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Three Phases of Vascular Smooth Muscle Cells in Cerebral Aneurysms: Early Hyperproliferative, Intermediate Dedifferentiated & Late Hypoproliferative

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Abstract

Vascular smooth muscles play a vital role in the growth and propagation of cerebral aneurysms. These highly dynamic cells, characterized by a high degree of plasticity, show structural and functional modifications in response to external environmental influences. Following sustained endothelial injury, vascular smooth muscles avail a new functional capability characterized by proinflammatory, and promatrix remodeling abilities, losing the normal contractile and synthetic ability. Switching of differentiated vascular smooth muscle cells into undifferentiated inflammatory vascular smooth muscle cells followed by eventual apoptosis decreases the production of collagen, a vital component of the structural matrix, rendering the vessel wall less responsive to cyclical hemodynamic pressure swings and more susceptible to aneurysmal dilatation and rupture. The goal of this review is to understand the structural and functional modifications that vascular smooth muscle cells undergo during the natural course of cerebral aneurysm formation with a particular focus on the contributory molecular mechanisms.

Introduction

A major contributor in providing structural support in arteries are the vascular smooth muscle cells (VSMCs). Normally, these cells contract to help transport blood, oxygen, and other nutrients throughout the cardiovascular system. However, during arterial disease states, VSMCs can undergo a phenomenon known as a phenotypic switch which is characterized by a decrease in the expression of contractile proteins that are responsible for contraction of the blood vessels and an increase in matrix metalloproteinases, enzymes that break down components of the vascular extracellular matrix. The breakdown of vascular structures leads to dilation and rupture of the blood vessels. When this occurs, cerebral aneurysms follow. Some causes of the phenotypic switch phenomenon of VSMCs, include the presence of pro-inflammatory factors (growth factors, cytokines, etc.) and changes in the structures of vascular extracellular matrices. When VSMCs undergo the switch from contraction-promoting contractile cells to a more proliferative and synthetic type of cell, many factors that lead to the development of cerebral aneurysms start to become more apparent. One such effect is the increase in vessel wall calcification in which the now synthetic VSMCs utilize vesicular structures to transport calcium phosphate crystals into the blood vessels causing arterial hardening. An acute or early disturbance of blood flow causes high wall stress, which is accompanied by the migration of smooth muscle cells from the tunica media into the tunica intima. In this case, the VSMCs proliferate heavily, thicken the intima, and deposit collagen in an effort to better balance the high hemodynamic pressures. Subsequently, unbalanced hemodynamic stresses cause the contractile phenotype to regress. By increasing endothelial production of nitric oxide and prostacyclin, normal laminar flow patterns induce protective vasodilatory and anti-inflammatory smooth muscle cell responses. A proinflammatory-induced phenotypic modulation of vascular smooth muscle cells results in a sequential weakening of the vascular wall, predisposing to further growth and rupture. Vascular smooth muscle cells may eventually fail to express any functional phenotype after dedifferentiation into more primitive vascular smooth muscles devoid of contractile function but with proinflammatory and promatrix functional capabilities.

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Discussion

Vascular smooth muscle plasticity

Vascular smooth muscle cells are stromal cells located in the tunica media of blood vessels [1]. VSMCs, in adults, are derived from precursor progenitor cells situated in the adventitia and media layers of blood vessels [2,3]. Premature vascular smooth muscle cells situated in arteries stabilize the structural integrity of the blood vessel during repeated cycles of contraction and relaxation to allow the vascular wall to adapt to hemodynamic flow alterations [4]. Further, vascular smooth muscle cells synthesize extracellular matrix, thus providing the vessel wall with structural integrity to prevent vessel deformation in response to high wall pressure [5]. The mature VSMC is characterized by an elongated spindle shape, coinciding with its main contractile function [1]. Mature VSMCs are characterized by expression of smooth muscle 22 alpha, smooth muscle alpha actin, smooth muscle myosin heavy chain, h1-calponin, and smoothelin, indicating the presence of a fully differentiated smooth muscle cell with a contractile phenotype [6-9]. In particular, myocardin influences vascular smooth muscle cell differentiation by transcriptionally activating CArG components present in the promoter regions of gene sequences of differentiated VSMC protein markers. CArG components of promoter regions of differentiated SMCs modulate expression of SMC gene expression leading to the promotion of a differentiated VSMC phenotype. More importantly, VSMCs exhibit a significant degree of plasticity marked by their ability to alter their phenotype from a nonmigratory contractile cell to a migratory synthetic cell. As a consequence, VSMCs temporarily transition from a differentiated contractile phenotype responsible for modulating of vessel wall diameter to a dedifferentiated synthetic phenotype with loss of differentiated SMC markers, such as smooth muscle myosin heavy chain, smooth muscle 22 alpha, and smooth muscle alpha actin. The ability of VSMCs to switch their phenotype depends on surrounding environmental factors in the vessel wall. In response to vessel wall injury, most commonly, VSMCs switch their phenotype in a compensatory measure to better adapt to their surrounding microenvironment and facilitate vessel wall repair. [10] Following the advent of dedifferentiation, VSMCs are marked by a loss of their contractile proteins, increase in extracellular matrix production, and a hyperproliferative response defined by inward migration to the tunica intima. Upon repair of the vascular injury, the dedifferentiated synthetic, proliferative and migratory VSMC reprogrammes to a stable, contractile phenotype [10]. VSMC dedifferentiation, in the normal vascular wall, represents a transient phenomenon, occurring at only a low rate, allowing sufficient vascular wall repair without the advent of untoward vascular wall derangements.

Vascular smooth muscle cell intimal migration and proliferation lead to an early adaptive increase in synthetic function

Vascular smooth muscle cells are highly differentiated contractile cells located in the arterial media that maintain the structural integrity of the arterial wall through the production of matrix proteins- namely collagen and elastin [11]. Collagen, the main matrix component produced by VSMSs confers a protective role by counteracting the continual cyclic hemodynamic stresses subjected upon the vessel wall. When subjected to the cyclical hemodynamic stresses within the arterial system, VSMCs respond by a compensatory increase in the production of collagen [12]. The initial behavior of vascular smooth muscle cells in response to an untoward perturbation of hemodynamic stress begins with an early adaptive increase in its synthetic ability to produce collagen [12,13]. High wall stress, triggered by an acute/early perturbation of blood flow, is attended by a migration of smooth muscle cells from the tunica media into the tunica intima. Prolonged and continual exposure to increased wall shear stress activates mitogen activated protein kinase pathways in the vascular smooth muscle cell leading to increased vsmc proliferation [14]. Likewise, heightened vasoconstrictor responses in cerebral aneurysms stimulate protein kinase C and ROCK molecular pathways initiating VSMC hypertrophy and a strengthened VSMC contractile response leading to increased ECM synthesis accompanying an initial hyperproliferative vascular remodeling process characterized by increased vascular rigidity [15]. Here, the VSMCs undergo extensive proliferation resulting in intimal thickening and lay down collagen, all in an attempt to better counterbalance the excessive hemodynamic stresses. Intimal thickening, represented by intimal hyperplasia with a dense concentration of smooth muscles in the intima, is the dominant response to an early disturbance in cerebral hemodynamics, bearing with it many similarities to the early vascular changes noted in atherosclerotic vessels [11]. Kosierkiewicz, et al., used immunohistochemistry techniques to substantiate a hyperfunctional role for vascular smooth muscles during early stages of cerebral aneurysms by corroborating similar changes observed in atherosclerotic lesions. Here, immunohistochemical analysis of small, immature early cerebral aneurysms displayed intimal hyperplasia with an increased density of smooth muscle cells in the intima [16]. Intimal thickening with an increased number of smooth muscle cells found in the intima postulates the migration of smooth muscle cells from other regions of the vascular wall in response to endothelial injury. To further corroborate this, Frosen, et al., performed studies on murine models of saccular aneurysms and confirmed the findings on earlier studies of intimal hyperplasia by identifying discrete regions of thickened intimal pads. In addition, the source for these cells was identified as the vascular wall rather than the bone marrow [17].

Mechanisms governing the precise response of vascular smooth muscle cells to endothelial injury following hemodynamic stresses are still primitive in its development; however few studies have delineated plausible mechanisms. Vascular smooth muscle cells respond to unbalanced excessive hemodynamic signals via perception of increased mechanical stretch input-mechanoreceptors [18,19]. Subsequently, an intracellular signaling cascade begins with heightened perception of mechanosensitive stretch of vascular smooth cells by integrins and notch receptors [20]. Following mechanosensitive input and activation, integrin and notch receptors convey input downstream to protein tyrosine

kinase 2, subsequently activating downstream Ras homolog A-ROCK1 dependent signaling pathways [21]. Increased flux through the RhoA/ROCK1 signaling pathway evokes migration of vascular smooth muscle cells from the tunica media into the tunica intima [22]. In addition to initiating vascular smooth muscle cell migration, activation of integrin upregulates expression of the Src/Ras/MEK ½ pathway, resulting in an eventual activation of the proinflammatory transcription factor-NFKB ligand [23,24]. Heightened activation of the NF-KB ligand facilitates increased inflammatory cell adhesion, tissue trafficking and structural remodeling of the arterial through the elaboration of proteases and cytokines. One cytokine of particular importance in orchestrating the subsequent response of VSMCs to hemodynamic stress following intimal migration is platelet-derived growth factor. Vascular smooth muscles when exposed to platelet derived growth factors undergo extensive proliferation manifesting as intimal hyperplasia [25]. Secondary to migration of VSMCs from the media into the intima and subsequent intimal proliferation, VSMCs acquire a new synthetic phenotype characterized by an overabundance of endoplasmic reticulum and Golgi apparatus with a corresponding loss in their normal contractile phenotype [26]. The abundance of endoplasmic reticulum and Golgi apparatus-prime mediators of the intracellular protein machinery- provide a structural basis for increased secretion of proteoglycans and collagen- structural proteins of the vascular wall [26].

Combinedly, these studies provide substantiating evidence for the hyperfunctioning of smooth muscle cells in the early stages of a cerebral aneurysm with an 1) Increase in synthetic function, characterized by increased production of collagen, and 2) Increase in intimal thickening, noted by intimal hyperplasia with a dense concentration of smooth muscle cells in the intima and 3) Thinning of the media, Corresponding with a loss of smooth muscle cells in the media.

Proinflammatory mediators & KLF4 induce dedifferentiation of vascular smooth muscle cells leading to a loss of vsmc differentiation markers

Structural change in the arterial media followed by loss of this layer appears to be conducive to the development of cerebral aneurysms. Meng, et al., demonstrated that thinning of the arterial tunica media facilitates aneurysm formation and progression [26]. Hazama and Hashimoto, et al., further elucidated a possible cause for tunica media thinning by suggesting that vessel wall changes in aneurysms arise as a consequence of underlying degenerative changes affecting vascular smooth muscle cells localized in the arterial media [27]. Further examination into the molecular crosstalk initiating destructive vascular smooth muscle changes begins with phenotypic modulation of vascular SMCs. Phenotypic modulation of VSMCs from a mature contractile phenotype, defined by a predominant expression of contractile proteins, including smooth muscle myosin heavy chain and smooth muscle alpha actin, to a dedifferentiated pro-inflammatory, pro-synthetic phenotype, characterized by a heightened expression of inflammatory factors and MMP, is the initial step [28-36]. Merei and Gallyas postulated that phenotypic VSMC modulation marked early histological evidence of cerebral aneurysm development, whereas normal parallely orientated spindle shaped VSMCs reorganize themselves into spider cells. Moreover, they observed that VSMCs that underwent a phenotypic modulation demonstrate a loss of their normal spindle shape arrangement, aligning with the contractile function of differentiated VSMCs, and shift towards a loosely adherent spider-like cellular arrangement with decreased cellular adhesion, now with non contractile properties [31]. Similarly, Kilic, Pera, & Sibon, et al., confirmed a phenotypic modulation of VSMCS in intracranial aneurysms by observing a reduced expression of contractile proteins- alpha actin-in ruptured and unruptured cerebral aneurysms compared to normal arteries [29,33,34]. Additionally, Nakajima demonstrated that phenotypic modulation of VSMCs is a well defined phenomena occurring in the walls of intracranial aneurysms using immunohistochemical techniques [32]. They observed that aneurysmal walls displayed a suppressed expression of contractile proteins, indicative of the presence of a differentiated VSMC. In an interesting observation, derived from the same study, ruptured IA aneurysms were shown to have a more significant VSMC phenotypic switching compared to unruptured IA aneurysms, with control arteries demonstrating minimal VSMC structural modifications [32].

Following prolonged endothelial injury, vascular smooth muscle cells undergo a structural rearrangement to a pro-inflammatory, pro synthetic remodeling phenotype. Vascular smooth muscle cells are remarkable in their ability to undergo structural reorganization from differentiated cells capable of contractile properties to undifferentiated cells suited for a pro-inflammatory, pro-matrix remodulative functionality [13]. A vital component of such an aggressive functional transformation is the loss of differentiation markers expressed by vascular smooth muscle cells. Fully differentiated vascular smooth muscle cells are defined by the expression of protein markers: smooth muscle 22 alpha, smooth muscle alpha actin, SM myosin heavy chain, h1-calponin and smoothelin [7-9]. Downregulation of these protein markers, consequently, leads to a de-differentiated phenotype with erratic remodeling properties [29,32,33,35]. Loss of VSMC differentiation markers-SM alpha actin, SM-myosin heavy chain, calponin and h-caldesmon- and a repression of contractile phenotype and cellular adhesion are universally agreed upon as a marker of VSMC dedifferentiation. Loss of VSMC differentiation markers is subsequently attended by an increase in cell cycle stimulating proteins (calmodulin, cyclins) and ECM remodeling proteins (collagen I, matrix metalloproteinases) [37]. The dedifferentiated VSMC phenotype, also, is marked by a loss of cytoskeletal and contractile proteins such as desmin. Desmin, a cytoskeletal intermediate filament of SMCs, is responsible for maintaining the structural integrity of SMCs [38]. In experimental models of arterial injury, including atherosclerosis and atherosclerotic plaques, fewer desmin-positive SMCs were observed, proposing a loss of desmin in response to arterial injury [10,39-41]. Finally, Mimata, et al., noted that SMCs in the aneurysmal wall failed to positively stain for desmin, a marker of differentiated contractile VMSCs [42].

Although the precise molecular mechanisms triggering dedifferentiation of vascular smooth muscle cells remains to be more clearly elucidated, various pieces of literature from experimental observations serve to offer some insight. Unbalanced hemodynamic stresses mediate a regression of the contractile phenotype. Normal laminar flow patterns invoke protective vasodilatory and anti-inflammatory smooth muscle cell responses by increasing endothelial production of nitric oxide and prostacyclin. More so, normally derived endothelial nitric oxide exerts several non-atherosclerotic and non-inflammatory actions resulting in downregulation of VCAM-1 and MCP-1 expression, suppression of MMPs, activation of vasodilation and decreased platelet aggregation, and repression of VSMC proliferation [43]. In response to unbalanced turbulent flow patterns, endothelial cells upregulate expression of chemokines (IL-8 and MCP-1) and cell adhesion molecules (VCAM-1, ICAM-1) procuring a proinflammatory phenotype. Upregulation of cell adhesion molecules and inflammatory chemokines on the endothelial cell surface facilitates inflammatory cell (monocytes) adhesion and transcellular migration subsequently resulting in the production of corresponding cytokines-TNFa and IL-1B [44]. As suggested by Chaoulini, murine rat models of cerebral aneurysm formation demonstrated proinflammatory changes suggestive of vascular smooth muscle cell phenotypic modulation as evidenced by decreased expression of contractile genes, increased expression of pro-inflammatory, pro-matrix remodeling genes (MCP-1, VCAM-1), and increased expression of transcription factors (NF-KB) [11,13]. Building on this, NF-KB p50 subunit deficient mice displayed a paucity of arterial inflammatory changes with an attendant disinhibition of aneurysmal development. Further, Aoki, et al., reached similar conclusions- NF-KB blockade prevents aneurysmal formation and development of an inflammatory foci within the arterial wall [45].

Additionally, during states of vascular injury, including atherosclerosis and perturbed hemodynamic stresses, phenotype modulation of the VSMC is mediated by KLF4 [46-48]. KLF4, a cellular dedifferentiation transcription activator, regulates the dedifferentiation of different cells, including smooth muscle cells [49,50]. More specifically, KLF4 is a pluripotent factor capable of mediating reprogramming of differentiated somatic cells - smooth muscle cells- in response to specific proinflammatory cytokines released by inflammatory cells [51,52]. Following ischemia and injurious insults, cerebral blood vessels upregulate expression of proinflammatory mediators, including TNF-alpha amongst others [53]. Several *in vitro* and *in vivo* studies, subsequently, corroborate the role of TNF-alpha in modulating the development of inflammatory vascular smooth muscle cells from observations of reduced expression of contractile genes- myocardin, SM-alpha-actin, smooth muscle heavy chain and smooth muscle 22 alpha- and increased expression of proinflammatory genes-MMP 3, MMP 9, MCP-1, VCAM-1, and IL-1B following exogenous TNF administration. Reversible changes in proinflammatory and contractile genes expression following the use of 3, 6 dithiothalidomide, a TNF-inhibitor, strengthen the argument for a proinflammatory mediated vascular smooth muscle phenotypic switch. TNF-alpha is exceedingly implicated in mediating VSMC phenotypic modulation through its interaction with KLF4. The role of TNF-alpha in mediating VSMC phenotypic switch is suggested by the abundant over-expression of TNF-alpha in aneurysms [54]. Similarly, in human aneurysms TNF-alpha was found to be significantly upregulated in the aneurysmal dome. The demonstration of a marked upregulation of TNF-alpha in the thinnest portion of the aneurysm lends further support to VSMC dedifferentiation, with the newer VMSC unable to resist hemodynamic forces due to inflammatory mediated vascular remodeling processes. Prior studies have documented that TNF-alpha orchestrates the downregulation of SMC differentiation markers as well the myocardin promoter, in order to allow phenotypic modulation of VSMCs. Wamhoff, et al., demonstrated that VSMC phenotypic modulation depends on expression of the G/C repressor element of the SM-22 alpha gene promoter sequence [47]. M Ali, et al., demonstrated that SMC phenotypic modulation is dependent on a similar mechanism. Here, TNF-alpha markedly upregulated KLF-4 expression with a concurrent decrease in myocardin, a VMSC differentiation marker. In the same study, chromatin immunoprecipitation assays demonstrated that KLF4 directly binds to specific promoter regions of myocardin following treatment with TNF-alpha. Predictably, KLF4 inhibition with the use of siRNA reverted VSMC dedifferentiation [13]. Salmon, et al., used chromatin immunoprecipitation assays to more clearly delineate the influence of KLF4 on SMC phenotypic switching [55]. They proposed that KLF4 binds to the G/C repressor component of the SM22 alpha gene leading to the recruitment of histone deacetylase 2 and eventual repression of SMC protein SM22 alpha expression, thereby initiating VSMC phenotypic switch [55]. Moreover, Yoshida, et al., observed that knockout mice devoid of KLF4 developed a temporary delay in the downregulation of differentiated SMC markers following vascular injury [50].

Fas Ligand - Fas receptor interactions, P53 and caspase activation drive vascular smooth muscle cell apoptosis leading to structural weakening and further aneurysmal dilation/rupture

A central determinant in the transformation of unruptured cerebral aneurysms into ruptured cerebral aneurysms is the modulation of the vascular smooth muscle cells in the tunica media of cerebral arteries. The net consequence of a proinflammatory induced phenotypic modulation of the vascular smooth muscle cells is a sequential weakening of the vascular wall predisposing to further growth and rupture. Following dedifferentiation into more primitive vascular smooth muscles devoid of contractile function with proinflammatory and promatrix functional capabilities, vascular smooth muscle cells may ultimately fail to express any functional phenotype. The loss of smooth muscle in the arterial wall, in cerebral aneurysms, initiates the process of thinning of the medial layer of the cerebral aneurysm. Thinning of the aneurysmal wall, predominantly in the tunica media, is explained by histological observations of a decrease in the number of smooth muscle cells [56,57]. Several pieces of experimental laboratory evidence support

a role of loss of VSMC following sustained endothelial cell injury and arterial wall inflammation. Merei and Gallyas, et al., in their histopathological analysis of smooth muscles in the vascular wall following chronic inflammation observed a transformation of spindle-like smooth muscle cells normally tightly arranged in a parallel configuration next to one another to loosely adherent separated cells resembling a "spider-like pattern" [31]. Similar conclusions can be drawn by Kondo, et al., investigations into the implications of vascular smooth muscle cell loss in murine rat models in the development and growth of cerebral aneurysms. Morphological analysis revealed ultrastructural changes- shrinkage and fragmentation of cells, clumping together of chromatin, and packaging of cytosolic and nuclear cellular components into apoptotic bodies- consistent with apoptosis of medial smooth muscle cells during aneurysm development. Kondo, et al., ligated the common carotid arteries of rats in an attempt to more closely elucidate the process of vascular wall remodeling of cerebral aneurysms in response to hypertensive conditions. Following the initial loss of the internal elastic lamina in cerebral aneurysms, the next target was the vascular smooth muscle cells. The progression of cerebral aneurysm development from the early stage was characterized by a decrease in the number of vascular smooth muscles, strongly correlating with the degree of vessel dilation. With continued dilation and immediately prior to rupture, a significant quantity of the vascular smooth muscle cells had disappeared, thereby highlighting that loss of vascular smooth muscle cells represents an important transition of cerebral aneurysms towards increased growth and expansion [56]. Further, Hara and Kondo, et al., supported previous observations of vascular smooth muscle cell loss with cerebral aneurysm growth by demonstrating that the presence of apoptotic cells localized to human or rat cerebral aneurysm walls was directly linked with a higher probability of cerebral aneurysm rupture [58]. Further, they attributed the disappearance of arterial wall smooth muscle cells in cerebral aneurysms to apoptosis of these cells. Bennett, et al., observed that rat vascular smooth muscle cells undergo apoptosis during the course of cerebral aneurysm development [59]. Likewise, Bjorkerud, et al., demonstrated that human vascular smooth muscle cells undergo apoptosis in order to facilitate further cerebral aneurysm growth [60]. Moreover, Aoki, et al., demonstrated that VSMC's displayed a marked impairment of collagen synthesis in experimental aneurysm models, proposing a loss of VSMCs during the development of cerebral aneurysms [37].

Vascular smooth muscle cells modulate continued vessel wall remodeling in cerebral aneurysms by undergoing apoptosis leading to structural weakness of the arterial wall and rendering the vasculature more susceptible to outward dilation under the influence of hemodynamic stresses [61-63]. Abnormal wall shear stress exerted by the growing end cerebral aneurysm drives the expression of a proatherogenic, proinflammatory expression of the vascular endothelial cells, influencing smooth muscle cell behavior. Low wall shear stress upregulates expression of leukocyte specific adhesion molecules on the vascular endothelium leading to vascular wall inflammation. Arterial wall inflammation begins with induction of VCAM-1 and ICAM-1 expression on the endothelial cell surface, permitting leukocyte adhesion [64]. VCAM-1, a granulocyte specific adhesion protein responsible for mediating inflammatory cell adhesion, is upregulated on both SMCs and endothelial cells in experimental aneurysm models [65]. Interestingly, VCAM-1 expression is most potently upregulated in humans following aneurysmal rupture [66]. Upregulation of VCAM-1 facilitates inflammatory cell adhesion to the vascular wall followed by consequent endothelial damage, leukocyte transcellular migration, and macrophage infiltration into the vessel wall leading to the release of proinflammatory cytokines (IL-1 and Tumor necrosis Factor). Infiltrating inflammatory cells- T lymphocytes and macrophages- represent a source of Fas Ligand, which interact with inflammatory cytokines (TNF and IL-1) released by these cells triggering apoptosis of vascular smooth muscle cells [67,68]. Apoptosis of vascular smooth muscle cells is mediated by a complex interaction between the Fas receptor and its downstream ligand, the Fas-ligand (Fas L). The Fas receptor has frequently been observed in regions of the vessel wall demonstrating the presence of inflammation with T-lymphocytes and macrophages [69]. Similarly, Fas receptor is expressed on both inflammatory cells and vascular smooth muscle cells in the arterial wall. Interaction of Fas Ligand with its downstream receptor the Fas Receptor upregulates the production of proinflammatory cytokines such as IL-1 and TNF-alpha by the surrounding inflammatory cells [11,13,34,70]. Consequently, macrophage and T-lymphocyte release of proinflammatory cytokines initiate vascular smooth muscle cell apoptosis [61-63]. In line with this, the vascular media of cerebral aneurysms commonly demonstrate an increased expression of IL-1 and IL-1B knockout mice are protected against cerebral aneurysm development. Mice devoid of IL-1 were observed to display a decreased occurrence of destructive aneurysmal wall changes and apoptosis by mediating expression of apoptotic promoting caspase molecules [71]. Additionally, released proinflammatory cytokines (IL-1 and TNF-alpha) act as chemotactic agents to increase activation of inflammatory cells with the consequent release of destructive matrix proteases such as matrix metalloproteinase involved in vessel wall breakdown in cerebral aneurysms. MMPs have commonly demonstrated to be over expressed in human cerebral aneurysms, with a greater predominance in ruptured aneurysms compared to unruptured aneurysms [72]. Further, blockade of MPPS inhibited propagation of aneurysmal growth, decreasing the likelihood of aneurysmal rupture [73].

Apart from directly mediating vascular smooth muscle cell apoptosis in cerebral aneurysms, proinflammatory cytokines also influence expression of NO. Specifically, these cytokines induce the synthesis of iNOS, a potent inhibitor of eNOS, alternatively initiating vascular smooth muscle cell apoptosis [74]. Decreased production of eNOS and aberrant production of iNOS leads to non physiological alterations of the arterial wall, one of which entails increased apoptosis of vessel wall smooth muscle cells leading to a marked decrease in cellular density of these cells and vessel wall thinning [58,75-77]. The net outcome is an inhibition of vascular smooth muscle proliferation and an induction of vascular

smooth muscle cell apoptosis. Supraphysiological levels of NO exerts its deleterious effects on vascular smooth muscle cells by activating p53, upregulating FAS, and activating c-Jun-N-terminal kinase [78]. Additionally, supraphysiological levels of iNOS trigger apoptosis through the activation of caspase 3, a signaling molecule involved in apoptosis, as well as damage to cellular nucleus with features suggestive of fragmentation of DNA and condensation of chromatin [79]. Idel, et al., demonstrated the use of phytanic acid, a fatty acid, initiated apoptosis of vascular smooth muscle cells through the upregulation of iNOS expression and induction of tumor necrosis factor-a synthesis [80]. Alternatively, hemodynamic influences on nitric oxide expression influence vascular smooth muscle cell apoptosis in cerebral aneurysms. Namely, low wall shear stress inside the growing end of cerebral aneurysms inhibits endothelial expression of eNOS, reducing production of functional quantities of nitric oxide [81]. Loss of endothelial derived nitric oxide inhibits vascular smooth muscle cell proliferation, shifting the balance towards inducing apoptosis of these cells by a mechanism involving increased surface expression of cellular apoptotic receptors [82]. Indirect evidence for the role of decreased eNOS in mediating vascular smooth muscle cell apoptosis in cerebral aneurysms comes from analyzing the influence of reactive oxygen species on the development of cerebral aneurysms. In the arterial vasculature, oxidative stress initiates nascent cerebral aneurysm formation through several actions on the vascular endothelium and adjacent vascular smooth muscle cells. Free radicals, in particular, have been demonstrated to initiate vascular smooth muscle cell apoptosis with a corresponding reduction of collagen synthesis and consequent structural weakening of the arterial wall [83-85]. The normal response of the arterial wall to states of increased oxidative stress is a compensatory increase in antioxidants responsible for neutralizing the reactive oxygen intermediates and minimizing vessel wall damage. This intrinsic antioxidant property of the arterial vasculature depends, to a large extent, on normal endothelial-derived nitric oxide. Here, oxidative stress mediates endothelial injury, upregulation of leukocyte adhesion molecules and chemotactic cytokines, activation of matrix metalloproteinases, ultimately culminating in a loss of endothelial-derived nitric oxide, thereby initiating smooth muscle cell apoptosis [86].

Loss of functional smooth muscle cells by apoptosis decreases the stability of the connective tissue matrix through reduced production of collagen and elastin. The decline in elastin and collagen renders the vascular endothelium more susceptible to hemodynamic stresses, setting into motion a complex process of arterial remodeling. Aneurysm formation, therefore, stems from arterial structural remodeling with an important contributory and detrimental precedent triggered by vascular smooth muscle cell apoptosis. Loss of functional smooth muscle cells by apoptosis decreases the stability of the connective tissue matrix through reduced production of collagen and elastin. The decline in elastin and collagen renders the vascular endothelium more susceptible to hemodynamic stresses, setting into motion a complex process of arterial remodeling. Aneurysm formation, therefore, stems from arterial structural remodeling with an important contributory and detrimental precedent triggered by vascular smooth muscle cell apoptosis.

Conclusions

The early adaptive increase in the vascular smooth muscle cells' synthetic ability to generate collagen marks the start of their first behavior in response to hemodynamic stress. The response of VSMCs is a compensatory increase in collagen formation in response to the cyclical hemodynamic stressors within the vascular system. Vascular smooth muscle cells undergo a structural rearrangement to a pro-inflammatory remodeling phenotype after sustained endothelial damage. Regression of the contractile phenotype is mediated by unbalanced hemodynamic stressors. A proinflammatory-induced phenotypic modification of the vascular smooth muscle cells results in a cumulative weakening of the vascular wall, making it more prone to future development and rupture. Through decreased production of collagen and elastin, loss of functioning smooth muscle cells through apoptosis reduces the integrity of the connective tissue matrix. The vascular endothelium becomes increasingly vulnerable to hemodynamic stressors when elastin and collagen levels decrease, which starts a complicated process of arterial remodeling. In conclusion, the remodeling of the arterial structure leads to aneurysm formation, with the death of vascular smooth muscle cells acting as a major contributor and unfavorable effect.

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Conflict of Interest

None.

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