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Global spotlights

Brain endothelium: a nexus for cerebral small vessel disease

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A focal point for vascular signalling

Brain endothelial cells (BECs) have unique roles in controlling cerebral blood flow (CBF) and as a cornerstone of the blood–brain barrier (BBB). For example, they influence baseline CBF and act as sensors of moment-to-moment changes in neural activity. They participate in vascular remodelling and regulate immune cell interactions, thereby contributing to the maintenance of brain homoeostasis. Despite such advances, we have only scratched the surface in understanding the contribution of BECs to vascular control and subsequently brain health. Brain endothelial cells are a signalling focal point, integrating cellular, blood-borne, and mechanical stimuli. Acutely, this input is translated into electrical (ionic) or molecular signals that control vascular resistance, re-directing local CBF to regions of increased cellular activity.[1] Brain endothelial cells also exert chronic effects on mural cells (pericytes and vascular muscle), glia, and neurons. Single-cell RNA sequencing (scRNAseq) studies in humans and mice have uncovered a largely unanticipated zonation- and organ-specific heterogeneity of endothelial cells,[2] the impact of which is relatively poorly defined in relation to brain health. For instance, capillary ECs show enrichment in transport, metabolism, and O_2-response genes in accord with their positioning at the BBB, whereas ECs from arteries, arterioles, and venules are enriched in genes related to remodelling, structural organization, and inflammation, respectively.[2–4] Accounting for this heterogeneity is critical when studying cerebrovascular disease and for therapeutic targeting. As an example, the cell type expressing the most Alzheimer's disease (AD) and AD-related trait genes [based on genome-wide association studies (GWAS) in humans] is BECs.[5]

Hypertension and brain endothelial cell dysfunction

The prominence of hypertension (HT) as the leading modifiable risk factor for small vessel disease (SVD), stroke, and dementia further implicates a key role for BECs and a vascular contribution to mechanisms that promote a progressive decline in brain health (e.g. mixed dementia). Hypertension produces diverse changes in the micro-vasculature, local haemodynamics, and BECs. These changes include loss of endothelium-dependent signalling, ion channel dysfunction, rarefaction of capillaries and arterioles, loss of pericytes, changes in the extracellular matrix, inward vascular remodelling and arteriolar hypertrophy, hypoperfusion, loss of BBB integrity and function (e.g. tight junctions, transcytosis, and transporters), and impaired regulation of local CBF (e.g. neurovascular coupling).[6] We propose a two-hit mechanism where HT synergizes with genetic predisposition to drive SVD, providing a more relevant model of human disease.

A nexus for cerebral small vessel disease

Cerebral SVD accounts for the majority of haemorrhagic strokes, ~25% of ischaemic strokes, and contributes to at least 40% of dementias.[7] Despite such profound impact on brain health, there are no proven treatments for SVD. Genome-wide association studies[8] implicate BEC dysfunction in disease initiation and propagation.[5] For instance, common variants of *FOXF2* are associated with small vessel stroke and white matter lesions (WMLs). In mice, *Foxf2* encodes a key

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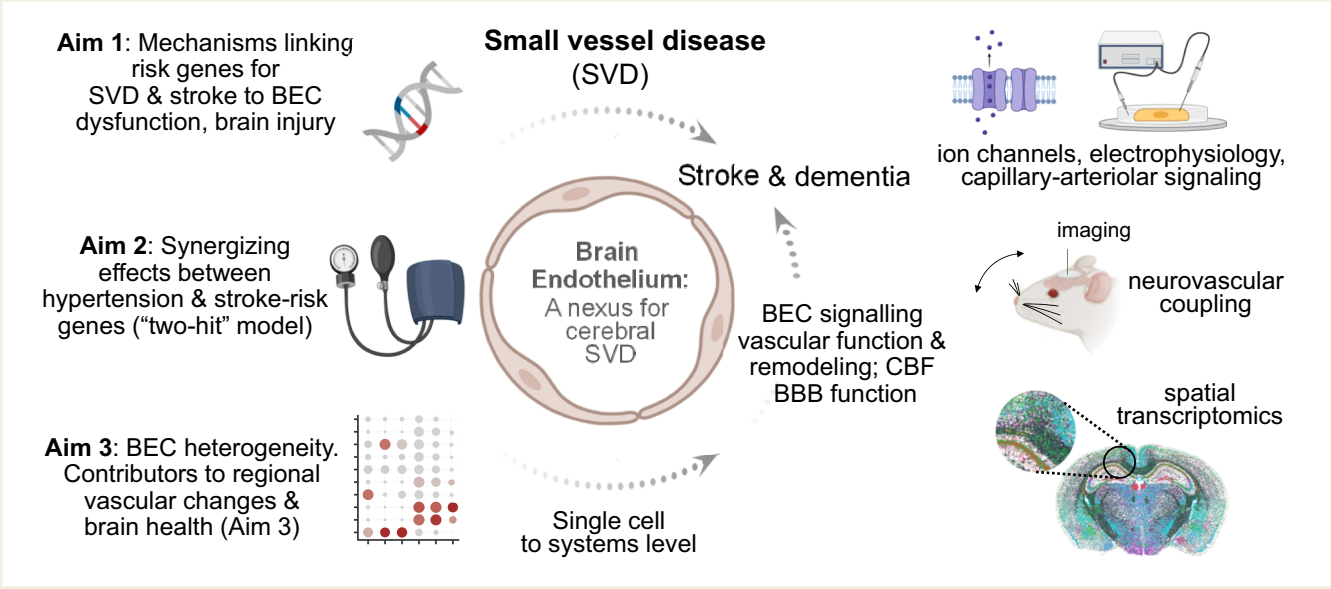

Figure 1 The BRENDA network will define mechanisms linking risk genes for cerebral small vessel disease and stroke to brain endothelial cell dysfunction and brain injury, applying cutting edge technology to novel disease models, including human inducible pluripotent stem cell–based models of the blood–brain barrier and neurovascular unit (Aim 1); test whether genetic predisposition synergizes with hypertension to augment brain endothelial cell dysfunction and brain injury (Aim 2, 'two-hit' model); and determine whether brain endothelial cell heterogeneity underlies differences in brain injury across regions (Aim 3). Advances in the understanding of brain endothelial cells and their impact on brain health are expected to facilitate the development of novel therapeutic approaches. BBB, blood–brain barrier; BEC, brain endothelial cell; CBF, cerebral blood flow; SVD, small vessel disease. Figure created with BioRender.com.

transcription factor primarily expressed in BECs and pericytes[2] and required for BBB development and maintenance.[9] Inactivation of *Foxf2* in mice causes BEC swelling, BBB breakdown, ischaemic infarcts, and intra-cerebral haemorrhage (ICH), thus phenocopying SVD. Studies in a model of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and capillary to arteriolar signalling revealed defects in BEC–BEC signalling that reflected impaired ion channel activity but could be restored by pharmacological intervention, highlighting the therapeutic potential of BEC-based interventions. Common and rare variants of collagen genes (*COL4A1*/*COL4A2*) are also associated with lacunar stroke, WML, and ICH, while EC-specific expression of mutant *Col4a1* causes ICH in mice. These findings support the concept that an essential integrator function of BECs is progressively degraded in SVD and that microvascular BEC dysfunction serves as a nexus for the loss of brain health.[7,10] Thus, BEC may be a target with significant, but largely unrecognized, therapeutic potential.

BRENDA network of excellence

The new Leducq Foundation International Network—Brain Endothelium: A Nexus for Cerebral Small Vessel Disease (BRENDA)—aims to further define BEC biology in an effort to unlock the translational potential of BEC-based mechanisms. In addition to being a major cause of stroke and dementia, SVD results in covert brain injury through micro-infarcts and micro-bleeds—stroke subtypes that often go undetected but are major contributors to disability and the decline of brain health.[11] Network investigators identified genetic variants in humans that increase the risk for SVD and stroke across multiple ancestries. They developed mice expressing such variants in BECs and found that these models exhibit features of SVD mimicking those in humans. Over the next 5 years, the network aims to (i) define mechanisms that link genetic variation in risk genes for cerebral SVD and stroke to BEC dysfunction and brain injury; (ii) test whether genetic variants synergize with HT to augment BEC dysfunction and brain injury; and (iii) determine whether BEC heterogeneity underlies differences in injury across brain regions (*Figure 1*). Addressing such questions should facilitate development of targeted therapeutics for prevention and treatment of SVD.

BRENDA brings together collaborative efforts and complementary expertise in genetics, vascular physiology, HT, *in vivo* imaging, *ex vivo* and *in vitro* approaches, human-induced pluripotent stem cell–derived models of the BBB, scRNAseq, and clinical studies—all with a focus on the microvasculature and BECs. The team is composed of Drs Martin Dichgans (European coordinator; University Hospital, LMU Munich), Frank Faraci (US coordinator; University of Iowa), Christer Betsholtz (Uppsala University), Elizabeth Hillman (Columbia University), Anne Joutel (INSERM Paris), Mark Nelson (the University of Vermont) and Dominik Paquet (University Hospital, LMU Munich).

Declarations

Disclosure of Interest

All authors declare no conflict of interest for this contribution.

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References

1. Hillman EM. Coupling mechanism and significance of the BOLD signal: a status report. *Annu Rev Neurosci* 2014;**37**:161–81. https://doi.org/10.1146/annurev-neuro-071013-014111
2. Vanlandewijck M, He L, Mae MA, Andrae J, Ando K, Del Gaudio F, *et al.* A molecular atlas of cell types and zonation in the brain vasculature. *Nature* 2018;**554**:475–80. https://doi.org/10.1038/nature25739
3. Schaeffer S, Iadecola C. Revisiting the neurovascular unit. *Nat Neurosci* 2021;**24**:1198–209. https://doi.org/10.1038/s41593-021-00904-7
4. Saunders A, Macosko EZ, Wysoker A, Goldman M, Krienen FM, de Rivera H, *et al.* Molecular diversity and specializations among the cells of the adult mouse brain. *Cell* 2018;**174**:1015–30.e16. https://doi.org/10.1016/j.cell.2018.07.028
5. Yang AC, Vest RT, Kern F, Lee DP, Agam M, Maat CA, *et al.* A human brain vascular atlas reveals diverse mediators of Alzheimer's risk. *Nature* 2022;**603**:885–92. https://doi.org/10.1038/s41586-021-04369-3
6. Koide M, Harraz OF, Dabertrand F, Longden TA, Ferris HR, Wellman GC, *et al.* Differential restoration of functional hyperemia by antihypertensive drug classes in hypertension-related cerebral small vessel disease. *J Clin Invest* 2021;**131**:e149029. https://doi.org/10.1172/jci149029
7. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol* 2019;**18**:684–96. https://doi.org/10.1016/S1474-4422(19)30079-1
8. Mishra A, Malik R, Hachiya T, Jürgenson T, Namba S, Posner DC, *et al.* Stroke genetics informs drug discovery and risk prediction across ancestries. *Nature* 2022;**611**:115–23. https://doi.org/10.1038/s41586-022-05165-3
9. Reyahi A, Nik AM, Ghiami M, Gritli-Linde A, Pontén F, Johansson BR, *et al.* Foxf2 is required for brain pericyte differentiation and development and maintenance of the blood–brain barrier. *Dev Cell* 2015;**34**:19–32. https://doi.org/10.1016/j.devcel.2015.05.008
10. Rajani RM, Quick S, Ruigrok SR, Graham D, Harris SE, Verhaaren BFJ, *et al.* Reversal of endothelial dysfunction reduces white matter vulnerability in cerebral small vessel disease in rats. *Sci Transl Med* 2018;**10**:eaam9507. https://doi.org/10.1126/scitranslmed.aam9507
11. Dichgans M, Leys D. Vascular cognitive impairment. *Circ Res* 2017;**120**:573–91. https://doi.org/10.1161/CIRCRESAHA.116.308426