Commentary

JCBFM

Journal of Cerebral Blood Flow & Metabolism
2020, Vol. 40(9) 1912–1914

DOI: 10.1177/0271678X20938146
journals.sagepub.com/home/jcbfm
SAGE

Leaky memories: Impact of *APOE4* on blood–brain barrier and dementia

Wenlu Li and Eng H Lo

Abstract

A new study suggests that the leading genetic risk factor for Alzheimer's disease, apolipoprotein E4 (*APOE4*), is linked to blood–brain barrier breakdown and subsequent cognitive decline. These findings broaden our understanding of how cerebrovascular mechanisms contribute to cognitive impairment and should stimulate new directions for pursuing therapeutic approaches for Alzheimer's disease and related dementias.

Keywords

Alzheimer's disease, dementia, apolipoprotein E4, blood–brain barrier, pericyte degeneration

Received 4 June 2020; Accepted 8 June 2020

Scientists continue to make great strides in understanding the molecular mechanisms of Alzheimer's disease (AD) and related dementias, but clinically effective therapies remain elusive. With the failure of several large trials of treatments designed to lower the amyloid load in the brain of patients with AD, a shift in thinking is taking place, and the role of vascular contributions to AD and dementia is increasingly recognized. A recent study by Montagne et al. now present exciting evidence in humans and mouse models that the leading genetic risk factor for AD, *APOE4*, may be directly linked to blood–brain barrier (BBB) breakdown that anticipates cognitive decline.[1]

Focusing on middle-aged individuals (≥45 years of age) who had either healthy cognition or mild cognitive impairment (a prelude to AD), the authors used dynamic magnetic resonance imaging (MRI) to map the blood-to-brain transfer coefficient of the MRI contrast agent gadolinium (K_{trans}).[1] Their results showed that BBB permeability in the hippocampus and parahippocampal gyrus were significantly increased in *APOE4* carriers. Moreover, BBB leakage was worse in *APOE4* carriers who exhibited mild cognitive decline. A recent study also revealed a higher prevalence of cerebral white matter hyperintensities (WMH) in *APOE4* carriers.[2] Since cerebral small-vessel-disease associated WMH and microbleeds are common in the elderly, it would be instructive to examine BBB alterations in white matter of *APOE4* carriers, and ask whether these mechanisms may more broadly contribute to cognitive disconnections throughout the entire brain.

Next, the authors examined cerebrospinal fluid (CSF) levels of the soluble form of platelet-derived growth factor-receptor-β (sPDGFR-β) that sheds from the surface of pericytes lining the BBB when they respond to cell stress or injury.[1] Elevated sPDGFR-β was found in the CSF of *APOE4* carriers, and these levels were positively correlated with cognitive impairment. These observations indicate that pericyte degeneration might serve as a useful biomarker that links BBB leakage with cognitive decline in neurodegenerative diseases. Associations between pericyte

Neuroprotection Research Laboratories, Departments of Radiology and Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Corresponding authors:
Wenlu Li, Neuroprotection Research Laboratories, Departments of Radiology and Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.
Email: wli23@partners.org

Eng H Lo, Neuroprotection Research Laboratories, Departments of Radiology and Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.
Email: Lo@helix.mgh.harvard.edu

degeneration, BBB perturbation, and cognitive dysfunction have also been detected in experimental models of traumatic brain injury and focal cerebral ischemia.[3,4] Moreover, PDGFR-β knockout mice display deformed tight junctions in brain endothelium and severe neurologic deficits.[4] These models may offer opportunities to further investigate the mechanisms that underlie the increased risk of developing AD and dementia years after brain injury in humans. Would brain injury-induced degeneration of brain capillary pericytes increase the overall risk of AD or dementia, or does it mainly predict cognitive impairment only in *APOE4* carriers?

An important question is whether *APOE4*-mediated BBB dysfunction may be connected to "standard pathways" of amyloid-β (Aβ) and/or tau. By using positron emission tomography, Montagne et al. demonstrated that *APOE4*-induced BBB breakdown was mostly independent of changes in Aβ or tau biomarkers.[1] Instead, the molecular pathway that drove *APOE4*-induced leakage was associated with the cyclophilin A-matrix metalloproteinase-9 (CypA-MMP9) signaling in degenerating pericytes.[1] Taken together, these findings may therefore provide a basis for developing CypA-MMP9-targeted therapies for *APOE4* carriers in AD and related dementias. Nevertheless, it may still be important to acknowledge that BBB integrity will depend on more than just pericytes, and cerebrovascular homeostasis is ultimately mediated by crosstalk between all cell types in the neurovascular unit. Indeed, crosstalk between endothelium and pericytes may mediate transporter trafficking in the BBB.[5] Evidence from human induced pluripotent stem cell-derived endothelial cells harboring different *APOE* genotypes suggests endothelial cells themselves contribute to vascular dysfunction in *APOE4* carriers.[6] Other pathways beyond MMP9 can also contribute. Robo4-paxillin-ARF6 signaling in endothelial cells has recently been identified as a key pathway for maintaining vascular integrity.[7] How other cell signaling pathways within the entire neurovascular unit are affected during cognitive impairment in *APOE4* carriers warrants further investigation.[8]

Finally, risks of dementia do not occur in isolation and are known to interact with age and sex. The BBB mechanisms identified by Montagne et al. may provide a conceptual framework to link these various factors. BBB permeability increases in the aging hippocampus.[9] A recent study indicates that *APOE4* may affect cognition more strongly in women than men.[10] Further studies validating whether BBB dysfunction in *APOE4* carriers is correlated with aging or affected by sex should be important in order to truly understand the neurovascular pathobiology of cognitive impairment.

Montagne et al. has uncovered a previously unrecognized mechanism for BBB dysfunction in *APOE4* carriers.[1] These remarkable findings reveal a complex loop of interactions between pericytes, BBB, and cognition. Future research that explores how signaling perturbations in entire neurovascular unit causes cognitive impairment in *APOE4* carriers may lead to novel opportunities for new biology and precision medicine in AD and dementia.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Montagne A, Nation DA, Sagare AP, et al. APOE4 leads to blood-brain barrier dysfunction predicting cognitive decline. *Nature* 2020; 581: 71–76.
2. Rojas S, Brugulat-Serrat A, Bargallo N, et al. Higher prevalence of cerebral white matter hyperintensities in homozygous APOE-varepsilon4 allele carriers aged 45–75: results from the ALFA study. *J Cereb Blood Flow Metab* 2018; 38: 250–261.
3. Choi YK, Maki T, Mandeville ET, et al. Dual effects of carbon monoxide on pericytes and neurogenesis in traumatic brain injury. *Nat Med* 2016; 22: 1335–1341.
4. Shen J, Xu G, Zhu R, et al. PDGFR-beta restores blood-brain barrier functions in a mouse model of focal cerebral ischemia. *J Cereb Blood Flow Metab* 2019; 39: 1501–1515.
5. Tome ME, Jarvis CK, Schaefer CP, et al. Acute pain alters P-glycoprotein-containing protein complexes in rat cerebral microvessels: implications for P-glycoprotein trafficking. *J Cereb Blood Flow Metab* 2018; 38: 2209–2222.
6. Rieker C, Migliavacca E, Vaucher A, et al. Apolipoprotein E4 expression causes gain of toxic function in isogenic human induced pluripotent stem cell-derived endothelial cells. *Arterioscler Thromb Vasc Biol* 2019; 39: e195–e207.
7. Li W, Chen Z, Yuan J, et al. Annexin A2 is a Robo4 ligand that modulates ARF6 activation-associated

cerebral trans-endothelial permeability. *J Cereb Blood Flow Metab* 2019; 39: 2048–2060.
8. Miners JS, Schulz I and Love S. Differing associations between Abeta accumulation, hypoperfusion, blood-brain barrier dysfunction and loss of PDGFRB pericyte marker in the precuneus and parietal white matter in Alzheimer's disease. *J Cereb Blood Flow Metab* 2018; 38: 103–115.
9. Montagne A, Barnes SR, Sweeney MD, et al. Blood-brain barrier breakdown in the aging human hippocampus. *Neuron* 2015; 85: 296–302.
10. Hobel Z, Isenberg AL, Raghupathy D, et al. APOEε4 gene dose and sex effects on Alzheimer's disease MRI biomarkers in older adults with mild cognitive impairment. *J Alzheimers Dis* 2019; 71: 647–658.