nature structural biology

The winning channels

On October 8, 2003, just days before this issue went to press, the Royal Swedish Academy of Sciences announced the winners of the 2003 Nobel Prize in Chemistry. The award acknowledges the contributions of two scientists—Peter Agre of Johns Hopkins University and Roderick MacKinnon of Rockefeller University—in understanding how water molecules and ions are selectively transported across cell membranes. In doing so, the Nobel committee has added another example to a growing list of contributions from the field of structural biology.

Agre's discovery of the water channel (called aquaporin) was serendipitous. What began in the mid-1980's as a search for proteins constituting the Rh-factor in the red blood cells turned up an abundant membrane protein. After cloning the DNA encoding this protein, Agre and co-workers demonstrated that the polypeptide directly mediates water transport across membranes. This discovery has led to the identification of more than 200 similar channels in various tissues and in many organisms, including mammals, plants and microbes.

Identification of the molecular entity that constitutes the water channel made it feasible to study the mechanism underlying channel function. As a step toward this goal, Agre collaborated with structural biologists and reported the first high-resolution structure of aquaporin in 2000. The structural features, most prominently the narrow passage and the electric field of the passage, explain how an aquaporin could selectively allow water but not other molecules, especially hydrated protons, to cross the membranes. These studies therefore provide the foundation for understanding how water channel defects may arise, as well as the starting point for therapeutic approaches that target such defects.

MacKinnon's research focuses on the understanding of the molecular mechanisms of ion channels. Initially, MacKinnon's group used site-directed mutagenesis to painstakingly map out residues crucial for potassium ions conduction through the channel. However, to understand how the channel selects potassium ions over other very similar monocations, it was clear that a high-resolution structure would be necessary.

To achieve this goal, MacKinnon—although not formally trained as a crystallographer—ventured into the field of membrane protein crystallography, one of the most challenging areas of structural biology. This effort paid off in an amazingly short amount of time. In 1999, his group reported the first structure of an ion channel—that of a bacterial potassium ion channel. The structure explains the basis for potassium ion selectivity. With additional experiments, MacKinnon and colleagues showed that the bacterial, mammalian and fly potassium channels likely share the same core structure. For his remarkable achievement, MacKinnon was one of the recipients of the Lasker award for basic medical research in 1999 (shared with Clay Armstrong and Bertil Hille).

In the next four years, MacKinnon's group provided several additional landmark studies about ion channels, addressing questions such as the gating of potassium ion channel and the structural basis for the transport of an anion (chloride). His work on a voltage-gated potassium ion channel challenged our thinking about the mechanism of voltage sensing. As ion channels' functions are crucial for many biological processes, such as setting the pace of the heart or generating an electric impulse in the nerveous system, the findings of MacKinnon's work represent significant advance in more than a single scientific discipline.

In the past 40 or so years, the Nobel committees have recognized the achievements of many structural biologists, a list that includes the likes of Perutz and Kendrew (Chemistry, 1962), Watson, Crick and Wilkins (Medicine, 1962), Hodgkin (Chemistry, 1964), Klug (Chemistry, 1982), Deisenhofer, Huber and Michel (Chemistry, 1988), Ernst (Chemistry, 1991), Walker (shared Chemistry, 1997) and, just last year, Wüthrich (shared Chemistry). Although most of these achievements were formally recognized as "the most important chemical discovery or improvement" (http://www.nobel.se/chemistry), these contributions also have significant implications in basic biological research and molecular medicine. In this sense, the work of Agre and MacKinnon crosses the boundaries of traditionally defined fields, and the Nobel once again highlights the significance of multidisciplinary research.

Looking forward, the maturation of techniques, such as cryo-EM and electron tomography will no doubt provide crucial details of large molecular complexes and cellular organization in the near future. With many fundamental questions in biology becoming accessible to molecular techniques, we believe that structural biologists will continue to provide prominent contributions in the next 40 years. ■