Solid State NMR Explorations of Protein-Lipid Interactions in Cardiovascular Disease

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Abstract

We have utilised and developed solid-state NMR (ssNMR) methods to investigate functionally important phospholipid-protein interactions associated with cardiovascular disease. This could be a common factor in the formation of arterial plaques and cholesterol transport. Medin is a highly prevalent polypeptide found in blood vessel amyloid plaques of individuals over the age of 50, and has possible associations with Alzheimer's disease via its co-aggregation with the Aβ peptide.[1, 2] Using the high-field ssNMR facility, we obtained the first structural details of medin fibrils.[3] Recently, we have used MAS and oriented ssNMR to characterise medin on the surface of liposomes mimicking extracellular vesicles isolated from smooth muscle cells.[4] The results provide insight into the aortic amyloid formation pathway and the role of phosphatidylserine lipids.

Secondly, we have developed ssNMR methods to probe protein-lipid interactions in high-density lipoprotein (HDL-C, "good cholesterol"), as HDL-C carries cholesterol to the liver for excretion. Our oriented ^{31}P ssNMR method can detect the rHDL-C morphology[5], and using the dynamically averaged ^{13}C-^{13}C and ^{13}C-^{1}H dipolar couplings we have determined the orientational distribution of [2,3,4-$^{13}C_3$]cholesterol in discoidal rHDL-C.[6, 7] We are now investigating differences in the structure and function of atheroprotective and dysfunctional variants of HDL-C containing mutants of the main protein (apoA-I), including at high-field (1 GHz). Our overarching goal is to use the structural knowledge to develop improved diagnostic and preventative approaches to cardiovascular disease.

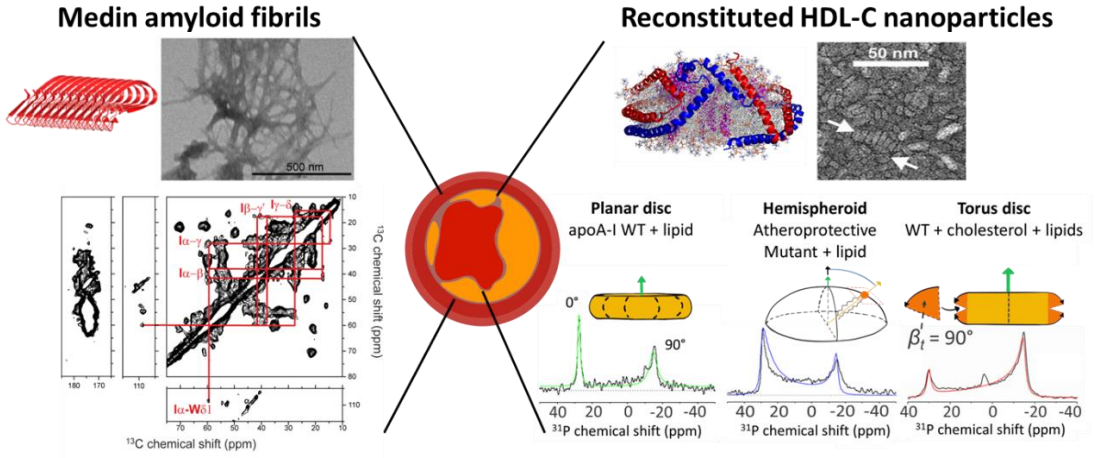

Figure 1. ssNMR can be used to detect site-specific structural features in aggregated medin amyloid fibrils and different HDL-C nanoparticle morphologies. Reproduced AAMD HDL model obtained from Pourmousa *et al*.[8]

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