

## Preface

Membranes define cells and many organelles within cells. Along with the genetic material, cellular membranes are arguably the most important cell components that carry out thousands of essential functions that define life, from the most primitive microorganisms through the plant and animal kingdoms up to man. Membranes are involved in such diverse cellular functions as transport of nutrients, ion conduction, photosynthesis, respiration and ATP synthesis, signal transduction, vision, hearing, cell migration, fertilization, development, and many more.

For about half a century now, we know that the basic building block of biological membranes is the lipid bilayer. Embedded in the fluid lipid bilayer are proteins of various shapes and traits. This volume illuminates from physical, chemical and biological angles the numerous – mostly quite weak – interactions between lipids, proteins, and proteins and lipids that define the delicate, highly dynamic and yet so stable fabric that gives biological membranes their shape and function.

Even though the basic bimolecular leaflet structure of membranes has been discovered many decades ago, more recent research has considerably refined the early “fluid mosaic” model of the structure of biomembranes. As briefly recounted in Chapter 1, it has been recognized that the membrane-water “interface” occupies a considerable fraction of the entire membrane volume that has many previously under-appreciated consequences, for example, on how proteins interact with membranes or become inserted into membranes. It has also become increasingly clear that the “fluid mosaic” model does not suffice to describe lateral heterogeneities that exist in biological membranes and that affect many membrane functions – for example, in signal transduction, protein sorting, endocytosis, or the budding of enveloped viruses. Biological evidence points to a membrane structure that is laterally highly organized, while still retaining predominantly liquid characteristics. In physical terms, membranes could be considered to consist of a mosaic of fluid grains of different degrees of pseudo two-dimensional liquid order. Our current level of understanding and consequences of this membrane structure of organized fluid domains on various micro- and nanoscopic length scales are summarized in Chapters 13 and 14. Some answers emerge from this research on why cells make many lipids with different properties, but the long-standing question why cells make as many lipids as they do (literally thousands) is still not answered by even the most recent research in this rapidly evolving field.

The four chapters collected in Part 1 illuminate how proteins are inserted into biological and model membranes. Since the crowded environment of a cell membrane, namely the laterally and vertically compartmentalized lipid bilayer, is so different from the crowded aqueous environment of the cytoplasm, the folding and insertion of membrane proteins proceeds along very different biological pathways and according to very different physical principles than the folding of soluble proteins. The major building blocks of membrane proteins are  $\alpha$ -helices and  $\beta$ -sheets and the generation and insertion of these elements of secondary structure are described in Chapters 1 to 3, respectively. Chapter 4 focuses on what happens when membrane protein folding goes wrong and causes disease.

Not only do lipids shape proteins, but proteins also shape lipids. The two chapters in Part 2 focus on this problem and illuminate how specific lipids can be dramatically distorted on membrane protein surfaces as seen by x-ray crystallography, but also how lipid-protein interactions can be highly dynamic at these interfaces when examined by nuclear magnetic resonance techniques.

Many diseases, including some that are unleashed by biological terrorism agents, are caused by protein toxins that have to breach the cell membrane to reach their point of action. Examples include diphtheria and anthrax toxins. Other toxins such as those from staphylococci, clostridia, or sea anemones are toxic because of their pore forming activities in membranes. Since these proteins are facultative membrane proteins that can exist in soluble and membrane-bound forms, they offer interesting avenues to study membrane protein insertion in addition to studying their mechanism of pore formation and toxicity. Chapters 7 and 8 deal with these mechanisms and Chapter 9 gives an overview of the action of antimicrobial peptides on membranes.

Viruses constitute another class of biological agents that cause disease. While very little is known on how non-enveloped viruses breach cell membranes, membrane-enveloped viruses enter cells by membrane fusion. Chapter 12 recounts how viral fusion proteins have evolved to orchestrate the formation of fusion pores through which viral nucleocapsids and viral genomes are delivered into the cell cytoplasm. Just as viruses gain cell entry by membrane fusion, some cells fuse with one another to generate multinucleated cells. This occurs in fertilization, but also in development – for example when myotubes are formed in muscle development or when epithelial cells fuse in nematode development as summarized in Chapter 10. The molecular mechanisms that govern intracellular membrane fusion, which is essential for the biogenesis of organelles, exocytosis and synaptic transmission are summarized in Chapter 11.

Many cellular proteins are targeted to membranes in response to signals from the outside or from within the cell. Switching between membrane-bound and soluble forms of these proteins regulates a huge number of metabolic responses that impact on cell growth, migration, and development. The volume closes with a collection of Chapters that describe how different protein modules are recruited and bind to membrane surfaces. Chapter 15 gives a broad overview over the many families of membrane targeting domains that are present in eukaryot-

ic cells. Chapter 16 focuses on the mechanisms of membrane interactions of one of these families, namely the C2 domains. Chapter 17 illustrates with two prominent examples how some of these domains cooperate to form allosteric molecular switches on membrane surfaces.

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