Preface

Membrane proteins account for roughly 30% of all open reading frames in fully sequenced genomes. These proteins are of central importance to living cells. They are required for transport processes, sensing changes in the cellular environment, transmission of signals, and control of cell–cell contacts. These proteins are implicated in numerous pathologies, like cancer, cystic fibrosis, epilepsy, hyperinsulinism, heart failure, hypertension and Alzheimer disease, but studies of these and other disorders are hampered by a lack of information about the proteins involved. Knowing the structure of membrane proteins is an essential prerequisite for understanding how these proteins function and, further, how their functions can be modified by small molecules. This is of paramount importance in the pharmaceutical industry, which produces many drugs that bind to membrane proteins (50% of all drug targets are G protein-coupled receptors [GPCRs]), and recognizes the potential of many recently identified GPCRs, ion channels and transporters as targets for future drugs. However, whereas high-resolution structures are available for myriad soluble proteins (more than 42,000 in the Protein Data Bank), three-dimensional (3D) structures have so far been obtained for only 204 membrane proteins, the majority of which are from prokaryotic organisms, with only 25 from mammalian membrane proteins (see http://blanco.biomol.uci.edu/Membrane_Proteins_xtal.html). The first membrane proteins were crystallized owing to their natural abundance, circumventing all the difficulties associated with overexpression. However, the majority of medically and pharmaceutically relevant membrane proteins are present in tissues at very low concentration, making overexpression of recombinant membrane proteins in heterologous cells suitable for large-scale production a prerequisite for structural studies. The development of heterologous expression systems capable of delivering high-quality recombinant protein for structural studies remains an essential goal. In 2005, the two first atomic structures of recombinant mammalian membrane proteins expressed in yeast were resolved. Since that time, extensive optimization of heterologous expression systems has begun to bear fruit, and 11 eukaryotic membrane protein structures have been solved to high resolution using recombinant material.

This volume proposes an overview of different heterologous expression systems that produce an adequate amount of membrane proteins for structural analysis. Methods and protocols are described for each heterologous expression system proposed. Some chapters of this volume treat membrane protein solubilization, purification and instability in solution and comment on the strategies that allowed the determination of the structure of the first heterologously expressed mammalian membrane proteins.

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