"New Insights into the Role of Lipoproteins in Alzheimer's Disease"

Alzheimer's disease (AD) is defined by amyloid beta (Aβ) plaques and neurofibrillary tangles and characterized by neurodegeneration and memory loss. Apolipoprotein E (apoE) is the major genetic risk factor for AD with multiple roles in AD pathogenesis, primarily assumed to occur within the brain. Importantly, as many AD patients also have vascular co-morbidities including Aβ deposition in cerebral vessels known as cerebral amyloid angiopathy (CAA) and microhemorrhages, promoting cerebrovascular resilience may therefore be a promising therapeutic or preventative strategy for AD. Plasma high-density lipoproteins (HDL) have several vasoprotective functions and are associated with reduced AD risk in epidemiological studies. In mice, deficiency of apoA-I, the primary protein component of HDL, increases CAA and cognitive dysfunction, whereas overexpression of apoA-I from its native promoter in liver and intestine has the opposite effect and lessens neuroinflammation. Similarly, acute peripheral administration of HDL reduces soluble Aβ pools in the brain. New animal model data support a role for apoA-I, the major apolipoprotein in HDL, in reducing astrocyte reactivity to parenchymal and vascular amyloid in the cortex and attenuating parenchymal and vascular ICAM-1 in the hippocampus. Studies using novel 3-dimensional engineered human cerebral vessels show that HDL, especially the fraction of HDL enriched in apoE, reduces Aβ deposition and Aβ-induced endothelial activation and is providing new insights into multiple mechanisms by which HDL can protect the cerebrovasculature. Taken together, HDL may be an attractive non-amyloid approach to prevent or treat cerebrovascular dysfunction for AD.