Apolipoprotein E/Lipoprotein Binding Mechanism

https://www.neurodegenerationresearch.eu/survey/apolipoprotein-e-lipoprotein-binding-mechanism/

Principal Investigators

NARAYANASWAMI, VASANTHY

Institution

CALIFORNIA STATE UNIVERSITY LONG BEACH

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Research Abstract

DESCRIPTION (provided by applicant): Apolipoprotein E (apoE) is an exchangeable apolipoprotein that plays a critical role in lipid transport and in maintaining plasma and brain cholesterol homeostasis. It mediates its role by serving as a ligand for the low- density lipoprotein receptor (LDLr) family of proteins, which facilitate receptor-mediated endocytosis of lipoproteins, thereby eventually lowering plasma lipid levels. It also plays a role in reverse cholesterol transport in atherosclerosis, by promoting cholesterol efflux from macrophages to

form high-density lipoproteins (HDL). In this proposal, we will focus on understanding the differences between the two major human apoE isoforms, apoE3 and apoE4, and their role in HDL formation. ApoE3 is associated with normal plasma lipid profiles (anti- atherogenic), while apoE4 is considered pro-atherogenic and is a risk factor for cardiovascular disease (CVD) and Alzheimer's disease (AD). However, neither the mechanism of lipid binding nor the molecular basis for the differences in the physiological behavior between the isoforms is known. We will test the overall hypothesis that there are isoform-specific variations in the conformation of apoE3 and apoE4, which lead to differences in lipid binding mechanism and in lipid (HDL)-bound conformation. To accomplish this, we will: (i) determine the unfolding pattern of recombinant apoE3 and apoE4 using a combination of fluorescence polarization (FP) and hydrogen deuterium exchange coupled to mass spectrometry (HDX-MS); (ii) compare the lipid binding mechanism between apoE3 and apoE4 by capturing 'snapshots' of the proteins during lipid binding by FP and HDX-MS, and identifying possible isoform-specific differences in the order of lipid binding of the different helices, and, (iii) examine the lipid-bound conformation of apoE in reconstituted and macrophage-generated HDL following cholesterol efflux by fluorescence spectroscopy and cross-linking analysis. Completion of these studies will significantly advance our understanding of the isoform-specific differences in the physiological behavior of apoE and the predisposition of apoE4 to CVD and AD. By determining the mechanistic basis of lipid binding, our studies will provide timely and much-needed opportunities to identify potential intervention strategies to treat CVD and AD. The developmental objectives of the PI are to establish and sustain a highly productive and scholarly research activity at CSULB, publish research findings, offer research training opportunities and mentorship for student trainees from diverse backgrounds in state-of-the-art biomedical research, actively participate in national and international meetings, initiate and continue collaboration with established investigators outside CSULB, and expand her expertise to address questions related to AD.

Further information available at:

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