Lipoprotein structure dependency on lipid cargo and exchange dynamics - Implications for atherosclerosis development

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Atherosclerosis and related cardiovascular disease constitute the leading cause of death in westernized societies [1]. In atherosclerosis, plaques of fat and fibrous elements accumulate in the arteries leading to heart disease and stroke [2]. The levels of different plasma lipoprotein particles, low density lipoprotein (LDL), oxidized LDL (oxLDL), high density lipoprotein (HDL), lipids and cholesterol have been associated with the disease and are therefore currently being used as key clinical markers [3]. However, the impact that the apolipoprotein isoform, the apolipoprotein oxidation state, the lipid cargo and the presence of divalent ions have on the structure and stability of the lipoprotein particles is still not fully known. Together with their subsequent effects on lipoprotein interactions with blood vessel components these parameters need to be thoroughly investigated in order to understand the molecular mechanisms behind the initial events of plaque-build up. This can in turn allow for the development of novel strategies for the diagnostics and treatment of cardio-vascular disease. Here we use small-angle x-ray scattering and small-angle neutron scattering in combination with selective deuteration to provide novel information on both structure of the lipoproteins and the molecular exchange which occurs between lipoprotein particles and cell-membrane mimics. Focusing on the lipid exchange kinetics between both native HDL and LDL and liposomes made of “invisible” PC lipids [4] we show that the apolipoprotein plays a key role in enhancing lipid exchange. Furthermore, we present a novel structural model for LDL and HDL and the effects that temperature and oxidation have on the particles overall structure as well as on the organization of their hydrophobic core and which now allows us to start relating the specific structural changes with the observed lipid exchange.

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