PREFACE

Receptors are the gateway through which our cells sense and respond to their changing environments. Cell surface receptors have the unique capacity to both engage exracellular ligands, as well as relay this information through the plasma membrane to intracellular components, and beyond. Some receptors, such as growth factor and cytokine receptors, contain only a single-transmembrane segment, connecting modular extracellular and intracellular domains that can be studied as soluble fragments retaining full ligand-binding activity. Other receptors, such as G-protein coupled receptors are multi-pass transmembrane proteins requiring a lipid bilayer for functional reconstitution. Others systems, exemplified here by the glutamate receptor, are combinations of autonomous ligand binding extracellular domains connected to multiple transmembrane helix polypeptide cores. Regardless of structural classification, the fundamental question persists, how is ligand engagement outside the cell coupled to receptor activation within the cell? This question remains elusive even for the most intensively studied systems, and remains one of the most challenging problems in biochemistry. Structural biology has made great strides in understanding this question through the determination of structures of receptors and their complexes with ligands. Ultimately a clear elucidation of a detailed mechanistic picture of receptor activation will require a combination of static biophysical methods such as x-ray crystallography, with dynamic methods such as NMR and single-molecule spectroscopy, which together can be dovetailed with functional studies.

While the structural database now has many examples of protein-protein complexes which have taught us about the first principles of molecular recognition, receptors remain somewhat enigmatic in that they are protein machines, rather than simple binding proteins. The chemistry of receptor-ligand recognition is part of an overall process by which ligand orients, or otherwise perturbs the structure of a receptor in such a way that the intracellular adaptor proteins initiate signaling cascades. The basis by which this phenomenon occurs appears far more complex than we originally thought based on simple models of receptor homodimerization. Not so long ago there was a common assumption that simply bringing receptors together is all one needs for activation. More recently, it is being appreciated that subtle orientational differences in the extracellular domains of dimerized receptors can translate into very significant downstream signaling differences. Thus, the transmembrane helices may

not simply be loose tethers between the extracellular and intracellular domains. Rather, in a number of receptors systems such as Erythropoetin, the connecting peptides and transmembrane helices appear capable of transmitting torque though the lipid bilayer to effect orientational strain in the intracellular parts of the receptors. It is a fact that most cell surface receptors are oligomerized in some fashion by their ligands, but the geometric and conformational details of this clustering are critical to the appropriate signals being transduced. Examples exist now of ligands inducing large-scale conformational changes in preformed receptors dimers, as well as receptor activation through disruption of dimerization. Most recently, GPCR are now being shown to require some form of ligand-induced dimerization, in concert with conformational change of the helices, for activation. Given the technical challenges inherent in studying receptors at a biophysical level, it is likely we have currently seen only a small fraction of the universe of potential mechanisms for receptor activation.

This issue of Advances in Protein Chemistry presents detailed chapters on several important receptor systems, with an emphasis on relating the structural basis of extracellular ligand recognition to the activation of intracellular signaling events. Some chapters focus on structural aspects of ligand recognition, while others are more focused on mechanistic questions. However in all cases there is an attempt to paint a structural portrait for how ligand engagement may activate the receptor. We have emphasized systems for which a significant amount of structural information is known on either the extracellular or intracellular regions of the receptors. In most cases the chemistry of ligand recognition relates in subtle, yet still unclear ways to receptor activation. The receptors discussed in this edition range from type-I receptors for growth factors hormones, and immunoregulatory ligands (Leahy, Nikolov, Garcia, Kossiakoff, Walter, Wu, Springer, Strong) to multi-pass integral membrane proteins (Oswald, Falke, Handel). For several of these systems structures are known for both extracellular domains and intracellular domains, allowing models to be constructed for the entire receptor. Clearly, these all-encompassing models are an important future direction for the field of receptor structural biology.

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