Preface

There are more than 90 known protein tyrosine kinase genes in the human genome; 58 encode transmembrane protein receptor tyrosine kinases (RTKs) distributed into 20 subfamilies. Among them, the ErbB receptor family, also known as the EGF receptor family or type I receptor family, includes the epidermal growth factor (EGF) receptor (EGFR) or ErbB1/Her1, ErbB2/Her2, ErbB3/Her3, and ErbB4/Her4. Among all RTKs, EGFR was the first RTK identified and the first one linked to cancer. Thus, EGFR has also been the most intensively studied among all RTKs.

ErbB receptors were first implicated in human cancer approximately three decades ago, when the avian erythroblastosis tumor virus was found to encode an aberrant form of the human epidermal growth factor (EGF) receptor (EGFR). Scientific communities have since developed a substantial understanding of the cell signaling mediated by ErbB receptors, and the biology underlying the dependence of cancers on aberrant ErbB receptor signaling. ErbB receptors are activated after homo- or heterodimerization. The ErbB family is unique among various groups of RTKs in that ErbB3 has impaired kinase activity, while ErbB2 does not have a direct ligand. Therefore, heterodimerization is an important mechanism that allows the activation of all ErbB receptors in response to ligand stimulation. The activated ErbB receptors bind to many signaling proteins and stimulate the activation of many signaling pathways, including the Ras-Raf-Mek-ERK, PI3K-Akt-Tor, PLC-γ1, STAT, and Src pathways. The specificity and potency of intracellular signaling pathways are determined by positive and negative regulators, the specific composition of activating ligand(s), receptor dimer components, and the diverse range of proteins that associate with the tyrosine phosphorylated C-terminal domain of the ErbB receptors. Through the control of these diverse signaling networks, ErbB receptors regulate many critical cellular processes, such as cell proliferation, cell differentiation, cell survival, cell metabolism, cell migration, and cell cycle.

Most of the research protocols have been developed to study the activation, dimerization, phosphorylation, interaction with other proteins, and the functions of RTKs. These protocols have been primarily developed in studying ErbB receptors, especially EGFR, as a model system. The protocols used to study the signaling of ErbB receptors may be easily adapted to study the signaling of all other RTKs and many non-receptor protein tyrosine kinases.

This volume contains protocols specifically designed for studying cell signaling mediated by ErbB receptors. These protocols apply to the study of a broad range of ErbB receptor-mediated signaling from basic research to clinic applications, from cultured cells to various animal models and primary cancer cells from patients. This book provides the most comprehensive protocols, not only for the study of cell signaling mediated by ErbB receptors but also for cell signaling which is mediated by other RTKs and beyond. This book includes five parts. Part I includes several reviews that provide a general overview of the field and updated knowledge regarding ErbB receptor signaling and its relevance to cancer. Part II provides the most common protocols for studying various aspects of ErbB receptor-mediated cell signaling. Part III includes newly developed methods in biomedical research that are also widely used in the study of ErbB receptor signaling. Part IV provides a protocol for studying

EGFR signaling in Drosophila. Finally, Part V provides important protocols for studying ErbB receptor signaling in various animal model systems.

This volume includes the most commonly used protocols for studying cell signaling that is mediated by ErbB receptors. All of the protocols have been obtained from researchers who either originally developed these protocols or modified and used these protocols. The protocols are very detailed and easy to follow. Thus, this volume may serve as a handbook for any researcher who is studying the cell signaling mediated by ErbB receptors and other RTKs. In addition, several reviews included in this volume provide the reader with up-to-date information in this continuously evolving field.

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