Repressed Autophagy in Aging Is Associated With Heightened Blood-Brain-Barrier Permeability and Altered Functional Hyperemia

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Cardiovascular disease and cognitive impairment are among the biggest healthcare challenges facing the elderly. Integrity of the blood brain barrier (BBB) and lining of the blood vessels require viable, healthy endothelial cells (ECs). Autophagy, the ability to remove damaged cells, appears repressed in the old. Studies suggest that an aging EC phenotype contributes to heightened BBB permeability and an inability to respond to functional demands. Our study demonstrates repressed EC mRNA and arterial protein indexes of autophagy in old mice ECs. Next, we showed that permeability across the BBB is increased when autophagy is repressed: greater infiltration of white blood cells and Evans Blue dye was detected in inducible-depletion of Atg3 in ECs (iecAtg3KO). Lower cell index in Human Brain Microvascular ECs was evident when treated with 3-Methyladenine (3-MA) and measured via Electric Cell-substrate Impedance Sensing System (ECIS) in vitro. To provide evidence of a compromised functional hyperemic stress response precipitating in arterial dysfunction, we demonstrate that 60-min treadmill-running increased Atg3, LC3B and p-eNOSS1177 activation in ECs from aorta of adult but not old mice. Reduction in vasodilation was evident in femoral arteries from old mice in response to stress. IecAtg3KO mice demonstrate similar suppression of Atg3, p-eNOSS1177 activation and vasodilation providing direct evidence that autophagy-linked p-eNOSS1177 activation may be important in functional hyperemia. Structurally, there is increased thickness of the tunica media layer in the vasculature of the old and iecAtg3KO mice. This study provides a glimpse into a mechanism of autophagy responsible for BBB permeability and functional vascular response in the elderly.

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