Preface

Why write a book on cell membranes? Being a full-time teacher now, writing this book on cell membranes brings together two loves—studying ion channels as a graduate and a postdoctoral student and, more recently, teaching biology to undergraduate students. Writing this book caps a scientific career in research into the structure–function relationship of ion channels using mostly model membrane systems. I first fell in love with cell membranes as a student at the University of Basel, Switzerland, when a graduate student in Hansgeorg Schindler's biophysics course demonstrated the reconstitution of single channels in planar lipid bilayers. The simplicity and beauty of the ensuing single-molecule activity—repeatedly sweeping across the green screen of an oscilloscope— elicited solely from reconstituted synthetic phospholipids and a small amount of gramicidin peptide solution, introduced me to a core truth about cell membranes as a complex system: their function is the result of lipids and proteins working together to produce an effect that neither could do on its own.

When I started writing the book around 2003, the existing fluid-mosaic model of cell membranes as conceived by Nichols and Singer in 1971 was ripe for revision in order to better account for the existence of lipid domains. The accelerating pace of determining high-resolution structures of membrane proteins enhanced the insight into the complex behavior of cell membranes. Particularly, progress in solving the atomic structures of channels has dramatically changed the field's rudimentary understanding of transport mechanisms. In the 1970s, kinetic models with multiple energy barriers along cylindrical pore models tried to explain ion selectivity and specificity of transport, but were sorely lacking structural evidence. Today, molecular modeling based on detailed high-resolution structures of transporters in various states of activity shows the sophisticated gating and selectivity mechanisms of proteins, which undergo conformational changes to capture substrates on one side of the membrane and release them on the opposite side.

Cell membranes are essential components of all living organisms—bacteria, animals, and plants. Membranes regulate nutrient uptake and waste removal, protect against environmental toxins and infectious microorganisms, store energy like batteries, catalyze chemical reactions, recognize stimuli from their surroundings, and transduce signals from external hormones and growth factors into intracellular responses. Two of the most fundamental biological processes—respiration and photosynthesis—are carried out by membrane-bound enzymes. Membranes being such centrally important structures of cells, it is thus not surprising that, on the one hand, teaching about membranes becomes an indispensable component of any course in the life sciences, from biophysics to neurobiology, from cell biology to physiology, from microbiology to medicine. On the other hand, learning about cell membranes expects from students an understanding of all the natural sciences, and a grasp of chemistry and physics, of mathematical modeling, and of engineering. With this textbook, faculty can use an interdisciplinary approach when preparing a lecture on cell membranes. A cell biologist can find information about the biophysical properties of membrane lipids and bilayer organization, and a structural biologist will find information about physiology and hormone receptors.

This book therefore offers a long-overdue synthesis of our knowledge of cell membranes. I organized the book to guide the reader first through basic descriptions and explanations of the molecular composition and physical properties of cell membranes, surveying the structural diversity of membrane proteins and lipids separately. The book then moves on to discuss how the functions of both membrane proteins and lipids depend on each other to promote the four basic functions of cell membranes: being barriers, mediating exchange of molecules and information to maintain cellular compartments, promoting signaling and adhesion, and being metabolically self-renewing cellular structures. Having always had an interest in the evolutionary history of life, I have included in the book a special emphasis on the biological diversity, evolution, and origins of membranes. Core questions in modern biology are in the understanding of the complex interactions of many molecular components to produce an orderly cellular process and how membranes contribute to information processing in living organisms. To this end, the book describes the use of model membrane systems to gain insights into membranes in living cells. With this reductionist approach, biologists are able to answer important questions about the structural organization of cells, and how this molecular organization contributes to the behavior of organisms.

The reader will also come across, and hopefully appreciate, the use of categories for proteins and lipids and the need to choose from alternative ways to categorize proteins and lipids by structure, function, secondary structure composition, membrane location, or membership in families and superfamilies. I hope that the corresponding tables are useful and function as an easy reference for the reader. Many more tables could have been generated, given the large numbers of known proteins and lipids, and relying mostly on examples was often the best option in order to stay on message and not overwhelm the topic with too many details. Occasionally, I perceived a real need to abandon or tweak existing categories, and one of the novel categories I use in this book employs the term 'surface-bound' membrane protein—that is, to combine peripheral, lipid-anchored, and monotopic membrane proteins into one group distinct from transmembrane proteins. Conventional terms like integral and intrinsic, while still valuable for methodological discussions, fall short of describing the variation in the ways membrane proteins are associated with lipid bilayers. Interestingly, reviewers sensed my occasional struggle and the work that went into making sense of existing but conflicting categories and nomenclature. A good example is the use of the terms phospholipids and glycolipids, both of which are ambiguous, yet have clear meaning to the veteran scientist, until they do not. Thus, I hope the 'veteran' reader will appreciate my approach of consolidating terminology and making choices in favor of some but not other terms.

There is yet another approach that I felt was necessary: an emphasis on concepts rather than methods, although each chapter ends with a list of reading materials where experimental information can be found about the topics covered. As a result, the appendices in the book include information, albeit concise, about amino acid properties important for protein structure prediction methods, the diversity and properties of detergents, and reconstitution strategies to solve high-resolution structures through X-ray crystallography, nuclear magnetic resonance (NMR), and electron diffraction techniques. Many other experimental methods in the biochemical, structural, and genetic analysis of membrane lipids and proteins are mentioned (and some are explained in more detail) throughout the chapters.

I want to thank many people who have helped me become the scientist and teacher I am today: Hansgeorg Schindler and Jurg P. Rosenbusch at the Biozentrum of the University of Basel, where I learned the ropes of membrane biochemistry and ion channel reconstitution and functional analysis; Richard Zimmermann and Matthias Falk who showed me the amazing world of *in vitro* synthesis of membrane proteins; and Maurice M. Montal and Reza Ghadiri who introduced me to the world of synthetic, channel-forming peptides. While always working with synthetic bilayers, these scientists all came from different backgrounds, allowing me to see and think like a physicist, a cell biologist, a chemist, or a neurobiologist. I worked with bacterial porins and mammalian gap-junction channels, with synthetic peptides mimicking the nicotinic acetylcholine receptor pore structure, and cyclic nanotubes, a non-natural peptide designed to mimic the channel architecture of gramicidin peptides. Thus, at the very end of my research career, I came full circle to my very first look at a cell membrane.

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