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Pathobiology of ApoE in Brain Aging and Alzheimer's Disease

Guojun Bu

Division of Life Science, The Hong Kong University of Science and Technology, Hong Kong SAR

Email: gbu@ust.hk

Alzheimer's disease (AD) is the leading cause of dementia in elderly, impacting an increasingly large population of our aging society. Despite progress in understanding the pathological events associated with AD, the complex molecular events that underlie the development of AD remain poorly understood and are the key to developing targeted therapies. The ε4 allele of the apolipoprotein E (APOE) gene is the strongest genetic risk factor for late-onset AD compared to the common ε3 allele or the protective ε2 allele. In the central nervous system (CNS), apoE4 inhibits the clearance and promotes the aggregation of amyloid-β (Aβ) and has several Aβ-independent effects including age-dependent inferior functions in transporting lipids, supporting synapses, and controlling neuroinflammation. In this presentation, I will discuss our current understanding on how APOE impacts AD risk with a focus on our own studies using animal models and iPSC-derived cellular and organoid models. Specifically, using human APOE allele-specific and cell type-specific mouse models, we found that apoE isoforms expressed in different cell types in the brain, vasculature, and periphery differentially modulate brain cognition and AD pathology. Highlights will include the effects of peripheral apoE and microglial apoE in brain function and AD pathogenesis in an isoform-dependent manner. Knowledge gained through studies from our group and others can help with designing individualized therapies targeting APOE in a genotype-specific manner.