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NMR structure determination of the 108kDa discoidal HDL particle - Stefan Bibow - University of Basel Germany

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Abstract

High-density lipoprotein particles (HDLs) are transport containers in the circulatory system that receive cellular cholesterol and lipids destined for the liver and other lipoprotein particles. Because low levels of HDL-cholesterol often indicate an increased risk for cardiovascular diseases, HDL particles are considered as important pharmacological targets for therapeutic strategies. Mature spherical HDLs develop from lipid-free apolipoprotein apoA-I through the formation of intermediate discoidal HDL particles which are the primary acceptors of cellular cholesterol. Although of high biophysical and medical importance heterogeneity in density, size, shape, as well as protein and lipid composition prohibited a detailed molecular and structural description of discoidal HDL particles. Here, we present the three-dimensional solution structure of reconstituted discoidal HDL (rdHDL) particles by combining nuclear magnetic resonance (NMR), electron paramagnetic resonance (EPR) and transmission electron microscopy (TEM) data.

By using amino acid selective labeling, methyl labeling, Lipid-PREs and long-range EPR data we found that rdHDL particles are composed of two helical apoA-I molecules that dimerise in an anti-parallel fashion to form a double belt around a lipid bilayer patch. The integrity of this unique structure is maintained by up to 28 salt bridges and an unusual zipper-like pattern of cation-Ї€ interactions between helices 4 and 6. In order to accommodate a hydrophobic interior a gross â€˜ right to rightâ€™ rotation of the helices upon lipidation is necessary. The structure relevant in our understanding of HDL-biology and metabolism reflects thereby the beauty and complexity of this type of biological shuttling container that is able to hold a fluid lipid/cholesterol interior at a protein lipid ratio of 1:50.