

*Characterising PC/cholesterol supported lipid bilayers and interactions with human HDL*

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Atherosclerosis is the leading cause of death in the west. In atherosclerosis, plaques of fat and fibrous elements accumulate in the arteries leading to heart disease and stroke. Current knowledge recognizes a range of indicators associated with the disease, including concentrations and ratios of different lipoprotein particles [1-2]. These lipoproteins act as carriers of cholesterol and triglycerides, which are otherwise insoluble in blood plasma. The main cholesterol transporters are the low-density lipoprotein (LDL) and high-density lipoprotein (HDL), and cardiovascular disease has been shown to be directly related to the plasma levels of LDL [3] and inversely related to the plasma levels of HDL. However, the guidelines are continuously being extended and the development of more accurate diagnostic tools as well as treatments are of highest importance in the fight against cardiovascular disease.

In contrast to LDL, the HDL particles have traditionally been considered the "good cholesterol", and are thought to remove fats from foam cells thus disrupting atherogenesis at several key stages. However, more recent studies have shown that even increasing levels of HDL increase the risk of cardiovascular disease. The mode of interaction between the various types of lipoproteins and the vessel wall is thought to occur via competition: atherosclerosis does not depend so much on the absolute blood lipoprotein concentrations of LDL and HDL but rather on their ratio (LDL/HDL), as well as numerous other factors such as the presence of Lipprotein(a), presence of oxidized forms, SOD (Superoxide dismutase) levels, and many other factors. Although we today know about the relative affinities of LDL and other particles to specific type of proteins, we know very little about the molecular events taking place upon binding. This is important since lipid accumulation occurs in the intima layer even at conditions of low grade of atherosclerosis. Indeed, bulk and interfacial exchange between LDL and HDL and different vessel wall components is likely to be critical for the protective effect of HDL against atherosclerosis and needs to be carefully studied.

Neutron reflection is a very useful tool for in situ measurements of lipid exchange processes between human fractions of LDL and HDL and supported lipid bilayers (SLBs) that mimic the plasma membrane. A methodology recently developed in our group allows us to study the surface interactions between human lipoprotein particles with supported lipid bilayers made of specifically deuterated, physiologically relevant, mono-unsaturated phosphatidylcholines in combination with perdeuterated as well as non-deuterated cholesterol. Through this approach, we can monitor the kinetics of both phospholipid exchange and cholesterol uptake and show that for HDL the exchange is dependent on the specific lipid type present. Thus, a slower exchange was seen when using the natural unsaturated lipids compared to a faster exchange seen when using fully saturated synthetic lipids. These results highlight the effect that the lipid environment exerts on the interaction with HDL particles - notably the level of saturation of the lipids on the degree of exchange.

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[3] Grundy, S. M., 2008, Circulation, 117 (4), 569-73; discussion 573.

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