EDITORIAL

nature structural & molecular biology

Cellular gatekeepers

In a common yet effective analogy, a cell can be compared to a fortified city, in which lipid membranes form the defensive walls, and membrane proteins function as gates and checkpoints that control the transit of molecules and information across these walls. We evoke this concept on the cover of this special Focus on Membrane Proteins.

Here's a knocking indeed! If a man were porter of hell-gate, he should have old turning the key.

—Shakespeare, *Macbeth*

Membrane proteins, the gatekeepers of cells, have been implicated in neurotransmission, sensing, and transport of nutrients and drugs into and out of cells. They are targeted by ~50% of all marketed pharmaceutical drugs to treat conditions as diverse as neurological disorders and cancer. Determining the three-dimensional structures of membrane proteins is essential to understanding their function and developing more effective drugs. Structures of important classes of membrane proteins have recently been solved, spurred by technical progress, thus yielding mechanistic insights into the membrane-protein function. In this issue, a special Focus on Membrane Proteins (http://www.nature.com/nsmb/focus/membraneproteins) highlights the most recent breakthroughs in determining the structure and mechanisms of two important classes of membrane proteins—the ATP-binding cassette (ABC) transporters and the neurotransmitter-gated ion channels—and explores the technical and methodological developments that are advancing the field of membrane proteins.

The first crystal structures of soluble proteins were those of hemoglobin (Perutz, M.F. *et al.*, *Nature* **185**, 416–422, 1960) and myoglobin (Kendrew, J.C. *et al.*, *Nature* **185**, 422–427, 1960). It was not until a quarter-century later that the first high-resolution structure of an integral membrane protein, the *Rhodopseudomonas viridis* photosynthetic reaction center, was determined (Deisenhofer, J. *et al.*, *Nature* **318**, 618–624, 1985). Although membrane proteins constitute up to 40% of eukaryotic and prokaryotic proteomes, they currently account for less than 2% of all known protein structures. Such disparity serves as a testimony that the structural determination of membrane proteins remains a daunting feat.

Nevertheless, recent years have witnessed unprecedented advances in the structural study of membrane proteins, as recounted in the Commentary by Hendrickson (page 464). Remarkably, approximately 80% of all known membrane-protein structures have been reported in the past decade, largely owing to developments in X-ray crystallography and in methods for the expression and purification of membrane proteins; the rapid progress in cryo-EM should expand the field even further.

Although it is perhaps less commonly used than other approaches, NMR spectroscopy is becoming an increasingly popular means of investigating membrane proteins. The Perspective by Liang and Tamm (page 468) provides an overview of recent successes and challenges as well as future opportunities for the application of solution and solid-state NMR methods not only in determining structures but also in assessing the dynamics and folding of membrane proteins and studying the binding of lipids, ligands and drugs.

Similarly to structure determination, computational design and structure prediction are still lagging for membrane proteins compared with soluble proteins. As Barth and Senes (page 475) discuss in their Perspective, encouraging progress has been achieved for α-helical membrane proteins, owing to the availability of faster and more powerful computational resources and to the growth of structural and genomic sequence databases. Major hurdles remain, particularly for the experimental characterization of the designs, but the emergence of new structural and biochemical methods is steadily accelerating progress.

The Perspective by Denisov and Sligar (page 481) summarizes the use of nanodiscs, small discoidal lipid bilayers encircled by scaffold proteins, in membrane-protein studies. It is well established that the lipids in the cell membrane are critical in shaping the conformation and modulating the function of membrane proteins. Detergents greatly facilitate solubilization, but they present membrane proteins with a physicochemical environment that differs from that of native phospholipids, often altering or even abrogating protein activity and function. Nanodiscs are an invaluable tool for structural and functional investigations of membrane proteins in controlled native-like lipid environments.

Carrying molecules and facilitating the passage of ions across the lipid barrier are major tasks undertaken by membrane proteins. Along with other types of active carriers, the ubiquitous ABC transporters are essential for cell survival because they preside over the uptake of nutrients and the export of cytotoxic compounds. Locher (page 487) reviews structural and functional insights on ABC transporters and discusses their mechanistic differences that have emerged from recent functional, crystallographic and cryo-EM analyses.

Fast synaptic transmission is mediated by neurotransmitter-gated ion channels, which are among the first membrane proteins ever characterized. Plested (page 494) reviews the numerous crystal and cryo-EM structures that have recently advanced understanding of the molecular mechanisms of activation and desensitization, as well as the pharmacology of the two major families of neurotransmitter-gated ion channels: the glutamate receptors and the Cys-loop receptors.

Given the current progress and intense research efforts, it is clear that this is a golden age for the field of membrane proteins. We look forward to presenting in our pages new developments that will reveal how these essential gatekeepers achieve their cellular functions. We also hope that this special Focus on Membrane Proteins will be useful to researchers in broad areas including structural and cellular biology, neurosciences and drug development. ■