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Unlocking pericyte function in the adult blood brain barrier one cell at a time

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The brain supports essential functions such as synaptic transmission and plasticity that are critical for long-term information storage and are easily disrupted by mis-regulation of its ionic, metabolic or cellular composition. In addition, its exquisitely high energetic demand is dependent on a precisely regulated regional blood flow[1, 2]. To simultaneously achieve efficient blood flow delivery and a tight homeostatic regulation of its microenvironment, the brain has evolved an intricate and dense network of specialized microvessels. These vessels are characterized by the presence of the blood brain barrier (BBB), an endothelial cellular specialization that allows regulated influx and efflux of diverse compounds, nutrients, peptides and drugs, while restricting the entry of plasma proteins and immune cells from the circulation[2]. This selectivity is achieved by the presence of impermeable tight junctions, low levels of endothelial transcytosis and selective expression of membrane transporters [3]. Disruption of these mechanisms has been involved in the pathogenesis of a variety of neurological disorders ranging from acute injury to autoimmune and neurodegenerative conditions[4] .

Much progress has been made in understanding mechanisms involved in the development of the brain vascular network and emergence of BBB properties. The recruitment of vascular mural cells (pericytes and smooth muscle cells) has been shown to be critical for the embryonic development of the BBB [5, 6] and for maintenance of microvascular integrity and adult properties of the BBB[7]. Interestingly pericytes in different brain regions have different origin with forebrain pericytes derived from the cranial neural crest and mid-, hindbrain, and

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spinal cord pericytes from mesoderm[8]. Despite their diversity in origin, the maintenance and function of all pericytes seems to be orchestrated by a master regulator, the platelet-derived growth factor-B (PDGFB) and its receptor[9]. In adults, PDGFB signaling pathway remains important in the maintenance of pericytes and defects in this pathway have been associated with various neuropathologies[10]. Despite these observations, the precise cellular and molecular mechanisms involved in BBB regulation and the role of interactions between endothelium and mural cells remains poorly understood.

In this article, Mae et al[11], used a multifaceted approach to systematically dissect the precise molecular signatures dependent on pericyte coverage that influence brain endothelial phenotypes. They implemented single cell RNA seq methodologies of the brain vasculature in Pdgfb ret/ret mice, which display significant loss of pericytes but are viable in adult life. They crossed these mice with reporter lines in which both endothelial cells and pericytes where fluorescently labeled. This allowed them to purify the endothelial cell population free of pericyte contamination, a major challenge for studying pericyte-endothelial interactions using gene expression profiling. In addition, they used detailed immunofluorescence confocal imaging of selected proteins of interest identified through scRNAseq analysis and correlated the patterns of expression with fluorescent tracer analysis of the BBB. Finally, they use additional tissue specific knockout models in combination with the Pdgfb ret/ret mouse to dissect the potential alterations in downstream signaling resulting from pericyte deficiency.

Consistent with a recent publication by the same group[6] they show that endothelial cells are transcriptionally diverse but their profile changes gradually within the arteriovenous (AV) zonation. In the current paper they reveal that pericyte loss in Pdgfb ret/ret mice disrupts this AV zonation, skewing the endothelial phenotype towards a venous fate. This is associated with the re-acquisition of angiogenic plasticity as manifested by the prominent presence of tip cells at sites of pericyte deficiency, suggesting a regression to a developmental phenotype. Some of these observations are sure to stimulate potential novel biological questions in the vascular biology field. First, it is fascinating that capillary endothelia cells within the AV zones while acquiring “developmental phenotype” choose a venous fate in a pericyte deficient brain. During development vascular mural cells including pericytes privilege arterial vasculature. Arterial endothelial cells by responding to blood flow shear stress promotes Pdgfb ligand expression and recruit Pdgfrb+ cells3. Recent data from Stratman et all[12], found that venous cells possess an intrinsic ability to inhibit mural cell recruitment by suppressing Pdgfb expression. It is therefore possible that the absence of pericyte might trigger a “venous developmental memory”. It is also possible that this process could be indirectly influenced by hemodynamics defects within the pericyte-deficient brain. Since most of the sc-RNA seq data required cell dissociation, molecular signatures driven by blood flow hemodynamics are difficult to capture, thus this aspect will require further investigation.

With respect to changes in the BBB, Pdgfb deficiency in Pdgfb ret/ret mice was associated with significant leakage of macromolecules into the brain parenchyma. Mae et al., noticed hotspots of leakage as well as an overall endothelial transcytotic uptake, as the main mechanisms of BBB dysfunction. Using their single cell and imaging methodologies as well

as mouse mutants, they investigated potential molecular mechanisms involved in these BBB changes. They analyzed candidate genes based on known markers of either BBB transcytosis or vascular maturation. They found that formation of leakage hotspots in Pdgfb ret/ret mice was independent of MFSD2A and Fgfbp1, known regulators of endothelial transcytosis and BBB permeability. In addition, contrary to the well-known function of ANGPT2 as a vascular stabilizer, they found that double Pdgfb ret/ret and ANGPT2 knockout mice had increased BBB leakage, suggesting a ANGPT2/Tie2-indpendent mechanism of pericyte control of BBB permeability. Because pericyte loss causes a multiplicity of vascular changes including formation of microaneurysms, changes in the basal lamina and hemodynamic alterations, their results shine light on the complexity of studying pericyte-endothelial signaling in health and disease.

Altogether, the use of single cell sequencing, protein analysis in individual cells and multiple genetic models, combined with assessment of endothelial and BBB function in vivo, is an exciting and promising approach. Application of this strategy will continue to advance our understanding of endothelial-pericyte signaling and will help elucidate mechanisms of neurovascular pathology.

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References

1. Hill RA, Tong L, Yuan P, Murikinati S, Gupta S and Grutzendler J. Regional Blood Flow in the Normal and Ischemic Brain Is Controlled by Arteriolar Smooth Muscle Cell Contractility and Not by Capillary Pericytes. Neuron. 2015;87:95–110. [PubMed: 26119027]
2. Daneman R and Prat A. The blood-brain barrier. Cold Spring Harb Perspect Biol. 2015;7:a020412. [PubMed: 25561720]
3. Langen UH, Ayloo S and Gu C. Development and Cell Biology of the Blood-Brain Barrier. Annu Rev Cell Dev Biol. 2019;35:591–613. [PubMed: 31299172]
4. Zlokovic BV. The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron. 2008;57:178–201. [PubMed: 18215617]
5. Daneman R, Zhou L, Kebede AA and Barres BA. Pericytes are required for blood-brain barrier integrity during embryogenesis. Nature. 2010;468:562–6. [PubMed: 20944625]
6. Vanlandewijck M, He L, Mae MA, Andrae J, Ando K, Del Gaudio F, Nahar K, Lebouvier T, Lavina B, Gouveia L, et al. A molecular atlas of cell types and zonation in the brain vasculature. Nature. 2018;554:475–480. [PubMed: 29443965]
7. Armulik A, Genove G and Betsholtz C. Pericytes: developmental, physiological, and pathological perspectives, problems, and promises. Dev Cell. 2011;21:193–215. [PubMed: 21839917]
8. Korn J, Christ B and Kurz H. Neuroectodermal origin of brain pericytes and vascular smooth muscle cells. J Comp Neurol. 2002;442:78–88. [PubMed: 11754368]
9. Soriano P Abnormal kidney development and hematological disorders in PDGF beta-receptor mutant mice. Genes Dev. 1994;8:1888–96. [PubMed: 7958864]
10. Bell RD, Winkler EA, Sagare AP, Singh I, LaRue B, Deane R and Zlokovic BV. Pericytes control key neurovascular functions and neuronal phenotype in the adult brain and during brain aging. Neuron. 2010;68:409–27. [PubMed: 21040844]
11. Mäe MA, He L, Nordling S, Vazquez-Liebanas E, Nahar K, Jung B, Li X, Tan BC, Foo JC, Cazenave-Gassiot A, et al. . Single-Cell Analysis of Blood-Brain Barrier Response to Pericyte Loss. Circ Res. 128: xx–xxx.

12. Chang L, Noseda M, Higginson M, Ly M, Patenaude A, Fuller M, Kyle AH, Minchinton AI, Puri MC, Dumont DJ and Karsan A. Differentiation of vascular smooth muscle cells from local precursors during embryonic and adult arteriogenesis requires Notch signaling. Proc Natl Acad Sci U S A. 2012;109:6993–8. [PubMed: 22509029]

13. Stratman AN, Burns MC, Farrelly OM, Davis AE, Li W, Pham VN, Castranova D, Yano JJ, Goddard LM, Nguyen O, et al. Chemokine mediated signalling within arteries promotes vascular smooth muscle cell recruitment. Commun Biol. 2020;3:734. [PubMed: 33277595]