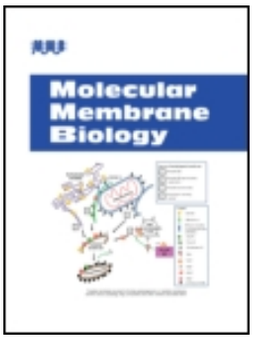

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Foreword: lipid rafts/biophysics, cell signalling, trafficking and processing

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Lipids and proteins are not distributed randomly and homogenously in biological membranes. Various domains exist in membranes in which particular lipids and proteins cluster together. One such domain is the cholesterol- and glycosphingolipid-rich lipid raft in which these lipids are in the liquid-ordered phase relative to the liquid-disordered surrounding lipids. Although originally implicated in lipid and protein trafficking, lipid rafts now appear to be involved in a range of biological processes including cell signalling, endocytosis, apoptosis, protein and lipid sorting and organization, and the regulation of proteolysis. Although questions remain as to the actual size of lipid rafts in living cells, whether all rafts are identical in composition, and where in the cell they form, an increasing body of evidence clearly indicates that certain lipids and numerous proteins are localized in discrete domains of the membrane and that this localization depends on the presence of cholesterol and the saturated glycosphingolipids. The analysis of the protein and lipid content of rafts has often relied upon exploiting their relative insolubility in non-ionic detergents at low temperature. However, recent work has shown that this technique may artefactually result in the aggregation of lipids and proteins which were not near neighbours in the original membrane. Increasingly, a range of biophysical imaging techniques are being used to visualize rafts in model and biological membranes. This issue brings together a series of review articles on lipid rafts by leading experts that focus on three key areas: the biophysics of rafts in model membranes and in living cell membranes, the role of lipid rafts in cell signalling, and the role of lipid rafts in the trafficking and processing of lipids and proteins.

In model membranes consisting of an unsaturated glycerophospholipid, sphingomyelin and cholesterol, the lipids readily partition into two separate phases, the liquid-disordered and liquid-ordered domains. John Silvius and Ivan Robert Navi describe how techniques based on fluorescence quenching and fluorescence resonance energy transfer (FRET) have been used to demonstrate the formation of nanoscale liquid-ordered domains in cholesterol-containing model membranes and to investigate the structural features of lipids and proteins that influence their partitioning between liquid-ordered and liquid-disordered domains. These authors also discuss how FRET-based methods have been used to test for the presence of rafts in the plasma membrane of mammalian cells and the further potential of FRET-based methods to test and refine current models of the nature and organization of membrane microdomains.

The planar nature of lipid bilayers makes them ideal for interrogation by atomic force microscopy (AFM). Lipid phases can be distinguished in the AFM due to changes in bilayer thickness caused by the differences in acyl chain packing. AFM can also image under physiological conditions and can resolve structures ranging from nanometres to tens of microns in size. Simon Connell and Alastair Smith review the results of AFM studies on model membrane systems, planar supported lipid monolayers or bilayers, with particular emphasis on phase separation, highlighting the relevance to understanding lipid raft formation in cell membranes.

Fluorescence Correlation Spectroscopy (FCS) provides exquisite sensitivity in measuring local concentrations, association/dissociation constants, chemical rate constants and, in general, in probing the chemical environment of the species of interest and its interactions with potential partners. Nicoletta Kahya and Petra Schwille review some applications of FCS to lipid and protein organization in model membranes with lateral heterogeneities which share some physicochemical properties with cellular rafts

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and how this relates to studies in more complex cellular membranes.

Katharina Gaus and colleagues review a 2-photon fluorescence microscopy approach which allows the visualization of membrane fluidity using the fluorescent probe Laurdan which exhibits a blue shift in emission with increasing membrane condensation. They give examples where Laurdan microscopy has been instrumental in quantifying the formation of condensed membrane domains and their cellular requirements and how microdomains identified by Laurdan microscopy are consistent with domains identified by other methodologies.

Cholesterol-rich lipid rafts have been implicated in a range of biological processes, for example, early events in signalling by the T cell receptor incorporate the function of lipid rafts. In T cells, molecules with a key role in T cell receptor signalling, including the tyrosine kinase Lck, localise to rafts. Panagiotis Kabouridis discusses current results and a model of how lipid rafts may regulate T cell receptor signalling, including data from the use of mutant forms of Lck that fail to localize to rafts and are unable to support signalling.

Functional polarization of leukocytes is required to accomplish immune function. Immune synapse formation or chemotaxis requires asymmetric redistribution of membrane receptors, signalling molecules and the actin cytoskeleton. There is increasing evidence that compartmentalization of the plasma membrane into distinct lipid microdomains is critical in establishing and maintaining this leukocyte polarity. Santos Manes and Antonella Viola discuss the roles of lipid rafts as organizers of T lymphocyte polarity during cell activation and migration, with particular reference to the assembly of specific rafts into large-scale domains to create plasma membrane asymmetries at specific cell locations, thus temporally and spatially coordinating cell signalling.

Polarized epithelial cells of multicellular organisms have a highly specialized apical cell membrane that faces the external environment and that differs in composition and function to the basolateral membrane that faces the internal milieu. In absorptive cells of the intestine and kidney, hydrolytic enzymes make up the bulk of the microvillar apical membrane proteins. Many of these are localized in lipid rafts where glycolipids, rather than cholesterol, together with the divalent lectin galectin-4, define these rafts. Michael Danielsen and Gert Hansen describe how the architecture of these rafts supports a digestive/absorptive strategy for nutrient assimilation, but also how they function in pathogen uptake and the protective role played by anti-glycosyl antibodies.

Infection of human erythrocytes by the malarial parasite, *Plasmodium falciparum*, results in complex membrane sorting and signalling events in the mature erythrocyte; events that rely on proteins resident in the erythrocyte lipid rafts. Kasturi Haldar and colleagues describe work that has been undertaken to characterize the major proteins present in erythrocyte detergent-resistant lipid rafts and which of these proteins traffic to the host-derived membrane that bounds the intraerythrocytic parasite. They discuss how these data suggest that raft association is necessary but not sufficient for vacuolar recruitment, and that there is probably a mechanism of active uptake of a subset of erythrocyte raft proteins.

Prions are the causative agent of the transmissible spongiform encephalopathies, such as Creutzfeldt-Jakob disease in humans. In prion diseases the normal cellular form of the prion protein (PrP^{C}) undergoes a post-translational conformational conversion to the infectious form (PrP^{Sc}). PrP^{C} associates with lipid rafts through association of its glycosyl-phosphatidylinositol anchor with saturated raft lipids and through interaction of its N-terminal region with an as yet unidentified raft associated molecule. David Taylor and Nigel Hooper review the role that lipid rafts play in the endocytosis of PrP^{C}, in signal transduction from PrP^{C} and in the conformational conversion of PrP^{C} into PrP^{Sc}.

Caveolae are flask-shaped membrane invaginations of the plasma membrane that have been implicated in endocytsosis, transcytosis, and cell signalling. Caveolae, often considered as a subset of lipid rafts, are involved in the uptake of some membrane components such as glycosphingolipids and integrins, as well as viruses, bacteria and bacterial toxins. Richard Pagano and colleagues review the accumulating evidence that endocytosis mediated by caveolae requires unique structural and signalling machinery, including the coat protein caveolin-1, and that the balance of glycosphingolipids, cholesterol, and caveolin-1 regulates caveolae endocytosis.

The amyloid-β peptide (Aβ), which accumulates extracellularly as plaques in the brains of Alzheimer's disease patients, is derived by sequential proteolytic cleavage of the integral transmembrane amyloid precursor protein (APP). A variety of studies indicate that cholesterol is an important factor in the regulation of Aβ production, with high cholesterol levels being linked to increased Aβ generation and deposition. Anthony Turner and colleagues review the evidence that amyloidogenic APP processing may preferentially occur in cholesterol-rich lipid rafts, and that changes in cholesterol levels could exert their effects by altering the distribution of

APP-cleaving enzymes within the membrane. In addition, they discuss that rafts may also be involved in the aggregation and clearance of Aβ by amyloid-degrading enzymes such as neprilysin and plasmin.

In conclusion, it should be evident from this issue that although we still have much to learn about lipid rafts, there is an increasing amount of biophysical data showing that lipids in membranes do exist in discrete domains, and that the segregation of lipids and proteins in such domains plays a critical role in a range of biological processes. Further technical developments will aid research on lipid rafts, and a greater understanding of their formation, structure and regulation may provide opportunities for therapeutic intervention in a number of diseases.

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