



Recent progress in membrane protein structures and investigation methods

Editorial overview

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Tamir Gonen is a Group Leader at the Janelia Farm Research Campus of the Howard Hughes Medical Institute. Prior to his current position, he was an Associate Professor of Biochemistry and the Director of the Molecular Electron Microscopy Laboratory at the University of Washington in Seattle where he was also a Howard Hughes Medical Institute Early Career Scientist. His research aims are to understand the structure and function of membrane proteins involved in nutrient uptake, cellular communication, water uptake and homeostasis. His group is currently focusing on the structure and function of voltage gated ion channels in biological membranes by electron crystallography.

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Gabriel Waksman is Director of the Institute of Structural and Molecular Biology at UCL and Birkbeck, Head of Department of Structural and Molecular Biology at UCL and Head of Department of Biological Sciences at Birkbeck. Over the past 20 years, he has developed a research programme into the structural and molecular biology of bacterial secretion. His current research aims to elucidate secretion mechanisms by large membrane-embedded macromolecular systems involved in pilus biogenesis and in DNA secretion.

Welcome to the Membranes section of *Current Opinion in Structural Biology* 2012. Membranes are vital cellular structures and threats to their integrity are lethal. Because cells must communicate with their environment, they have evolved a myriad of membrane-embedded proteins that serve as channels, pumps or receptors to selectively carry out crucial cellular functions. Studying these devices has evolved into a vigorous field of study. Not surprisingly more than 30% of the total human genome encode for membrane proteins and 90% of all pharmaceuticals target membrane proteins for ailments from epilepsy to diabetes, hypo and hyper glycemias to blindness. More and more structures of membrane proteins are determined and the field of membrane biology is gaining momentum. In this special section of the *Current Opinion in Structural Biology* we have assembled an array of contributions to share the recent breakthroughs and excitement in the field of membrane biology.

Paula Booth writes about transition states in membrane protein folding. Understanding how membrane proteins fold is critical for understanding how they are made to perform certain well-defined functions. In this review the folding of alpha helical membrane proteins is described detailing how a transmembrane helix is formed within the unforgiving hydrophobic environment of the membrane.

Sciara and Mancia highlight exciting findings from recently determined structures of membrane proteins while focusing on channels and transporters. The authors present an overview of some of the most exciting novel structures of channels and transporters that were determined by X-ray crystallography in the last two years. A lengthy discussion follows drawing analogies and mechanistic implications based on the new structures.

Lebon, Warne and Tate describe agonist bound structures of G protein coupled receptors (GPCRs). The vast majority of all pharmaceuticals that target membrane proteins, in fact, work by targeting GPCRs. These protein assemblies play a major role in intracellular communication following excitation (or inhibition) by extracellular ligands. This review details the structures of nine agonist bound GPCRs that were published in the last year detailing the mechanism of action of these receptors at the atomic level.

Thogersen and Nissen highlight the role membrane components play in modulating the activity of membrane embedded nanomotors. Their review

focuses on the crucial family of P-type ATPases, a family of integral membrane proteins that play important roles in maintaining electrochemical gradients and asymmetric lipid distributions across membranes.

[Allen, Phan and Waksman](#) write about pilus biogenesis at the outer membrane of Gram-negative bacterial pathogens. The chaperone-usher pathway is the best characterized pilus biogenesis system, able to synthesize and display structures at the outer membrane without the use of endogenous energy sources. This review showcases recent exciting new developments in our understanding of this complex nanomachine.

[Taraska](#) highlights how fluorescence techniques can be used to map the structures of membrane proteins at high resolution in real time and without the constraints of crystal formation and crystallization artifacts. Fluorescent methods such as intensity mapping, fluorescent resonance energy transfer (FRET) and photo induced electron transfer are used as examples for measuring the structures, folding and orientation of domains within membrane proteins. Using these approaches the dynamic transitions of membrane proteins can be probed.

[Pope and Unger](#) highlight electron crystallography as a valuable tool in determining the structures of membrane proteins within the lipid bilayer, in an environment that closely mimics biological membranes. They highlight

some of the methodological and technological advances in the field and demonstrate that structures can be determined at high resolution even from very small crystalline patches – as small as 20 unit cells.

[Ubarretxena and Stokes](#) also write about electron crystallography but focusing more on the technological advancements that have ushered the field into a new decade. Here the atomic structures of membrane proteins can be determined and lipid-protein interactions probed directly. Automated crystallization robotics and crystal screening hardware and software are discussed as they facilitate electron crystallography. Finally, new high throughput methods for structure determination by electron crystallography are discussed.

[Jiang and Gonen](#) describe the influence of lipids on the structure and function of voltage gated ion channels. This important class of ion channels are responsible for transmitting electrochemical signals in excitable and non-excitable cells. X-ray structures of voltage gated ion channels such as potassium and the recent sodium channels are highlighted. A new lipid-mediated regulation in voltage gated ion channels is highlighted suggesting that the structures of such channels should be studied by electron crystallography from two-dimensional crystals of the channels embedded in membranes.

We thank all authors for contributing to this exciting volume and we hope you enjoy this selection.