Astrocytic apoE4 and tau: Deadly combination for neurons

Paramita Chakrabarty1,2,3 and David R. Borchelt1
1Department of Neuroscience, Center for Translational Research in Neurodegenerative Disease, McKnight Brain Institute, University of Florida, Gainesville, FL 32610, USA
2Correspondence: pchakrabarty@ufl.edu
https://doi.org/10.1016/j.xcrm.2021.100316

New data from Wang and colleagues1 suggest that astrocyte-derived apoE4 drives tau-mediated neurodegeneration. This research highlights how a genetic risk factor for Alzheimer’s disease is a major determinant of neurodegeneration in tau-expressing neurons by regulating non-cell-autonomous pathways.

The ε4 allele of the Apolipoprotein E (APOE) gene remains the strongest genetic predictor of Alzheimer’s disease (AD) risk.2,3 Although most research has focused on apoE as a modifier of amyloid β (Aβ) pathology,4,5 a series of recent publications,3,4 including an article appearing in a recent issue of Neuron, provide compelling evidence that apoE can modulate tau pathology. Led by Dr. Holtzman at Washington University, this study provides new insights into the non-cell-autonomous mechanisms by which apoE4 modulates neurodegeneration in the PS19 mouse model of tauopathy.

Many functions have been ascribed to apoE, including lipid homeostasis, Aβ aggregation and clearance, mitochondrial metabolism, receptor trafficking, neuronal activity, neurodegeneration, and synaptic regulation.6 While astrocytic apoE plays a major role in these conditions, apoE4 derived from other cell types could also potentially contribute to neurodegeneration. Indeed, an intriguing link between microglial apoE and neurodegeneration has been revealed through single-cell transcriptomic analysis in mouse models of neurodegeneration.7 This gene expression signature, commonly referred to as disease-associated microglia (DAM) or microglial neurodegenerative (MGNd) phenotype, suggests that both apoE and a microglial receptor, Trem2, are required for the transition of microglia from a homeostatic to neurodegenerative phenotype in AD. The involvement of TREM2 as a key player in apoE-associated neurodegenerative phenotype is notable as the R47H variant TREM2 increases AD risk comparable to the effect of APOE4, though the TREM2 variant is much rarer in the population. Studies in mouse models of Aβ led to the discovery of AD-associated R47H TREM2 worsens Aβ-induced neurtic tauopathy.8 Surprisingly, in the PS19 model, the R47H TREM2 variant delayed tauopathy and neurodegeneration.9 This exposes an interesting dichotomy in how immune cells and their interactome (apoE and TREM2 in this context) regulate intraneuronal (tau) and extracellular (Aβ) proteinopathy through non-cell-autonomous communication with neurons. Such a paradigm, whereby cross-talk between neurons and immune cells could regulate AD proteinopathy and disease progression, is expected to be dependent on disease stage, the co-occurring pathologies, genetic susceptibility, and the functional state of the immune cells. Thus, an important question emerging from ongoing studies of neuroimmune regulation of AD is the following: how do genetic susceptibility factors synergize with immune cell function leading to AD-typical neurodegeneration?

Wang and colleagues address this critical question by conditionally knocking out astrocytic expression of apoE in the biallelic PS19 model of tauopathy with loxp site-flanked APOE alleles inserted in the Apoe locus.1 The PS19 model, which expresses the P301S mutant 1N/4R human tau shows cortical atrophy and paralysis around 9 months of age.10 Immunosuppression lowered tauopathy in these mice, implicating innate immunity in disease progression.11 In the current paper, astrocytic apoE expression was suppressed by starting tamoxifen treatment at 5.5 months of age (pre-symptomatic) and ceasing the treatment at 9.5 months of age. Reduction in astrocytic apoE4 reversed brain atrophy (improving hippocampal and cortical volume) to levels comparable to age-matched control mice with APOE3 allele but not to pre-symptomatic levels (5.5 months). Tamoxifen treatment also reduced formic-acid-associated phosphorylated tau preferentially in female APOE4 mice. Further, removing astrocytic apoE4 rebalanced astrocytic gene expression patterns to homeostatic levels. There was a normalization of the DAM phenotype and oligodendrocyte reactivity as well as improved synaptic integrity in these APOE4-deleted mice. The finding that the neuroprotective phenotype produced by eliminating astrocytic apoE4 was more apparent in female mice is notable in terms of translational significance, given that the apoE4 effect on tauopathy was more pronounced in females.11 Interestingly, though eliminating astrocytic apoE3 had no significant effect on neurodegeneration, phosphorylated tau was reduced in these mice, again only in females. Overall, this study suggests that lowering astrocytic apoE4 could be beneficial in tauopathies. Because reduction in astrocytic apoE3 did not rescue neurodegeneration, the most likely mechanism by which astrocytic apoE4 affects neurodegeneration is probably via a gain of toxic property phenotype.

Previous data from the Holtzman group showed that pharmacologically removing microglia in PS19×APOE4 mice rescues brain atrophy and reduces hippocampal tauopathy.11 Intriguingly, this study showed that microglial ablation resulted...
in increased apoE4 in astrocytes and neurons. That microglial ablation can induce apoE to accumulate in neurons is intriguing, as neuronal apoE has been associated with tissue injury and excitotoxicity-related cell death. Comparing this finding with the present study, which shows no change in microglial apoE expression but a reduction in the
DAM/MGnD signature following apoE ablation in astrocytes, would suggest that both microglia and astrocytes may be working in concert to regulate the apoE4-tau-neurodegeneration nexus. Notably, the present study suggests that microglial apoE4 is neuroprotective in the absence of astrocytic apoE4. Collectively, these findings suggest that the gain of toxic function of astrocytic apoE4 results in specific patterns of microglial dysfunction that then exacerbates neuronal tauopathy and neurodegeneration caused by mutant tau (Figure 1). An important take home message is that the neurodegenerative phenotype is more susceptible to apoE4 than apoE3. This is supported by two independent observations. The original PS19 cohort expressing mouse apoE, which is considered functionally similar to human apoE4, also showed substantial degeneration. Second, knocking out mouse ApoE showed a protective effect in PS19 mice. Determining whether tau-mediated tauopathy is dependent on direct cross-talk between astrocyte and microglial apoE4 or some other factors are involved will be a matter of importance as the data so far suggests differential toxicities of immune cell-derived apoE3 or apoE4 in the context of tauopathies. In particular, establishing whether the astrocyte-microglia cross-talk in the context of APOE4 is TREM2 dependent is expected to provide some translational insights into the human-typical AD neurodegenerative cascade and lead the way to precision medicine-oriented manipulations.

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