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# Vascular hypothesis of Alzheimer's disease: role of apoE and apoE receptors

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## Background

Alzheimer's disease (AD) is a progressive neurodegenerative disease that has emerged as the most prevalent form of late-life dementia in humans [1]. Production of amyloid- $\beta$  (A $\beta$ ) from the amyloid precursor protein (APP) and its subsequent accumulation, aggregation and deposition in the brain are central events in the pathogenesis of AD [1]. Cerebral amyloid angiopathy (CAA) is a major pathological feature of AD where amyloid spreads and deposits throughout the blood vessel walls in the central nervous system. These pathogenic events induce a specific clinical presentation profile including cerebral hemorrhage, stroke, ischemic infarctions, subarachnoid hemorrhage, seizures, cognitive impairment and dementia [2]. While A $\beta$  is a key molecule in AD, epidemiological studies have shown that several well-established risk factors for AD, including diabetes mellitus, atherosclerosis, stroke, hypertension, transient ischemic attacks, microvessel pathology and smoking, have a vascular component that reduces cerebral perfusion [3]. In fact, detection of regional cerebral hypoperfusion through neuroimaging techniques can preclinically identify individuals at risk for AD. Further, cerebral hypoperfusion precedes hypometabolism, cognitive decline, and neurodegeneration in AD [3]. Therefore, disturbance of cerebrovascular system is likely a major contributor to AD pathogenesis. Among the three human apolipoprotein E (apoE) isoforms (E2, E3 and E4), *APOE4* is the strongest genetic risk factor for late-onset AD. The most consistent finding that differentiates apoE4 from apoE3 is their respective roles in brain A $\beta$  clearance, where apoE4 is less efficient than apoE3 in promoting A $\beta$  clearance [4]. In addition, *APOE4* also increases the risk for CAA and vascular dementia [4]. Because apoE4 is known to damage blood-brain barrier (BBB) integrity and reduces small cerebral vessels [5], apoE is likely involved in

the maintenance of cognitive function through regulating the function of cerebrovascular systems.

## Materials and methods

We generated conditional knockout mice deleting a major apoE and A $\beta$  receptor LRP1 in vascular mural cells (smLRP1-KO), which include smooth muscle cells and pericytes. These mice were further bred to the background of amyloid model mice APP/PS1. Cerebral blood flow, behaviors and A $\beta$  metabolism were compared among human *APOE* isoform (E2, E3 and E4)-targeted replacement (TR) mice and between smLRP1-KO mice and wild-type littermate controls at young and old ages.

## Results

We found that cerebral blood flow and memory performance are reduced, while endogenous A $\beta$  levels are elevated, in aged *APOE4*-TR mice compared to *APOE3*-TR mice and in smLRP1-KO mice compared to controls. When crossed with APP/PS1 mice, deletion of LRP1 in vascular mural cells exacerbated A $\beta$  deposition both in the cortical parenchyma as amyloid plaques and along the cerebral vessels as CAA [6].

## Conclusions

Our results demonstrate that the presence of *APOE4* or an absence of apoE receptor LRP1 leads to cerebrovascular defects, which compromise A $\beta$  clearance machinery resulting in A $\beta$  accumulation in the brain. The resulting A $\beta$  aggregation and deposition further exacerbate cerebrovascular dysfunction in AD.

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