APOE PROMOTES Aβ TRAFFICKING AND DEGRADATION BY MODULATING MICROGLIAL
CHOLESTEROL LEVELS
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Introduction: Apolipoprotein E (ApoE) is recognized as the major risk factor of Alzheimer's disease (AD). Intracellular degradation of β-amyloid peptides (Aβ) by microglia is facilitated in the presence of ApoE. However, the underlying mechanism remains unclear. Epidemiologic studies suggest a link between elevated plasma cholesterol levels and increased risk of AD and that use of cholesterol synthesis lowering drugs is associated with reduced prevalence of AD later in life. Since maintaining brain cholesterol homeostasis is an important function of ApoE, its ability to promote Aβ degradation may be correlated with this property.

Aims: To test the hypothesis that ApoE promotes proteolysis of Aβ by modulating cellular cholesterol levels.

Methods: We performed ELISA to analyze microglial Aβ degradation in the presence of cholesterol modulating drugs. Cellular cholesterol levels were monitored. Confocal microscopy was performed to analyze the trafficking of Aβ.

Results: We report that promoting Aβ degradation is the common feature of HDL apolipoproteins, including ApoE and ApoA-I. Cholesterol lowering drugs enhanced Aβ degradation, recapitulating the effects of ApoE. Conversely, elevated cellular cholesterol levels were associated with impaired Aβ degradation. This effect is not by regulating the expression of Aβ degrading enzymes. Importantly, we observed that reducing cellular cholesterol levels by ApoE resulted in faster delivering Aβ to lysosomes, where it is degraded.

Conclusions: ApoE-induced intracellular Aβ degradation is related to the cholesterol efflux function of ApoE, which in turn, facilitates the intracellular trafficking of Aβ to lysosomes for degradation. These findings suggest a direct role of cholesterol in AD pathogenesis.