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Electron crystallography of membrane proteins

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High-resolution structure determination of membrane proteins is currently one of the greatest challenges of cell biology. These important proteins account for approximately a third of our proteome and form the responsive interface between cellular and subcellular compartments and their environment. More specifically, they mediate material and information transfer and include a number of protein families such as receptors, signal transducers, channel-forming proteins, active transport pumps, electron transport systems, and adhesive proteins, as well as a considerable number of enzymes. Given the obvious importance and diversity of membrane proteins, their structure determination is of fundamental importance in developing our understanding of molecular cell biology and is of immense value to the pharmaceutical industry for the design of new and highly specific drugs.

Despite their importance, to date fewer than 400 near-atomic-resolution ($<4 \text{ \AA}$) membrane protein structures have been deposited in the Protein Data Bank (PDB), compared to almost 30,000 structures of soluble proteins. Despite the fact that the global effort to solve membrane protein structures has produced important results, the rate of structure determination is still lagging behind expectations and requirements for pharmaceutical research, cell biology, structural biology, and proteomics.

Electron crystallography has been used to analyze a large number of membrane proteins at lower resolution and to determine 2D projection maps. High-resolution 3D data from electron crystallography have also led to the determination of atomic models of eight proteins so far. Besides structure determination by X-ray crystallography and nuclear magnetic resonance (NMR), the young method of electron crystallography is becoming increasingly important in membrane protein research.

Since its first application to study the structure of bacteriorhodopsin (Henderson and Unwin, 1975), substantial progress has been made in 2D crystallization methods, cryo-EM sample preparation, low-temperature imaging technology, and data processing. The recent structure determination of mammalian Aqp0 at 1.9 \AA resolution by electron diffraction on 2D crystals and molecular replacement (Gonen et al., 2005) demonstrated impressively the potential of this method to solve the structure of membrane proteins and their detailed interaction with individual lipid molecules of a near native bilayer.

To increase the rate and quality of structure output by electron crystallography, progress is needed in a range of areas, including crystallization methods, automation of sample screening, cryo sample preparation, high-resolution data processing, and the automation of data

processing. Furthermore the electron crystallography field would benefit from coupling these into a streamline process for structure determination.

This special issue of the *Journal of Structural Biology* on electron crystallography of membrane proteins aims to highlight key recent developments in this field and to summarize the state of this method. The order of papers in this issue reflects the position in the electron crystallography pipeline. In addition to the articles presented here, we would like to point the readers' attention to the recently published image processing system IPLT (<http://www.iplt.org>; Philippsen et al., 2007) and to the recently published book on this topic (Glaeser et al., 2007).

We would also particularly like to thank the many dedicated reviewers who gave so freely of their time and expertise during the preparation of this special issue.

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