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Editorial

Membrane protein structure

Membrane protein structure represents the next frontier in structural biology. Perhaps 30% of the proteins coded by the human genome are membrane proteins. By some estimates, 60% of drug targets in the pharmaceutical industry are membrane proteins. The importance of membrane proteins as drug targets follows from the wide range of functions that occur in or on the membranes of cells. For example, at the plasma membrane, one finds transport proteins building the electrical and chemical gradients across cells, channel proteins enabling action potentials, receptors supporting signal transduction from extracellular signals, proteins that bind the membrane skeleton, and proteins promoting cell–cell recognition, to mention a few. Intracellular membranes, such as mitochondrial membranes, contain membrane proteins that synthesize ATP utilizing a transmembrane electrical and chemical gradient created by other membrane proteins, as well as proteins involved in import of newly synthesized protein and transport of small metabolites. Some outer bacterial membrane proteins facilitate diffusion of small to medium-sized nutrients through pores, while proteins of the inner bacterial membrane coordinate the active transport of sugars. Mutations in some membrane proteins have been identified as being important in specific diseases such as, for example, CFTR in cystic fibrosis, rhodopsin in retinitis pigmentosa, and the insulin receptor in diabetes and many more examples will likely be identified in the near future.

Despite the importance of membrane proteins in cell function, a cursory examination of the PDB structural database will reveal that very little information is available on membrane protein structure. The number of soluble protein structures in the database exceeds the number of membrane protein structures by approximately 1000:1! This represents a huge deficit of information about membrane protein structure.

The reason behind this extraordinary deficit of membrane protein structures is largely due to the insolubility of membrane proteins in aqueous solution. Membrane proteins contain large hydrophobic patches on their surfaces that enable the proteins to inhabit the hydrophobic interior of a lipid bilayer in a membrane. As a result, membrane proteins cannot dissolve (generally) in water. Normally, detergents are required to stabilize membrane proteins in an aqueous environment. But detergents inhibit crystallization, and crystallization is required for the most highly used means of determining atomic structures of proteins, X-ray crystallography. The first successful structure determination for a membrane protein was obtained using two-dimensional crystals (of bacteriorhodopsin, which spontaneously forms two-dimensional crystals suitable for electron diffraction analysis). Higher resolution structural information has been obtained by X-ray crystallography for those few membrane proteins that can be crystallized. The size of membrane protein–detergent mixed micelles inhibits the effectiveness of the other highly used means of protein structure determination, NMR.

Solid-state NMR methods have, however, been developed to solve the structures of simple membrane proteins in lipid bilayers, providing in some cases information that X-ray crystallography cannot. And solution NMR methods have been used to obtain structural information about helical bundle membrane proteins by studying soluble fragments that behave as sub-domains.

Despite all the difficulties, impressive progress has been made in determining membrane protein structures over the last few years. This special issue of Biochimica et Biophysica Acta is designed to summarize some of this new information in a way that we hope will be helpful to those with an interest in membrane protein structure.

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