

Hemodynamics, inflammation, vascular remodeling, and the development and rupture of intracranial aneurysms: a review

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ABSTRACT

The central nervous system is an immunologically active environment where several components of the immune and inflammatory response interact among them and with the constituents of nervous tissue and vasculature in a critically orchestrated manner, influencing physiologic and pathologic processes. In particular, inflammation takes a central role in the pathogenesis of intracranial aneurysms (IAs). The common pathway for aneurysm formation involves endothelial dysfunction and injury, a mounting inflammatory response, vascular smooth muscle cells (VSMCs) phenotypic modulation, extracellular matrix remodeling, and subsequent cell death and vessel wall degeneration. We conducted a literature review (1980-2014) by Medline and EMBASE databases using the searching terms "IA" and "cerebral aneurysm" and further search was performed to link the search terms with the following key words: inflammation, hemodynamic(s), remodeling, macrophages, neutrophils, lymphocytes, complement, VSMCs, mast cells, cytokines, and inflammatory biomarkers. The aim of this review was to summarize the most recent and pertinent evidences regarding the articulated processes of aneurysms formation, growth, and rupture. Knowledge of these processes may guide the diagnosis and treatment of these vascular malformations, the most common cause of subarachnoid hemorrhage, which prognosis remains dismal.

Key words: Inflammation, hemodynamics, vascular remodeling, intracranial aneurysms

INTRODUCTION

Saccular intracranial aneurysms (IAs) are the most frequent cause of subarachnoid hemorrhage (SAH), the stroke type with the higher morbidity and mortality.^[1,2] A precise evaluation of their rupture risk is crucial to orient treatment of unruptured IAs relatively to the risk of endovascular or surgical treatment.^[2-7] Statistic studies involved patients suffering from aneurysm rupture found that cigarette smoking, arterial hypertension, ethnic origin, age, previous SAH, size ≥ 7 mm, localization of IAs at the posterior circulation and aneurysm's shape are the most important variables regarding the rupture risk.^[2-7]

However, the majority of IAs diagnosed following their rupture is small and located on the anterior circulation,^[8,9] which indicates that the statistical approach does not allow individualizing the risk of rupture. Elucidating the pathogenic pathways inherent to the development and rupture of IAs may allow identifying more reliable markers of rupture-prone IAs. A growing body of evidence supports the correlation between modification of hemodynamic factors and arterial wall alteration leading to IAs development and rupture.^[10-13] Particularly, wall shear stress (WSS) gradient might be an important factor of vascular remodeling through multiple mechanisms involving endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) modification of gene expression triggered by local inflammatory reaction and leading to degenerative changes of arterial wall.^[14] In this article, we summarize the existing data, extracted from a review of the pertinent literature, regarding inflammation and hemodynamic stress in the pathogenesis of IAs. Our endeavor is to explore the causative relationships that may link hemodynamics, inflammation, vascular

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remodeling and the development and rupture of IAs. This approach may provide effective tools to predict the individual risk of aneurysmal rupture more reliably than statistical methodology.

METHODS OF THE REVIEW

The literature review was conducted using Medline and EMBASE searches that included works published between 1980 and 2014. The terms “IA” and “cerebral aneurysm” were used as text words and MESH headings with appropriate subheadings. A further search was performed to link cerebral and IAs and the following key words: inflammation, hemodynamic(s), remodeling, macrophages, neutrophils, lymphocytes, complement, VSMCs, mast cells, cytokines, and inflammatory biomarkers. Textbooks, journal bibliographies, and conference proceedings were also included. Language restrictions were not used.

INFLAMMATION AND INTRACRANIAL ANEURYSMS REMODELING

The central nervous system is an immunologically active environment where a complex set of interactions links the various constituents of the immune and inflammatory system with the constituents of nervous tissue and vasculature.^[15] Aneurysm formation begins with a hemodynamically triggered endothelial dysfunction where inflammation initiated by nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) activation and imbalance between nitric oxide (NO) and peroxynitrite anion (ONOO⁻) in favor of ONOO⁻ seem to hold a key role.^[16] The following mounting inflammatory response implicates several inflammatory cells and mediators and phenotypic modulation of VSMCs from a contractile to a pro-inflammatory/pro-matrix remodeling phenotype with myointimal hyperplasia, inflammation and wall degeneration.

Several *in vitro* and *in vivo* studies found evidences that infiltration of inflammatory cells in the arterial wall initiates aneurysm formation and promotes its rupture through production of inflammatory cytokines, adhesion molecules, immunoglobulins, reactive oxygen species (ROS), complement and inflammatory cell-induced upregulation of matrix-degrading proteinases, among which macrophages, neutrophils, and lymphocytes hold a central role.^[17,18]

Macrophages

Monocytes originally produced in bone marrow enter circulation and infiltrate endothelium at the site of the hemodynamic injury, where they differentiate into macrophages.^[18] Macrophage is one of the first cell

types to respond to injury, but it also regulates the later immune response.^[18] The role of these inflammatory cells in IAs formation is demonstrated by the fact that macrophage depleted mouse displays a lower risk of IAs.^[19] Macrophage action on the arterial wall is mediated by secretion of cytokines and proteinases.

Cytokines are peptides, proteins, and glycoproteins that mediate inflammatory and immune response.^[20-22] Several cytokines secreted by macrophages have been found involved in the pathogenesis of IA especially monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor alpha (TNF- α), stromal cells derived factor-1 (SDF-1/CXCL12). MCP-1 is a chemotactic cytokine, also known as chemokine, for monocytes, lymphocytes, and some granulocytes secreted by macrophages.^[23] Its implication in the development of IAs is demonstrated by a decrease of IAs and arterial wall inflammation in MCP-1 knockout mice.^[24] TNF- α is another proinflammatory cytokine secreted by macrophages.^[18] Experimental data suggest a critical role of TNF- α in the formation and rupture of aneurysms in a murine model of cerebral aneurysm formation induced by hypertension and a single stereotactic injection of elastase into the basal cistern.^[25] TNF- α knockout mice and those pre-treated with 3,6'-dithiothaldomide (DTH), a synthesized TNF- α inhibitor, had significantly decreased the incidence of aneurysm formation and rupture as compared to sham mice. Protein and mRNA expression of TNF- α in the cerebral vasculature were not significantly different in TNF- α knockout mice and in those pre-treated with DTH. However, TNF- α expression was higher in unruptured and the highest in ruptured aneurysms when compared to other conditions of aneurysms, where it co-localized to both smooth muscle cells and macrophages. SAH occurred between 7 and 21 days following aneurysm induction. Initiation of DTH treatment 6 days after aneurysm induction did not alter the incidence of aneurysm formation but resulted in aneurysmal stabilization and a significant decrease in rupture. Therefore, it can be inferred that inhibitors of TNF- α could be beneficial in preventing aneurysmal progression and rupture.^[25] TNF- α upregulates the adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin in ECs, fibroblasts, and SMCs.^[26] These adhesion molecules attract and facilitate migration of leucocytes through the arterial wall, predisposing to atherosclerosis and IAs development.^[26] Macrophages secrete also another potent chemoattractant cytokine, such as SDF-1/CXCL12.^[27-29] Besides promoting angiogenesis by recruiting endothelial progenitor cells from the bone marrow through a CXCR4 dependent mechanism,^[30] SDF-1 is associated with angiogenesis and migration

and proliferation of macrophages in the walls of human and murine aneurysms, possibly playing a role in the development of IAs.^[31] Macrophages also directly promote degradation of ECM by secreting a zinc and calcium-dependent family of endopeptidases known as matrix metalloproteinases (MMPs) and modulate their activity by producing tissue inhibitors of metalloproteinases (TIMPs), MCP-1 and TNF- α .^[32-34] Beside from degrading all kinds of ECM proteins, these proteinases, particularly MMP-9 secreted also by VSMCs,^[35,36] induce macrophage migration and infiltration across ECM.^[37] Overexpression of MMP-9 in the wall of excised IA was first documented by Kim *et al.*,^[38] followed by Takemura *et al.*^[39] who later showed by immunohistochemical analysis of the overexpression of MMP-1, -2, and -9 in aneurysm walls. Moreover, the levels of MMP-2 and -9 were found to be higher in ruptured compared with unruptured aneurysms in a series of 30 patients, suggesting that MMP-mediated excessive breakdown of vessel ECM eventually leads to aneurysmal rupture.^[40] The central role of MMPs in the pathogenesis of IAs is further demonstrated by the fact that inhibition of TIMPs promotes aneurysm formation in a rodent model.^[41] Under physiological conditions, MMPs production is regulated at the level of transcription. An imbalance between the active MMPs and TIMPs leads to the accelerated destruction of connective tissue associated with several vascular diseases including IAs.^[42]

Neutrophils

Other important inflammatory cells migrating to the site of arterial injury are neutrophils. As for macrophages, they secrete cytokines and MMPs. In addition, they produce peroxidases.^[18] The array of neutrophil-derived cytokines is similar to that of macrophages, including TNF- α and cxc-chemokines such as interleukin (IL)-1 β . However, unlike macrophages, they do not secrete cc-chemokines such as MCP-1.^[39] IL-1 β and cxc-chemokines are involved in various inflammatory cellular activities such as cell proliferation, differentiation, and apoptosis. Upregulation of IL-1 β in animal models of IAs is associated with aneurysm formation and progression by reduced collagen biosynthesis in the aneurysm wall both at the transcriptional and post-transcriptional levels.^[43,44] In addition, neutrophils secrete macrophage inflammatory protein 1- α , which reinforces cytokines' action to promote inflammatory cell recruitment, migration, activation, and differentiation.^[45]

Lymphocytes

Other first-responding inflammatory cells found in IAs wall are lymphocytes. They infiltrate arterial wall in early phases of aneurysm formation and rupture.^[46] They are involved in the production of

proinflammatory cytokines such as TNF- α , interferon- γ (IFN- γ) and IL-6.^[47]

Complement

The role of complement in the mechanism of IA formation is not fully elucidated. In one study by a Helsinki group that compared ruptured with unruptured IA, the expression and activation of complement membrane attack complex were greater in ruptured samples and was associated significantly with aneurysm wall degeneration and inflammatory cell infiltration.^[48] These authors showed in another study that complement activation occurs via the classical pathway as evidenced by the presence of classical pathway activators (IgG, IgM, C reactive protein, oxidized low-density lipoprotein) in the IA wall.^[49]

Vascular smooth muscle cells

As mentioned above, VSMCs are crucial in the process of IAs formation, and rupture. They are mostly found in the medial layer and synthesize the matrix for the structural integrity to the arterial wall. Thinning of this layer contributes to aneurysm formation and rupture.^[50] In response to endothelial injury VSMCs first migrate into the intima where they multiply and give rise to myointimal hyperplasia.^[51] Successively, VSMCs from a differentiated phenotype whose primary characteristic is contraction, dedifferentiation, losing capacity of expressing contractile genes, like myocardin, acquiring the capacity to express genes that may affect the rigidity or elasticity of the vascular wall such as collagen $\alpha 2(I)$ gene (*COL1A2*) and upregulating proinflammatory genes, such as MMPs, MCP-1, VCAM 1, and IL.^[52,53] This phenotypic modulation of VSMCs is induced by TNF- α and mediated by Kruppel-like transcription factor 4.^[54] Phenotypically modulated VSMCs are no longer in spindle shape forming tightly compacted bands, but spider-like cells dissociated from each other, nonproliferating and noncontractile.^[55] Likewise, aneurysmal rupture is associated with degeneration and caspase-mediated apoptotic loss of VSMCs of the aneurysm wall.^[17,56,57]

Mast cells

Although best known for their role in allergy and anaphylaxis, mast cells play an important role in the inflammatory reaction leading to IAs formation and rupture mainly via cytokines release and expression and activation of MMPs.^[58] Indeed, IAs formation is associated with the proliferation and degranulation of mastocytes, and ruptured aneurysms wall is richer in mast cells than unruptured IAs.^[59] The finding that inhibitors of mast cell degranulation decrease the inflammatory reaction in aneurysm walls and block the progression of IAs in mice further support the

participation of mast cells in the pathogenesis and rupture of IAs.^[58]

Inflammatory cells interaction and arterial wall degeneration

Inflammation of arterial wall leading to formation of IAs is initiated by the infiltration of inflammatory cells (macrophages, neutrophils and lymphocytes), which release proinflammatory cytokines and proteinases as well as chemokines and chemoattractant cytokines, for the upregulating recruitment of inflammatory cells into the aneurysm wall.^[60,61] In particular, levels of MCP-1, chemokine (C-C motif) ligand-5 (CCL5), monokine-induced-by-[gamma]-interferon, interferon-[gamma]-induced protein-10, Eotaxin, 2 other chemokines, IL-8 and IL-17 have been found to be higher in blood samples taken from the lumen of human IAs than blood samples from femoral arteries of the same patients.^[61] Inflammatory cytokines lead to degradation and apoptosis of ECs and VSMCs through activation and upregulation of immune cells migration and activity.^[21] Immune cells target not just cells but also ECM, the scaffolding structure that provides the arterial wall with tensile strength, elasticity, compressibility, adhesiveness as well as communicability between cells constituting the vessel wall.^[17,18] In particular, macrophages secrete MMPs resulting in excessive proteolytic activity against connective tissue proteins, including collagens, elastin, and proteoglycans, which causes focal degradation of the vascular ECM and may contribute to aneurysm formation and growth.^[31] Macrophages, in conjunction with lymphocytes, also act on VSMCs, for vessel wall remodeling.^[21] Cytokines and growth factors secreted by macrophages and T-lymphocytes affect VSMCs phenotype changes^[62] and promote their apoptosis.^[48,63,64] One of the key initiators of apoptosis is interaction between the Fas receptor, which is expressed on the surface of both inflammatory cells and VSMCs, and its ligand (Fas-ligand, FasL), which is expressed on the surface of macrophages and T-lymphocytes.^[65] Their interaction induces VSMCs apoptosis through upregulation of cytokines such as TNF- α and interferons expressed by inflammatory cells.^[17,54,56,57] These cytokines promote also the synthesis of NO, another factor inducing apoptosis.^[66] Apoptotic loss of VSMCs induces arterial wall weakening by reducing matrix synthesis.^[63,64]

HEMODYNAMIC FACTORS INDUCE ARTERIAL WALL INJURY AND INITIATE WALL INFLAMMATION

Endothelial dysfunction initially and vascular remodeling subsequently are triggered by shear stress.^[67] This explains why IA is commonly found at arterial junctions, bifurcations or abrupt vascular angles where excessive hemodynamic stresses are exerted on

arterial walls.^[68] There is a close relation between WSS, endothelial dysfunction, and the downstream inflammatory reaction.^[69,70]

Computational flow dynamic studies coupled with histological studies of the aneurysm wall demonstrated a correlation between hemodynamic conditions and inflammatory changes of intracranial arterial wall leading to aneurysm formation and rupture.^[10-13,70] The most highlighted, even though, controversial factor studied is WSS,^[12,71,72] which is the component of the forces coplanar with the cross-section of the artery, originating from blood circulation and acting on arterial walls.^[73] WSS is related to dynamic viscosity of blood, flow velocity parallel to the arterial wall and distance of the vector to the wall.^[73] Whether high or low WSS is involved in the arterial wall inflammatory damage, and development and rupture of IA are still matter of debate.^[74] Hemodynamics in IAs is complex and includes areas of low and high WSS.^[71,72] Several studies show that exposure to abnormal WSS drives endothelium-mediated proinflammatory reactions,^[75] MMPs activation,^[76-79] apoptosis of ECs and VSMCs,^[80] ECM degradation, and arterial wall remodeling.^[36,81] Spatial gradients and changes in WSS magnitude regulate ECs gene expression through the upregulation of transcription factors such as NF- κ B under the conditions responding to cytokines, free radicals and other stimuli implicated in cell survival.^[82-84] Oxidative stress in the arterial wall promotes IAs formation inducing direct endothelial injury, VSMCs phenotypic modulation and apoptosis, recruitment and invasion of inflammatory cells through upregulation of chemotactic cytokines and adhesion molecules, and MMPs activation.^[85] Oxidative stress reflects an imbalance between the production of ROS and the arterial wall's ability to readily detoxify the reactive intermediates or to repair the resulting damages. The ability of the arterial wall to counteract oxidative stress effects largely repose on NO action.^[16] NO is an endothelium-derived relaxing factor that has several actions translating in anti-atherosclerotic properties: it modulates vasomotor tone, inhibits expression of MCP-1 and VCAM-1, prevents propagation of lipid oxidation, inhibits VSMC proliferation, decreases platelet aggregation^[86] and inhibits expression and activity of MMPs.^[86] Practically, all risk factors for arterial wall damage (hypercholesterolemia, diabetes, insulin resistance, arterial hypertension, cigarette smoking) reduce production of endothelial NO through increased production of superoxide and other ROS.^[16,86-90] These strong oxidants both disrupt NO-mediated arterial wall protection decreasing availability of NO and promote arterial wall inflammation increasing ONOO⁻ production.^[16,86-90] Under physiological conditions, unidirectional laminar

shear stress increases NO availability through a biphasic action: within seconds after stress the endothelial nitric oxide synthase (eNOS) enzyme expressed in ECs is activated by a calcium-independent mechanisms.^[91] Subsequently, eNOS expression is upregulated through NF- κ B activation by a transient, one hour lasting, increase in eNOS mRNA transcription and a sustained increase in eNOS mRNA stability.^[92] However, NF- κ B activation leads also to an increased expression of pro-inflammatory genes encoding cytokines, VCAM-1, ICAM-1, tissue factor and MCP-1.^[16,86-90] At a first glance, the NF- κ B mediated protective and damaging effect appears to be contradictory. Nonetheless, the evidence of a negative feedback pathway on NF- κ B activation mediated by NO production resolves this apparent paradox. If eNOS levels are relatively high, sufficient NO is produced to shut down NF- κ B activation soon after shear is applied to endothelium through a classical negative feedback pathway.^[16] Conversely, if eNOS levels are relatively low, NF- κ B activation persists enough to restore eNOS to normal levels in order to ensure a long-lasting protection to ECs. The double effect of NF- κ B activation also explains why shear stress may reveal both harmful and protective to endothelium. As a matter of fact, in case of alteration of the inhibitory limb of the NO-mediated negative feedback, the proinflammatory action of shear stress prevails, leading to endothelium damage, with elongation, migration, change in density, and loss of ECs and to VSMCs phenotype change with acquisition of pro-inflammatory/pro-matrix remodeling properties.^[17,50,61] ROS may also play a role in the pathogenesis of IAs.^[93,94] Aoki *et al.*^[95] demonstrated the upregulation of genes producing ROS and the downregulation of ROS-eliminating genes in a murine model of IAs. Moreover, the same study showed a similar effect of edaravone, a free radical scavenger, and of the deletion of ROS-producing gene: in two separate groups of animals both effectively inhibited IAs formation by suppressing inflammation in aneurysmal walls.^[95] Moreover, low WSS may provide upregulation of proinflammatory cytokines and their receptors, such as IL-1 α , IL-1 receptor, IL-6, and MCP-1.^[96] In addition, an *in vitro* study showed that WSS on ECs causes a differential modulation of TNF- α -induced expression of adhesion molecules such as ICAM-1, VCAM-1, and E-selectin by reducing intracellular ECs ROS levels.^[97] This may cause inhibition of TNF- α -induced VCAM-1 and E-selectin expression in ECs through inhibition of NF- κ B activation.^[97] However, the same authors showed that WSS-induced production of TNF- α stimulates the expression of another adhesion molecule, ICAM-1.^[97] These apparently discordant findings indicate that a more thorough study of the cross-talk between these signaling molecules may shed further light onto the biological end-points produced

by the WSS in modulating cytokine-induced adhesion molecule expression in ECs. Although the processes by which hemodynamic factors affect inflammation of the artery wall is incompletely known, vascular remodeling in response to abnormal WSS correlates with increased ECs and VSMCs apoptosis,^[98,99] with upregulation of MMPs activity in both ECs^[33] and VSMCs^[36] and with upregulation of several transcription factors and inflammatory cytokines by inflammatory cells.^[18] Along these lines, Wang *et al.*^[82] showed in canine models that in areas of high shear stress (arterial bifurcations), aneurysm wall remodeling is associated with IL-1 β and MMPs expression along with a loss of eNOS expression. In line with these findings, EC injury was found by Jamous *et al.*^[100,101] to be the earliest change in aneurysm wall, followed by the formation of an inflammatory zone that leads to proteolytic destruction of the vascular ECM by MMPs and ultimately to aneurysm formation.

In summary, under physiologic condition shear stress promotes both endothelial NF- κ B upregulation and immediate eNOS activation. In turn, NF- κ B triggers both transient upregulation of eNOS and increased eNOS stability. This results in increased NO synthesis. NO protects arterial wall through a “direct” action on it as well as “indirectly” through a negative feedback on NF- κ B activation. When the chain of events in red prevails, shear stress sustains arterial wall protection. Failure of NO-mediated direct and/or indirect arterial wall protection shifts the balance towards inflammation.

When the degeneration in the arterial wall, including loss of endothelial and smooth muscle cells and degradation of ECM are not healed, chronic remodeling of tissue takes place to alter the biomechanical properties of arterial wall and aneurysm formation, which eventually rupture [Figure 1].^[63,64]

INFLAMMATORY BIOMARKERS AND ESTIMATION OF RISK OF RUPTURE

Giving that considerable evidence suggest the involvement of inflammation in development and rupture of IAs,^[19-25,31,35-41,48-64,70,76-81,93,94,99-101] preoperative noninvasive assessment of inflammatory status of the aneurysm wall may guide management of unruptured IAs.^[102-105] One possible tool to identify rupture-prone IAs is ferumoxytol-enhanced magnetic resonance imaging (MRI).^[102-104] Ferumoxytol is an ultrasmall superparamagnetic particle of iron oxide that reveals phagocytic activity of inflammatory cells because it is cleared by macrophages.^[102-104] Ferumoxytol is hypointense on MRI T2*-weighted gradient echo sequences and hyperintense on T1-weighted spin echo sequences. It is detected inside blood vessels for ≤ 72 h and begins to clear within 24 h from injection. Its early

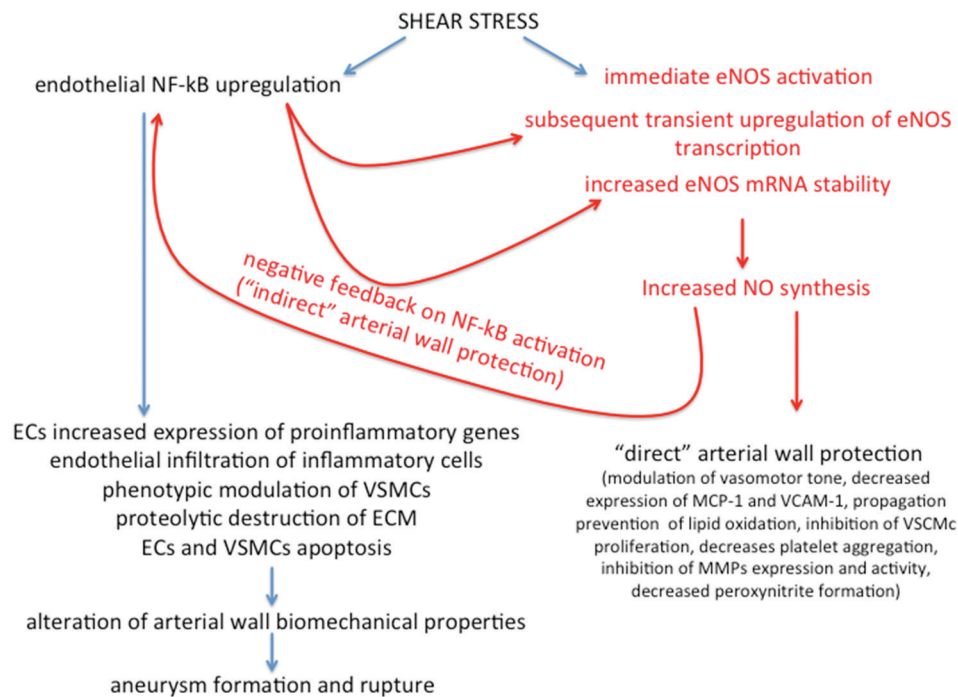


Figure 1: Impact on arterial wall condition of balance between shear stress-mediated endothelial nuclear factor kappa B-cell upregulation and nitric oxide synthesis

uptake, within 24 h, is secondary to macrophage uptake and considering the crucial role of such inflammatory cells in development and rupture of IAs, it indicates active inflammation in aneurysm walls of unstable aneurysm, as suggested by one recent study.^[102] These authors found that early ferumoxytol uptake was significantly higher in aneurysms with marked upregulation of inflammatory molecules such as cyclooxygenase-2 and microsomal prostaglandin E synthase-1 and macrophages, independently from site and size of the aneurysms.^[101] Moreover, all three unruptured IAs of their series with early ferumoxytol uptake that were managed conservatively ruptured less than 6 months after diagnosis, which supports the hypothesis that inflammation is the cause but not the consequence of the rupture.^[102] Another line of research aiming at differentiating ruptured and unruptured IAs on the basis of distinctive patterns of expression of inflammatory markers is the analysis of gene expression profile.^[103] A recent study compared the gene expression arrays of ruptured and unruptured aneurysms and found a significant difference of expression of genes encoding macrophage-mediated inflammatory molecules according to the age of patients.^[105] In particular, genes involved in vascular remodeling, inflammation, and atherosclerosis such as S100/calgranulin genes (*S100A8*, *S100A9*, and *S100A12*), cluster of differentiation 163, myeloperoxidase (MPO), were upregulated, while genes for Krüppel-like family of transcription factors (*KLF2*, *KLF12*, and *KLF15*) and *CDKN2*, which are respectively anti-inflammatory regulators and inhibitors of cellular proliferation, were downregulated, together with cell adhesion molecules and cytoskeletal proteins of arterial

wall.^[105] Therefore, the authors conclude that some of these identified genes may help identifying IAs at risk of rupture, which warrant early treatment.^[105]

CONCLUSION

Aneurysm formation begins with a hemodynamically triggered endothelial inflammatory dysfunction, which is the cause rather than the consequence of aneurysms' development and rupture. The proinflammatory action of shear stress prevails over its endothelium protective action when the balance between NF-κB-mediated production of NO and proinflammatory mediators (ROS, cytokines, adhesion molecules) shifts in favor of inflammation because of alteration of the inhibitory limb of the NO-mediated negative feedback on NF-κB activation. Targets of the inflammatory reaction are, besides ECs, ECM, and VSMCs. Endothelial injury, VSMCs phenotypic modulation with acquisition of pro-inflammatory/pro-matrix remodeling properties and subsequent Fas-mediated apoptotic cell death lead to the arterial wall weakening and aneurysm formation and rupture. Clarifying the causative relationships that link hemodynamics, inflammation, vascular remodeling, and the development and rupture of IAs may provide effective tools to predict the individual risk of aneurysmal rupture and aid the treatment decision-making process.

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