Journal of Clinical Neuroscience 21 (2014) 28–32

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Review

The role of vascular remodeling and inflammation in the pathogenesis of intracranial aneurysms

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ARTICLE INFO

Article history:
Received 23 June 2013
Accepted 12 July 2013

Keywords:
Aneurysms
Inflammation
Matrix metalloproteinases
Vascular remodeling

ABSTRACT

While the mechanisms triggering pathogenesis of intracranial aneurysms have not been fully elucidated, different mechanisms have been proposed ranging from hemodynamic mechanisms to genetic predispositions. One mechanism that has been thoroughly explored is the physiological and pathological vascular remodeling that occurs in conjunction with inflammatory reactions resulting in the initiation and progression of these lesions. Both hemodynamic stimuli and vascular inflammation can trigger a series of biochemical reactions resulting in vascular smooth muscle cell apoptosis and migration causing thinned, dilated areas of the cerebral vasculature. In addition, an imbalance between extracellular matrix remodeling proteins, such as matrix metalloproteinases and their inhibitors, can result in accelerated degradation of the internal elastic lamina and the adventitial layers, further weakening the vessel. While these processes occur under normal physiological conditions, situations that alter their balance such as inflammation caused by cigarette smoking or cocaine usage or hypoxia induced under chronic hypertensive conditions can alter the delicate balance of these reactions potentiating pathological remodeling and aneurysm development. The present study represents a thorough literature review of the vascular remodeling and inflammatory components to aneurysmal pathogenesis.

1. Introduction

Intracranial aneurysms are a cerebrovascular disorder with significant neurological risk and high rates of morbidity and mortality. Aneurysms are arterial lesions defined by thinned, dilated regions of the vessel wall. Histopathologically, the defining characteristics of aneurysmal genesis and propagation are disappearance of the internal elastic lamina (IEL), thinning of the tunica media, and subsequent remodeling and degradation of extracellular matrix (ECM) proteins throughout the vessel wall. Pathological and angiographic techniques reveal that approximately 3.6–6.0% of the population over age 30 have unruptured intracranial aneurysms [1]. Rupture of these lesions resulting in subarachnoid hemorrhage (SAH) has an overall mortality of approximately 40 to 50% and approximately one-quarter of cerebrovascular deaths are the result of ruptured aneurysms [2].

Risk factors predisposing aneurysm formation include cigarette smoking, hypertension, heavy alcohol consumption, cocaine usage, familial history, ethnicity, sex and age. In particular, cigarette smoking has been demonstrated to raise the relative risk of SAH to between 1.9 and 5.2 and some studies have demonstrated dose dependent risks [3–5]. Some mechanisms through which cigarette smoking and cocaine usage cause aneurysm formation are hypothesized to be secondary to inflammatory effects on the vasculature [6].

While the detailed pathological mechanisms of intracranial aneurysm formation and rupture have not been completely elucidated, inflammation can activate vascular smooth muscle cell (VSMC) apoptosis and migration, as well as ECM remodeling proteins which accelerate the rate of protein degradation weakening the arterial wall [7]. One group of proteins that is of particular interest is the matrix metalloproteinases (MMP) that are the main regulators of ECM remodeling and are capable of destroying both collagen and elastin [8,9].

Determining how vascular and ECM remodeling and inflammation interact in aneurysm formation could help shed light on preventing the pathogenesis of cerebral aneurysms pharmacolo gically or through alterations in lifestyle. Additionally, further knowledge could help prevent the occurrence of SAH and limit the devastating neurological effects of this common disorder. The present study represents a compilation of current literature surveying the underlying vascular remodeling and inflammatory mechanisms causing aneurysm formation and growth.

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http://dx.doi.org/10.1016/j.jocn.2013.07.004

2. Physiological and pathological vascular remodeling

Pathological conditions altering normal blood flow in the cerebral vasculature can initiate vascular remodeling characterized by VSMC apoptosis and migration, accelerated degradation of ECM constituents, and inflammation compromising the structural integrity of the vessel and causing local dilation of the wall [3]. One of the primary pathological findings in cerebral aneurysms, the disappearance of the medial layer of smooth muscle in the arterial wall, is caused by signals that initiate apoptosis or induce migration of these cells to other areas of the wall. Apoptosis of VSMC is fundamental to normal vascular development and remodeling, as well as the development of numerous pathological conditions, such as atherosclerosis, restenosis, and aneurysms.

In order to closely examine the progressive deterioration of the media during aneurysm pathogenesis, Konda and colleagues ligated the common carotid arteries in rats, exposing one group of rats to aneurysm-inducing hypertensive conditions for 3 months and another group for 6 months [10]. This technique allowed researchers to observe the histological changes in arteries classified at various stages of pathological development. It was found that just after the disappearance of IEL, VSMC density remained similar to controls; however, the cells became disarranged. These changes are observed prior to dilation of the vessel. As the early aneurysm continued to progress, the wall began to dilate and thin as VSMC numbers decreased and cells exhibited volume reduction and morphological changes. Finally, as the aneurysm became more dilated and reached near full growth, most VSMC disappeared. This work showed the progressive thinning of the media, decreased density and number of VSMC, and irregularity in cellular morphology and organization occurring during aneurysm formation.

Furthermore, Konda and colleagues used nuclear DNA labeling techniques and electron microscopy to demonstrate that these changes were the result of apoptosis of VSMC [10]. Arterial tissue samples from control and experimental rats were treated with TdT-mediated dUTP-biotin nick end labeling (TUNEL) stain, a technique designed to label fragmented DNA and identify apoptotic cells. It was shown that vessels not undergoing aneurysmal genesis exhibited virtually no apoptotic cells, while groups of vessels that were exhibiting changes consistent with aneurysm development were found to contain apoptotic VSMC. Additionally, as aneurysm formation progressed, the mean number of apoptotic cells decreased demonstrating that VSMC apoptosis is a key process in the initial destruction of the vessel wall. These findings were further solidified using electron microscopy to visualize structural characteristics unique to apoptotic cells including cell shrinkage, chromatin condensation, dense actin fibers, budding of cytosolic and nuclear components into membrane-bound apoptotic bodies, and phagocytosis of VSMC by neighboring cells.

Hemodynamic stimuli and inflammatory reactions are among the primary occurrences that are thought to induce VSMC apoptosis in aneurysmal pathogenesis. Flow-dependent nitric oxide (NO) release inhibits VSMC proliferation and NO may actually induce apoptosis via mechanisms that increase cell death receptor expression [11]. By increasing the number of these receptors, the opportunity for other inflammatory factors to bind these receptors and induce apoptotic cascades increases. Also, NO may initiate apoptosis by activation of caspase 3, a molecule involved in apoptotic signaling pathways specifically responsible for cleavage of intracellular substrates that are used to maintain cell vitality, as well as DNA fragmentation, chromatin condensation, and apoptotic body formation [12]. Mechanical stretch has also been demonstrated to induce apoptosis through the activation of a transcription factor, p53, which inhibits cell growth through induction of a cyclin-dependent kinase inhibitor [13]. Finally, inflammation in the vascular wall caused by endothelial damage and infiltration of leukocytes, monocytes, and macrophages into the vascular wall induces the release of cytokines, such as interleukin-1β (IL-1-β), interferon γ, and tumor necrosis factor α (TNF-α), which bind to death receptors and initiate signaling cascades triggering apoptosis in VSMC [12,14,15].

Inflammatory responses leading to VSMC apoptosis can also be initiated by oxidative stress induced by chronic hypertension. Under normal physiological conditions, when the metabolic demand of the surrounding tissue increases, resistance vessels dilate to supply adequate oxygen. During chronic hypertension, vessels remain in a constricted state or are partially stenosed, which prevents the tissue from receiving the oxygen it needs creating hypoxia which causes the production of free radicals that can destroy endothelial function and induce inflammatory responses. Particularly, when oxygen becomes low the concentration of superoxide radicals in the cell increases and increases production of hydrogen peroxide and peroxinitrate through superoxide dismutase. Hydrogen peroxide causes the upregulation of nuclear factor-kappa B (NF-κB), a transcription factor that increases expression of intercellular adhesion molecules and inducible NO synthase. The transcription of these molecules increases leukocyte infiltration and inhibits VSMC proliferation. Additionally, peroxynitrite diffuses into the nucleus destroying the cellular DNA and preventing its repair, beginning the processes involved in VSMC death and inducing further inflammation. Cocaine also induces oxidative stress which not only initiates inflammatory reactions, but also causes damage to endothelial cells further up-regulating adhesion molecules, via NF-κB and allowing leukocyte infiltration.

In addition to apoptosis, VSMC migration occurs in normal vascular remodeling in response to vascular injury and pathological signals. During normal vascular development, the migration of VSMC precursors is stimulated by the release of platelet-derived growth factor (PDGF) which triggers the collection of smooth muscle progenitor cells around an endothelial cell tube [16]. There are many groups of molecules that act as promigratory or antimigratory signals, such as small amines, peptide growth factors, cytokines, and ECM components, and release of these signals can be influenced by hemodynamic stresses [17]. This evidence provides reason to believe that pathological alterations of blood flow in the brain can trigger the release of signaling molecules promoting migration away from the site of the aneurysm or inhibiting migration to the site.

Although it has long been known that subintimal migration of VSMC occurs in many arterial diseases resulting in narrowed arteries, it has only recently been observed and documented that this occurs in aneurysm pathogenesis [18]. Jamous and colleagues demonstrated that endothelial injury from hypertension in the cerebral circulation causes migration of VSMC and formation of a localized inflammatory zone. Damage to the endothelial surface and exposure of subendothelial structures triggers the release of growth factors and proinflammatory molecules from the platelets in the blood, such as PDGF. As stated above, PDGF is a promigratory molecule and release of this molecule could trigger migration of VSMC away from the site of damage where this molecular signal can penetrate deeper layers of the vessel wall. Prior to vessel dilation, it was observed that this migration initially occurs at the luminal surface and appears as endothelial swelling which could partially occlude the vessel, creating hypoxia and subsequent generation of free radicals, potentiating the process of VSMC apoptosis and medial thinning. Also, as the arterial wall begins to dilate, the migration of VSMC occurs away from the initial site of swelling, causing further thinning of the wall [18].

Another mechanism of interest in the formation and progression of aneurysms is the role of ECM remodeling proteins. The