ApoE4, Astrocyte priming, and Alzheimer's disease

Apolipoprotein E4 (ApoE4) is one of the most substantial risk factors for Alzheimer's disease (AD). Previously, we showed that human-induced pluripotent stem cells (iPSCs)-derived astrocytes carrying *APOE4* isoform nicely recapitulate some AD-related phenotypes such as impaired amyloid-beta clearance and intracellular cholesterol accumulation. An exaggerated immune response of astrocytes is another well-known common pathology of AD, but whether/how ApoE4 affects immune response in astrocytes has not been defined yet. We identified a primed status in human iPSCs-derived astrocytes after recovery from immune stimulation, displaying an exaggerated immune response to a subsequent immune challenge. Primed astrocytes displayed altered transcript profiles similar to those from the brain of the elderly. We observed that primed astrocytes reduced their phagocytotic activity against Aβ but increased the secretion of cytokines known to influence microglia. Indeed, conditioned media from Aβ-treated primed astrocytes increased Aβ clearance by microglia. Interestingly the comparison between isogenic ApoE3/E4 hiPSC-derived astrocytes revealed that stimulation-induced priming in ApoE4 astrocytes was significantly attenuated compared to ApoE3 astrocytes. We further observed that secretory factors from Aβ-treated primed ApoE4 astrocytes significantly reduced microglia-dependent clearance of Aβ. We are currently validating our observations *in vivo* using a mouse model. Our study will elucidate the role of astrocyte priming in AD pathogenesis and how ApoE4 impacts this process.