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Preface

Cholesterol is one of the major lipid components of the plasma membrane of mammalian cells. This lipid, with its fused ring structure, has very different physical properties from the phospholipid and sphingolipid components of the cell membrane. There has been a long interest in the role of cholesterol in determining the physical properties of a membrane and affecting biological functions. In recent years there has been a resurgence of interest in the physical properties of cholesterol and its relationship to biological function. Much of this interest has been focused on the question of the presence of cholesterol-rich domains in biological membranes that have particular biological functions [1]. In this issue several specific biological function that are related to the presence of cholesterol-rich domains are discussed. These functions are discussed along with reviews of our current understanding of the nature of cholesterol interactions with other membrane lipid components.

In order to understand the molecular properties of cholesterol in membranes, one has to begin with simpler mixtures than those of biological membranes. In relation to the formation of cholesterol-rich domains, the miscibility of cholesterol with other lipids is of particular relevance. This topic has been studied for many years. Cholesterol has long been known to restrict the motional properties of phospholipids in membrane. More recently, this has led to a description of a new phase, the liquid ordered phase, which has the properties of both the solid and liquid phase. The acyl chains are extended, with largely trans rotamers in the hydrocarbon chain, as in the solid phase. In addition, however, the rate of lateral diffusion is rapid and mimics that of the liquid phase. In addition to the effects of cholesterol on the bulk physical properties of the membrane, it has also been proposed that cholesterol forms specific complexes with phospholipids. The article in this issue by McConnell and Radhakrishnan makes a case, based on a consideration of the phase behavior and miscibility in monolayers, for the formation of condensed complexes of cholesterol and phospholipids having specific stoichiometries.

Silvius discusses the effect of phospholipid structure, both the headgroup as well as the degree of unsaturation of the hydrocarbon portion. They also review the evidence for the formation of cholesterol-rich domains in model membranes.

It is not surprising that cholesterol and phospholipids are not miscible in all proportions, with the two lipids being so different structurally as well as having different polarities. As a consequence, when cholesterol passes a certain mole fraction it forms crystallites that can be detected by calorimetry, diffraction and MAS NMR. Bach and Wachtel discuss the application of these methods in detecting cholesterol crystals. The dramatically lower solubility of cholesterol monohydrate crystals in bilayers of phosphatidylserine compared with phosphatidylcholine has recently been demonstrated by MAS NMR [2]. This may have particular relevance for the arrangement of cholesterol on the cytoplasmic face of cholesterol-rich domains in plasma membranes. A detailed understanding of the physical basis of this phenomenon is lacking. The biological relevance of the formation of crystalline domains is discussed by Mason, Tulenko and Jacob. They particularly focus on the plasma membranes from arterial smooth muscle cells and from ocular lens fiber cells. They present diffraction evidence that the cholesterol crystallites are part of the membrane bilayer and not as physically separate crystals. It is also suggested that the cholesterol crystallites of arterial smooth muscle cells may play a role in atherosclerosis, while in the case of the ocular lens fiber cells, they may be essential for the normal physiology. The phenomenon of the formation of ordered, crystalline-like domains of cholesterol in biological specimens is also discussed by Addadi, Geva and Kruth using recognition by cholesterol antibodies as the criterion for the presence of ordered cholesterol domains. Some of these cholesterol antibodies have been shown to interact with crystals of cholesterol monohydrate but not with monomeric cholesterol. Some of the antibody labeling patterns are responsive to agents or mutations that effect cholesterol trafficking.

Cholesterol is the only major lipid component in mammals that is not oxidized as a source of energy. A large fraction of the cholesterol in the body, apart from the liver, is delivered and removed by circulating lipoprotein particles. The relationship of this cholesterol traffic to the formation and stability of cholesterol-rich domains in membranes is outlined by the Fieldings. In their review, the composition and properties of the two types of cholesterol-rich domains, rafts and caveolae, are discussed. They suggest that changes in free cholesterol, through cholesterol trafficking processes, can modulate signal transduction processes by modulating the formation of protein complexes in cholesterol-rich domains.

There is considerable evidence for the formation of cholesterol-rich domains in model membranes and of cholesterol-rich invaginations in regions of cell plasma mem-

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branes also containing caveolin, i.e. caveolae. However, the characteristics of the putative "floating" rafts, or even their very existence in biological membranes, are less well defined. Subczynski and Kusumi review the applications of pulse EPR spin labeling and single molecule fluorescence tracking techniques for the study of the size, lifetime and dynamics of rafts in both model and biological membranes. They indicate the heterogeneity of the size and lifetime of rafts in biological membranes. One of the concepts that these authors emphasize is that the sequestration into raft domains is not all or none, but rather a preferential partitioning of certain molecules toward one environment compared with another. In the small volume of a membrane, the relative affinity for one phase over another does not have to be very high to result in an increased concentration of a component in a particular domain.

One of the functions of rafts that have been suggested in several contexts is its role in signal transduction. There has been speculation about the physical environment of cholesterol-rich domains modulating the activity of proteins as well as the role of "rafts" in recruiting proteins into a specific location in the plasma membrane where they will interact with each other in a more efficient manner. This latter mechanism has been extensively described with regard to signaling in lymphocytes [3–5]. The role of rafts in concentrating specific proteins into a smaller domain is described by Bodin, Tronchère and Payrastre for signal transduction in platelets. These domains also contain specific lipids required for signal transduction and the concentration of these molecules into a domain will lead to an efficient and coordinated activation mechanism.

The largest pool of cholesterol in the body, as well as the highest concentration of cholesterol in any tissue, is in the brain [6,7]. There is growing evidence to suggest that lipid rafts play an important role in neuronal signaling as well as in neuronal cell adhesion, axon guidance and synaptic transmission [8]. Evidence from the fraction of the membrane that is insoluble in Triton suggests that brain rafts differ in both lipid and protein composition, compared with the detergent-insoluble fraction of other cells. There is less sphingomyelin in the raft fraction from brains, compared with other cells. One of the proteins of rafts is NAP-22, a 22-kDa acidic protein that is myristoylated at the amino terminus. This protein has the unusual property of binding to liposomes containing a high mole fraction of cholesterol but not to liposomes composed only of phosphatidylcholine [9]. Maekawa discusses the properties of this protein and other proteins of brain rafts. NAP-22 shares a unique role with another raft protein, GAP-43, in neurite outgrowth and anatomical plasticity [10]. Another observation indicating the importance of cholesterol for brain development is that glia-derived cholesterol is required for synaptogenesis. The role of cholesterol in the development and stability of synapse is discussed by Pfrieger. There is also a role for cholesterol in the brain pathology accompanying Alzheimer's disease. There is evidence that cholesterol-lowering drugs reduce the risk of Alzheimer's disease. The relationship of cholesterol to the disease appears to be the result of the role of this lipid in the interaction of the amyloid β-peptide with membranes. Wood and colleagues discuss the relationship between the amount and distribution of cholesterol in the brain and the accumulation and synthesis of the amyloid β-peptide.

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