G M Anantharamaiah et al., J Clin Exp Cardiolog 2016, 7:6(Suppl)
http://dx.doi.org/10.4172/2155-9880.C1.029

Apolipoprotein E mimetic: From theory to therapy

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Apolipoprotein E (apoE) has a dual-domain structure, with a four helix bundle containing the receptor binding region in the amino terminal domain and a carboxyl terminal lipid binding domain. Peptides derived from the LDL receptor (LDL-R) binding region of apoE have been studied by a number of groups, with the primary focus being on the binding of the peptides to LDL-R. Based on the dual-domain structure, a peptide was designed with the highly cationic residues 141-150 from human apoE (hE) covalently bound to the lipid-associating Class A α-helical peptide 18A and the amino and carboxyl termini blocked with acetyl and amide groups, respectively. This peptide, called Ac-hE18A-NH2 (in clinical development as AEM-28), was found to have striking cholesterol- and triglyceride-reducing and anti-inflammatory properties. Unlike statin drugs and proprotein convertase subtilisin/kexin type-9 (PCSK-9) inhibitors, these properties exist even in the absence of a functional LDL-R, with cholesterol reduction being mediated by binding to heparan sulfate proteoglycans (HSPG). Ac-hE18A-NH_2 is currently undergoing Phase 1a/1b clinical trials, and has shown acceptable tolerability and promising efficacy. Thus, this and similar peptides have great potential for treatment of statin-resistant conditions such as familial hypercholesterolemia and acute hypertriglyceridemic pancreatitis.

Biography

G M Anantharamaiah is a Professor in the Department of Medicine since 1982. He received his Post-doctoral training at Ohio State University in Columbus, OH in 1979 and a Research Associate in 1982 before coming to UAB as a faculty. His research has focused on structure and function of plasma Apolipoproteins, Apo-A1 Structure and Function, Apo-E Structure and Function, Structure of Apo-A-1 in Alzheimer Disease Research. He initiated studies of peptide mimetics of apolipoproteins A-I and E, both of which are licensed to two different companies for further development as therapies for lipid-mediated inflammatory disorders. He has published more than 200 papers in this field of research.

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