Preface

TAKING A LOOK BACK, I GLANCED THROUGH the index of the biochemistry textbook from my medical school days to search for cell membranes. There was nothing. I found 20 pages on the lipid constituents of tissues and chapters on lipid metabolism and nutrition, but nothing about the structures that those lipids form or their functional importance. The book was published in 1957. From a current standpoint this is quite shocking and reflects how curricula are continually changing.

By 1925, Gorter and Grendel had already performed their classic experiment revealing that the red blood cell membrane is a lipid bilayer. They used acetone to extract the lipids, determined the surface area of the extracted lipid in a Langmuir trough, and compared this value with the surface area of erythrocytes calculated from dried smears. We now know their studies had two errors. Acetone does not extract all the lipids, but this error was offset by their error in measuring the red cell surface area. Nevertheless, Gorter and Grendel came to the conclusion that the ratio of surface area occupied by lipid to the area of the cell is around 2, a number consistent with the idea that the cell is enveloped by a bimolecular leaflet.

From then on, lipids dominated membrane research. In the Davson–Danielli unit membrane model, proteins were plastered on both sides of the bilayer but no protein was thought to penetrate through the two lipid leaflets. The permeability of cell membranes to ions was postulated to be governed by electrostatic interactions and membrane potential. Because this model could not account for various forms of accelerated ion transport observed across membranes, lipid pores were postulated to extend through the bilayer. This all sounds amazing, but it illustrates how radically our understanding of biology has changed in the past 100 years.

The next phase in membrane research came in the 1960s, when studies of mitochondria and chloroplasts started to challenge the unit membrane concept. Detergent solubilization revealed the existence of lipoprotein subunits in these membranes. In addition, electron microscopy seemed to support a new model of membranes in which they were built from lipoprotein subunits. Thus, membrane proteins had moved center stage and started to attract more and more attention.

It was not until the early 1970s, however, that experiments showed that one and the same protein could be labeled from both sides of the red blood cell plasma membrane; thus the concept of transmembrane proteins was born. The composition of the two lipid leaflets was also found to be asymmetric, with choline-containing lipids in the outer leaflet and phosphatidyl ethanolamine, phosphatidyl serine, and phosphatidyl inositol on the inside. Freeze-fracture studies demonstrated that the cell membranes can be split down the middle, and the fracture planes revealed intramembrane particles thought to represent individual transmembrane proteins.

Also groundbreaking were studies demonstrating that proteins and glycolipids can move laterally in the plane of the membrane, revealing the fluid nature of the lipid bilayer. At that time, my colleagues and I were studying the budding of an enveloped virus, Semliki Forest virus, through the host cell plasma membrane. This budding process was enigmatic because during the assembly of the viral envelope into a specific domain in the plasma membrane, host proteins were excluded but viral envelope proteins were specifically included. Because the dogma in virology was that envelope proteins cannot penetrate the bilayer, no plausible model for the formation of an envelope virus could be formulated. Henrik Garoff and I solved the problem by demonstrating that envelope proteins are transmembrane proteins that connect to the underlying nucleocapsid, which functions as a template for the budding process.

This research culminated in the Singer–Nicolson model for cell membranes. In this model, transmembrane proteins were embedded in the bilayer, with peripheral proteins binding to the membrane on both sides. The lipid bilayer became the sea in which protein "icebergs" were free to float around. This is the model that dominated membrane research in the years to come. Meanwhile, recombinant DNA technology caused a revolution in membrane protein research. Quickly, membrane proteins went from being extremely difficult to purify, and therefore to work with, to being characterized in ever-increasing numbers and having their atomic structures determined. Meanwhile, from studies on lipid metabolism, research on membrane biosynthesis moved to the forefront, specifically focusing on assembly of proteins into membranes. The roles of transport vesicle formation and fusion in membrane trafficking became hot areas of research, again with a focus on protein cargo and on the protein machineries involved.

This focus on proteins led to a near-total neglect of the role of lipids in the function of biological membranes. These were relegated backstage and viewed as a boring, inert solvent for hydrophobic proteins. The early insights that specific lipids can regulate membrane protein function were forgotten. In the vast field of signal transduction, roles for lipids as potential allosteric regulators of signaling processes were no longer proposed—indeed, even today, lipids rarely appear in reviews on signal transduction.

The introduction of the "lipid raft" concept that postulated the existence of dynamic membrane subcompartments was a turning point and stirred up the field. From being a passive solvent, the lipid bilayer took on an active role in membrane function. The concept caused controversy, naturally so in an area of research plagued by a lack of technologies to study dynamic processes in two-dimensional fluids. Indeed, the skepticism was evident in the titles of some reviews: "Lipid rafts: Elusive or illusive"[1] or "Lipid rafts: Now you see them, now you don't."[2] The accelerating development of novel and sophisticated spectroscopic and imaging technology, however, has allowed cell membrane research to pick up speed. Moreover, the deadlock in generation of analytical tools to study lipid diversity has been broken. Now, cellular lipidomes can be analyzed by sensitive high-resolution mass spectrometry. The question of why our cells make so many different species is beginning to be answered.

It is this excitement that this book tries to catch. Membrane researchers are now starting to include lipids in their repertoire. The protein-only focus will soon be gone. Cell membranes are two-dimensional fluids, composed of a lipid bilayer crowded with proteins; thus, we have to study both the lipids and the proteins together to come to grips with this fascinating fluid.

I wish to thank Richard Sever for persuading me to edit this book, and Barbara Acosta for her untiring support to make it a reality. I also thank all of the authors who agreed to contribute chapters and Kostas Margitudis for drawing the cover.

KAI SIMONS

[1]Munro S. 2003. Lipid rafts: Elusive or illusive? *Cell* **115:** 377–388.

[2]Shaw AS. 2006. Lipid rafts: Now you see them, now you don't. *Nat Immunol* **7:** 1139–1142.

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