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## Neuroinflammation and subarachnoid hemorrhage: a revised look at the literature

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### Abstract

A key topic for aneurysmal subarachnoid hemorrhage is neuroinflammation. Neuroinflammation can predispose to aneurysm formation and rupture. Neuroinflammation can also result from the blood breakdown products after aneurysm rupture. Recent evidence has shown that perpetual neuroinflammation can contribute to vasospasm and hydrocephalus. Targeting neuroinflammation is a novel mechanism for preventing subsequent neurologic sequelae. In this review, we highlight the pathophysiology of aneurysm formation, the neuroinflammatory surge after rupture including the involved cytokines, and ultimately tie in the contributory clinical relevance. In the last sections, we look at the pre-clinical data and novel avenues for further discovery. This paper will be a useful resource to both the clinician and scientific investigator.

### Keywords

neuroinflammation; subarachnoid hemorrhage; treatment approach; aneurysm formation

### Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a significant source of morbidity and mortality resulting from vessel damage with an overall prevalence of 3.2% [1]. Aneurysm rupture can lead to brain damage, hydrocephalus, dramatic cognitive decline, and vasospasm [2]. A key feature in aSAH pathophysiology is inflammation. Neuroinflammation and aSAH are intricately related with a mutually causal relationship: inflammatory changes both lead to formation of aSAH and are evident in the period following subarachnoid hemorrhage.

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Competing interests

The authors declare no conflicts of interest.

## Neuroinflammation causes aSAH

There are several mechanisms that contribute to aSAH progression (Figure 1). Increased oxidative stress in the period preceding aneurysm formation, for one, is thought to disrupt the endothelial regulation of vessel tone, compounding the issue of hemodynamic wall stress [3]. Certain genetic conditions such as polycystic kidney disease, which leads to impaired smooth muscle and blood vessel strength [4], and connective tissue disorders such as Ehlers-Danlos, which impair the integrity of collagen [5], also lead to aSAH progression. Despite this, neuroinflammation occupies a central role in the initiation of aSAH, directly leading to endothelial and smooth muscle dysfunction as well as vessel wall damage, which we describe here.

Several inflammatory changes have been observed to contribute to aneurysm formation. Namely, elevated hemodynamic shear stress has been shown to activate the pro-inflammatory transcription factor- $\kappa$ B (NF- $\kappa$ B) pathway in endothelial cells [6, 7]. NF- $\kappa$ B is a key inflammatory transcription factor which, in turn, engenders an inflammatory pro-death autophagy state in endothelial cells and vascular smooth muscle cells, leading to the thinning of vessel walls and eventual aneurysm rupture [8]. NF- $\kappa$ B has also been implicated in the inhibition of procollagen expression in the aSAH, leading to further weakening of vessel walls [9]. Further, NF- $\kappa$ B promotes macrophage recruitment by upregulating cell adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [10]. In turn, these macrophages infiltrate into the vessel wall and secrete more pro-inflammatory cytokines, setting up a vicious inflammatory positive feedback loop that causes vessel ballooning [11]. For example, microglia, the resident macrophages of the central nervous system, can adopt a pro-inflammatory M1 configuration or a neuroprotective M2 configuration [12]. Aneurysm formation is thought to be mediated by polarization of microglia towards the M1 phenotype. Proinflammatory neutrophils are thought to play a role in this polarization, since antibodies against CXCL1 – a neutrophil recruitment chemokine – reduce the M1 phenotype [13]. Complement activation has also been observed as an inflammatory change preceding aSAH, as membrane attack complex (MAC) localization to saccular aneurysm has been observed both prior and following rupture [14]. Clearly, several inflammatory molecular pathways triggered by changes in hemodynamic flow result in damage to the cerebral vessel wall prior to rupture.

## Neuroinflammation is a result of aSAH

Though inflammation is abundant in the period leading to aneurysm rupture, an increasing amount of evidence points to the inflammatory changes in the period following aneurysm rupture. Cell death markers such as caspase-3 are elevated in parenchymal and vascular cells just 10 minutes after aneurysm rupture [15], and inflammatory proteins such as high-mobility group box 1 (HMGB1) are elevated in as little as 2 hours following aSAH rupture [16], underscoring the swift response to intracranial hemorrhage. Blood brain barrier (BBB) disruption precipitated by inflammation is also a hallmark in the post-hemorrhage period and has been observed as soon as 24–48 hours after aneurysm rupture [17]. In the first 72 hours following aSAH rupture, microglia polarization into the pro-inflammatory M1 configuration has been observed [18, 19]. This microglial reaction is thought to have a temporal component. Early brain injury following aneurysm rupture is associated with this

early microglial inflammatory reaction, which precedes a later monocytic infiltration [20]. Blockade of this microglial reaction or polarization away from the M1 phenotype conveys a neuroprotective effect [21, 22]. In one study, neuronal apoptosis was avoided with microglia depletion 7 days following aneurysm rupture but was not avoided with microglia depletion 15 days following aneurysm rupture [23]. Taken together, this suggests that inflammatory agents in the early phase following aneurysm rupture are key drivers of injury.

### Current and Emerging Treatments for aSAH

Current management of aSAH can be understood in terms of surgical and medical treatment approaches. If vessel rupture has not occurred yet, coil embolization or aneurysm clipping is a surgical option used to prevent delayed aneurysm rupture and resultant ischemia [24]. Medical management of aSAH focuses on control of hypertension and reduction of bleeding. Blood pressure control is a central theme of medical management to avoid risk of stroke and further bleeding. In fact, antihypertensives such as nimodipine may even be used in the acute period following aSAH [25]. Early endovascular clipping of ruptured aneurysms is associated with improved clinical outcome [26] and represents a surgical modality in the acute management of a ruptured SAH. Counseling to reduce pro-aneurysmal risk factors such as smoking and high alcohol intake is also part of the management regimen [25].

In addition to the current treatments for aSAH, several emerging drug candidates are poised to target neuroinflammation, removing a central mediator in the progression of brain injury after aSAH. Levosimendan, a calcium channel sensitizer, has been used for several years in the treatment of heart failure [27], though recently has been investigated for its anti-inflammatory effects which have been shown to ameliorate cerebral vasospasm following aSAH [28]. Milk fat globule epidermal growth factor 8 (MFG-E8) is a glycoprotein which mediates phagocytosis of apoptotic cells [29], that has recently been implicated in diminishing the inflammatory response [30]. One recent study employed the use of a recombinant MFG-E8 in a SAH rat model and discovered that MFG-E8 downregulated the proinflammatory HMGB1 and attenuated early brain injury caused by subarachnoid hemorrhage (SAH) [31]. Indeed, targeting the proinflammatory HMGB1 is a focus of recent work and has been shown to diminish early brain injury following SAH [32, 33]. The lipid-derived resolvins have also been investigated recently for their neuroprotective and anti-inflammatory effects following SAH rupture. Resolvin-D1 administration in a rat model of SAH not only downregulated inflammatory markers such as matrix metalloproteinase-9 (MMP-9) and ICAM-1, but it also prevented inflammatory cell infiltration and improved neurological function [34]. Taken together, these recent advances represent promising therapeutic targets in the de-escalation of the neuroinflammatory response following SAH rupture.

### Inflammatory cytokines and SAH

Inflammatory cytokines play a key role in the pathogenesis and resolution of SAH [60]. Some, such as interleukin-1B (IL-1b), interleukin-1(IL-6) and TNFa have well defined roles in the cellular and environmental changes following SAH (Table 1). Other cytokines have shown to be elevated at various time points following the inciting event but without a

clear understanding of their actions (Table 1). Further understanding of these cytokines along with their levels and timeframes could lead to targeted therapies aimed at preventing SAH complications such as vasospasm and hydrocephalus [36, 52, 61]. Although both the timeframe [60, 61] and the levels [62] of cytokines following SAH have been studied, there remains a lack of consensus on how and when to measure these cytokines following SAH to improve clinical outcomes and develop targeted therapies [61].

Cytokines were first identified in brain injury by Giulian et al in 1986 when interleukin-1 (IL-1) was shown to be secreted by microglia to upregulate astroglia [63]. This was shortly followed by a study showing microglia secreting TNF $\alpha$  under certain pathological states [64]. Aloisi et al then demonstrated that astrocyte secretion of IL-1 $\beta$  leads to the secretion of other cytokines such as IL-6, IL-8, IL-1 $\beta$ , and colony stimulating factors. To a lesser degree astrocytes also were shown to secrete TNF $\alpha$  leading to the release of similar cytokines [65]. From there, IL-6 was shown to be elevated in cerebrospinal fluid (CSF) following SAH in 1993 [35]. IL-6 and IL-8 were both thought to be important immunomodulators following SAH [36]. Kikuchi et al postulated that IL-6 functions as an important vasoconstrictor in post-SAH vasospasm [36]. This hypothesis was supported by further studies showing that higher levels of IL-6 and TNF $\alpha$  increased the risk of vasospasm following SAH [52]. IL-6 has also been implicated in delayed ischemic deficits [45] and as a general marker for post-SAH complications [53, 55]. Cytokine IL-1 was shown to mediate fever, leukocytosis, and NO synthesis following SAH [37]. Mathiesen T et al. also demonstrated that high CSF cytokine levels correlated with brain damage [37]. Although individual cytokines had been studied following SAH, Takizawa et al were first to demonstrate the cascade of cytokines following SAH [41]. They found that elevated levels of CRP and TGF- $\beta$  were associated with communicating hydrocephalus [41]. Fassbender et al found that both blood flow velocity and intrathecal secretion of these cytokines contributed to the compartmentalized inflammatory response following SAH [40, 66]. This compartmentalized response could also be driven by vasoconstrictors such as endothelin 1 [66]. Although astrocyte and microglial involvement was elucidated early on, only recently has the mechanism for neutrophil recruitment following SAH been understood. Coulibaly et al found that increased CSF IL-17 leads to the recruitment of neutrophils to the site of inflammation following the initial insult [60]. Other cytokines following SAH have been shown to play roles in immunosuppression such as TGF- $\beta$  [41] and IL-10 [53]. Chaudhry SR et al. found that elevated IL-10 was associated with immunodepression leading to increased nosocomial infections following SAH [53]. Other cytokines play critical roles as neuroprotective factors following SAH [67].

Several papers have looked at the association of cytokine levels and outcome at various time points following SAH. Levels of IL-1 $\alpha$ , and TNF $\alpha$  have been shown to be associated with outcome in both the subacute and acute timeframes [37, 39]. Further, high CSF levels of IL-6 in the subacute time frame has been shown to correlate with poor 3- and 6-month outcomes [39, 46, 51, 61]. Clinical use of these cytokine profiles could guide clinical decisions if standardized, but there is not yet a consensus on how or when to collect these markers in clinical practice [61].

Whether being secreted from leukocytes [66] or glial cells [63–65], cytokines play a key role in the response of the brain parenchyma following SAH. Cytokines are directly responsible for the numerous structural and chemical changes that occur minutes to months following SAH [62]. By better understanding the temporal nature and which cytokines predominate, clinicians may be better equipped to manage and prevent common complications following SAH.

## Clinical relevance

About one third of patients with acute SAH develop ischemia caused by narrowing of the blood vessels supplying the brain [68, 69], making it one of the main causes of morbidity and mortality among patients with SAH. Proper risk prediction and adequate management of the problem reduces morbidity and mortality, but the pathogenesis of cerebral vasospasm is multifocal and not well understood. Researchers have investigated many risk factors associated with developing vasospasm such as age, sex, cigarette smoking, alcohol intake, heart disease, diabetes, and body mass index (BMI) [70, 71]. Radiological and laboratory data have also been studied to depict any correlation or risk stratification for the prediction of post SAH vasospasm [72, 73]. Symptomatic vasospasm may present with recent onset or worsening neurological insults without causes being explained by angiography [72, 74] and is defined in two ways: radiological or clinical. Radiological vasospasm is defined as narrowing of the major cerebral vessels and may be focal or diffuse [74, 75]. It starts usually on the third day after SAH and usually lasts for 2–3 weeks [74–76]. Clinical vasospasm is identified by a delayed neurologic effect and presents as a gradual loss of consciousness with focal motor and speech deficits [75].

Pathogenesis of cerebral vasospasm: The mechanism of SAH induced vasospasm is not clear. Several pathways seem to be involved in the pathogenesis of vasospasm and delayed cerebral ischemia [77]. Here, we provide an overview of these mechanisms and the updated strategies for possible therapies.

## Mechanisms involving vascular smooth muscles

Intracellular calcium is known to regulate smooth muscle contraction [78]. In case of vasospasm, contraction of vascular smooth muscles occurs in both calcium dependent and independent manners [77]. For one, smooth muscle calcium regulation is thought to be disrupted following SAH [79]. Further, the products of blood in the subarachnoid space are suggested to stimulate G protein coupled receptors which may further increase intracellular calcium [77].

## Endothelial factors

Endothelial cells regulate the tone of vascular smooth muscles by secreting different mediators as NO, prostacyclins and endothelins. There is a balance between vasoconstrictors and vasodilators under normal physiological conditions. The shift of this balance towards the vasoconstrictive side is thought to be highly involved in cerebral vasospasm [80]. Endothelin-1 (ET-1) is a potent natural vasoconstrictor secreted by endothelial cells, and ET-1 receptor expression is upregulated in the cerebral vessels of patients with SAH in a

hypoxia-dependent process [81, 82]. Some clinical trials have demonstrated that endothelin-1 inhibition reversed SAH-associated decrease in cerebral blood flow [83]. The conscious trials reported that inhibition of the endothelin-1 pathway reduced the degree of vasospasm without any pronounced effect on functionality [84, 85].

### **Neurogenic mechanism**

Transient global cerebral ischemia is the first pathologic insult that occurs immediately after SAH and in this case the intracranial pressure is so close to the mean arterial pressure [86]. Stimulation of the sympathetic system is most prominent at this stage resulting in catecholamine surge [87]. The catecholamine levels remain high in the blood of patients with SAH several days after the bleed and their levels correlate with poor prognosis [87, 88].

### **Glymphatics role**

The lymphatic vessels within the lining of the venous sinuses of the brain [89] are also thought to contribute to vasospasm. Oxidative stress after SAH was exaggerated after cervical lymph node blockage that was observed before discovery of brain lymphatics [90]. Paravascular glymphatic channels are located close to cerebral arteries and represent a direct interface between CSF and brain interstitial environment [91]. Blood products can pass through these channels and initiate parenchymal inflammatory reactions [92]. Magnetic resonance imaging reported reduced glymphatics perfusion following acute SAH [93].

### **Hydrocephalus**

Hydrocephalus is a common complication of spontaneous SAH with acute onset presenting in 15–87% of cases [25, 94], and chronic in 9–64% [95, 96]. Management of increased intracranial pressure is crucial for the survival of these patients. Early intervention using an external ventricular drain (EVD) reduces the long-term effect of blockage of CSF pathway with blood clots, however, it may complicate treatment and cause infection [97, 98].

Various mechanisms are involved in the pathogenesis of acute and chronic hydrocephalus following aneurysmal SAH. Ventricular system adhesions, abnormal CSF dynamics, and blocked arachnoid granulations are possible mechanisms [99, 100]. It is reported that fibrosis in the subarachnoid space is responsible for the pathogenesis of chronic hydrocephalus following aneurysmal SAH [101]. Various cytokines secreted by inflammatory cells recruit fibroblasts initiating a fibroproliferative reaction in the subarachnoid space [41]. Therefore, both inflammatory and fibroblastic responses are culprit in the pathogenesis of post aneurysmal SAH.

### **Fibrosis involvement in hydrocephalus**

Fibrosis at the arachnoid granulations reduces CSF absorption and impairs its circulation, resulting in hydrocephalus. Levels of fibrosis promoting factors such as TGF $\beta$ 1 are upregulated in the CSF of patients with SAH with chronic hydrocephalus indicating a possible relation with hydrocephalus [102]. TGF $\beta$ 1 is the predominant profibrotic factor in the CNS and is secreted by glia and neurons [103]. A pathway involved in fibrosis is highly dependent on the activity of TGF $\beta$ 1 [104]. Experimental studies have shown that TGF $\beta$ 1 inhibition reduced the burden of hydrocephalus in rats with SAH [105].

## Pre-clinical findings

Several models are used for SAH including mouse, rat, rabbit, and dog models [106]. However, rat and mice models are by far the most commonly used [107]. While several rodent models are available, these models are unable to be translated from preclinical studies to clinical trials, mainly since the models are unable to replicate human pathophysiology (e.g.: cerebral vasospasm and delayed cerebral ischemia) [108].

## Current preclinical SAH models

To better understand areas of possible improvement, it is important to understand the main types of SAH models available. Currently, even though most SAH occur via spontaneous rupture of cerebral aneurysms, most rodent models mimic non-aneurysmal SAH [109]. This is because it is difficult to induce cerebral aneurysms in rodents, which is a significant challenge that will be elaborated herein [108, 110]. Non-aneurysmal SAH models are mainly created via two methods: (1) prechiasmatic and cisterna magna blood injection models or (2) endovascular perforation [108]. These models are widely used, as evidenced by a recent study that used them to test mesenchymal stem cells-derived therapies for SAH as well [111].

## Aneurysm induction in animal models

However, it is important to distinguish non-aneurysmal SAH models from aSAH models (Figure 2). Not only because aSAH represents a majority of human SAH cases, but also because aSAH has additional consequences, as previously described, of endothelial and inflammatory changes due to the spontaneous rupture of an intracranial aneurysm [108]. Without true aSAH models, it is hard to evaluate preventative and/or therapeutic paradigms in experimental models [108]. To tackle this challenge, efforts have focused on trying to induce aneurysms in rodent models through a few methods. First, hypertension and hemodynamic stress has been shown to induce aneurysms, but this method can take up to three months and the resulting aneurysms are small [110, 112]. Another method is to inject elastase to degrade internal and external lamina of cerebral vessels, which results in aneurysms in approximately three weeks [113–115]. This triad of hypertension, hemodynamic stress, and elastase injections has been used to develop the first intracranial aneurysm mouse model [116]. C57BL/6J mice were injected with elastase at the right basal cistern and continuously infused with angiotensin-II to produce the desired hypertension and hemodynamic stress [11, 108]. This method resulted in 500  $\mu\text{m}$  intracranial aneurysms (dose-dependent on concentration of elastase and angiotensin-II) [108]. The use of angiotensin-II has been supported by the attenuation of aneurysm rupture while using angiotensin I-converting enzyme (ACE) inhibitors [112].

While the aforementioned triad model was effective in inducing aneurysms, it utilized angiotensin-II, which may cause confounding systemic effects due to inflammation and reactive oxygen species within vessel walls [117]. Thus, one factor to keep in mind is the hypertensive agent that is utilized [108]. An alternative compound is deoxycorticosterone acetate (DOCA). The original methodology included a DOCA pellet being implanted post unilateral nephrectomy along with an elastase injection and 1% saline drinking intake [118].

While this method resulted in intracranial aneurysm rupture in the circle of Willis between 7–16 days, the unilateral nephrectomy posed the problem of depleting blood pressure affecting hormones, such as renin and others [117]. Thus, a newly proposed idea is to implant DOCA and 1% saline without nephrectomy, although this has not been investigated yet in the setting of cerebral aneurysms [108].

### Future directions for preclinical studies

Given the summary of current SAH models, there are still areas of improvement needed mainly because the current models do not allow for studying long-term outcomes and known complications of aSAH, including cerebral vasospasm and/or delayed cerebral ischemia [108]. Starting with cerebral vasospasm, several methods exist to examine this (histological analysis to measure intraluminal diameter and gel casting of cerebral vasculature), but require sacrificing rodents, preventing the study of long-term outcomes or the progression of cerebral vasospasm [119–121]. In vivo imaging, such as synchrotron radiation angiography and digital subtraction angiography, has been used to study rodent cerebral vessels to avoid this issue [122]. However, use of angiography is quite limited due to the toxicity of contrast agents. A research study in 2005 turned to using MRA to overcome the lack of utilizing serial angiography images, which produced similar results to previous methods [123]. But this also posed new concerns in that the technique is quite time consuming, expensive, and requires anesthesia, which can affect the SAH pathophysiology [108]. Thus, there isn't an ideal method of studying cerebral vasospasm currently and would be a good area of future research.

Another complication of aSAH with limited investigation via preclinical models is delayed cerebral ischemia (DCI). A systematic review of 78 preclinical studies showed that only 38% of models (with the most prevalent method being cisterna magna injection) reproduced DCI, but these instances were never investigated with imaging [124]. Given that DCI is a major prognostic factor of poor outcomes or disability after aSAH, it is imperative to find a preclinical model that reproduces DCI well [124, 125].

To summarize, the current models for aSAH do not allow for translation to clinical trials due to difficulty of inducing spontaneous aneurysmal rupture, the lack of temporal control, the inability to follow long-term outcomes, and the limited ability to study the severity and progression of noted complications of aSAH such as cerebral vasospasm, delayed cerebral ischemia (DCI), early brain injury, and neurological deficits [108, 126]. Thus, the goal should be to create a model that encompasses all these aspects. Future research efforts, beyond the forementioned points, should also focus on creating a standardized protocol/preclinical model so that comparison of results across studies can be more easily facilitated.

### Future directions and conclusion

In a patient with an aSAH due to a ruptured intracranial aneurysm, the initial goal is stabilization of the patient in which their hemodynamic status and ability to protect their airway is assessed [127]. Once this is accomplished, treatment options of the inciting vascular defect can be addressed. Generally, two different methods exist for treatment of an intracranial aneurysm leading to SAH, either microsurgical clipping or endovascular

coiling [128]. The choice of which treatment to pursue depends on anatomical factors such as the location of the affected artery, characteristics of the aneurysm, the characteristics of the hemorrhage and its subsequent mass effect [25]. Beyond the anatomy of the vascular injury, other factors that are considered when choosing a method of treatment are the overall health of the patient and they able to undergo invasive surgery, as well as the preference and comfort level of the neurosurgeon providing treatment [127]. Regardless of what treatment method is chosen, providing treatment in a timely fashion remains of utmost importance with the goal of preventing rebleeding [25, 129].

Microsurgical repair of aneurysmal SAH once was the primary means of repair prior to the development of specialized endovascular repair methods [130]. Surgical repair is an invasive method of aneurysm repair and thus confers greater risk intraoperatively and postoperatively than endovascular repair. It entails performing a craniotomy and visualizing the aneurysm while evacuating the extravasated blood. The aneurysm is then mechanically occluded using titanium clips while care is taken to preserve blood flow through the adjacent arteries [131]. Due to the invasive nature of the procedure, it has fallen out of favor when compared to endovascular repair. Additionally, endovascular coiling is a means of aneurysm repair in patients that are poorer surgical candidates such as those that are older or have cardiovascular comorbidities. Prior to the endovascular intervention, neuroimaging is conducted to ensure that there is no hydrocephalus, hemorrhage or recent infarction [132]. The procedure entails catheter insertion using fluoroscopic guidance. Metal coils are then placed in the lumen of the aneurysm with the goal of interrupting blood flow to the aneurysm while acting as a nidus for thrombotic occlusion of the aneurysm.

Neuroinflammation plays a critical process in both aneurysm rupture, injury progression, and ultimately the healing process. It is still a topic that is poorly understood but has significant clinical relevance. In this review, we looked at the role of inflammatory cytokines and contribution to vasospasm and hydrocephalus. Pre-clinical literature provided important guidance on important pathways and the inflammatory surge. We also presented further guidance regarding areas of needed investigation. This is a topic that will gain ongoing relevance in the quest for improved treatment options.

## Abbreviations

<b>aSAH</b>	aneurysmal subarachnoid hemorrhage
<b>NF-<math>\kappa</math>B</b>	transcription factor- $\kappa$ B
<b>BBB</b>	blood-brain barrier
<b>CRP</b>	C-reactive protein
<b>CSF</b>	cerebrospinal fluid
<b>DCI</b>	delayed cerebral ischemia
<b>SAH</b>	subarachnoid hemorrhage
<b>DOCA</b>	deoxycorticosterone acetate

<b>ET-1</b>	endothelin 1
<b>HMGB1</b>	high mobility group box 1
<b>EVD</b>	external ventricular drain
<b>HMGB1</b>	high-mobility group box-1
<b>ICAM-1</b>	intercellular adhesion molecule-1
<b>MAC</b>	membrane attack complex
<b>MFG-E8</b>	milk fat globule epidermal growth factor 8
<b>MMP-9</b>	matrix metalloproteinase-9
<b>NF-<math>\kappa</math>B</b>	nuclear factor kappa B
<b>TGF<math>\beta</math>1</b>	transforming growth factor beta-1
<b>ACE</b>	angiotensin I-converting enzyme
<b>VCAM-1</b>	vascular cell adhesion molecule-1
<b>BMI</b>	body mass index

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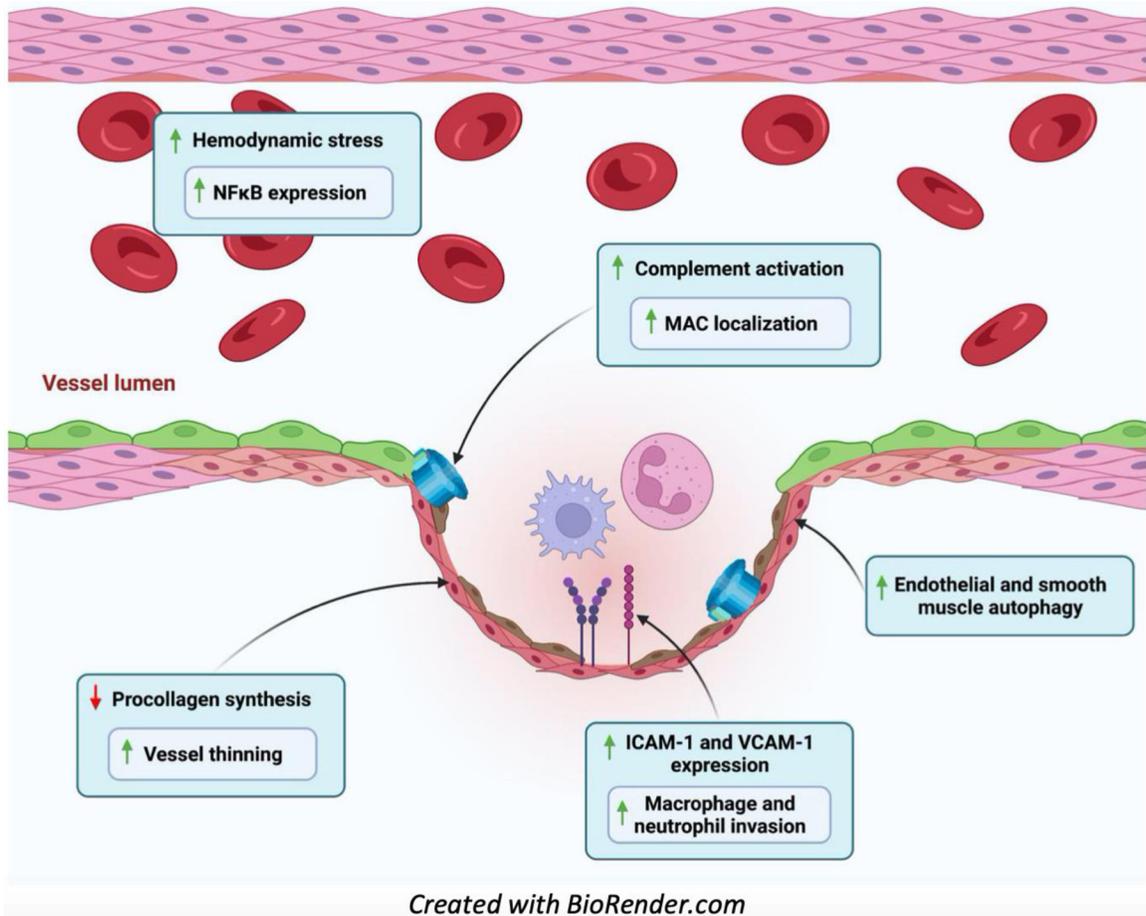
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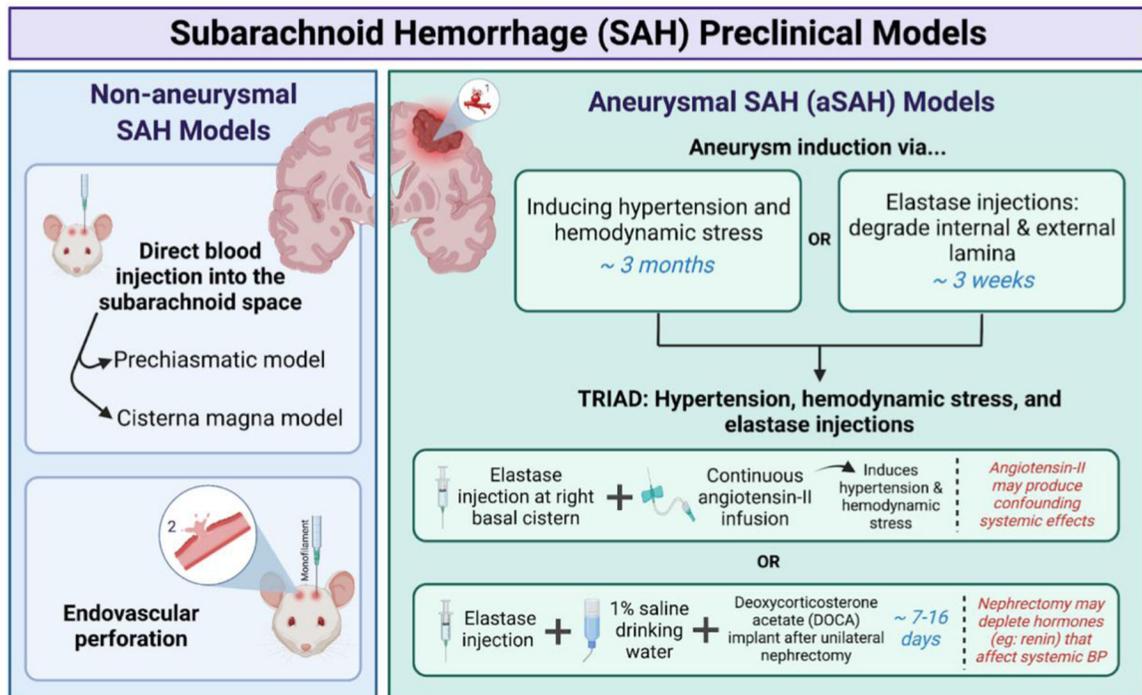
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**Figure 1.**  
Inflammatory changes leading to aneurysm formation



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**Figure 2.**  
Summary of current preclinical SAH models

**Table 1**

Summary of inflammatory cytokines studied in articles concerning SAH

Paper	Year	IL-1ra	IL-1a	IL-1b	IL-6	IL-8	IL-10	IL-18	TNFa	ICAM-1	HMGB-1	TGF-b1
Mathiesen et al. [35]	1993				x							
Kikuchi et al. [36]	1995		x	x	x	x			x			
Mathiesen et al. [37]	1997	x	x	x					x		x	
Osuka et al. [38]	1998				x	x						
Gruber et al. [39]	2000	x	x	x					x			
Fassbender et al. [40]	2001			x	x				x			
Takizawa et al. [41]	2001			x	x							x
Kwon et al. [42]	2001			x	x				x			
Hendryk et al. [43]	2004			x	x							
Nakahara et al. [44]	2009				x	x			x			
Sarrafzadeh et al. [45]	2010				x							
Graetz et al. [46]	2010				x							
Hanafy et al. [47]	2010								x			
Mellergard et al. [48]	2011			x	x		x					
Sokol et al. [49]	2015										x	
Hollig et al. [50]	2015				x					x		
Niwa et al. [51]	2016				x		x					
Wu et al. [52]	2016				x				x			
Chaudhry et al. [53]	2017				x							
Garcia et al. [54]	2017						x					
Duris et al. [55]	2018			x	x				x			
Lv et al. [56]	2018			x				x	x			
Vlachogiannis et al. [57]	2019				x							
Chaudhry et al. [58]	2020						x					
Ridwan et al. [59]	2021				x							

IL-1ra, Interleukin-1 receptor antagonist; IL-1a, interleukin-1A; ICAM-1, intercellular adhesion molecule-1; HMGB1, high-mobility group box-1; TGFb1, transforming growth factor beta-1.