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Editorial overview: Membranes

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Bruno Miroux is research director at INSERM and is heading the Laboratory of Physical and Chemical Biology of Membrane Proteins (Institut de Biologie Physico-Chimique, CNRS, Paris, France). During his PhD in Daniel Ricquier's lab he established the first experimental topological map of the mitochonchondrial uncoupling protein 1. As post-doc in John Walker's lab he isolated bacterial mutants, namely C41(DE3) and C43(DE3), adapted to the overproduction of soluble and membrane proteins that are widely used in structural biology of membrane proteins. Over the last fifteen years he worked on the physiological functions of the mitochondrial uncoupling protein 2 and on membrane protein production in bacteria.

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Eva Pebay-Peyroula is a professor at the Grenoble Alpes University (UGA). Shortly after a PhD in physics, she moved into structural biology. Membranes and membrane proteins are her favourite topics. She worked on crystallization (highlighting the detergent structure in porin crystals with neutron diffraction), and contributed to the very early developments of crystallization in lipidic cubic phases. She pioneered micro-crystallography, and solved high resolution structures of bacterial rhodopsins, and the 1st structure of the mitochondrial ADP/ATP carrier. Along her carrier, she enjoyed nice international collaborations that were important in this multidisciplinary field.

Biological membranes are essential in all life processes. They are not only walls surrounding cells and cellular compartments, but also control the passage of ions and molecules, or any other signals, and therefore ensure the communication between cells and compartments.

Since the early days of structural biology, membrane proteins have kept the attention of scientists. However, due to their natural environment, their surfaces highlight dual properties, partly hydrophobic but also partly hydrophilic, making these proteins impossible to handle in aqueous solutions. In the 1980s new concepts for the purification of such proteins based on the use of detergents emerged and physical chemistry of detergents was essential to progress in purification and crystallization of membrane proteins. Thanks to strong collaborations between chemists and biologists, new amphiphilic molecules were designed as exemplified by the emergence of amphipols. The first structures of membrane proteins were obtained from natural sources. They should still be considered, in particular when studying large molecular assemblies. Although heterologous expression of membrane proteins is still a challenge, using several strategies in parallel is often rewarding. Most of the known high-resolution structures were obtained by X-ray crystallography. Crystallization also a major bottleneck is now slightly facilitated by alternative methods based on lipidic phases. Very recently, electron microscopy is becoming of major importance in the field and no more restricted to large and highly symmetrical particles. In parallel to structural biology, chemists, physical-chemists or biophysicists studied model membranes, consisting of a chemically well-defined medium made from pure lipids, mixtures of lipids, or lipids with additives. Phase diagrams and a certain number of mechanic parameters were studied in light with physical concepts.

For many years, a simplistic view of membranes prevailed, depicting them as two separate components. On one side were the lipids forming a bilayer and providing the shape and the mechanical properties to the membrane surrounding the compartment, on the other side the proteins embedded in the lipidic bilayer providing the function (transport, signaling, ion exchange, etc.). In many cases, both communities ignored each other. Only in the last decades, it became obvious that membranes are perfect examples where only integrated biology will provide the clues to understand the mechanisms of action. In addition, it was also demonstrated in several examples, that the use of physical concepts can be adapted to biological membranes and explain their behavior. Membranes are peculiar and fascinating media where multiscale behaviors coexist. They are organized from the atomic (0.1 nm) to the micron (up to 100 μm) scales in a continuous

manner, so that their properties can only be approached by integrated methods. Although, methods to study the two extreme scales are available, studying the junction between both, in particular when molecular properties and mesoscopic properties overlap, is still a challenge. We feel that in the very recent years science in that field has made tremendous progresses, and will continue to do so. Structural biology of individual membrane proteins will continue to develop, and for some of these proteins part of the mechanism of action will come out from the structures alone combined with functional data. For other systems, classical structural data will have to be complemented with additional information. Indeed, the function can be sensitive to the mechanic stress imposed by the surrounding membrane. Conformational changes in proteins ensuring transport across the membrane might necessitate the physical properties of the surrounding membrane. When larger remodeling at the level of the membrane occurs, then integrated methods are clearly indispensable.

This issue has the ambition to illustrate several aspects described in this introduction. However, the list is not exhaustive and many other facets could have been covered. For example, NMR based methods are also progressing and provide important insights on structure and dynamics of membrane proteins. Molecular modeling and numerical simulations from atomic description to coarse grain approaches continuously improve and provide essential information on membrane proteins within membranes and probably in the near future on whole membranes.

The first part of the issue, describes three different families of membrane proteins for which recent structural data arose. However, this issue does not intend to be a catalog of recent structures and we selected topics, which illustrate nicely the contribution of structural biology to elucidate fundamental question, and at the same time open the way to medical applications. Bacterial multidrug transporters are largely responsible for resistance to medical treatments. Dijun *et al.* report on the mechanistic models that were derived from structures, explaining drug efflux achieved by the main classes of multidrug transporters. Water is the most essential molecule of life. It cannot freely cross membranes in sufficient amounts. Aquaporins catalyse this process and are ubiquitous in all living organisms. From the large body of structures from various aquaporins that are now available, Kreida *et al.* discuss the structural features leading to the transport of individual water molecules. The exceptional sub-Ångstroem data obtained for a yeast aquaporin is particularly valuable to experimentally visualize hydrogen atoms, an indispensable information to understand water translocation. The third illustration concerns NMDA (N-methyl-D-aspartate) receptors, which belong to the family of ionotropic glutamate receptors, well known for their role in brain functions. Combining different sets of experiments, Regan *et al.* were able to obtain structural data of the whole heterotetramer. They explain herein the function and pharmacology of these ligand-gated ion channels as inferred from their data.

The second part illustrates two aspects of membrane fusion. Understanding this important process in membrane remodeling obviously needs multiple experimental approaches and also fundamental concepts in physics. Kozlov *et al.* show how physical concepts, based on the existence of membrane tension, can drive the fusion. The paper also addresses the question of the origin of the membrane tension, and proposes a mechanism that leads to fusion. Baquero *et al.* discuss the role of specific proteins in viral fusion, a process that will allow enveloped viruses to enter the cell. Based on the current structural knowledge from proteins belonging to different viruses, they discuss the mode of action of class III viral glycoproteins in the catalysis of membrane fusion, involving structural rearrangements from the pre- to the post-fusion states.

Two aspects of mitochondrial membranes are shown in the third part. Mitochondria are surrounded by two membranes and fulfill elementary tasks for the cell. Both examples are related to large molecular machineries. Bohnert *et al.* discuss how membrane proteins are inserted into the mitochondrial membranes. Indeed, most of them are encoded by nuclear DNA and expressed in the cytosol. In particular, based on the current functional and structural knowledge, they compare different machineries that are necessary for the insertion of proteins having different topologies. Letts *et al.* report on recent structural data obtained on respiratory complex I, the first element of the oxidative respiratory chain that will lead to the synthesis of ATP. They compare the structures of a bacterial complex obtained by electron microscopy, to the bovine one obtained by crystallography.

The fourth and last part of this issue is focused on two technics that are currently revolutionizing the field of membrane structures (for individual protein structures, and for large molecular assemblies). Electron microscopy is a well-known approach which provided extensive data on viruses. Until recently, only large particles with high internal symmetry led to quasi-atomic data. Now the dogma was broken thanks to tremendous technological improvements on the detection of electrons. Vinothkumar shows how membrane proteins benefit from such developments. Working on single particles (or nanocrystals with a limited amount of particles) is conceptually very attracting, and becomes now possible with the emergence of X-ray free electron lasers. The paper by Neutze *et al.* updates the recent achievements on membrane proteins. They also show how the use extremely strong X-ray

pulses opens the way to time-resolved experiments in unprecedented short time-scales. This new tool should therefore not only bring structural information but also new insights in structure and dynamics of membrane proteins.

All the findings discussed in this issue are based on studies that represent real *tours de force*. We are delighted that the authors we have contacted accepted to contribute to this issue and hope that it will be a source of inspiration to the readers.