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Inflammation in human cerebral aneurysms: pathogenesis, diagnostic imaging, genetics, and therapeutics

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ABSTRACT

Intracranial aneurysms are a life-threatening cerebrovascular pathology with a probability of spontaneous rupture. Current intervention techniques carry inherent risk. Recent investigation has reinforced inflammation's role in the pathophysiological process of cerebral aneurysms. These data suggest alternative diagnostic and noninvasive therapeutic strategies. Furthermore, novel characteristics of the underlying disease have been elucidated through distinct bioinformatic and gene expression profile analyses. This article will emphasize the most recent investigation, highlighting findings of clinical significance and etiological relevance.

Key words: Diagnostic imaging, genetics, intracranial aneurysms, pathogenesis, therapeutics

INTRODUCTION

Intracranial aneurysms (IAs) are a common multifactorial cerebrovascular disease. While having a 3.2% prevalence rate in the general population and 1.1% annual rupture risk, aneurysms remain lethal upon rupture in 40% of cases.[1-3] Risk for aneurysmal subarachnoid hemorrhage (SAH) is higher in hypertensive patients, smokers, heavy drinkers, and females.[2,4] The current interventional techniques, surgical clippings and endovascular occlusions, remain invasive despite advancements in technology. Although SAH risk factors are known, a more complete understanding of the complex pathophysiology underlying IA formation, progression, and rupture is needed. The majority of evidence from intensive investigation has implicated a mounting inflammatory response during the aneurysm pathogenesis.[5,6] This data ultimately provides promising targets for *in vivo* molecular imaging and noninvasive IA therapeutics. This article will discuss inflammation as it pertains to IA pathogenesis, with a focus on the most recent investigation. Furthermore, it will offer a review of recent genetic and bioinformatic analyses, highlighting findings of pathological significance and methodological diversity. The final sections will further illuminate both innovations in diagnostic imaging of aneurysmal inflammation and experimentally efficacious noninvasive attempts at IA prevention and regression.

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PATHOGENESIS

Hemodynamic insult is considered to be one of the first steps in activating the cerebral vessel wall's inflammatory response.[7] There is a continuous balance between hemodynamic stress and the integrity of the vessel wall.[5] Upon the hemodynamic insult, this balance is perturbed, leading to vessel wall weakening. Dilation results, as extracellular matrix is degraded by increased levels of matrix metalloproteinases (MMP) compounded by concomitant apoptotic death of vascular smooth muscle cells (VSMCs).[7] Initially, the vessel wall is highly organized. Integral disturbances lead to less organization within the aneurysm wall and fewer distinct layers.[5] Simultaneously, MMP activation has been found to facilitate flow-induced internal elastic lamina (IEL) fragmentation.[8] Similar IEL fragmentation is a feature commonly observed in atherosclerotic lesions.[9]

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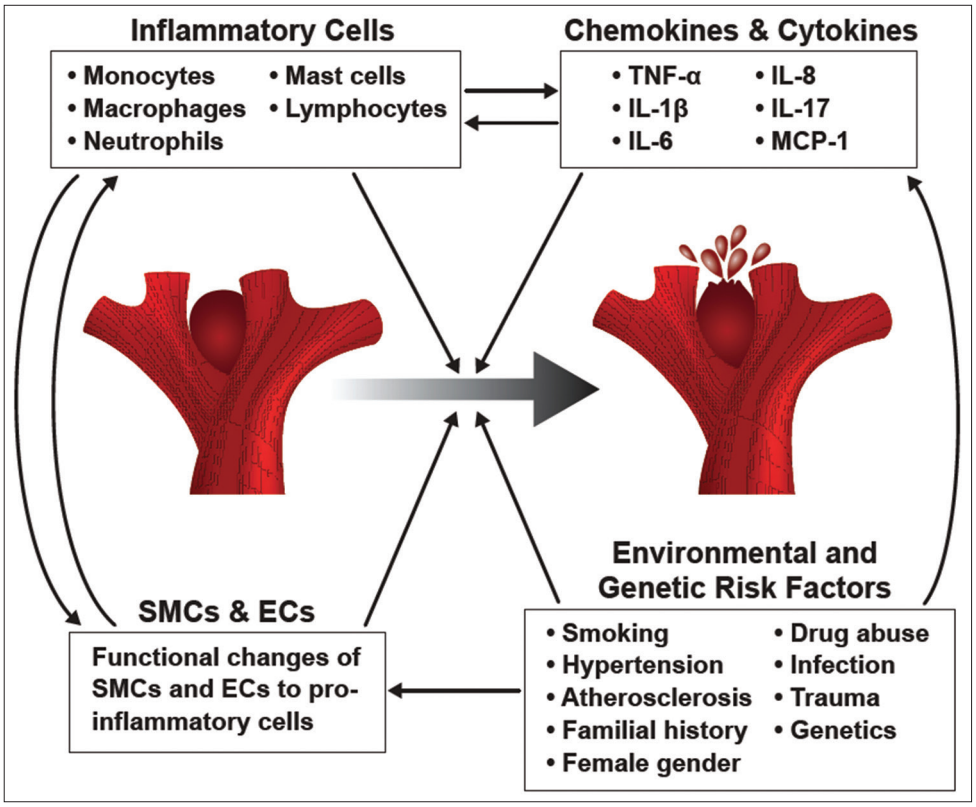

Figure 1: Summary of the factors contributing to cerebral aneurysm pathogenesis. Inflammatory cells, cytokines, chemokines, changes to the vascular smooth muscle cells and endothelial cells, and environmental as well as genetic risk factors all play a role in the development of cerebral aneurysms and their progression to rupture

macrophage presence and aneurysm rupture. Hasan *et al.*[22] showed that in human cerebral aneurysms, M1 and M2 macrophages were found to be in equal proportions; however, M1 macrophages presented in higher levels than M2 macrophages in ruptured human cerebral aneurysms. This means that there were more macrophages promoting inflammation, M1 macrophages, than macrophages working to repair the vessel tissue and decrease inflammation, M2 macrophages. This imbalance was also correlated with an increase in mast cell presence in ruptured aneurysms.[22]

The role of the inflammatory mediators, chemokines, has been studied in aneurysm formation. Chemokines promote chemotaxis in particular, the migration of inflammatory cells during the inflammatory response. In recent years, Chalouhi *et al.*[23] demonstrated that plasma concentrations of RANTES, MIG, IP-10, eotaxin, interleukin 8 (IL-8), IL-17, and the monocyte chemoattractant protein-1 were significantly increased in the lumen of unruptured human cerebral aneurysms when compared to femoral arterial plasma of the same 16 patients. In addition, the study found increased plasma concentrations of MCP-1 in unruptured aneurysms.[23] This reaffirms the work of Aoki *et al.*[24] who observed increased MCP-1 expression in rat arterial walls. These data indicate that inflammatory cells are being actively recruited to the aneurysm wall as a result of high chemokine levels, further contributing to IA formation and eventual rupture.[23]

Aoki *et al.*[25] confirmed in rodent models that tumor necrosis factor-α (TNF-α) levels are higher in cerebral aneurysms, particularly in the endothelial cells of these lesions, during their formation and progression when compared to the TNF-α levels of control cerebral arteries. Aoki *et al.*[25] further investigated the TNF-α-TNFR1 signaling pathway and found that IA formation was suppressed in rodents deficient in TNFR1. The authors concluded that TNFR1 deficiency blocks NF-κB activation and MCP-1 expression, ultimately inhibiting macrophage infiltration. Intervening with this signaling pathway may serve as a future therapeutic strategy.[25] TNF-α has been previously identified as a contributor to the phenotypic modulation of VSMCs *in vivo* following hemodynamic stress.[26] The transcription factor, NF-κB, has also been found to be essential in the activation and recruitment of macrophages as it influences the expression of a number of pro-inflammatory genes.[5,6] Aoki *et al.*[27] demonstrated the activation of NF-κB and expression of downstream genes; these changes seen in the vessel wall of the early stages of aneurysm development in a rat model. The study specifically showed that mice deficient in NF-κB p50 subunit had a lower incidence of aneurysm formation and macrophage infiltration into the aneurysm wall. Furthermore, Aoki *et al.*[28] showed that the up-regulation of interleukin-1β (IL-1β) and activation of NF-κB significantly reduced collagen biosynthesis, a process linked to IA progression and rupture.

cells (primarily neutrophil granulocytes), may potentially be used as a tissue-specific biomarker of inflammation and cerebral aneurysm instability.[55] Previously, Deleo *et al*.[56] developed a method to access MPO enzymatic activity as an inflammatory biomarker in a rabbit model of IA. The group used clinical field strength MRI and an MPO specific paramagnetic substrate, di-5-hydroxytryptamide of gadopentetate dimeglumine, as an MR contrast agent. Following endovascular injection of *Escherichia coli* lipopolysaccharide, which resulted in inflammatory cell infiltration into the aneurysm wall and increased active MPO expression, the investigators found the MR enhancement ratios were consistent with the inflammatory changes.[56] Ultimately, these studies suggest enzymatically specific MR imaging may help identify aneurysms with a significant rupture propensity.

These studies further highlight inflammation's role in the progression and rupture of cerebral aneurysms. *In vivo* targeted molecular imaging may ultimately provide the needed noninvasive metric required for optimal management of IA. Given the strong association of inflammation and macrophage infiltration with IA rupture, IA experts have agreed on the importance of these findings and suggested that larger scale studies are needed.[53]

THERAPEUTICS TARGETING INFLAMMATION

Studies focused on developing noninvasive IA therapeutics reaffirm inflammation's pathophysiological role in IA formation and progression. Hasan *et al*.[57] investigated the anti-inflammatory effect of acetylsalicylic acid (aspirin) on the progression of aneurysm to rupture. A secondary analysis of the ISUIA study revealed that the aspirin decreased patients' risk of aneurysm rupture by 60%. Furthermore, the group found ruptured aneurysms had higher levels of cyclooxygenase-2 (COX-2) and microsomal prostaglandin E2 synthase 1 (mPGES-1) expression.[58] An exploration of acetylsalicylic acid's effect on inflammatory mediators through ferumoxytol enhanced MRI and immunostaining found aspirin-treated patients to have both decreased macrophage infiltration and COX-2 and mPGES-1 expression.[52] These pro-inflammatory enzymes were found to be overexpressed in ruptured IA tissue. Taken together, these findings suggest that low doses of aspirin (81 mg daily for 3 months) may effectively attenuate inflammation in IA, preventing acute SAH.[57]

Angiotensin 1-7 has also been explored as a potential therapeutic option as Ang 1-7 is an antagonist to Ang 2. Ang 2 has been shown to increase the expression of various pro-inflammatory cytokines as well as promote blood vessel extracellular matrix remodeling.[59] Peña Silva *et al*.[60] explored the therapeutic effect of Ang 1-7 in aneurysm-induced mice and found that Ang 1-7 decreased the frequency of morality and IA rupture. The authors believe that Ang 1-7 acts through a Mas receptor-dependent pathway as Ang 1-7 administration did not decrease the frequency of aneurysm rupture in Mas KO mice.[60] To investigate the applicability of Ang 1-7 as a therapeutic option, immunostaining was performed on human cerebral aneurysms to confirm Mas receptor presence. Immunostaining for Mas receptors was found to be positive in unruptured and ruptured aneurysms. The expression of Mas receptors was also identified in the intima and media layers of control human cerebral arteries.[60] These data suggest Angiotensin 1-7 mediated targeting of the Mas receptor pathway may be an efficacious noninvasive treatment modality.

Aoki *et al*.[27] found that in aneurysm-induced rats, the activation of NF-κB in the arterial wall of earlier stages of aneurysmal development corresponded with the expression of the downstream pro-inflammatory genes, vascular cell adhesion molecule-1 (VCAM-1) and MCP-1. The group explored the inhibitory effects of NF-κB through the use of a synthesized decoy oligodeoxynucleotide (ODN) in a rat model. Investigators found that the facilitation of ODN 1-week following aneurysmal induction inhibited VCAM-1 and MCP-1 expression and overall, reduced aneurysm size and IEL disruption.[27] In a follow-up study, the authors used chimeric decoy ODNs against both NF-κB and proinflammatory transcription factor Ets-1.[61] Aoki *et al*.[61] found that chimeric decoy ODNs reduced IA size and thickened the walls of existing IAs in a rat model. Rats treated with chimeric decoy ODNs also showed a reduction in MCP-1 expression and macrophage infiltration into the aneurysm wall. If nuclease resistant ODNs can be administered transorally or transvenously, these findings suggest that NF-κB and Ets-1 are both potential therapeutic targets in human IAs.[61]

Additionally, Aoki *et al*.[19] tested the effects of tolylsam, a selective inhibitor of the gelatinases MMP-2, MMP-9, and MMP-12, in a rat model. Facilitation of tolylsam did inhibit aneurysm progression, as the rate of advanced aneurysms in the tolylsam group was lower; however, the incidence of aneurysm development in the tolylsam group and control group was not different. The authors concluded that the tolylsam may delay aneurysm progression rather than formation.[19]

Granulocytes were found to be present in the cerebral aneurysm wall.[17] Specifically, Ishibashi *et al*.[17] reaffirmed mast cells' role in aneurysm pathogenesis by administering in a rat model the mast cell inhibitor, tranilast (N-(3,4-dimethoxycinnamoyl) anthranilic acid; Kissei Pharmaceutical, Nagano, Japan) and emedastine

difumarate, (1-(2-ethoxyethyl)-2-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)-benzimidazole difumarate; Kowa, Tokyo, Japan). The facilitation of these inhibitors proved mast cells' contribution to IEL and media degeneration as both of these processes were suppressed.[17] Ultimately, the facilitation of these inhibitors reduced the size of the induced aneurysms and the thinning of the vessel's media layer. Inhibitors of mast cell degranulation have shown to be useful in the treatment of other inflammatory processes such as allergies.[17] As a result, the authors believe mast cell inhibitors may prove to be a practical and safe future anti-inflammatory treatment for IAs.[17]

TNF-α-TNFR1 cascade inhibition is a strategy that has been recently explored by Aoki *et al*.[25] Anti-TNF-α antibody or soluble TNF receptor has been successfully used in the treatment of an inflammatory disease, such as rheumatoid arthritis.[25] The authors note that the use of these inhibitors in the treatment of aneurysms would be likely efficacious; however, the expense of these drugs makes an alternative inhibitor of the TNF-α-TNFR1 signaling cascade desirable.[25] In addition, increased levels of TNF-α in unruptured and ruptured IAs in an *in vivo* model were reconfirmed by Starke *et al*.[62] This follow-up study focused on the therapeutic strategy of the TNF-α-TNFR1 signaling cascade by analyzing TNF-α knockout mice and mice administered an inhibitor of TNF-α synthesis, 3,6'dithiothalidomide (DTH). Both groups showed a lower incidence of aneurysm formation and rupture when compared with control mice.[62] The study also found that the inhibitor DTH led to an increase in aneurysm stabilization and consequently, a decrease in aneurysm rupture upon formation.[62] Although DTH is an inhibitor of TNF-α synthesis, the authors noted that the inhibitor's actions are not fully understood as other properties of the inhibitor may explain aneurysm stabilization and prevention of rupture.[62]

CONCLUSION

Intensive investigation has implicated the inflammation in the complex pathophysiological processes that underlie IA development, progression, and rupture. Ongoing research shows how these inflammatory mechanisms can be clinically accessed and therapeutically modulated. Although advances in microsurgical and endovascular management of IA will inevitably lead to lower procedural complication rates, the need for a safe and effective noninvasive therapeutic strategy to prevent aneurysmal SAH will remain. Overall, these data suggest potential alternative medical treatment strategies for patients with human cerebral aneurysms.

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