

Inflammation of the cerebral arteries: lifting the veil on the pathobiology of intracranial aneurysms

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Cerebral aneurysms (CAs) are the most common cause of spontaneous subarachnoid hemorrhage (SAH).^[1] Despite significant improvements in microsurgical and endovascular aneurysm therapies and in neurocritical care since the turn of the century, the outcomes after CA rupture remain dismal. The mortality associated with aneurysmal SAH is approximately 50%, and of the survivors, approximately one-third have long-term neurocognitive deficits and one-half require permanent assistance.^[2,3] Since post-SAH management outcomes have seemingly plateaued in the past decade, the ideal window for improving overall outcomes in CA patients is prior to rupture.^[4]

However, interventions for unruptured CAs are not without risk, so their risk to benefit profiles must be compared to the natural history of unruptured CAs.^[5,6] Naggara *et al.*^[7] performed a systematic review of endovascular treatment outcomes for unruptured CAs and found a 5% rate of unfavorable outcomes. Similarly, Kotowski *et al.*^[8] performed a systematic review of surgical outcomes for unruptured CAs and reported a 7% rate of unfavorable outcomes. Even as advances in neurointerventional techniques and endovascular technologies, including newer generation flow-diverting stents (i.e. Surpass, flow redirection endoluminal device), intermediate coverage stents (i.e. LVIS), aneurysm neck and bifurcation reconstruction devices (i.e. PulseRider, Barrel, Eclips), and intrasaccular flow disruptors (i.e. WEB, Luna),

continue to improve interventional outcomes for CAs, treatment of unruptured CAs continues to expose patients to potential morbidity and mortality.^[9,10] Therefore, a medical therapy that effectively reduces the hemorrhage risk of an unruptured CA with a reasonable safety profile may improve the long-term outcomes for patients harboring these lesions. Unfortunately, such a therapy does not currently exist, although the efficacies of novel and existing pharmacologic agents have been investigated.^[11]

A crucial component to the development of an effective drug to stabilize or induce regression of CAs is acquiring an understanding of their pathogenesis. Two common pathogenic features shared by CAs and extracranial aneurysms are (1) chronic inflammation, with an accompanying increase in the expression of pro-inflammatory cytokines and matrix metalloproteinases, initiates and exacerbates CA development, and (2) progressive loss of smooth muscle cells (SMCs) in an artery's tunica media, which are critical for providing contractility and mechanical stability of the vessel wall. One of the difficulties in evaluating CA pathophysiology is the lack of animal models that accurately recapitulate the human disease. A mouse CA model is advantageous over models in other animals, due to the plethora of different genetic knockouts that are available in mice. An increasingly popular mouse CA model was initially devised by Nuki *et al.*,^[12] in which CAs are generated by a combination of induced systemic hypertension and intracranial elastase injection into the basal cisterns. A number of recent studies have used this mouse model to investigate the role of various endogenous factors in CA pathogenesis.^[13-16]

Inflammation has been shown to be a central contributor to the pathogenesis of CAs. Hasan *et al.*^[17] showed that ferumoxytol-enhanced magnetic resonance

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imaging (MRI) can be used to evaluate inflammation and destabilization of the CA wall by utilizing ferumoxytol uptake as a surrogate indicator of macrophage turnover. More recently, Edjlali *et al.*^[18] found that circumferential enhancement of the CA wall on MRI can identify CAs prone to rupture. Although our knowledge of CA pathobiology has improved significantly over the past decade, there remains much to be learned and tested. One challenge in determining the role of the immune system in CA pathogenesis is the phenotypic plasticity exhibited by SMCs, a unique phenomenon not observed in cardiac and skeletal muscle cells. In the setting of vascular injury or inflammation, SMCs undergo phenotypic modulation, a process by which markers of mature SMCs are downregulated and markers of inflammatory cells, such as macrophages, are upregulated.^[19] Given the inability of conventional immunohistochemical staining methods to identify transdifferentiated SMCs, evaluation of SMC epigenetic signatures and SMC lineage tracing studies are necessary to accurately assess the contribution of SMCs to vascular lesions, such as CAs.^[20] Thus, the respective roles of cells of SMC and myeloid lineage in CA formation, progression, and rupture remains incompletely defined.^[21]

Despite the current limitations in our understanding of CA pathogenesis, the future of CA translational and clinical research is promising. In this special issue of *Neuroimmunology and Neuroinflammation* on the topic of “The Role of Inflammation in Cerebral Aneurysms”, we have assembled a collection of articles from renowned experts in the field of cerebrovascular disease, and attempt to lift the veil on the pathobiology of intracranial aneurysms.

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