Pericyte-associated hemorrhage in arteriovenous malformations

TO THE EDITOR: We read with pleasure the article by Winkler et al.7 (Winkler EA, Birk H, Burkhardt JK, et al: Reductions in brain pericytes are associated with arteriovenous malformation vascular instability. J Neurosurg [epub ahead of print January 5, 2018. DOI: 10.3171/2017.6.JNS17860]) regarding the findings of reduced populations of perivascular macrophages (pericytes) in brain arteriovenous malformations (bAVMs). We commend the authors for their thorough evaluation of the histological findings in both pathological and normal brain biopsy specimens from patients with and without bAVMs, respectively.

The authors found that pericytes are reduced in both cell quantity and capillary coverage in bAVM specimens compared to tissue of patients undergoing anterior temporal lobectomy. Ruptured bAVMs demonstrated a significant reduction in pericyte coverage compared to unruptured bAVMs. When comparing pericyte coverage to nidal blood flow on preoperative angiograms, there was a positive correlation of pericyte coverage to transit time through the bAVM nidus. The authors’ findings are without a doubt interesting, particularly given our increasing appreciation of the role of pericytes in capillary blood flow (CBF) in both health and disease.2–4,9

Pericytes are bone-derived macrophages implicated in neuro-inflammation and blood-brain barrier (BBB) integrity and CBF.1,8,10 Recent evidence suggests that pericyte coverage and activity may be significantly upregulated following hyperacute exposure to subarachnoid blood, following stroke, or even in chronic CNS injury. However, there is some controversy over the role of pericyte activation in mediating cerebral blood flow. Pericyte contractility is thought to be mediated by α-smooth muscle actin (α-SMA), but its expression is variable between proliferative CD90+ cells and pro-inflammatory (and contractile) CD90− cells.5 Furthermore, there are different reports of the constitutive expression of α-SMA in pericytes, and so not all pericytes are capable of restricting capillary flow. It would be of significant interest if the authors could comment on the expression of α-SMA in the CD90 status of pericytes found in bAVMs. Additionally, the use of in situ hybridization techniques of mRNA would further solidify the relationship of α-SMA and contractility of pericytes to the delayed blood flow appreciated on radiography. Knowledge of the natural state of bAVM pericytes is of particular interest because they may be induced to change their expression of α-SMA through signaling cascades, which may provide a mechanism of treatment in reducing hemorrhage risk in the future.6

Additionally, the findings of reduced pericyte quantity and coverage are not altogether unexpected given the aberrant capillary architecture and inconsistent glial components of bAVMs. Because pericytes are bone derived and require migration and signaling to arrive at the capillary interface, the abnormal cytoarchitecture and unpredictable glial or endothelial interactions of bAVMs may prevent appropriate pericyte migration. Still, the authors should be commended for their thorough, well-designed, and topical work that further highlights the importance of pericyte activity in mediating both CBF and neuroinflammatory processes.

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References

Disclosures
The authors report no conflict of interest.

Response
We thank Taylor et al. for their interest in our recent article showing reduced pericytes in bAVMs. Pericytes are versatile vascular mural cells that regulate important neurovascular functions, including BBB integrity, CBF, neuroinflammatory responses, and brain angiogenesis. Although the authors of this letter refer to pericytes as “perivascular macrophages” derived from bone, the literature does not support their description as macrophages. They are capable of phagocytosis in certain disease states, but are distinct from macrophages.

Recent work with fluorescent transgenic reporter mice has identified subpopulations of brain pericytes with variable structure and expression of specific proteins, such as the contractile protein α-SMA. However, comprehensive single cell sequencing has not been performed to characterize and delineate these pericyte populations. As suggested in their letter, pericyte contractile protein expression is also altered in a number of disease states, such as ischemic stroke or subarachnoid hemorrhage. We conducted the experiments suggested by Taylor et al. and observed an increase in α-SMA positivity in bAVM-associated pericytes (unpublished observations). The relationship between nidal transit time and pericyte coverage, and how this relates to pericyte contractile protein expression, remains unclear and requires further investigation, both in bAVM specimens and in bAVM rodent models.

As with other published works, our paper studied pericyte abundance globally. We agree with Taylor et al. that future studies are needed to determine whether different subpopulations of pericytes are differentially affected in bAVMs or other neurological diseases in which pericytes are implicated, such as stroke, traumatic brain injury, fetal intraventricular hemorrhage, and cavernous malformations. Similarly, additional studies are needed to determine which disruptions of endothelial-pericyte signaling cascades contribute to pericyte loss in bAVMs. Pericytes may represent a novel therapeutic target for stabilizing bAVMs, and these multifaceted cells are the focus of ongoing investigation.

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