https://doi.org/10.1038/s41594-024-01303-9

Membrane-embedded machines

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The first membrane protein structure was reported almost 40 years ago. In this issue, we are publishing a set of papers that serve to underline the incredible advances in our understanding of the biology of these multifaceted molecular machines.

While the structure of soluble myoglobin was determined in 1958 (ref. 1), it was almost 30 years later in 1985 that the structure of the first membrane protein, the photosynthetic reaction center, was solved by Michel and colleagues[2]. Membrane proteins are challenging to work with, owing to their preference for a hydrophobic environment such as those found inside lipid bilayers. Today, thanks to advances in sample preparation and structure determination, structures of membrane proteins can finally be solved more easily. In this issue, we showcase a collection of papers reporting structures and the mechanisms underlying functions of membrane proteins involved in signal transduction, transport and energy generation.

Cells are organized into membrane delimited compartments. While certain aspects of separation enable different functions, communication between organelles and the cytoplasm, and between cells and their environments, is needed. For example, exchange of water, ions and larger molecules must occur across membranes. One well-known example of intercellular communication is between neurons, in which one cell releases neurotransmitters that are received by a second neuron to propagate signals across long distances in macroorganisms.

Communication between compartments and cells is facilitated by integral membrane proteins, which can function as receptors or enable exchange of molecules in active or passive transport. Membrane proteins also function as cargo receptors in vesicular trafficking or as insertases in membrane protein biogenesis. Moreover, members of the same family can carry out a diverse set of roles. In his Perspective article, Newstead outlines functions of solute carriers, including their non-conventional roles.

Considering their multitude of functions, it is not entirely surprising that membrane proteins make up 20–30% of the proteome. However, the progress in studying the mechanisms of their action by structural determination has been lagging behind that of soluble proteins. Today, there are almost 220,000 unique protein structures in the Protein Data Bank[3], but only around 1,700 unique membrane protein structures are specifically annotated.

Our April cover features a spectacular specimen of the annelid worm *Malacoceros fuliginosus*, from which Kalienkova et al. cloned the FMRFamide-gated sodium channel 1 for analysis by cryo-electron microscopy. Their work reveals the basis of peptide activation of excitatory DEG/ENaC channels. Notably, the history of ion channels is intertwined with the use of model organisms. In a Comment, Jan and Jan recall their early work on *Shaker* mutants in *Drosophila*, which led to the identification of Shaker as a potassium channel. Our issue this month also includes structural work on ion channels, including a paper from Nakagawa et al., who uncover a hidden calcium ion binding site in the open gate of the AMPA receptor, which controls ion permeation.

With respect to novel insight into transporters, the work from Fortea and other members of the Accardi lab focuses on the prototypic *Escherichia coli* CLC-type Cl^-/H^+ exchanger to determine the basis of its activation. The authors suggest this mechanism could be related to the common gating mechanism of human CLC-7. In this theme, Pourmal et al. present insights into prostaglandin efflux by the transporter MRP4, and Qiu, Gao et al. show us the mechanism through which CHT1 reuptakes choline into the presynaptic terminal after termination of synaptic transmission.

Communication and signal propagation, however, do not always involve passage of molecules through a membrane. Receptors act by propagating a conformational change after a ligand-binding event to act on other effector proteins. G-protein-coupled receptors (GPCRs) are of particular importance, as they are attractive drug targets. In their Comment, Smith and Murray reflect on the focus of the field on GPCR endogenous ligand determination for receptors with unknown ligands – 'orphan receptors'. The authors call for a more holistic approach, in which determination of activation mechanisms via multidisciplinary approaches takes the lead.

Providing further insights into orphan GPCR activation, Hoppe, Harrison, Hwang et al. present the structure of GPR161, involved in Hedgehog signaling, which allowed them to identify a sterol-binding pocket that stabilizes the conformation required for G protein coupling. Shin, Park et al. progress our conceptual understanding of another orphan GPCR, GPR156, involved in sound detection, and provide the basis for its constitutive activation.

However, it is not just GPCRs that facilitate signaling. The Savvides group unveils the basis of extracellular receptor assemblies mediated by pro-inflammatory cytokines interleukin-12 and interleukin-23. Furthermore, work from Jiao, Pang et al. and from Felt et al. provide structural insights into chemokine receptor and serotonin 3 receptor agonism, respectively.

To showcase the functions of membrane proteins in energy production, this issue features work from Sharma et al. in which the authors found intermediates in the reaction cycle of ATP synthase, which inform on the elastic coupling mechanism of this enzyme.

Finally, as well as this set of papers focused on membrane proteins, we highlight some clinically relevant work from Steinthorsdottir et al. that shows that a missense mutant in the protein SYCE2 is associated with random crossovers, decreased recombination and pregnancy loss. An accompanying News & Views by Carioscia & McCoy discusses the advances reported in this study, as well as the challenges of understanding the genetic basis of human pregnancy loss.

We are proud to be at the forefront of reporting recent discoveries in the study of membrane proteins, and we look forward to the next 30 years of progress in this fascinating field.

Published online: 18 April 2024

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