# The role of inflammation in cerebral aneurysms

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**ABSTRACT**

The natural history of unruptured intracranial aneurysms (IAs) is poorly understood. At present, risk factors for aneurysm rupture are limited to demographics and rudimentary anatomic features of the aneurysm. The first sign of aneurysm destabilization and rupture may be subarachnoid hemorrhage, a potentially devastating brain injury with high morbidity and mortality. An emerging body of literature suggests a complex inflammatory cascade likely promotes aneurysm wall remodeling and progressive ballooning of the arterial wall, ultimately terminating in aneurysm rupture. These events likely begin with hemodynamic, flow-related endothelial injury; the injured endothelium stimulates inflammation, including the recruitment and transmigration of inflammatory cells, particularly macrophages. Various proteases are secreted by the inflammatory infiltrate, resulting in degradation of the extracellular matrix and the structural changes unique to IAs. Detailed understanding of these inflammatory processes may result in (1) early identification of patients at high risk for aneurysm rupture, perhaps via arterial wall imaging, and (2) targeted, noninvasive therapies to treat or even prevent cerebral aneurysms.

**Key words:** Aneurysms, atherosclerosis, inflammation, intracranial

## INTRODUCTION

Subarachnoid hemorrhage due to intracranial aneurysm (IA) rupture is a devastating disease. Initial mortality may be as high as 40-50%, and of those who survive, one-third to one-half are left with permanent neurologic deficits.[1] When an unruptured aneurysm is discovered in a patient, current therapeutic options to prevent aneurysm rupture include invasive endovascular occlusion versus surgical therapy, or close radiologic follow-up with intervention when the risk of rupture is deemed high enough. That being said, risk stratification of patients with an unruptured IA is based on a limited understanding of natural history, size appears to contribute to aneurysm destabilization,[2] but there are likely other, poorly understood factors at play. And as demonstrated in the International Study of Unruptured Intracranial Aneurysms (ISUIA), invasive endovascular or surgical treatments are associated with an overall 1-year morbidity/mortality of 10%.[3]

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In order to appropriately tailor treatment decisions, further understanding of the pathophysiology behind aneurysm growth and rupture is needed. In recent years, a growing body of literature has identified inflammation as a key player in the pathogenesis of intracranial aneurysms (IAs), from aneurysmogenesis and vascular remodeling to aneurysm destabilization and rupture. Here, we will review the pathology of IAs along with the literature supporting a role for inflammation in this pathology; we will also examine potential inflammatory targets for noninvasive treatment of IAs.

## STRUCTURAL CHARACTERISTICS OF INTRACRANIAL ANEURYSMS

Intracranial aneurysms are believed to be acquired vascular lesions; they are exceedingly rare in children and their incidence increases with age.[4,5] As IAs are preferentially located at bifurcations and sharp curves, hemodynamics (e.g. various shear stressors) are believed to trigger aneurysmogenesis. From a structural perspective, compared to extracranial vessels, intracranial vessels have less elastic fiber in the tunica media and adventitia, less smooth muscle in the media, and a thinner adventitia.[6] At vessel bifurcations, the apical portion of the intracranial vessel lacks smooth muscle cells (SMCs), a gap referred to as the "medial raphe".[7] During the initiation of aneurysms, the luminal surface of the vessel becomes

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irregular and often damaged, even denuded, a probable consequence of disturbed hemodynamic stress.[8]

Although shear stressors likely trigger the initial injury, further degradation and disorganization of the vascular wall leading to the aneurysmal growth is likely the result of an inflammatory cascade.[9-11] In general, the vessel wall is transformed into a disorganized array, with fragmentation/loss of the internal elastic lamina, myointimal hyperplasia, and disorganization of muscle fiber structure.[12-14] SMCs transition from a contractile phenotype to a pro-remodeling, pro-inflammatory synthetic phenotype, and finally to a dedifferentiated phenotype prior to aneurysm rupture.[15] Though the initial vascular injury was from high shear stress, the cavity of the aneurysm is subjected to low, atheroprone-like shear stress, the type conducive to inflammatory cell adhesion and infiltration.[16] In large aneurysms (e.g. those prone to rupture), there are often advanced atherosclerotic changes, phenotypically modified SMCs, lipid-laden macrophages, and lymphocytes.[17]

## INFLAMMATORY MEDIATORS OF ANEURYSM WALL REMODELING

The histological findings in the walls of IAs, those of degeneration and pathologic vascular remodeling, are similar to the findings evident in inflammatory atherosclerotic lesions. Summarized here and depicted in Figure 1 are the mediators of inflammation likely to play a role in IA pathogenesis.

### Endothelial dysfunction

Flow-mediated endothelial dysfunction is likely pivotal in aneurysm formation.[18] Several mechanosensors, such as ion channels, integrins, cell adhesion molecules, G-protein-coupled receptors, have been identified at the apical and basal surfaces of the endothelium;[14] these sensors can identify variations in wall shear stress and adapt lumen diameter accordingly. High shear stress can result in activation of inflammatory mediators, such as the master regulator of inflammation, nuclear factor-kappaB (NF-κB).[19,20] Mechanical stressors can denude the endothelium, triggering the expression of chemoattractants, pro-inflammatory cytokines, and cell adhesion molecules at the surface of endothelial cells.[21] Absent from normal control arteries, monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8) are expressed in human and experimental IAs[22] and vascular cell adhesion molecule-1 (VCAM-1) is expressed in the walls of human and rat model IAs.[23]

### Macrophages and other inflammatory infiltrates

Numerous studies have demonstrated the presence of inflammatory cell infiltrates, particularly macrophages, in IAs.[24] In one study, inflammatory infiltrates were present in half of all unruptured aneurysms (10/20) versus 100% of all ruptured aneurysms (40/40).[25] And in a study by Frösen *et al.*[26] whereby 42 ruptured IAs were histologically compared with 24 unruptured IAs, infiltration of the aneurysm wall by macrophages correlated strongly with aneurysm rupture. Macrophages are thought to be a key mediator of IA vascular remodeling as they release matrix metalloproteinases (MMP) such as MMP-9 and MMP-2.[27,28] In one study by Kanematsu *et al.*,[29] macrophage-depleted mice had a substantially lower risk of IA development compared with control mice (10% *vs.* 60%).

### Extracellular matrix remodeling

An essential feature of IAs is fragmentation of the internal elastic lamina (IEL) and thinning of the arterial media. These changes alter the mechanical properties of the aneurysm wall; in response to further shear stress, the destabilized arterial wall may progressively balloon. MMPs are proteolytic enzymes secreted by activated macrophages and by phenotypically modified SMCs. MMPs are capable of degrading the principal structural components in the artery wall, collagen, and elastin, and are, therefore, likely responsible for the structural

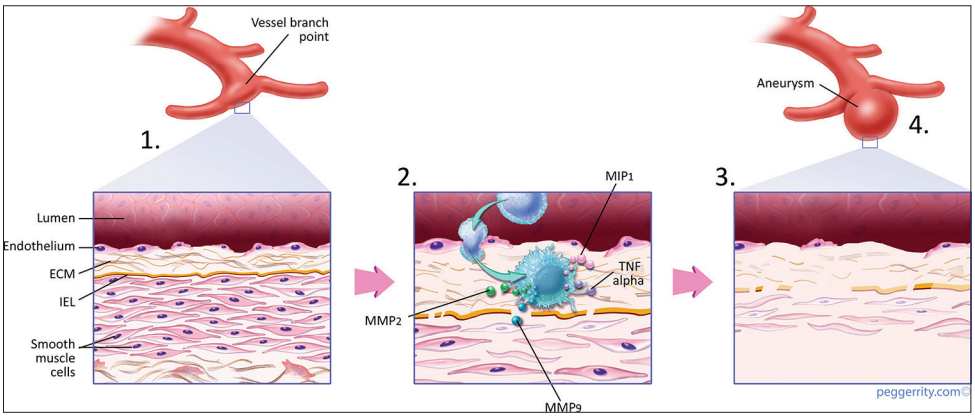


**Figure 1:** (1) Flow-related endothelial injury; (2) triggers an inflammatory response whereby cells (macrophages) infiltrate the arterial wall and secrete pro-inflammatory cytokines and metalloproteinases; (3) the mounting inflammatory response results in proteolytic destruction of the extracellular matrix and smooth muscle cell phenotypic modulation; (4) macroscopically, the arterial wall is remodeled into an aneurysm wall with progressive aneurysmal ballooning

changes in the internal elastic lamina and media in IAs.[30,31]

### Thrombus formation

Normally, an intact endothelial wall protects the luminal surface from thrombosis and platelet aggregation, in part via the expression of CD39, nitric oxide, and prostacyclin.[32] In contrast, damaged or denuded endothelial cells may instead activate thrombosis and platelet aggregation pathways. Altered hemodynamic flow within the IA cavity may also promote thrombus formation.[33] Neutrophils and macrophages are recruited to the site of endothelial injury and thrombosis. These cells often release proteolytic enzymes, MMPs, cathepsin G, and elastase, to try and promote fibrinolysis and thrombus degradation. Instead, these proteolytic enzymes may further degrade the IA wall.[34] SMCs and myofibroblasts may invade the thrombus, incorporating the thrombus into the IA wall itself.[35]

### Complement cascade

The complement cascade has also been studied as a contributor to the pathogenesis of IAs. Activation of complement leads to robust and efficient proteolytic cascades, typically terminating in opsonization and lysis of pathogens as well as in the generation of the classic inflammatory response through the production of potent pro-inflammatory molecules. Immunostaining of IA walls both in humans and animal models have identified complement components, particularly C3 and C9.[36] Two studies using microarray analysis have demonstrated variable expression of complement-related genes in IAs as compared with control arterial tissue.[37,38] And in another study comparing ruptured with unruptured aneurysms, the expression of the complement cascade end product (the membrane attack complex) was greater in ruptured samples and correlated significantly with aneurysm wall degeneration and inflammatory cell infiltration.[39] It continues to be unclear, though, how complement activation results in IA rupture, further studies are needed to define the exact pathways linking the two.

## IMAGING OF ARTERIAL WALL INFLAMMATION

Noninvasive imaging of vascular inflammation within the aneurysm wall may in the future help differentiate stable IAs from destabilized IAs at greater risk for rupture. For instance, protocols have been developed to visualize arterial wall inflammation in patients with intracranial atherosclerosis. Preliminary studies of atherosclerotic plaques suggest vulnerable plaques prone to rupture have arterial wall imaging profiles separate from stable, asymptomatic plaques.[40-42] Regarding IAs, DeLeo *et al.*[43] published a pilot study whereby active inflammation was imaged *in vivo* in a rabbit model of common carotid artery aneurysms. This group utilized a myeloperoxidase-specific paramagnetic contrast agent in conjunction with magnetic resonance imaging (MRI). Several years ago, Hasan *et al.*[44] reported on the use of ferumoxytol-enhanced MRI to image macrophages within aneurysm walls in 11 patients with unruptured IAs. Ferumoxytol is an iron oxide nanoparticle theoretically macrophage-selective as it is cleared by reticuloendothelial system macrophages. Interestingly, early ferumoxytol-associated imaging changes (24 h postinfusion) were identified in five patients, and several of these patients had "symptomatic" IAs (progressive headache; rapid aneurysmal enlargement; aneurysm rupture). Further studies with larger sample sizes are needed to confirm whether ferumoxytol-associated imaging changes correlate with greater IA rupture risk.

## POTENTIAL ANTI-INFLAMMATORY PHARMACOLOGIC TARGETS

Advances in our understanding of the inflammatory cascade leading to aneurysm destabilization and rupture may result in the designing of novel therapies individualized to specific patients. Preliminary data in animal models of IA suggest therapies targeting the inflammatory response may have efficacy in the future treatment of IA. For instance, in their rat model of IA, Aoki *et al.*[45,46] demonstrated reduction of IA wall inflammation and cessation of aneurysm progression via various statin agents. The expression of MCP-1, VCAM-1, IL-1β, inducible nitric oxide synthase, and MMP-9 were all reduced in statin-treated rats, likely via inhibition of NF-κB. However, other studies have demonstrated dose-dependent effects of statins on IAs, including aneurysm growth and/or rupture with high doses of statins.[47] A case-control study by Marbacher *et al.*[48] did not find a reduction in the incidence of IAs in patients with a history of statin use. Additional prospective studies are needed to clarify the role statins may play in patients with IAs. Other promising therapeutics include edavarone, a synthetic free radical scavenger, and nifedipine, a calcium channel antagonist.[45,49] In an experimental model of IA, nifedipine inhibited DNA binding of NF-κB, preventing progression of IA wall degeneration and limiting IA size.

Recently, aspirin has emerged as a candidate for noninvasive pharmacotherapy in patients with unruptured IAs. Depending on the dose, aspirin can inhibit several inflammatory mediators via its irreversible inhibition of cyclooxygenase-2. Among patients enrolled in ISUIA, those with a history of aspirin use 3 times weekly, or greater had a lower risk of cerebral

aneurysm rupture and subarachnoid hemorrhage compared with those who never used aspirin.[50] These findings were reproduced in a retrospective study of 747 patients with IAs by Gross *et al*.[51] subarachnoid hemorrhage occurred in 28% of patients with a history of aspirin use versus 40% of patients without a history of aspirin use. In the previous section, we described an imaging protocol (ferumoxytol-enhanced MRI) whereby macrophages in IA walls can be visualized. In one ferumoxytol-enhanced MRI study, patients were imaged pre- and post-daily aspirin therapy (for several months). Ferumoxytol signal within the IA walls was decreased in these patients postaspirin therapy, suggesting IA inflammation may have decreased.[52]

## CONCLUSION

Inflammation has emerged as a probable key mediator of both aneurysmogenesis and aneurysmal destabilization and rupture. The inflammatory cascade is likely interrelated with mechanical flow-induced vascular dysfunction. Further studies will, hopefully, further define these pathways, aid in our prediction of the natural history of an IA in a patient-specific manner, and identify novel pharmacologic targets to prevent aneurysm growth and rupture.

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