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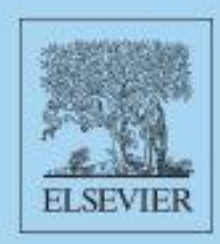

Special Issue
Properties and Functions of Cholesterol

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Editorial

Introduction to the Special Issue on "Properties and Functions of Cholesterol"

Cholesterol has attracted the attention of biophysicists, biochemists and physiologists over many years. As a prevalent lipid molecule in the membranes of most animal species, cholesterol and its homologs in yeast and in plants are thought to play an important role in the organization of molecules within membranes and the formation of membrane domains. Cholesterol has also received considerable attention in cardiac disease because of its appearance in high concentrations in atherosclerotic plaques. In spite of this intense interest the biological importance of cholesterol, there are still many unanswered questions about the properties functions of this lipid. This special issue covers many aspects of the roles of cholesterol. The issue is divided into four sections.

The first section deals with the behavior of cholesterol in model systems. The complexity of biological systems often prevents a detailed study of the molecular interactions among distinct molecular species. Cholesterol has a particular molecular structure that is very different from the other lipids of biological membranes and it is thus expected that cholesterol will mix differently with other components of the membrane. Cholesterol has a much greater tendency to form crystals than other molecules of biological membranes. This results in the appearance of cholesterol crystals in some pathological states. Some of the potential complications that must be considered in measuring the solubility limit of cholesterol in different lipid mixtures are reviewed in the first article of this issue (Epand et al., 2016). Although cholesterol is generally absent from bacterial membranes, there are bacteria that can incorporate exogenous cholesterol into their membranes resulting in the formation of raft-like domains (Huang and London, 2016). Cartoons of membrane structures almost always show cholesterol aligned along the bilayer normal with the hydroxyl group at the interface. However, new evidence shows that in some membranes cholesterol can be incorporated within the membrane (Marquardt et al., 2016). Cholesterol shares with sphingolipids the capability of forming hydrogen bonds with some phospholipid head groups. The consequences of this and the role of such a hydrogen bond in forming sphingomyelin and cholesterol-rich domains in membranes, as well as evidence for the direct interaction between ceramide and cholesterol are considered (García-Arribas et al., 2016). It is well recognized that biological membranes are asymmetrical with regard to the lipid composition of the two monolayers. Sphingolipids are known to be mostly on the extracellular monolayer of the plasma membrane. Because of possible interactions with this class of lipids, cholesterol would be considered *a priori* to also be largely in this monolayer. The sidedness of cholesterol has been difficult to measure because of its rapid rate of flip-flop. However, some experimental evidence and theoretical arguments suggest that the distribution may be greater on the cytoplasmic monolayer in the absence of sphingomyelin (Giang and Schick, 2015). The role of cholesterol in modulating membrane elastic fluctuations has been studied by NMR methods (Molugu and Brown, 2016).

For many years the effects of cholesterol on membrane properties had been considered largely from the point of view of the reduction of "fluidity" caused by the sterol. However, over the years it has been shown that there can be specific interactions between cholesterol and certain proteins. Two papers in this issue address this question. Evidence for a general peptide motif facilitating cholesterol binding to proteins is discussed (Fantini et al., 2016). In addition, some proteins co-crystallize with cholesterol, allowing for a detailed structural determination of the nature of this protein lipid interaction. The example of the family of G protein coupled receptors is discussed, along with the role of this interaction in altering the compactness of the protein structure (Gimpl, 2016).

It is known from chemical principles that the reactivity of a compound is determined by its activity and not by its bulk concentration. This is also the case of cholesterol in cell membranes and this may have physiological consequences by determining the availability of cholesterol for different processes (Lange and Steck, 2016). Cholesterol concentration also varies on the disk membranes of the retinal rod outer segment as the disks mature. This interesting phenomenon is discussed (Albert et al., 2016). The distribution and dynamics of cholesterol in the plasma membrane and the methods used to study this is reviewed (Wüstner et al., 2016). Particular emphasis is given to the role of fluorescence microscopy in imaging these phenomena. Cholesterol also has a role in membrane fusion. The multiple roles of cholesterol both in modulating membrane physical properties as well as interacting with specific membrane proteins is described for SNARE-mediated and viral envelope glycoprotein mediated membrane fusion (Yang et al., 2016).

The role of specific oxysterol products of cholesterol oxidation can lead to pathological consequences (Kulig et al., 2016). Perhaps the most recognized pathological role of cholesterol is in the formation of arterial plaques. High density lipoprotein plays an important role in decreasing cell damage caused by high levels of cholesterol (White et al., 2016). This build up of cholesterol is also lessened by regulatory mechanisms responding to high cholesterol

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concentrations (Howe et al., 2016). A little recognized role of cholesterol is in its promotion of the uptake on intracellular parasites. A general mechanism, involving cholesterol binding sites in host cell surface receptors is proposed (Kumar et al., 2016).

There are thus many aspects of cholesterol that are currently being studied to understand its molecular interactions in membranes, its binding to specific membrane proteins and its many roles in human biology and medicine. We hope that the combination of information and knowledge from these articles would help to develop a comprehensive working model for the role of cholesterol in biological membranes in healthy and diseased states. We would also like to make use of this opportunity to thank all the contributors for their efforts in making this an exciting and important issue.

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