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Apolipoprotein E mimetic: From theory to therapy

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-NH₂ 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. He joined the UAB faculty in 1982. His research involves use of apoA-I mimetic and apoE mimetic peptides, both these peptides to inhibit atherosclerosis in atherosclerosis sensitive mice, mechanisms of action of anti-atherogenic and anti-inflammatory peptides in relation to anti-inflammatory proteins present in HDL. In addition, apoE mimetic peptides enhance secretion of apoE and thus exert its additional beneficial effects not only in atherosclerosis but also in Alzheimer's disease and in diabetes. He has published more than 200 papers on his research.

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