phosphorylated tyrosines serve as docking sites for a variety of intracellular adaptors and effector kinases that transmit signals to the nucleus, resulting in changes in cell function or fate. Termination of RTK activation is tightly controlled through the activation of a variety of tyrosine phosphatases, receptor-mediated endocytosis, and subsequent receptor degradation. Indeed, the importance of many RTKs in mammalian development has been displayed through the study of genetically altered mice, resulting in either severe developmental abnormalities or embryonic lethality. Collectively, RTK activation of signaling networks provides an essential mechanism by which cells communicate to regulate a multitude of different cellular responses.

Since RTKs regulate both developmental and regulatory cellular processes, it is not surprising that abnormalities in RTK structure or activity can result in human diseases. Several diseases result from RTK mutation, constitutive activation, and/or overexpression such as cancer, diabetes, inflammation, arteriosclerosis, angiogenesis, autoimmune disorders, and skeletal diseases. Due to this causal relationship,

therapeutic targeting of RTK activity is clinically approved for treatment of several human diseases.

The focus of this book is to provide a comprehensive outline for the role of RTKs in mammalian cell development, with a focus on RTK evolution over time, cell-signaling networks, with a focus on RTK structure and function, and finally how RTKs play fundamental roles in human disease. In the opening chapter, **Tony Hunter and Gerard Manning** provide a comprehensive overview of the eukaryotic protein kinase superfamily and the emergence of RTKs. Further, they discuss the human kinome and the role it plays in pathology.

In the next chapter, **Manfred Schartl, Jean-Nicolas Volff, and Frederic Brunet** dovetail and expand the discussion of the evolution of RTKs. This chapter provides a useful reconstruction of the evolutionary history of the mammalian RTKs and the interrelationship of RTK families and their individual members, and how the emergence of RTKs grew in parallel with the increasing complexity of cell types and their individual functions in development and disease. After a thorough discussion on the emergence and evolution of RTKs **Ben-Zion Shilo** describes the role of RTKs in invertebrates. Specifically, the chapter highlights lessons learned from invertebrates and primitive signal transduction pathways and how they relate to higher level signaling in vertebrate animals.

Building on RTK signaling in invertebrates, **Pierre De Meyts** advances this discussion on classical signaling mechanisms emanating from RTKs localized to the plasma membrane. Specifically, he highlights what is known about ligand requirements and dimerization events resulting in the activation of the kinase domain and phosphorylation of C-terminal tyrosines. Further, he provides an in-depth analysis of downstream signaling cascades activated by RTKs and how these events regulate cellular homeostasis, cell cycle, and apoptosis. Extending the conversation of RTK signaling, **Yi Du, Jennifer L. Hsu, Ying-Nai Wang, and Mien-Chie Hung** highlight an emerging novel signaling role of RTKs localized from within the nucleus. Here they highlight families of RTKs that have been identified in the nucleus, namely the HER/ERBB, FGFR, VEGFR, insulin and insulin-like growth factor receptor, HGFR, ROR, and EPH receptor families. Further, they provide a comprehensive analysis, notably centered on the epidermal growth factor (EGFR), and the events associated with EGFR translocation from the cell membrane to the nucleus. They further discuss novel functions of nuclear RTKs, such as their ability to function as co-transcription factors and nuclear kinases, and how these functions lead to poor prognosis of cancer patients and resistance to cancer therapeutics.

Yehoshua Eneka, Morris E. Feldman, and Yosef Yarden build upon these two chapters and describe in-depth computational modeling of RTK signaling networks. Specifically they discuss the complexity of signaling and how a single ligand-receptor interaction can lead to a complex layered signaling network with both positive- and negative-feedback loops controlling this signaling network, ultimately feeding the output layer. Closing this section on RTK signaling, **Alexander Sorkin and Arola Fortian** provide an in-depth review of the events occurring after RTK activation, highlighting the EGFR as the prototypic experimental model. Specifically, they highlight the process of receptor-mediated endocytosis, a critical cascade

necessary for RTK attenuation. In conclusion they discuss other RTK systems and deviations from lessons learned from EGFR trafficking.

To better understand the structural features necessary for RTK activation and signaling, **Michael C. Lawrence and Colin W. Ward** discuss in depth the structural features shared among the ectodomains of RTKs. In this chapter they describe the modular structure of the ectodomains of each RTK and how these structural features define the 20 phylogenetic families of the RTK superfamily. As important as the ectodomains for ligand binding, the tyrosine kinase domain is just as critical for coupling extracellular signals across the membrane resulting in a signaling output. **Dániel Süveges and Natalia Jura** present a thorough review of the kinase domain and the architecture of the ATP-binding site. Further, they describe shared mechanisms for the activation of the kinase domain and provide discussion on the structural basis for regulation of kinase activity, including receptor oligomerization, the intracellular juxtamembrane segment, and regulation by the C-terminal tail.

In the penultimate chapter **Wolfgang J. Köstler and Christoph C. Zielinski** advance our knowledge of how RTKs are being identified and pursued as molecular targets in the clinical arena with a thorough discussion on how RTKs drive tumor progression, approaches to target RTKs in the clinic, and the development of resistance to advanced therapeutics targeting RTKs. Further, this chapter elaborates on the approaches taken in the clinic to inhibit RTK activation, highlighting the next generation of RTK inhibitors. In the closing chapter of this book, **Maria Sibilía and colleagues** systematically review the contribution of genetic mouse models, including transgenic, knockout, and knock-in mice for several RTKs, used to elucidate the functions of individual receptors and their roles in mammalian development, embryogenesis, immune function, and pathophysiological processes. This chapter represents the most comprehensive summary of mouse models leading to the advancement of our understating of RTKs. Collectively, the chapters presented in this book provide the reader with a cumulative summary of how RTKs function and behave in mammalian systems, with hopes of fostering new endeavors by the next generation of RTK researchers.

Madison, WI, USA
Rehovot, Israel

Deric L. Wheeler
Yosef Yarden

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