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TRANSCRIPTOMIC DISSECTION OF IMPAIRED ANGIOGENESIS AND BLOOD BRAIN BARRIER FUNCTION IN AD

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Aims: Brain perfusion and blood brain barrier (BBB) integrity are reduced in Alzheimer's disease (AD). We hypothesized that dysfunction of pathways regulating the structure and function of the BBB endothelial cells (EC), pericytes (PC) and fibroblasts (FB) is related directly to the pathological protein load.
Methods: We performed single nucleus RNA sequencing (snRNAseq) of vascular cells isolated from *post mortem* samples from AD patients and controls. We developed a meta-analytic approach to integrate these data with related publicly available datasets. First, we explored vascular cell-type enrichment for the expression of genes associated with genetic risk for AD. We then performed a differential gene expression (DGE) analysis using two approaches: a categorical comparison of AD vs controls and a regression of transcriptomic alterations to either regional total beta-amyloid (Aβ) or neurofibrillary tangle (NFT) burden.
Results: EC are enriched for expression of genes related to AD genetic risk. Among them, *PICALM* was downregulated in AD and *CTGF* positively correlates to Aβ in EC. EC transcriptional signatures also identified mechanisms for impaired Aβ clearance and increased apoptosis and interferon signalling genes were upregulated in the EC, as well as in PC. In the AD vs control comparison, an imbalance of angiogenic signalling, with an enhanced pro-angiogenic response driven by *HIF1A* and *ANGPT2* and a downregulation of the effectors of this response, notably including the angiopoietin receptor, *TEK,* and associated growth factor pathways, were observed in association with downregulation of extracellular matrix genes in FB.
Conclusions: Transcriptional signatures of brain vascular cells suggest a potentially causal role for EC in AD. They identify early vascular mechanisms of disease include impaired angiogenesis, reduced Aβ clearance and impaired integrity of the microvascular extracellular matrix composition.