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Driven by the hydrophobic effect, phospholipids, sphingolipids and – in many cases - sterols spontaneously assemble into non-covalent polymeric structures that are known as biological membranes. The self-sealing properties of membranes form the basis of macroscopic compartmentalization that enabled life through the formation of cells and intracellular organelles. Although the principles that govern membrane formation are simple, the resulting double-layered structures are chemically and physically more complex than any other cellular structure, posing tremendous challenges for experimental and computational exploration even today. The vast complexity of biological membranes is caused not only by the large number of different lipids that coexist in any membrane, but also by the presence of integral and peripheral membrane proteins that functionalize membranes and compensate for their intrinsic impermeability to the water soluble molecules that are found on either side of these boundaries.

Going beyond the molecular complexity of biological membranes, many cellular processes depend on the cell's ability to change the shape, or curvature, of their membranes at will and with astounding spatial and temporal accuracy (Figure 1).

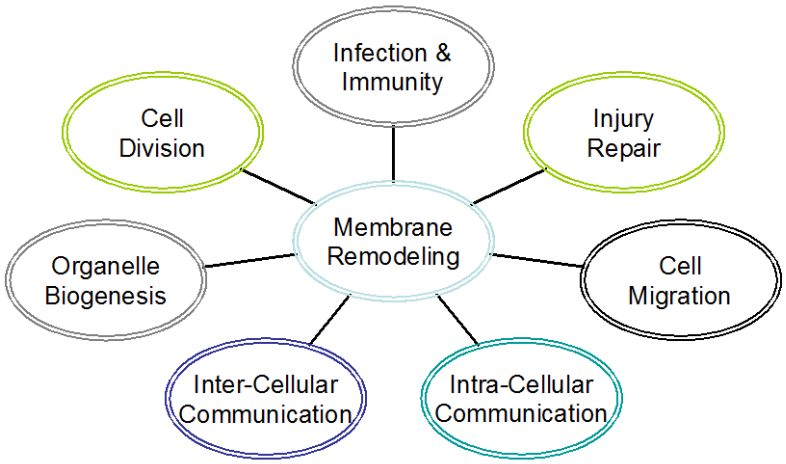

Fig. 1: Physiological functions related to membrane remodeling.

At the biochemical level, many of the players that participate in these processes have been identified over the past two decades. However, mechanistic understanding of how membrane shapes are changed – a process also known as membrane remodeling – lags significantly behind our knowledge of inventory, and understanding of both the spatial and temporal dynamics that control membrane remodeling processes is only in its beginnings.

What are key factors that slow progress in understanding this important part of biology? A first reason is rooted in the fact that structural biology of the bilayer:water interface remains a largely unmet challenge. Despite a few remarkable exceptions, this area of investigation does not currently have a clear path forward because the reconstitution of complex membrane remodeling processes in the presence of ideally asymmetric bilayer substrates has yet to be accomplished. A second reason lies in the physical chemistry of membranes themselves. Despite tremendous progress in some areas, thermodynamic description and computational modeling of asymmetric bilayers that approach the chemical diversity of actual bilayers is beyond of what can currently be accomplished. Related to this lack in understanding of bilayer physics is a third challenge: standardization and validation of experimental approaches. As the pace of investigation has increased over the past few years, conflicting mechanistic models

have begun to emerge that very well may turn out to be victims of circumstance, dealing with processes that act on a substrate we do not yet fully understand. Lastly, new membrane-dependent processes and proteins/protein complexes acting at and on the membrane are still being discovered, emphasizing the dynamic character and complex regulatory roles that membranes have far beyond the classical realms of membrane fusion, fission and endocytosis.

For this focused issue, we have invited both established and new investigators to contribute short reviews about various very active research topics in the area of membrane remodeling. We particularly asked them to identify open questions and challenges in their fields, discuss approaches to tackle them and to provide their vision how their research areas will develop in the coming years:

In the first review of the series, Low, Bohuszewicz and Liu focus attention on recent discoveries of membrane remodeling processes in prokaryotes, where they mediate, amongst others, the formation of outer membrane vesicles or allow cell division. Whilst many of the proteins players acting on prokaryotic membranes are still to be discovered, already now alternative membrane remodeling strategies compared to eukaryotes can be recognized.

In the second review, Henne discusses membrane-remodeling processes at contact sites between organelles, and how these processes contribute to organelle function. Due to their complex architectures and often transient nature, these contact sites are particularly challenging to study. Only lately, some protein players have been identified at membrane contact sites, pushing the expansion of this highly active research field.

The third review by Barbot and Meinecke continues the focus on membrane dynamics in organelles by looking at membrane-remodeling processes in mitochondria, especially on cristae membranes that constitute invaginations of the inner mitochondrial membrane. They discuss how reconstitution experiments and structural biology approaches have shed first light how different protein machineries work together to form the various cristae shapes.

Shifting attention from membrane dynamics of preformed organelles to de novo organelle formation, Turco and Martens examine reconstitution approaches of autophagic processes in the fourth review of this mini series. Many of the involved protein players in autophagy have been identified by various screening approaches, but the basic principles how they work in concert to mediate membrane-dependent protein degradation processes are just emerging now.

Focusing on the role of membrane remodeling defects in disease, the fifth review by Hohendahl, Roux and Galli discuss how mutations in the membrane remodeling proteins dynamin and amphiphysin interfere with membrane homeostasis of muscular T-tubules. As a recurring theme, this manuscript highlights the necessity of tightly regulated protein interplay at the membrane surface for proper physiology.

In the sixth review, Lampe, Vassilopoulos and Merrifield revisit the field of clathrin-mediated endocytosis, which has been extensively examined by many different groups; intriguingly, there is still no consensus how membrane curvature is created in clathrin-coated pits. The review explores how flat clathrin plaques found in certain cell types challenge the canonical model of clathrin-mediated endocytosis.

Last but not least, the seventh review in this series by Davtyan, Simunovic, and Voth describes the development of innovative computational approaches in the field of membrane remodeling. Using newly developed coarse-graining methods and employing vastly increased computational resources, complex membrane-dependent processes are now becoming tractable by computational approaches and are producing remarkable convergence with actual experimental data. These developments are extremely exciting because the marriage between experiment and computational approaches holds the potential to provide true mechanistic understanding of membrane remodeling in complex systems.

We believe that this broad collection of articles related to membrane remodeling will serve as an exciting primer for a general audience, students and teachers alike, while providing a glimpse of

things to come for those already involved in one of the most rapidly evolving fields of contemporary life sciences.

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