Available online at www.scholarsresearchlibrary.com

Extended Abstract

Journal of Computational Methods in Molecular Design, 2020, 10(1)
https://www.scholarsresearchlibrary.com/journals/journal-of-computational-methods-in-molecular-design/

ISSN 2231-3176

NMR structure determination of the 108kDa discoidal HDL particle

Stefan Bibow

University of Basel

E-mail: stefan.bibow@unibas.ch

High-density lipoprotein particles (HDLs) are transport containers in the circulatory device that get hold of cell cholesterol and lipids destined for the liver and other lipoprotein particles. Because low tiers of HDL-cholesterol frequently point out a multiplied risk for cardiovascular diseases, HDL particles are regarded as essential pharmacological goals for therapeutic strategies. Mature spherical HDLs increase from lipid-free apolipoprotein apo-I through the formation of intermediate discoidal HDL particles which are the foremost acceptors of cell cholesterol. Although high biophysical and scientific importance heterogeneity in density, size, shape, as well as protein and lipid composition prohibited a particular molecular and structural description of discoidal HDL particles. Here, we present the 3-dimensional answer structure of reconstituted discoidal HDL (rdHDL) particles via combining nuclear magnetic resonance (NMR), electron paramagnetic resonance (EPR), and transmission electron microscopy (TEM) data. By the use of amino acid selective labeling, methyl labeling, Lipid-PREs, and long-range EPR facts we located that HDL particles are composed of two helical apo-I molecules that dimerize in an anti-parallel trend to structure a double belt around a lipid bilayer patch. The integrity of this unique structure is maintained via up to 28 salt bridges and an uncommon zipper-like sample of cation-Ï€ interactions between helices four and 6. In order to accommodate a hydrophobic indoors a gross â€˜ right to rightâ€™ rotation of the helices upon lipidation is necessary. The structure applicable in our appreciation of HDL-biology and metabolism reflects thereby the beauty and complexity of this type of biological shuttling container that is in a position to keep a fluid lipid/cholesterol indoors at a protein-lipid ratio of 1:50.

Conversion of discoidal phospholipid (PL)-rich excessive density lipoprotein (HDL) to spheroidal cholesteryl ester-rich HDL is a central step in reverse cholesterol transport. A particular perception of this system and the atheroprotective position of apolipoprotein A-I (apo-I) requires an understanding of the shape and dynamics of these a range of particles. This study, combining computation with experimentation, illuminates structural elements of apo-I permitting it to contain various amounts of PL. Molecular dynamics simulated annealing of PL-rich HDL fashions containing unesterified cholesterol effects in double belt buildings with the same conventional saddle-shaped confirmation of each of our previous molecular dynamics simulations at 310 K and the x-ray structure of lipid-free apo-I. Conversion from a discoidal to a saddle-shaped particle involves loss of helicity and formation of loops in opposing antiparallel parts of the double belt. During floor expansion precipitated via the temperature-jump step, the curved palmitoyl oleoyl phosphatidylcholine bilayer surfaces method planarity. Relaxation again into saddle-shaped structures after cool down and equilibration further support the saddle-shaped particle model. Our kinetic analyses of reconstituted particles show that PL-rich particles exist in discrete sizes corresponding to neighborhood vigorous minima. Agreement of experimental and computational determinations of particle size/shape and apo-I helicity provide extra help for the saddle-shaped particle model. Truncation experiments blended with simulations propose that the N-terminal proline-rich domain of apo-I influences the balance of PL-rich HDL particles. We advocate that apo-I accommodates increasing PL in the form of minimal floor bilayers via the incremental unwinding of an at first twisted saddle-shaped apo-I double belt structure.

High-density lipoprotein (HDL) represents a heterogeneous population of particles with apolipoprotein A-I (apo-I) as the major protein. HDL biogenesis proceeds with the formation of phospholipid (PL)-rich HDL particles through the addition of cell membrane-derived PL and unesterified cholesterol (UC). At this time, HDL is an underexplored and necessary new target for the pharmacological remedy of coronary artery disease. Whether HDL plays a direct position in coronary artery ailment prevention (e.g. removal of cholesterol from clogged arteries) or an indirect function (e.g. acts as a platform for the clustering of protective molecules, such as an anti-inflammatory or antioxidant proteins), information of HDL structure and dynamics are incredibly desirable.

Bottom Note: *This work is partly presented at 10th Edition of International Conference on Structural Biology* March 15-16 2018 Barcelona, Spain