Apolipoprotein E, Receptors and Modulation of Alzheimer's Disease

Supplemental Information

ApoE in tauopathy

Tau is a microtubule-associated protein encoded by *MAPT* gene, which has a role in stabilizing neuronal microtubules. Hyperphosphorylation and aggregation of tau are characteristics of several neurodegenerative diseases known as tauopathies, including AD (1). Findings from clinical PET imaging, CSF, and post-mortem studies suggest that the pathological aggregation of tau is closely linked to patterns of neurodegeneration and clinical manifestations of AD (2, 3). AD patients who carry the *APOE4* genotype have greater medial temporal lobe vulnerability and post-mortem tau pathology compared to non-carriers (4-6). Preclinical studies concerning how apoE isoforms affect tauopathy in AD are limited. A transgenic animal study revealed that neuronal, but not astrocytic, apoE4 overexpression increases tau phosphorylation, suggesting a neuron-specific effect of apoE4 on tauopathy (7). An earlier study showed that tau binds avidly to apoE3, but not to apoE4, indicating that the isoform-specific interactions of apoE with tau might contribute to differential effects on tau metabolism (8).

Tauopathy in the absence of Aβ may reflect a pathological process that is distinct from AD. Patients with primary age-related tauopathy (PART) develop cognitive impairment that can be indistinguishable from AD, but in contrast contain none or only minimal Aβ deposition (9, 10). Interestingly, there is no association between PART and *APOE* genotype (10). It was also reported that the *APOE4* is associated with tau tangles in the brains with Aβ, whereas no such association is found in brains without Aβ (11). Understanding how apoE isoforms affect

tauopathy in the presence and absence of amyloid pathology *in vivo* will help us to develop appropriate therapeutic strategies for AD and other tauopathies.

ApoE and apoE receptors in brain lipid transport

The brain is the most cholesterol-rich organ, and about 30% of cholesterol in the brain is metabolically active and found in membranes of glial cells and neurons, where it undergoes recycling for neuronal repair and remodeling (12, 13). ApoE is critical in redistributing cholesterol and lipids to neurons through LRP1 and LDLR to maintain the synaptic function (13, 14). It was shown that the cholesterol levels in AD brains are lower than in healthy brains (15). The association between apoE, cholesterol and AD has been intensely reviewed (14, 16-20), and it is recognized that the isoform-specific effects of apoE in AD is at least partially due to their differential ability of transporting cholesterol to neurons, with apoE4 being less efficient than apoE3 (21-23).

ApoE in glucose metabolism and mitochondrial function

Glucose is the primary energy resources for the brain, and mitochondria are recognized as subcellular organelles that are essential for generating the energy for the cells (24). Cerebral glucose hypometabolism, as assessed by FDG-PET scan, exists in pre-symptomatic AD patients long before the clinical onset of disease and has become one of the early biomarkers of AD (25-28). Multiple studies have also suggested that mitochondrial dysfunction and oxidative damage might have early and preponderant roles in AD (29-31). *APOE4* has been associated with

glucose hypometabolism and mitochondrial dysfunction in the brain (32-34). FDG-PET studies have clearly shown that *APOE4* carriers, either as healthy adults or with dementia, have lower cerebral glucose metabolism compared to non-carriers (34-41). Moreover, *APOE4* genotype, not Aβ aggregation, contributes to reduced glucose metabolism in aging (42). *APOE4* carriers also have lower mitochondrial cytochrome oxidase activity than non-carriers (43). Studies revealed that apoE4 might affect the neuronal mitochondrial respiration due to its C-terminal-truncated fragmentation or domain interaction. In addition, it has been shown that neuronal LRP1 not only modulates lipid metabolism, but also plays a critical role in regulating insulin signaling and glucose metabolism in the brain (44). Whether LRP1 maintains both lipid and glucose homeostasis in an apoE isoform-dependent manner in the brain deserves further investigation. Together, more studies are required to understand the biological mechanisms that link the glucose hypometabolism and development of AD, and how apoE isoforms modulate these events (45-47).

ApoE and apoE receptors in vascular integrity and function

AD often co-exists with CAA, and is associated with microvascular dysfunction and degeneration in the brain (48). *APOE4* shows an association with CAA and CAA-related hemorrhages (49). Interestingly, *APOE2* is also a risk factor for CAA although it is protective against AD (50). ApoE4 interrupts cerebrovascular functions likely through both Aβ-independent and Aβ-dependent manner (51). ApoE4-TR mice showed an age-dependent progressive BBB breakdown by activating CypA-nuclear factor (NF) κB-MMP-9 pathway in brain capillary pericytes (52). The accelerated pericyte loss contributing to BBB damage was also found in human *APOE4* carriers (53). ApoE4-TR mice showed compromised BBB transport

function and cerebral vascular dysfunction and atrophy (54). Furthermore, it was shown that apoE produced by pericytes modulates Aβ removal and cytotoxicity near the vasculature in the brain, which might contribute to the development of CAA (55). Thus, it is possible that vascular defects in apoE4 precede neuronal dysfunction and could initiate neurodegenerative changes. However, a recent study reported no evidence of widespread BBB dysfunction in AD mouse models and apoE4-TR mice (56). Whether apoE4-mediated deficit impacts the global homeostatic capacity of the BBB which contributes to AD pathogenesis remains to be elucidated (57).

ApoE and apoE receptors in modulating neuroinflammation

Neuroinflammation is observed in both normal aging and AD (58-60). Resident immune cells, microglia and astrocytes, are activated by Aβ (61, 62), and joined by blood-borne monocytes that traverse the BBB and convert into activated macrophages, to release various cytokines, chemokines and proteolytic enzymes (63, 64). ApoE receptors, LRP1 and LDLR, mediate Aβ-induced astrocyte activation, initiating and modulating the inflammatory response induced by Aβ (65). By using a transgenic mouse overexpressing heparanase, an endoglucuronidase that specifically degrades HS side chains, it was found that all aspects of immune cell recruitment and activation are significantly attenuated in both lipopolysaccharide (LPS)-treated or microinjection of aggregated Aβ elicited inflammation models, which indicates that HSPGs are required to mediate neuroinflammatory responses (66). ApoE likely modulates the neuroinflammation in an isoform-dependent manner. It was reported that apoE4 amplifies the proinflammation (toll-like receptor 4-p38α) pathways induced by Aβ, and suppresses the anti-inflammtory (IL-4R-nuclear receptor) pathway, resulting in an adverse neuroinflammatory

phenotype that causes neuronal dysfunction (67, 68). Additionally, a specific apoE4 fragment (residues 186-299) detected in human AD brains can increase the level of inflammatory molecules in SHY5Y neuronal cell line (69). Following intracerebroventricular injection of LPS, it was shown that microglial and NF-κB activation are more pronounced in apoE4-TR than in apoE3-TR mice, indicating that NF-κB signaling pathway might mediate brain inflammation in apoE4-TR mice (70).

The missense mutation (R47H) of Triggering Receptor Expressed on Myeloid Cells 2 (TREM2), a protein expressed specifically in microglia in the brain, is associated with AD risk by dysregulating neuroinflammation and increasing AD pathology (71-76). Interestingly, apoE is an endogenous ligand of TREM2 (77). The uptake of apoE-Aβ complexes is reduced in macrophages from human subjects carrying the *TREM2* variant (78). It will be informative to further investigate whether apoE affects TREM2-mediated neuroinflammatory responses in an isoform-specific manner in the pathogenesis of AD.

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