

PREFACE

The intent of *The G Protein-Coupled Receptors Handbook* is to provide a comprehensive overview of recent advances in the G protein-coupled receptor (GPCR) field. From the basics of GPCR structure to dimerization and drug discovery, this book reviews much of the recent advances and current knowledge regarding GPCRs.

The first few chapters focus on the fundamentals of GPCR structure and function. GPCR function is now known to be regulated by a number of mechanisms: ligand-induced conformational changes, stabilizing intramolecular interactions, pharmacological chaperones, and membrane trafficking all play a role in regulating GPCRs. Specific ligand binding causes changes in GPCR conformation, which ultimately result in the activation of intracellular signaling cascades. Meanwhile, the inactive state of the receptor is maintained by stabilizing intramolecular interactions; disruption of these interactions is necessary for receptor activation. Pharmacological chaperones play a role in GPCR folding and maturation, and appear to be involved in a number of human genetic diseases. Finally, membrane trafficking of GPCRs in endocytic and biosynthetic pathways also contribute to the physiological regulation of GPCRs.

GPCRs are present in every cell and interact with a multitude of downstream effectors: heterotrimeric G proteins, regulators of G protein signaling (RGS), arrestins, G protein-coupled receptor kinases (GRKs), and many other GPCR interacting proteins. Heterotrimeric G proteins are among the most important signaling transducers involved in GPCR activity, directly coupling to the receptor and transmitting its information about activation/inactivation to the cell. RGS proteins are involved in the regulation and termination of the signaling process. GRKs catalyze GPCR phosphorylation, promoting receptor desensitization and internalization. Arrestins mediate the desensitization and uncoupling of GPCRs from their G proteins, and may also function as signal transducers. In addition, β -arrestin regulates the sequestration, intracellular trafficking, degradation, and recycling of most GPCRs. More than 50 other GPCR interacting proteins have been identified that function as modulators of GPCR function at various stages of signaling.

The next section of this book explores our current understanding of GPCR dimerization. The emerging concept of dimerization has modified our views of GPCR structure, function, and regulation tremendously. The existence of GPCR dimers has been demonstrated using biochemical

methods, such as co-immunoprecipitation, and biophysical approaches, such as fluorescence (FRET) and bioluminescence resonance energy transfer (BRET). Potential domains of GPCR dimerization have been described using computational and experimental approaches. Functional complementation studies have been used to analyze the basis, selectivity, and mechanisms of dimerization. It is now evident that dimerization plays a role in receptor maturation, as many GPCRs have been shown to dimerize prior to their trafficking to the cell surface. There is also some evidence suggesting that dimerization alters the endocytotic and postendocytotic trafficking properties of GPCRs. More importantly, heterodimerization has been shown to modify the pharmacological properties of GPCRs; a finding that could have an enormous impact on the future of drug design.

The final chapters of this book describe some of the most recent developments in the GPCR field, leading to advances in drug discovery. It is now thought that a number of GPCRs functionally interact as heterodimers to mediate analgesic responses. Elucidating the role of GPCRs in mediating pain is also crucial to the development of superior analgesic drugs. Thus, a new wave of drugs specifically targeting heterodimeric receptor complexes may be on the horizon. Another important area of current research consists of investigating the structural plasticity of receptor activation by examining the conserved motifs contributing to the overall receptor structure (and variability among subtypes); this would confer ligand-binding specificity and, thus, could lead to the development of receptor-type selective drugs. Finally, the last chapter describes the identification of natural ligands of orphan GPCRs, i.e., deorphanization. Orphan receptors may represent an untapped drug target. Understanding the evolutionary diversity in GPCR ligand recognition is fundamental to understanding the potential of GPCRs as therapeutic targets.

I thank all the authors for their timely and insightful contributions, the series editors Helen Baghdoyan and Ralph Lydic for suggesting this book as a part of their series, and Ms. Elyse O'Grady at Humana Press for keeping things moving along. I also thank Noura Abul-Husn, Fabien DeCaillot, and José Morón for their extensive input into the chapters. Finally, I am grateful to Dr. Ivone Gomes for her excellent assistance throughout all of the editing and formatting stages. From planning the list of chapters/authors to the realization of this book, it has been a rewarding experience; I hope this book will serve as a helpful guide for those who are interested in learning more about the function and regulation of GPCRs.

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