Defective autophagy impairs endothelial cells' function and blood-brain barrier integrity.

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Cerebral small vessel disease (SVD) is a common form of vascular dementia, where dysfunctional endothelial cells (ECs) lead to white matter changes, an early feature of the disease. ECs' dysfunction has been established as an early event in the pathogenesis of SVD, occurring before blood-brain-barrier (BBB) breakdown. In this context, identifying novel genes associated with ECs' dysfunction will help understand the role of ECs in BBB integrity. Recently, it has become apparent that autophagy is associated with the pathophysiology of neurodegenerative and vascular disease. However, the role of autophagy in endothelial barrier function in the blood-brain barrier (BBB) is not clear. Mounting evidence shows that autophagic flux within the endothelium has an essential role in maintaining the vascular function, whereas defective autophagy within endothelial cells (ECs) can promote a pro-inflammatory phenotype.
Trichoplein (TCHP) was initially characterised as a ubiquitously expressed keratin filament binding protein associated with cell division and cilia formation. Moreover, TCHP has been reported to regulate ER-mitochondria tethering and promote mitophagy, a specialised form of autophagy necessary for the turnover/remodelling of mitochondria. We previously demonstrated a pivotal role for the centriolar protein TCHP in linking ECs' function with the control of autophagy, showing that the depletion of TCHP in ECs impairs migration and sprouting and triggers cellular inflammation. We then generated endothelial-specific knock-out mice for Tchp ($Tchp^{EC}$). The analysis of the permeability of the ECs isolated from the brain of $Tchp^{EC}$ mice and of Human Brain Microvascular ECs with Tchp Knock-down (KD) by Electric Cell-substrate Impedance Sensing (ECIS®) revealed an impaired barrier function associated with the KD of Tchp. Furthermore, $Tchp^{EC}$ mice administered with the fluorescently labelled tracer dextran presented a higher accumulation of tracer in the brain compared to WT mice, demonstrating a loss of Blood-Brain barrier (BBB) integrity. Moreover, RNA sequencing demonstrated the activation of matrix-metalloproteinases and chemokine signalling pathways in ECs from $Tchp^{EC}$ mice. Analysis of immune cells recruitment by flow cytometry revealed the presence of $CD11B^{+}/CD45^{+}/LY6G^{-}/LY6C^{-}/P2Y12^{+}$ cells (reactive microglia) and recruitment of $CD11B^{-}/CD45^{hi}/CD19^{-}/CD3^{+}$ T cells in the brain of $Tchp^{EC}$ mice. Finally, a pharmacological screening identified an FDA-approved compound activating autophagy and, thus restoring ECs' function and reducing expression of inflammatory genes in ECs lacking Tchp.
In conclusion, TCHP-mediated defective autophagy in ECs could lead to inflammation and impaired BBB integrity.