

## Preface

CELL MEMBRANES ARE PRIME EXAMPLES OF SYSTEMS BIOLOGY. Only by considering the collective behavior of the lipid bilayer, including the ways that proteins interact with the lipids, the capability of lipids to form polymorphic structures, and the properties of the outer and inner surfaces of the bilayer, can one unravel how this biological system works. Today, all areas of cell biology are confronted with the complexity of the biological systems under study. This is the major challenge that molecular biology is trying to cope with. Cell membrane research is a forerunner in handling biological systems because membranes had to be considered as systems from the start. Membranes are wonderworlds of meso-scale organization, providing a perfect arena for dealing with dynamics and context. All the molecules involved in a membrane process are kept localized and functional by physical and chemical properties of the system. We learned earlier than other fields that to gain access to the workings of membrane processes, it is not sufficient to make use of only one method; multidisciplinary is required to open the Pandora's box of membrane secrets that membranes house. This will be the same in all systems biology approaches.

Particularly illuminating has been the way the physics of the molecules involved are shaping the behavior of membranes. Examples are planar diffusion in the bilayer and the role of phase separation in membrane subcompartmentalization, first observed in model membranes and then extended to complex cell membranes, demonstrating how collective behavior can be employed to regulate cell organization. Membrane nanodomains are formed and dissolved with the lipid in the bilayer playing a dominant role. Lipid research is gathering strength but there is much more to do. We hope that this book will promote interest among young researchers to leave the mainstream and enter a field full of possibilities for pioneering discoveries. Thirty percent of all proteins are transmembrane proteins and many other proteins spend part of their lifetime at either side of cell membranes. The membranes are indeed vital hubs of activity and are certainly worthy of more attention. One entry point could be the role lipids play in cell metabolism. Cell metabolism plays a key role in regulating cellular processes and health. Nevertheless, we know embarrassingly little of how metabolism functions. The biochemistry of cell metabolism rests on pioneering work done over 50 years ago. It is time to take a deeper look with all the capabilities of today. Lipid, sugar, and amino acid metabolism are functioning as a system but how is not known. Most metabolites are intermediates in the anabolism and catabolism of proteins, nucleic acids, and carbohydrates. Lipids, however, are end products and are built into cell membranes where they function. Mapping and understanding lipid metabolism will be the easiest way to open up new vistas to metabolism function. By studying how lipid metabolism changes during disease pathogenesis, light will be thrown on lipid diversity and open up totally new perspectives on how to combat disease.

In compiling this second edition of *The Biology of Lipids* we focus on the membrane lipidome, bringing together the latest cutting-edge approaches that are providing new insights into the nature of this complexity, uncovering the biophysical properties bestowed on diverse lipids species and the resulting functional consequences for membrane function. Analysis of the roles of lipids in specific membrane domains such as exosomes (Skotland et al.) and caveolae (Kenworthy et al.), and in specific processes such as endocytosis (Johannes et al.), exocytosis (Kim and Burd), Ras signaling (Liu et al.), endoplasmic reticulum stress (Ernst et al.), transmembrane signaling (Girysh et al.; Shi et al.), and memory (Wallis and Meunier) demonstrates the diversity of locations and functions of membrane lipids and uncovers fundamental new principles of lipid function. Understanding these processes requires new methods and huge advances have been made in this area in recent years

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(Uematsu and Baskin). These and other new cell biological and biophysical approaches are uncovering how these roles rely on the diverse properties of individual lipids but working within dynamically interacting assemblies of lipids (Mayor et al.; Doktorova et al.; Shelby and Veatch). The dynamics of lipid interactions are not only at the level of individual membrane systems but are maintained or modulated by the flow of lipids between compartments, as exemplified by the cellular mechanisms involved in the trafficking of cholesterol (Ikonen and Olkkonen). Further complexity of membrane lipids is achieved through modifications, the epilidome (Penkov and Fedorova). Phosphatidylinositol lipids represent a well-understood example of how specific lipid modifications lead to distinct functions (Davies et al.). We are also learning about the role of more enigmatic modifications, such as lipid unsaturation, and how they contribute to membrane function across evolution and in response to different environmental conditions (Harayama and Antonny).

A new understanding of membrane lipid biology, as exemplified in this volume, will also have immense implications for understanding human disease. Humankind is afflicted by a pandemic, dysmetabolism, worse than Covid-19. Overweight and obesity are spreading around the world. Unhealthy weight leads to diseases such as diabetes, cancer, and dementia. While plasma lipids have received great attention from biomedical researchers we must also understand the crucial role of membrane lipids in the pathogenesis of these diseases. Here the plasma lipoproteins are key players delivering lipids from the liver to cells in the body tissues and simultaneously removing them from the periphery. The LDL and HDL family of proteins form an amazing surveillance system to regulate the different molecular species in the cellular lipidomes to maintain their functionality, perhaps explaining why the plasma lipidome mirrors changes in the whole body lipidome. But exactly how is unknown. The field is underresearched. High time for lipid researchers to get involved!

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