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Review of Cerebral Aneurysm Formation, Growth, and Rupture

Nohra Chalouhi, MD; Brian L. Hoh, MD; David Hasan, MD

Cerebral aneurysms (CAs) occur in 3% to 5% of the general population and are characterized by localized structural deterioration of the arterial wall, with loss of the internal elastic lamina and disruption of the media.¹ The most dreaded complication of CAs is rupture, the likelihood of which is related to several modifiable and nonmodifiable risk factors. Despite advances in surgical techniques and perioperative management, the mortality and morbidity associated with aneurysm rupture remain high.² Current therapeutic options are limited to invasive therapies, namely microsurgical clipping and endovascular treatment, both of which carry a non-negligible risk of procedural morbidity.

In recent years, it has become obvious that CAs are not passively enlarging vascular structures but exhibit prominent features of inflammation and tissue degeneration. Other factors mainly hemodynamic, genetic, hormonal, and environmental may also play an important role. Knowledge of the pathogenic pathways of CAs may pave the way for the development of noninvasive therapies. The purpose of this review is to summarize the most relevant data on the molecular mechanisms, genetics, and risk factors for aneurysm formation, growth, and rupture. Although there are different forms of CAs, the present discussion focuses on saccular aneurysms, which represent the most common type of CAs and are also the most common cause of subarachnoid hemorrhage (SAH).

Cerebral Aneurysms: an Inflammatory Disease

Increasing evidence points to inflammation as the leading factor in the pathogenesis of CAs. The inflammatory process is initiated by a hemodynamic insult and leads to matrix metalloproteinases (MMPs)-mediated degradation of the extracellular matrix and apoptosis of smooth muscle cells (SMCs), which are the predominant matrix-synthesizing cells of the vascular wall. These processes act in concert to weaken the arterial wall progressively, resulting in dilatation, aneurysm formation, and ultimately rupture (Figure; Table 1). The data supporting a major role for inflammation in CA pathogenesis are strong and derive from both experimental and human studies. The 2 main constituents of the inflammatory response and the associated degenerative response are macrophages and SMCs.

Macrophages are invariably noted in human aneurysm samples.³ The tissue-infiltrating macrophages not only release pro-inflammatory cytokines that lead to recruitment of additional inflammatory cells, but also release MMPs that digest arterial wall extracellular matrix and cause further damage via upregulation of other proteinases. As such, Aoki et al⁴ elegantly demonstrated that the expression of macrophages and macrophage-derived MMPs was closely associated with aneurysm growth, and that selective inhibition of these MMPs blocked aneurysm progression. Likewise, macrophage-depleted mice were found by Kanematsu et al⁵ to have a substantially lower risk of developing CAs. Along similar lines, the inhibition of monocyte chemoattractant protein-1 (MCP-1), a chemokine regulating the migration and infiltration of macrophages, halted CA formation in mice.⁶ In a comparative study of ruptured and unruptured human CAs, macrophage infiltration was strongly associated with aneurysm rupture.⁷ Interestingly, macrophages seem to be present in human CAs in 2 different forms that exert opposite effects on inflammation.⁸ Whereas the proinflammatory M1 cells and the anti-inflammatory M2 cells are present in equal proportion in unruptured aneurysms, the balance shifts toward M1 cells in ruptured aneurysms, suggesting a role for M1/M2 imbalance in the progression of human CAs to rupture.⁸ Also, the critical role of macrophages in CAs has allowed the development of targeted molecular imaging for identifying rupture-prone aneurysms,^{9,10} and this will be discussed in further detail below. Therapies targeting macrophage activation and MMP release in aneurysm walls or preventing the M1/M2 imbalance may potentially halt aneurysm formation and rupture.

SMCs play a pivotal role in the formation, progression, and rupture of CAs. As discussed above, SMCs, mostly concentrated in the media, are the predominant matrix-synthesizing cells of the vascular wall. The media provide structural integrity to the arterial wall, and the thinning of this layer contributes to aneurysm formation and rupture. Early in aneurysm formation, SMCs migrate into the intima in response to endothelial injury and proliferate, producing myointimal hyperplasia.¹¹ Subsequently, SMCs undergo phenotypic modulation from a differentiated phenotype concerned with contraction

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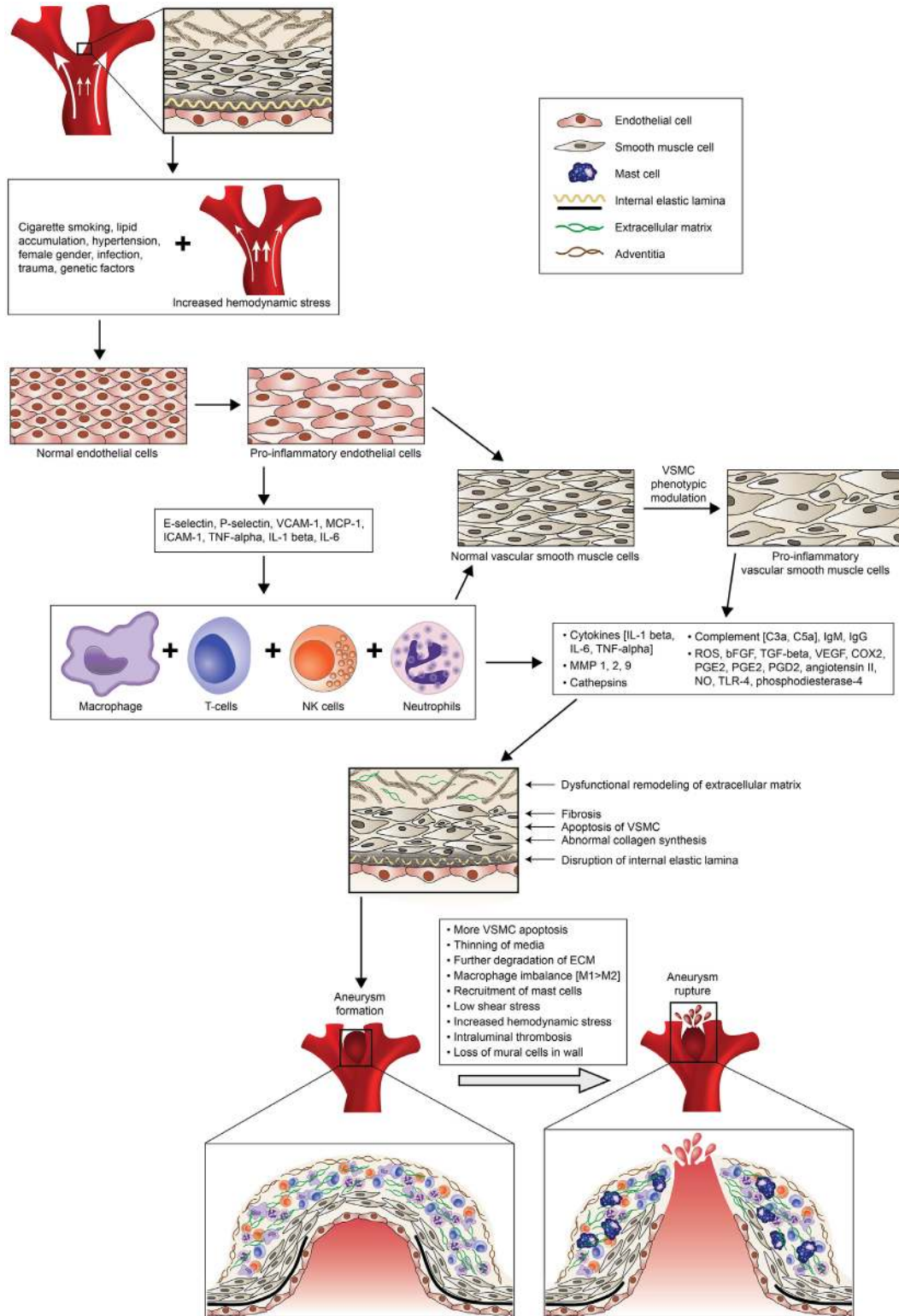


Figure. Cerebral aneurysm (CA) formation and rupture. Aneurysm formation is initiated by hemodynamically triggered endothelial dysfunction. An inflammatory response implicating several cytokines and inflammatory mediators as well as macrophages, T cells, and mast cells ensues. Concurrently, smooth muscle cells (SMCs) undergo phenotypic modulation to a proinflammatory phenotype. The inflammatory response in vessel wall leads to disruption of internal elastic lamina, extracellular matrix digestion, and aneurysm formation. Loss of mural cells and further inflammation and vessel wall degeneration ultimately lead to CA rupture. bFGF indicates basic fibroblast growth factor; COX2, cyclooxygenase-2; ECM, extracellular matrix; ICAM, intercellular adhesion molecule; IL, interleukin; MCP, monocyte chemoattractant protein; MMP, matrix metalloproteinase; NK, natural killer; NO, nitric oxide; PGD, prostaglandin D; PGE, prostaglandin E; ROS, reactive oxygen species; TGF, transforming growth factor; TLR, toll-like receptor; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor; and VSMC, vascular smooth muscle cell.

Table 1. Inflammatory Pathways and Mediators Implicated in CA Formation and Rupture

Pathway	Mediators
Endothelial dysfunction	IL-1 β NF- κ B Ets-1 MCP-1 Reactive oxygen species Nitric oxide (NO), endothelial NO synthase, inducible NO synthase Angiotensin II Phosphodiesterase-4 Prostaglandin E2 E selectin, P selectin, vascular cell adhesion protein 1 (VCAM1), intercellular adhesion molecule 1 (ICAM1)
Phenotypic modulation and loss of SMCs	TNF- α KLF-4 IL-1 β P47phox MCP-1 MMPs Adhesion molecules
Macrophages, M1/M2 imbalance, leukocyte infiltration	MCP-1 NF- κ B Ets-1 MMPs IL-1 β TNF- α Normal T cell expressed and secreted Monokine induced by γ -interferon Interferon- γ -induced protein-10 Eotaxin IL-8 IL-17
Vascular remodeling, cell death	MMP and cathepsins TNF α IL-1 β , IL-6 Toll-like receptor 4 Fas NO Complement IgG, IgM Basic fibroblast growth factor, transforming growth factor α and β , and vascular endothelial growth factor Reactive oxygen species

IL-1 β indicates interleukin 1 β ; KLF-4, Kruppel-like transcription factor 4; MCP-1, monocyte chemoattractant protein-1; MMP, matrix metalloproteinase; NF- κ B, nuclear factor- κ B; SMC, smooth muscle cell; and TNF α , tumor necrosis factor- α .

to a dedifferentiated phenotype, promoting inflammation and matrix breakdown (downregulation of contractile genes, such as myocardin, and upregulation of proinflammatory genes, such as MMPs, MCP-1, vascular cell adhesion molecule 1, and interleukins).^{12,13} Morphologically, modulated SMCs are no longer arranged in tightly compacted bands but dissociate from each other to be transformed into spider-like cells in aneurysm walls.¹⁴ The ability of these SMCs to synthesize collagen is severely impaired. A late event commonly seen in ruptured aneurysms is the loss of SMC with thinning of the media.³ Guo et al¹⁵ found decreased SMC density and

a significant increase in the activity of caspases in ruptured aneurysms compared with control vessels, whereas Sakaki et al¹⁶ added that SMCs in the wall of ruptured aneurysms were much more degenerated/apoptotic than those in the wall of unruptured aneurysms. A series of in vitro and in vivo studies by the Jefferson group found that the phenotypic modulation of SMCs in CAs was induced by tumor necrosis factor- α (TNF- α).^{17,18} Specifically, TNF- α inhibited the contractile phenotype of SMCs and induced proinflammatory/matrix-remodeling genes, namely MCP-1, MMPs, vascular cell adhesion molecule 1, and interleukin 1 β (IL-1 β).¹⁷ This process was mediated by Kruppel-like transcription factor 4, a known regulator of SMC differentiation. In a follow-up study, the same group found that phenotypic modulation of SMCs was reversed with a TNF- α inhibitor after aneurysm induction.¹⁸ Collectively, these data indicate that SMCs under the influence of inflammatory mediators, particularly TNF- α , promote aneurysm formation, progression, and rupture.

Although best known for their role in allergy and anaphylaxis, mast cells seem to be involved in the pathophysiology of CAs mostly through the release of various proinflammatory cytokines. The number of mast cells is significantly increased during CA formation, and their degranulation induces the expression and activation of MMPs.¹⁹ Additionally, mast cell degranulation inhibitors attenuate the inflammatory reaction in aneurysm walls and block the progression of CAs in mice.¹⁹ Furthermore, Hasan et al⁸ found that mast cells are invariably present in CA walls and were more prominently upregulated in ruptured than in unruptured human CAs, suggesting a role for mast cells in aneurysm rupture.

Several cytokines and inflammatory mediators are involved in the pathogenesis of CAs. IL-1 β and TNF α are the 2 most studied cytokines in CAs. IL-1 β is induced in the early stages of CA formation in mice, and its expression promotes SMC apoptosis and aneurysm progression.²⁰ Additionally, IL-1 β inhibits collagen biosynthesis both at the transcriptional and post-transcriptional levels, thus further contributing to the progression and weakening of CAs.²¹ TNF- α promotes the crucial SMC phenotypic modulation in aneurysm walls and directly activates MMPs while also reducing the expression of tissue inhibitor of metalloproteinase-1.²² Moreover, Jayaraman et al²³ demonstrated that TNF- α has a proapoptotic and proinflammatory action in CA walls through its downstream target FAS. In a recent study, Starke et al²⁴ highlighted the critical role of TNF- α in both aneurysm formation and rupture. Specifically, they demonstrated that CA formation (through induced hypertension and elastase injection) occurred in 81.8% of animals receiving only vehicle as compared with only 25% of TNF- α knockout mice and 33% of those treated with TNF- α inhibitor. Furthermore, TNF- α knockout mice were >12 \times less likely to have aneurysm rupture as compared with those receiving vehicle only.

Chemokines are chemoattractants for leukocytes that direct them toward sites of tissue inflammation. Their contribution to CA pathogenesis is recently being investigated. Chalouhi et al²⁵ compared the concentrations of chemokines and other inflammatory molecules in blood samples drawn from the lumen of human CAs of 16 patients with blood samples from the femoral arteries of the same patients and found higher plasma concentrations of

5 chemokines (MCP-1, regulated on activation, normal T cell expressed and secreted [RANTES], monokine-induced-by- γ -interferon, interferon- γ -induced protein-10, and Eotaxin) and 2 chemoattractant cytokines (interleukin 8 and interleukin 17) in the lumen of CAs. These findings suggest that there may be an active chemokine-driven recruitment of inflammatory cells into the aneurysm wall. The findings match well with those of Krischek et al²⁶ who reported in a networked-based gene expression analysis of CA tissue that chemokines were among the most significant canonical pathways involved in aneurysm tissue. Thus, chemokines may be a central factor in the inflammatory reaction in aneurysm walls, and this may open new therapeutic perspectives in the treatment of CAs.

With regard to the role of complement in the inflammatory response leading aneurysm formation, Tulamo et al²⁷ found the expression of membrane attack complex to be greater in ruptured aneurysm samples as compared with unruptured samples. Complement expression was also associated with aneurysm wall degeneration and inflammatory cell infiltration. The same group later reported that activation of complement in CAs occurs primarily via the classical pathway.²⁸ However, an explanation of how complement activation may contribute to aneurysm formation remains to be determined.

Reactive oxygen species (ROS) may also have a role in the pathogenesis of CAs.²⁹ Aoki et al³⁰ showed that ROS-producing genes were upregulated, and that ROS-eliminating genes were suppressed in CAs in mice, which indicated that overproduction of ROS occurred in aneurysm walls. Moreover, both a free radical scavenger (edaravone) and the deletion of ROS-producing gene (p47phox) effectively inhibited CA formation by suppressing inflammation in aneurysmal walls. In a critical review of the literature on ROS, Starke et al²⁹ found that oxidative stress can induce important processes leading to CA formation including direct endothelial injury, SMC phenotypic modulation and apoptosis, recruitment and invasion of inflammatory cells through upregulation of chemotactic cytokines and adhesion molecules, and MMPs activation.

Several studies have profiled gene expression in CAs, using microarray or polymerase chain reaction techniques, in an attempt to characterize the mechanisms underlying aneurysm formation, growth, and rupture. Although the results were somewhat heterogeneous across studies, alteration in expression genes related to the inflammatory and immune responses as well as the extracellular matrix were frequently observed in CAs and more so in ruptured than in unruptured aneurysms. Aoki et al³¹ compared the gene expression profile between normal cerebral arteries and experimentally induced CAs in rats and found upregulation of gene expression for MMPs, ROS, growth factors, chemokines, complement, adhesion molecules, and apoptosis in CAs. Kurki et al³² compared the whole-genome expression profile of 11 ruptured and 8 unruptured CAs using oligonucleotide microarrays and reported that response to turbulent blood flow, chemotaxis, leukocyte migration, oxidative stress, vascular remodeling, and extracellular matrix degradation were significantly upregulated biological processes in ruptured aneurysms. Significantly enriched genes were toll-like receptor signaling, nuclear factor- κ B, hypoxia-inducible factor-1A, and ETS transcription factor-binding sites. Conversely,

Pera et al³³ examined transcription profiles in ruptured CAs, unruptured CAs, and control middle meningeal arteries and paradoxically found downregulation of genes involved with the immune system and inflammation in ruptured samples. These results suggested a protective role of inflammation against aneurysm rupture. However, the study had limitations pertaining to sample size, baseline comparability, and extracerebral control tissue. Overall, gene expression studies provide useful data for understanding the pathophysiology of CAs; however, differences in microarray technique, statistical analysis, control tissue, type of aneurysm, and studied population make comparison across studies difficult.

Given the critical role of inflammation in aneurysm pathogenesis, several therapeutic strategies have been investigated with overall mixed but promising results (Table 2).³ Perhaps the most promising of all strategies has been acetylic acid (ASA), more commonly referred to as aspirin. ASA exerts its antiplatelet and anti-inflammatory actions by irreversible acetylation of cyclooxygenase-1 and -2, and possibly also through the formation of nitric oxide radicals and the modulation of inflammatory signaling pathways by the main ASA metabolite, salicylic acid. In a case-control study from patients enrolled in the International Study of Unruptured Intracranial Aneurysms, Hasan et al³⁴ found that patients using aspirin had a lower risk of hemorrhage than those who never used aspirin. Building on this work, the same group reported that ruptured aneurysms have higher immunohistochemical staining for cyclooxygenase-2 and microsomal prostaglandin E2 synthase 1, thus concluding that the protective effect of aspirin against rupture of CAs is mediated in part by inhibition of cyclooxygenase-2/microsomal prostaglandin E2 synthase 1.²⁸ Indeed, in a trial comparing 5 patients treated with ASA and 5 other control patients, the expression of macrophages and

Table 2. Noninvasive Therapies for Preventing Formation, Growth, or Rupture of Cerebral Aneurysms

Therapies Showing Efficacy	Therapies With No Effect
Aspirin (human studies) ^{34,36}	Statins (human studies) ³⁷
Nuclear factor- κ B decoy ODN (rats) ³⁸	Valsartan (rats) ³⁹
Pravastatin, low dose (rats) ⁴⁰	Pravastatin, high dose induces aneurysm formation (rats) ⁴⁰
Simvastatin (rats) ⁴¹	Simvastatin (rats) ⁴⁰
Infliximab (TNF- α inhibitor; rats) ²⁴	Clodronate liposomes (deplete circulating monocytes; rabbits) ⁴²
MMP inhibitor (Tolylsam; rats) ⁴	
MCP-1 inhibitor (7ND; rats) ⁶	
Phosphodiesterase-4 inhibitor (Ibudilast; rats) ⁴³	
Cathepsin inhibitor (NC-2300; rats) ⁴⁴	
Mast cell degranulation inhibitor (Tranilast, emedastine difumarate; rats) ¹⁹	
Free radical scavenger (Edaravone; rats) ³⁰	
Doxycycline (MMPs inhibitor; rabbits) ⁴²	

MCP-1 indicates monocyte chemoattractant protein-1; MMP, matrix metalloproteinase; ODN, oligodeoxynucleotide; and TNF- α , tumor necrosis factor- α .

inflammatory molecules in CAs after clipping was found to be significantly decreased in the ASA group.³⁵ Although this study provided novel data that ASA may attenuate the inflammatory process in the walls of human CAs, larger studies with long follow-up periods are needed to address whether ASA also prevents aneurysmal SAH. Bringing confirmation to the work of Hasan et al³⁴ is a recently published study from Europe that showed that chronic low dose aspirin therapy has a protective effect against SAH and does not increase the risk of intracerebral hemorrhage.³⁶ Furthermore, there was a particularly pronounced trend toward decreased risk of SAH among those on long-term aspirin therapy (>3 years). Collectively, these data suggest that aspirin may be a serious noninvasive strategy for prevention of SAH. If the efficacy of aspirin is confirmed in a randomized controlled trial, aspirin could potentially be offered as a treatment for those patients in whom the risk of invasive therapy exceeds the risk of aneurysm rupture. For example, a 75-year-old man with a 5-mm CA would be a perfect candidate for aspirin treatment. Likewise, aspirin may be used to decrease the risk of aneurysm rupture in patients refusing any sort of invasive therapies or in countries where invasive, specialized therapies are not available. The fact that aspirin is an inexpensive and widely available and used drug makes it an ideal candidate in this setting.

Besides ASA, statins have extensively been investigated as possible therapeutic agents for CAs but the data have been conflicting thus far. Although a lower dose of statins (5 mg/kg per day) reduced endothelial damage and inhibited aneurysm formation in mice, higher doses (25–50 mg/kg per day) facilitated aneurysm growth and promoted aneurysm rupture.³ Further study will be needed to determine whether statins may have a future role in the treatment of CAs. Despite evidence for a potential role of angiotensin in the pathophysiology of CAs, angiotensin-receptor blockers have shown little-to-no efficacy in preventing aneurysm formation and growth.³

Hemodynamics, Endothelial Dysfunction, and CAs

Hemodynamic stress is the initiating factor for CA formation.³ This is best illustrated by the observation that CAs occur at arterial junctions, bifurcations, or abrupt vascular angles where excessive hemodynamic stresses are exerted on arterial walls. In a well-designed study, Meng et al⁴⁵ created new branch points in the carotid vasculature of 6 dogs and observed destructive remodeling in the adjacent region of flow acceleration that resembled the initiation of an intracranial aneurysm, characterized by disruption of the internal elastic lamina, loss of medial SMCs, reduced proliferation of SMCs, and loss of fibronectin. They concluded that a combination of high wall shear stress (WSS) and a high gradient in WSS strongly predisposes to CA formation. The same group extended their previous findings by demonstrating a correlation between the degree of destructive remodeling accounting for internal elastic lamina loss, medial thinning, and luminal bulging with the magnitude of WSS at arterial bifurcations.⁴⁶

Although it is clear that high WSS drives CA formation, the question of whether low or high WSS promotes aneurysm progression and rupture remains unanswered. Whereas Cebal et al⁴⁷ found that high and concentrated WSS was associated

with aneurysm rupture, several computational fluid dynamic studies have shown that the WSS at the tip or bleb of an aneurysm, where rupture most commonly occurs, is in fact low.^{48,49} It is thought that low WSS may induce apoptosis of endothelial cells, thus promoting the structural remodeling/fragility of the aneurysm wall and ultimately leading to CA rupture. In an attempt to reconcile the conflicting data, some authors have proposed that low WSS may trigger the growth and rupture of large, atherosclerotic aneurysm phenotypes through an inflammatory reaction, whereas high WSS may trigger the growth and rupture of small or bleb aneurysm phenotypes through a mural response (MMP production, mural cell apoptosis, medial thinning).⁵⁰ However, the proposed mechanisms remain purely speculative, and further investigation is needed to answer this crucial question.

Endothelial dysfunction is a hallmark of CA biology. As discussed above, endothelial dysfunction and vessel wall inflammation and remodeling are directly triggered by WSS. Kadirvel et al⁵¹ elegantly revealed endothelial cell loss and differential expression of biological markers of vascular remodeling namely MMPs in areas of low WSS in elastase-induced saccular aneurysms. Likewise, Wang et al⁵² showed that WSS induces endothelial dysfunction, as evidenced by the loss of endothelial nitric oxide synthase expression, and upregulation of inflammatory markers in a canine model of CAs. Jamous et al³¹ reported that endothelial cell injury induced by hemodynamic abnormalities was the earliest change in aneurysm wall, followed by the formation of an inflammatory zone that leads to proteolytic destruction of the vascular extracellular matrix by MMP. Some investigators also suggest that the activation of nuclear factor- κ B in endothelial cells pursuant to hemodynamic stress may be the earliest step in CA formation because dramatic blockade of aneurysm formation was seen after inhibition of nuclear factor- κ B in mice.³⁸ As discussed above, the expression of MCP-1 by endothelial cells is pivotal in recruiting macrophages and other leukocytes into the aneurysm wall. Along these lines, endothelial tight junctions were found to be disrupted in CAs and were associated with the migration of leukocytes through endothelial gaps into aneurysm walls.⁵³ Collectively, these data indicate that endothelial dysfunction, driven by hemodynamic stress, is an early event in CA physiopathology that initiates and nurtures the inflammatory reaction in arterial walls.

Genetics of CAs

Despite extensive research, relatively little is known about the genetics of CAs. The role of genetics in CAs may be highlighted by the increased risk of aneurysms and SAH in first-degree relatives of patients with SAH. As such, CAs are noted in 2.3% of the general population versus 4% of those with 1 affected first-degree relative and 8% of those with 2 affected first-degree relatives.⁵⁴ Some heritable diseases of the connective tissue and extracellular matrix are also associated with an increased risk of CAs and SAH. Autosomal dominant polycystic kidney disease is the most common heritable disease associated with SAH. CAs may occur in 10% to 13% of patients with autosomal dominant polycystic kidney disease and in \leq 23% of those >60 years old, but routine screening is not recommended

in this population.⁵⁴ Ehlers-Danlos type IV (caused by mutation of collagen type III), fibromuscular dysplasia, and possibly Marfan syndrome (mutation of fibrillin-1 gene) are also heritable disorders associated with CAs and SAH.⁵⁴

Whether genetics contribute to CA formation and rupture is not certain. The largest twin cohort to date, the population-based Nordic Twin Cohort, which followed 79 644 complete twin pairs of Danish, Finnish, and Swedish origin for 6.01 million person-years did not find a significant degree of genetic contribution to SAH.⁵⁵ Based on these data, it might be tempting to conclude that aneurysmal SAH has little-to-no genetic basis, and that modifiable risk factors are the major determinants of SAH risk. In this case, familial CAs would be attributable to the familial clustering of modifiable risk factors. On the contrary, the powerful genome-wide linkage studies have identified several genetic loci for CAs, namely 7q11, 14q22, 5q22-31 in a Japanese study and 19q13.3 in a Finnish study.⁵⁶ Although no specific gene has been shown thus far to be associated with CAs, these genetic loci include some promising candidate genes coding for extracellular matrix proteins such as elastin and collagen. Other candidate genes that have been studied are those associated with vascular wall formation, matrix degradation, and response of the cerebral artery to increased stress (including inflammation).⁵⁶ Among those genes are lysyl oxidase, fibrillin 2, α 1 antitrypsin, MMPs, tissue inhibitor of metalloproteinase-1, endoglin, angiotensin-converting enzyme, nicotinamide adenine dinucleotide phosphate-oxidase, p22phox, phospholipase C, endothelial nitric oxide synthase, transforming growth factor- β receptors, and polycystin.⁵⁶ It should be noted that none of the findings of genetic association studies have been consistently reproducible, and this may be related to the fact that these studies dealt with different populations and were probably underpowered to detect a significant genetic association. Large multicenter studies will be needed to more clearly elucidate the genetic platform of CAs; however, it is likely that both genetic factors as well as environmental factors play a role in CA pathogenesis, complicating efforts at disease gene identification.

In clinical practice, genetic approaches may have application in identifying aneurysm-prone patients and rupture-prone aneurysms or even in controlling aneurysm development and rupture. Gene therapy, a technique that consists of inserting a functioning gene into a cell to correct a genetic error or to introduce a new function may be a potential therapeutic strategy for CAs.⁵⁷ For example, gene therapy for inhibiting the overexpression of MMPs, the activation of macrophages, or the phenotypic modulation of SMCs may theoretically have efficacy in preventing aneurysm rupture. Unfortunately, however, gene therapies have the best chance of success only if a specific defective gene is identified, as in cystic fibrosis, for example. Promoting healing after coil embolization is another application of gene therapy, and coils carrying antibody-tethered adenovirus may enhance direct gene transfer.⁵⁷ Candidate genes are those involved in vascular remodeling and include growth factors, metalloproteinase inhibitors, and MCP-1.^{57,58}

Common Risk Factors for CAs

There are several risk factors for CAs. A recent, large meta-analysis that included 1450 unruptured CAs in 94 912 patients

from 21 countries identified autosomal dominant polycystic kidney disease, a positive family history of CA or SAH, female sex, and older age as significant risk factors for harboring CAs.⁵⁹ The meta-analysis did not find a higher prevalence of CAs in Finnish and Japanese populations, which suggests that the higher incidence of SAH in those countries⁶⁰ is related to higher risks of aneurysm rupture. Smoking and hypertension are 2 well-established risk factors for CAs that were not included in this meta-analysis.⁵⁴ However, the same group later reported in a well-designed case-control study (206 patients with CAs and 574 controls) that active smoking (odds ratio, 3.0) and hypertension (odds ratio, 2.9) were strong risk factors for CAs and had an important additive effect (odds ratio, 8.3).⁶¹ It is important to note that cigarette smoking may particularly increase the susceptibility for CA formation in patients with certain gene variants namely on chromosomes 8q and 9p.⁶² A recent case-control study found a 10-fold increase in the prevalence of CAs in patients with bicuspid aortic valve (10% versus 1.1%).⁶³ An abnormality of cells derived from the neural crest could explain the association of bicuspid aortic valve with CAs because the aortic valvular cusps and the media of the aortic arch and its branches including cervicocephalic arteries are all composed of cells of neural crest origin.⁶³ Patients with Ehlers-Danlos syndrome type IV, a rare disease caused by abnormal synthesis of collagen type III, have a structural vascular fragility predisposing to CA formation as well as arterial dissection and carotid-cavernous fistulas.⁶⁴ Concerning ethnicity, the risk of harboring an aneurysm seems to be equivalent in whites, blacks, and Hispanics.⁶⁵ Finally, regular physical exercise may decrease the risk of harboring an aneurysm.⁶¹

It is well known that women are at higher risk of aneurysm formation, but the female preponderance becomes evident only in the perimenopausal and postmenopausal periods.⁶⁰ Indeed, an earlier age at menopause is associated with the presence of a CA, and hormone replacement therapy protects against SAH.^{66,67} Additionally, animal studies have shown a significant protective role of estrogen against the formation and progression of CAs.⁶⁸ The protective role of estrogen is likely related to its beneficial effects on the inflammatory reaction in cerebral vessels and the function of endothelial cells. These effects may involve the inhibition of nuclear factor- κ B and IL-1 β -mediated expression of adhesion molecules, with reduction of adhesion of leukocytes into cerebral endothelium. Thus, estrogen is undoubtedly one of the numerous therapeutic strategies that may potentially prove efficient in SAH prevention.

Currently, it is recommended to screen for CAs in patients with a positive family history. Experts recommend screening all individuals with 2 affected first-degree relatives because of the high frequency of CAs in this group.^{54,69} It may also be reasonable to screen patients who have 1 affected first-degree relative if they possess other risk factors for harboring CAs such as (1) female sex, (2) older age, (3) active smoking, (4) hypertension, (5) sibling of the affected relative, and (6) affected relative harbors multiple aneurysms at a young age.

Common Risk Factors for SAH

The annual rupture rate for CAs is 0.95%, as identified by the recent well-designed Japanese cohort.⁷⁰ The same study

also found that larger aneurysms, aneurysms arising from the posterior and anterior communicating arteries, and aneurysms with a daughter sac have higher rates of rupture. Specifically, the annual rupture rate by location was 0.26% for paraclinoid, 0.67% for middle cerebral artery, 1.31% for anterior communicating, 1.72% for posterior communicating, and 1.90% for basilar artery aneurysms.⁷⁰ The annual rupture rate by size was 0.36% for 3 to 4 mm, 0.50% for 5 to 6 mm, 1.67% for 7 to 9 mm, 4.37% for 10 to 24 mm, and 33.4% for giant aneurysms (≥ 25 mm). A similar association between size and risk of rupture was observed in the International Study of Unruptured Intracranial Aneurysms.⁷¹ The threshold for treating aneurysms arising from anterior/posterior communicating arteries and the posterior circulation should be lower than that for other locations. In our experience, most ruptured aneurysms at those locations tend to be small lesions (≤ 7 mm).

Besides aneurysm size and location, cigarette smoking is a strong risk factor for SAH that has been consistently reported in several studies.^{72,73} Juvela et al⁷⁴ recently reported the results of long-term follow-up (median, 21 years) of 142 patients with 181 unruptured CAs and found that cigarette smoking in addition to anterior communicating artery location, decreasing patient age, and aneurysm size ≥ 7 mm independently predicted aneurysm rupture. Interestingly, a case-control study reported that smoking may interact with a positive family history of SAH to increase the risk of SAH further than their individual risks.⁷⁵ Cigarette smoke may lead to CA formation and rupture through a variety of mechanisms that were recently reviewed by Chalouhi et al.⁷² Most of these mechanisms are related to inflammation. On closer inspection, smoking may cause hemodynamic stress on arterial walls, induce endothelial dysfunction/apoptosis, promote SMC phenotypic modulation through Kruppel-like transcription factor 4, increase inflammatory cell infiltration and cytokine release, and most importantly generate ROS.⁷² In other terms, cigarette smoke may affect every step in the cascade of events leading to aneurysm formation, growth, and rupture. Patients harboring CAs should be strongly counseled to quit smoking especially when observation is elected. The importance of this simple intervention cannot be overemphasized. Even in those who undergo embolization, cigarette smoking is a risk factor for aneurysm recurrence, and patients should also be urged to quit smoking.⁷⁶ In addition to smoking, hypertension was found to predispose to SAH in prospective population-based follow-up cohorts.⁷³ Therefore, blood pressure control is another simple intervention that may help decrease the risk of aneurysm rupture. For some investigators, however, hypertension is a risk factor for CA formation but does not affect the risk of rupture once the aneurysm has been formed.

Although heavy alcohol consumption has been shown to increase the risk of SAH, it does not predispose to aneurysm formation and growth.⁵⁴ The increased risk of SAH with alcohol use is likely the result of transient increases in blood pressure. Data from case-control studies suggest that frequent intake of fat increases the risk of SAH while frequent use of skim or reduced-fat milk and fruit as well as dietary antioxidants and soy products is protective against SAH.⁷² Further studies are needed to confirm these observations. Finally, Vlsek et al⁷⁷ identified coffee consumption and cola consumption in

addition to anger, startling, straining for defecation, sexual intercourse, nose blowing, and vigorous physical exercise as trigger factors for aneurysmal SAH.

Overall, aneurysms ≥ 7 mm in diameter should be treated because of their propensity to rupture, except in older patients and those with significant medical comorbidities and short life expectancy. Factors that warrant strong consideration for treatment regardless of the size of the aneurysm include young patient age, change in the size or configuration of the aneurysm, and the presence of multiple, daughter sac, or symptomatic aneurysms. Factors that may favor intervention over observation are active smoking, hypertension, posterior circulation aneurysm, anterior/posterior communicating artery aneurysms, previous SAH, history of familial SAH, and high aspect ratio.

Aneurysm Geometry and Risk of Rupture

A multitude of geometric indices of CAs have been studied as possible determinants of rupture risk. Although sophisticated mathematical models accounting for the 3-dimensional shape of the aneurysm have been used, only simple indices that can be calculated in the office setting are most useful in clinical practice. The aspect ratio defined as CA height divided by neck diameter is the most studied and perhaps the most useful shape parameter. In their initial work on aspect ratio, Ujiie et al⁷⁸ reported that 80% of ruptured aneurysms had an aspect ratio of >1.6 , whereas 90% of unruptured aneurysms had an aspect ratio of <1.6 . An optimal aspect ratio threshold value, however, above which CAs may be deemed as dangerous remains to be determined because different researchers have reported different thresholds for the aspect ratio. The rationale behind the aspect ratio is that blood flow is sluggish, and WSS is low in aneurysms with a high aspect ratio (ie, a large fundus and a small neck), which as discussed above promotes aneurysm wall remodeling and fragilization. In the clinical setting, although aspect ratio cannot be relied on as a sole predictor of aneurysm rupture, an aspect ratio >1.6 should favor intervention over observation in borderline cases.

Another simple and useful geometric index, particularly suitable for small aneurysms, is the aneurysm-to-vessel size ratio more commonly referred to as size ratio. In a recent large study by Kashiwazaki et al⁷⁹ that included 854 ruptured and 180 unruptured CAs, size ratio strongly correlated with aneurysm rupture and was found to be the only predictive factor for small CAs rupture. In clinical practice, this means that a 3-mm aneurysm arising from the anterior communication artery has a higher risk of rupture than a 3-mm aneurysm of the paraclinoid internal carotid artery.

Hoh et al⁸⁰ analyzed 30 patients with multiple CAs where each patient harbored 1 ruptured lesion and ≥ 1 unruptured lesions. The authors found that aneurysms with high bottleneck factor were more likely to rupture as were those with a high height-width ratio (ie, long and thin). Other indices not covered in this review have also been proposed and showed some correlation with aneurysm rupture. Overall, because unruptured aneurysms are being detected with increasing frequency, simple and reliable measurements and indices such as aspect ratio, size ratio, and bottleneck factor may be valuable to formulate an optimal treatment plan for a given patient.

Growth of CAs

The growth of a CA is a strong risk factor for future rupture. As such, many clinicians recommend treating any aneurysm that has increased in size during the follow-up period. The approach is justified because the same factors that drive aneurysm growth, namely inflammation and matrix degeneration, eventually lead to its rupture. This hypothesis is also supported by findings from prospective cohorts. In a recent large study that followed 258 unruptured aneurysms with computed tomography angiography, the annual risk of rupture was found to be 2.4% in aneurysms with growth versus only 0.2% in those without growth (ie, 12-fold increase in risk of rupture).⁸¹ The risk of aneurysm growth itself was associated with tobacco smoking and initial size. The authors concluded that aneurysm growth was not uncommon, and that all incidental aneurysms require longitudinal follow-up imaging to monitor for possible growth, including small lesions.⁸¹

An aneurysm grows either by expansion of the wall because of proliferation of mural cells with production of extracellular matrix and myointimal hyperplasia, or by distension attributable to hemodynamic pressure in degenerated CAs, or most commonly by a combination of these 2 mechanisms.⁸² The inflammatory reaction is a major factor in this process because it drives both mural cell growth with extracellular matrix production and degeneration of the aneurysm wall. Indeed, inhibition of nuclear factor- κ B, ROS, MMPs/cathepsin, and MCP-1 was shown to decrease aneurysm growth.³ Mitogen-activated protein kinases, a family of intracellular signaling proteins that have a critical role in cell growth, proliferation, differentiation, and apoptosis, have also been shown to be actively involved in aneurysm growth. Specifically, the proapoptotic p54 Jun N-terminal kinase and the proinflammatory p38 seem to be closely associated with CA growth, although the involved pathways remain poorly understood.⁸³ Overall, the mechanisms underlying CA growth seem to be complex. Although, most CAs will grow before rupturing, many aneurysms will not. This may suggest that the processes driving aneurysm progression and rupture may not be entirely identical.

In patients managed conservatively, periodic follow-up (every 6–12 months) with noninvasive imaging studies (magnetic resonance angiography or computed tomography angiography) is recommended. Strong consideration for treatment should be given to any aneurysm that grows over the follow-up period because this suggests active inflammatory processes in the aneurysm wall.

Targeted Imaging of Inflammation: the Emerging Role of Ferumoxytol-Enhanced MRI

Targeted imaging of inflammatory cells and molecules involved in CA pathogenesis is an interesting strategy that may provide important information on the natural history of these lesions. Ferumoxytol-enhanced MRI is one such technique that is recently being investigated. Ferumoxytol is a member of the class of nanoparticles known as ultrasmall superparamagnetic iron oxide and is approved by the Food and Drug Administration as a treatment for iron deficiency anemia in patients with chronic renal failure. It also is useful

as an intravascular contrast agent and an inflammatory marker when imaging is delayed because it is cleared by macrophages (usually within 24–72 hours). Hasan et al^{9,35,84} have investigated the possibility of using ferumoxytol-enhanced MRI for noninvasive assessment of the inflammatory status of CAs through the detection of the activity of macrophages. In their initial work, they found that the optimal technique for imaging macrophages in human CA walls is infusion of 5 mg/kg of ferumoxytol and imaging at 72 hours after injection.¹⁰ Later, they demonstrated that the findings of ferumoxytol-enhanced MRI may well predict the risk of aneurysm rupture.⁹ Combining radiological and histological findings, they found that CAs with early uptake of ferumoxytol (at 24 hours) exhibited more intense inflammation in their walls and had a higher risk of rupture than aneurysms with no or only late uptake of ferumoxytol (at 72 hours).⁹ Thus, if validated in larger studies, the technique may allow physicians to differentiate unstable aneurysms that require intervention from stable aneurysms where observation is appropriate. Specifically, this technique could prove particularly useful in identifying rupture-prone aneurysms in patients that often pose a therapeutic dilemma, namely elderly patients (>70 years old) and patients harboring small aneurysms (<5–7 mm). Moreover, ferumoxytol-enhanced MRI may allow noninvasive monitoring of the effects of anti-inflammatory pharmacological interventions (such as ASA) on CAs.^{35,84} As discussed above, if aspirin is adopted as a therapy for CAs, the technique may be used to identify those who respond to medical treatment versus those who will require more invasive treatment. Future improvements in technique and MRI signal quantification may allow efficient use of ferumoxytol-enhanced MRI in clinical practice.

Conclusions

Inflammation plays a central role in the pathogenesis of CAs. The common pathway for CA formation, growth, and rupture includes initially an endothelial dysfunction induced by hemodynamic stress, followed by an inflammatory reaction in arterial walls involving primarily macrophages and SMCs, and finally a degradation of the extracellular matrix by MMPs, which paves the way for aneurysm rupture. Knowledge of these mechanisms has allowed the conception of promising molecular-based imaging studies identifying rupture-prone CAs. Pharmacological therapy targeting the inflammatory reaction is also being investigated as a potential therapeutic strategy for CAs. Future experimental studies and clinical trials will be needed to further deepen our knowledge of this complex disease and to provide patients with efficient and innocuous therapies.

Disclosures

None.

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KEY WORDS: aneurysm ■ growth and development ■ inflammation ■ macrophages ■ rupture