PREFACE

This book presents an overview of membrane organization and lipid rafts in the cell and artificial membranes. The topics analyzed in this book cover a broad spectrum of functions played by lipid rafts in membrane organization within the cell and artificial membranes, and presents new information in this area of research. The topics analyzed include: fluid-mosaic cell membrane structure from cellular control and domains to extracellular vesicles; lipid rafts in binary lipid/cholesterol membranes; membrane assembly and lipid rafts in the cell and artificial membranes; the effect of lipid peroxidation; drugs, delivery systems and membrane organization in model and cell membranes; role of sphingomyelin on membrane domain formation and its influence in protein interaction focusing on the nanometer scale; lipid rafts and cell adhesion; mutual modulators of cell signaling; and finally, roles of glycosphingolipids in the regulation of the membrane organization and cell signaling in lipid rafts.

Chapter 1 - Living cells are surrounded by a fluid-mosaic plasma membrane that provides a barrier and a communication filter with the extracellular microenvironment. Plasma membranes are also essential for transport into and outside cells, and they provide important recognition structures, receptors and enzyme platforms for cells. Plasma and other cellular membranes assemble because of their physical properties, which allow the basic constituents to form a lipid bilayer with intercalated proteins and glycoproteins. These components can move laterally and selectively within the membrane plane and associate with similar or different constituents to form specific, small and large functional domains. In describing the macrostructure and dynamics of plasma membranes, membrane peripheral components, membrane-associated cytoskeletal structures and extracellular matrix are also important in maintaining membrane structure and dynamics by constraining the motions of membrane components and acting as traction points for cell motility. Plasma membrane components can be released from cells as secretory molecules, enzymes, receptors, large macromolecular complexes, membrane vesicles and exosomes that can modify the microenvironment and initiate specific molecular cross-talk between cells and tissues.

Chapter 2 - The lipid membrane was once modelled as a homogeneous two-dimensional fluid, however it is in fact a patchy, inhomogeneous state of matter. Inhomogeneities in membranes are now understood to be crucial to their function. These so-called lipid rafts are described as lateral lipid assemblies enriched in cholesterol, which have a greater degree of molecular order. They are believed to play a role in membrane bound protein insertion, sorting, and function. However, size, lifetime, and even the existence of rafts are still the

subject of debate. This chapter discusses a role for lipid rafts in membrane homeostasis, experimental techniques to detect rafts, and the authors' current physical models of how rafts may form. In particular, recent X-ray and neutron scattering experiments will be highlighted, which have revealed the lateral molecular ordering of cholesterol in lipid membranes, and have enhanced the authors' understanding of lipid rafts. Those experiments have in particular demonstrated that a drug, such as aspirin, can interrupt membrane homeostasis by influencing the formation of lipid rafts.

Chapter 3 - The adaptability of biological membranes is dependent on their structures and biophysical properties, which are determined by the types of lipids and proteins that make up the membranes. In terms of lipids, the heterogeneous membrane is believed to consist of a mixture of a dispersed "lipid raft" phase, enriched in cholesterol, raft-associated proteins, and saturated lipids (such as sphingolipids), and the "non-raft" matrix phase enriched with phospholipids containing polyunsaturated fatty acids. Lipid peroxidation of membrane lipids is accompanied by addition of numerous polar moieties on polyunsaturated fatty acyl chains present in the "non-raft" matrix phase. Thus, phospholipid oxidation products are very likely to alter the properties of bio-logical membranes, because their polarity and shape may differ significantly from the structures of their parent molecules. Thus, they may modify lipid-lipid and lipid-protein interactions and, as consequence, also membrane protein functions.

Chapter 4 - Evidence places lipid-lipid interactions and membrane structural alterations as central mechanisms underlying the action of membrane lipids. In the past decades several studies have shown that sphingolipids (SLs) have a fundamental role in several cellular events such as endocytic trafficking, apoptosis and cell migration. Membrane models containing different lipid composition have been contributing to a detailed knowledge of sphingolipid-induced membrane biophysical alterations. The segregation of SLs into specialized domains, such as lipid rafts and ceramide platforms, is a major event influencing membrane organization and regulation of cell functions. Particularly, the interaction between these compositionally and functionally distinct membrane compartments with drugs and delivery systems has shown to play a pivotal role in the efficacy of such treatments, namely in cancer therapy. In this chapter the authors will critically discuss the impact of membrane compartmentalization on different cancer therapeutic approaches.

Chapter 5 - The advent of novel experimental techniques based on physical principles opens a window to the nanometer world facilitating a renewed and detailed study of membranes. These specific techniques enable an understanding of how biologic-membrane functioning is related to membrane physical properties on various scales of time and dimension.

A preferential interaction between sphingomyelin (SM) and cholesterol (Cho) in both cell and model membranes has been proposed as a key influence on the formation of Cho- and SM-rich membrane domains. This chapter provides insights into the lateral structure and molecular organization of lipid membranes on the nanometer scale. The authors focus on how the specific molecular structure of SM affects the lateral behavior and physical properties of both model and natural membranes.

In addition, the lateral structure controls the mechanical properties of the membrane and thereby protein-membrane interactions. Many proteins, targeted to membrane microdomains by favorable associations with ordered lipids, are linked to the saturated acyl chains that partition well into these domains. This chapter shows, on the nanometer scale, the interaction with membranes of α-hemolysin (HlyA), an acylated protein. Atomic-force–microscopy

images indicated that the HlyA interaction appears not to conform to the general strategy described for other invasive proteins.

Chapter 6 - Not long after the publication of Singer and Nicolson's theory on the fluid mosaic model of the cell membrane did the intriguing possibility arise that the seemingly heterogeneous 'pool' of the lipid bilayer was, in fact, dotted with 'rafts' of more ordered lipid/protein domains. The plasma membrane is no longer thought as simply a stochastic admixture of lipids, proteins, and sterols but as dynamic 'sea' filled with ordered microdomains of membrane constituents, the so-called lipid rafts. It is the ordered state of the lipid rafts that confers functional relevance to a variety of inter- and intracellular processes including protein trafficking, signal transduction, and cell-cell/matrix adhesion. Indeed, the parallels between lipid rafts and other membrane trafficking systems that modulate the activity of cell signaling species have been extensively surveyed. However, the precise interplay between cell adhesion molecules and lipid rafts is still being actively explored. Specifically, the association between junctional components and signaling effectors in the lipid raft environment is emerging as an increasingly relevant interaction for defining normal epithelial cell homeostasis. As a result, perturbing the balance of adhesion molecules and lipid raft constituents at the cell membrane–as often observed in skin disorders and malignancies–may synergize to promote pathogenic signaling. This commentary will explore the functional relevance of adhesion protein-lipid raft interactions in modulating essential signaling pathways, and the detrimental consequences of deregulating one or both components.

Chapter 7 - Glycosphingolipids (GSLs) are enriched in the membrane microdomains such as lipid rafts or glycolipid-enriched microdomains (GEM), hereafter, named as GEM/rafts. Polymorphic carbohydrate structures in GSLs have been demonstrated to regulate composition of GEM/rafts, and to determine the intracellular signaling and subsequent cell fates. Generally, disialyl gangliosides tended to enhance malignant properties of cancer cells, while monosialyl gangliosides often suppressed those phenotypes. Analysis of knockout (KO) mice of various glycosyltransferase genes involved in the ganglioside synthesis revealed that many functions of gangliosides deleted in some KO might be compensated by the remaining GSLs in the individual KO mice. However, some functions could not be replaced by other GSLs. Thus, the authors concluded that there are 2 main groups of GSL functions, i.e., 1. those with non-specificity, can be compensated with other structures, their total amounts are important, and no specific ligands have been identified, and 2. those with specificity, can not be replaced with other GSLs, their absolute amounts are critical, and probably specific ligands are present. Mechanisms for the regulation of cell signals by GSLs have been analyzed, and their novel actions based on the interaction between GSLs and membrane molecules remain to be elucidated.