Signaling by Receptor Tyrosine Kinases

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EDITED BY

Joseph Schlessinger
Yale University School of Medicine

Mark A. Lemmon
University of Pennsylvania
Perelman School of Medicine

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Front cover artwork: Stylized representations of the 20 different receptor tyrosine kinase (RTK) families found in humans—accounting for a total of 58 different receptors. The common intracellular tyrosine kinase domain (lower part of each receptor) is shown as a red rectangle. Domains in the extracellular region (upper part of each receptor) are much more variable across families and include immunoglobulin domains (blue), fibronectin type III domains (orange), and many others. The chapters in this volume describe mechanisms by which ligand binding to the extracellular region controls activity of the intracellular kinase domain, which vary substantially across the family and drive a variety of intracellular signaling pathways. (Cover illustration created by J. Schlessinger and M. Lemmon.)

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Contents

Preface

Since their discovery in the late 1970s, the receptor tyrosine kinases (RTKs) have been the subject of intensive study in both the basic and clinical arenas. With 58 RTKs in the deduced human proteome, this family of receptors accounts for around two-thirds of all tyrosine kinases and ~10% of all protein kinases. Recognition of their importance in disease, notably the insulin receptor in diabetes and several growth factor receptors in cancer, predated sophisticated mechanistic understanding. As time has passed, all (or almost all) RTK families have been associated with one disease or another—most predominantly cancers—and they have become major therapeutic targets. In this arena, RTKs have the advantage that approaches to their inhibition (which is typically desired in cancers) have benefited greatly from development of small molecule kinase inhibitors. Moreover, because RTKs are cell surface molecules they can be targeted with antibodies that may act as inhibitors or mediate immunotherapy.

In putting together this volume, we were acutely aware that the majority of literature on RTKs is driven by disease context, clinical evaluation, and efforts to identify and target cancer drivers. This can make an overview of RTKs as a class of molecules difficult to discern. One of our primary goals, therefore, was to draw together the extraordinary recent advances in mechanistic, structural, and biochemical understanding of RTKs. The collection also highlights several new areas of biology in which RTKs play crucial roles. Our goal was to emphasize conceptual developments and mechanistic insights into RTK activation and signaling that will stand the test of time.

In Section I, Joseph Schlessinger and Tony Hunter give conceptual and historical perspectives on the discovery of RTKs and of tyrosine phosphorylation itself, respectively, setting the stage for understanding of the distinct biologies and mechanisms of the individual RTK families. Chapters in Section II describe the conceptual basis for common signaling and regulatory mechanisms employed by most RTKs. These include "canonical" mechanisms through which RTK activation is linked to downstream signaling via SH2 domains (chapter by Tony Pawson and colleagues), as well as more receptor-specific (and emerging) mechanisms of nuclear signaling (chapters by Graham Carpenter and Hong-Jun Liao and by Gabriel Corfas and colleagues). Section II also considers trafficking and internalization of RTKs (chapters by Alexander Sorkin and Lai Kuan Goh and by Marta Miaczynska)—a crucial part of their regulation—and the related (and burgeoning) area of RTK ligand processing (chapter by Matthew Freeman and Colin Adrain). Finally, in this section, Boris Kholodenko and Natalia Volinsky provide a systems perspective on RTK signaling.

Our intention in the remaining sections of the book was—with this stage set—to provide a useful resource for comparing the characteristics of different RTK families. There are 20 different families of human RTKs, and few (if any) resources with which they can be compared and contrasted at the level of biology and mechanism. In the remaining 18 chapters, we have tried to be as comprehensive as possible in covering these families. Some families (such as the EGFR, insulin receptor, and VEGFR families) are represented in more than one chapter—where the volume and diversity of work warrants this. Others have a single chapter. Only a few families—where work remains quite preliminary or RTK function is ill-defined—are not represented. With this organization, we believe that this book represents a unique resource for comparing the features of different RTKs, which we hope will provide the inspiration for new approaches to therapeutic targeting and the discovery of new RTK biology. We are deeply indebted to all of the authors who wrote superb chapters in their areas of

expertise. We also greatly appreciate their excellent scientific contributions to this field, and their patience in the process of completing this project.

We thank Richard Sever at CSHL Press for initiating this project and, in particular, Barbara Acosta, who has shown a level of patience and support that ought not to have been necessary and without whom this volume would never have been completed.

Joseph Schlessinger
Mark A. Lemmon

In memory of Tony Pawson (1952–2013)