The vasa vasorum are a specialized microvasculature that play a major role in normal vessel wall biology and pathology. Under physiological conditions, the adventitial vasa vasorum take up molecules that are transmitted from the blood to the adventitia by mass transport through the arterial wall. The adventitia is the primary early site for vessel wall response to arterial injury that occurs on the luminal side. The vasa vasorum expand in response to the injury, which alters vessel homeostasis. This review focuses on the impact the vasa vasorum expansion has on development of vascular pathology, particularly neo-intima development and growth of atherosclerotic plaque.

Vasa Vasorum and the Adventitia
The adventitia, the outermost layer of the vessel wall, has received considerable attention in recent years. It contains a heterogeneous population of cells, including macrophages, T cells, B cells, dendritic cells, progenitor cells, and fibroblasts that can differentiate into myofibroblasts. It also contains an adrenergic nervous system, a lymphatic network, and vasa vasorum, a specialized microvasculature that plays a major role in normal vessel wall biology and pathology that is the subject of the present review.

Under physiological conditions, the adventitial vasa vasorum and lymphatic vessels take up molecules that are transmitted from the blood to the adventitia by mass transport through the arterial wall. Vascular injury at the luminal side of the vessel wall significantly impacts the adventitia by convection of soluble factors, microparticles and macroparticles, mediators such as products of oxidation, tissue cytolysis, and proteolysis from the intima to the adventitia by hydraulic conductance. As a result, the adventitia becomes the primary early site for the vessel wall response to arterial injury, which includes myofibroblast migration into the vessel wall, inflammatory cell accumulation, and expansion of vasa vasorum. The latter process has the potential of affecting many aspects of the vessel homeostasis, including the development of neo-intima and growth of atherosclerotic plaque.

Vasa Vasorum Structure/Function
The vasa vasorum are specialized vessels found in the vessel wall. Two types of arterial vasa vasorum (AVV) are recognized. The first type are the vasa vasorum interna, which originate from the intima or media and branch into the adjacent artery wall. The second type are the vasa vasorum externa, which are found primarily in the adventitia at its border with the media and originate from various anatomic locations. These include the brachiocephalic and coronary arteries in the ascending aorta, the intercostal branches in the descending thoracic artery, the lumbar and mesenteric arteries in the abdominal aorta, and bifurcation segments of epicardial vessels in coronary arteries.

In addition to its function of transporting molecules from the blood to the adventitia, the vasa vasorum externa respond to oxygen and nutrient needs of the adventitial and outer medial layers when the supplies are not met by diffusion from the luminal surface. This occurs when the vessel wall exceeds a certain thickness, which in mammals is 0.5 mm, or 29 lamellar units. Under these circumstances, the vasa vasorum externa become angiogenic and expand deeper into the media. However, vasa vasorum neovascularization may be induced by stimuli other than vessel wall thickness. These include inflammation and atherosclerosis that results in extensive vascularization of mouse arteries even though the murine arterial wall does not exceed the 0.5 mm diffusion limit. Atherosclerosis studies in pigs demonstrated that growth of the vasa vasorum in coronary arteries occurs before vessel wall thickening and plaque development.

Differences in the vasa vasorum structure in nondiseased versus diseased arteries were noted as early as 1984. Although low-resolution x-ray images failed to detect the vasa vasorum in the absence of human coronary artery atherosclerotic plaque, a dense microvascular plexus was evident in diseased vessels. Subsequently, high-resolution microscopic computed tomography images of coronary arteries in hypercholesterolemic pigs showed that the longitudinal vasa vasorum externa (first-order vasa vasorum) originate from the coronary artery and branch to form a circumferential plexus (second-order vasa vasorum). Normal hearts have significantly greater first-order than second-order vasa vasorum density (ratio 3:2). However, in hypercholesterolemic pigs, the second-order vessel density is 2-fold greater than the first. Furthermore, whereas vasa vasorum branching patterns in nondiseased porcine vasculature show a dichotomous tree structure with a hierarchical branching pattern similar to the vasculature of systemic circulation structure, vasa vasorum in diseased arteries present a much more disorderly image.

High-resolution confocal microscopy demonstrated the presence of adventitial vasa vasorum structural differences.
hierarchy in hypercholesterolemic low-density lipoprotein receptor–deficient/apolipoprotein B100–only mice (LDLR−/−ApoB100/100) mice. The vasa vasorum tree consists of a large main vessel from which smaller vessels branch; these in turn branch to form a plexus that occupies the space between 2 larger vessels. The vessels within the plexus collapse in response to an angiogenesis inhibitor, whereas the larger vessels of the tree remain intact. The vasa vasorum are also detectable in chow-fed mice but do not exhibit a branching pattern. The cumulative data from studies using various animal models and imaging modalities clearly indicate that under disease conditions, AVV expand, frequently in a disorderly fashion.

The venous vasa vasorum (VVV) drain the arterial wall into companion veins34 that are parallel to the AVV feeder or into the largest branches of the main vein, where they penetrate every 5 to 15 mm.35 There are distinct qualitative differences between the AVV and the VVV.36,37 The AVV are many fewer in number, with diameters ranging from 11.6 to 36.6 μm compared with the VVV diameter range of 11.1 to 200.3 μm. Vascular corrosion casts coupled with scanning electron microscopy show that the VVV change course at acute angles and form kinks, constrictions, and outpouchings. This spatial distribution enables the VVV to withstand vessel wall distension with increased blood pressure or vessel stretching without a dramatic effect on the VVV function.37

The autonomic nervous system is thought to control blood flow in the human saphenous vein vasa vasorum.35,37 Use of the saphenous vein for coronary artery bypass graft surgery is associated with spasm of vascular smooth muscle cells (SMCs) of the vein that can develop into vein-graft disease.38,39 The conventional surgical technique for saphenous vein harvest involves stripping the connective tissue from the vein, which injures the adventitial autonomic nerves and vasa vasorum37,38 and may trigger venospasm.40 Moreover, studies suggest that the VVV play a role in vein vasorelaxation; any VVV damage during saphenous vein harvesting may impair flow-induced vasodilation in the graft.39,41,42

Adventitial Angiogenic Growth Factors

Studies performed in hypercholesterolemic LDLR−/−ApoB100/100 mice suggest that fibroblast growth factor-2 (FGF2) is the primary angiogenic growth factor expressed in the adventitial vasa vasorum. Quantitative polymerase chain reaction measured an 8-fold increase in FGF2 mRNA copy number in the hypercholesterolemic mice compared with age- and sex-matched chow-fed mice, whereas vascular endothelial growth factor mRNA was at control levels.41 Furthermore, fluorescein isothiocyanate–labeled lectin infusions in hypercholesterolemic mice have shown that FGF2 is associated with a well-developed vasa vasorum plexus. On the other hand, the vasa vasorum in nondiseased mice do not form a plexus, and diffuse FGF2 staining is observed in the matrix. An FGF2/perlecan complex appears critical for specifying FGF2 spatial distribution.42 It remains to be determined whether FGF2 provides a pattern for the vasa vasorum to form a plexus-like network or whether the vasa vasorum form a plexus and then produce and release FGF2 into the matrix. In 1 study, FGF2 delivered to the adventitia of apolipoprotein E–deficient (ApoE−/−) mice results in vasa vasorum expansion and accelerated plaque progression.43

Another potentially important player is a placental growth factor (PIGF), a member of the vascular endothelial growth factor family of proteins. Delivery of placental growth factor into the carotid artery periadventitial space in hypercholesterolemic rabbits significantly increased adventitial neovascularization and macrophage accumulation,44 whereas the absence of placental growth factor significantly reduced plaque size and macrophage number in ApoE−/−PIGF−/− mice.45

Adventitial Vasa Vasorum and the Stem/Progenitor Cells Niche

Recent studies have suggested the existence of a stem/progenitor cell niche in the adventitia of arterial wall. Such a niche is thought to contain mural cell progenitors, which may be positioned to respond to injury in the vessel wall to promote either repair or disease.47

Accumulation of SMCs in the neointima of atherosclerotic plaque has been thought to be triggered by their transformation from a quiescent, contractile state to a proliferating, synthetic phenotype, which enables them to migrate from the media to the intima. Recent studies have demonstrated that a DNA demethylation protein, ten-eleven translocation-2 (TET2) enzyme, plays a significant role in reversible SMC differentiation in human SMCs, human arterial tissue, and mouse models of atherosclerosis and injury-induced intimal hyperplasia.48 Mechanistic studies show that TET2 regulates SMC phenotype by converting 5-methylcytosine to unmethylated cytosine, which results in DNA demethylation and activation of key SMC differentiation genes; knockdown of TET2 increases expression of synthetic SMC phenotype markers. Furthermore, knockdown studies indicate that TET2 differentially regulates the chromatin accessibility of contractile and dedifferentiation genes. The collective data suggest that TET2 is a master epigenetic regulator of SMC differentiation.49

An alternative theory suggests that adult SMCs in the plaque originate from a variety of sources that include adventitial vessel wall progenitor cells49 and can migrate from the adventitia into the media and intima after arterial injury.50 The labeling of adventitial cells in rat common carotid arteries with β-galactosidase before a balloon catheter injury demonstrated their appearance in the media then the intima 7 and 14 days later.51 Analysis of cellular content of the adventitia in aortic roots of ApoE−/− mice demonstrates the presence of cells with a number of stem cell markers, including Sca-1. The latter are thought to have the ability to differentiate into SMCs when stimulated with platelet-derived growth factor-BB4 and to contribute to progression of atherosclerotic lesions in ApoE−/− mice.4 Adventitial vasa vasorum may be a conduit for mobilized progenitor cells into the intima, where they differentiate into SMCs.52

Regulators of Vasa Vasorum Expansion

Vasa vasorum are thought to proliferate and grow to meet the nutritional needs of the artery’s outer medial layer when metabolic needs exceed the amount of oxygen that can diffuse from the luminal blood.21,22 The hypoxia-inducible transcription
factors HIF-1 and HIF-2 induce transcription of hypoxia-responsive genes\(^5\) such as proangiogenic vascular endothelial growth factor,\(^5\) which promotes vessel growth. Hypoxia also stimulates increased expression of key enzymes required for heparan sulfate chain synthesis in microvascular endothelial cells. This leads to creation of new binding sites for FGF2,\(^5\) a potent mediator of endothelial cell growth and vasa vasorum stability.\(^3\)

Experimental evidence in hypercholesterolemic pigs\(^1\) suggests that the vasa vasorum begin to sprout before aortic wall thickening and that the sprouting is in turn preceded by infiltration of inflammatory cells into the adventitia. One likely possibility is that infiltrating adventitial inflammatory cells secrete a number of angiogenic growth factors, including vascular endothelial growth factor. Periadventitial fat may also contribute to this process via stimulation of inflammation\(^2\) or release of angiogenic growth factors.\(^3\)

The impact of cardiovascular risks on vasa vasorum dynamics and adventitial remodeling differs in various experimental models.\(^6\) Hypercholesterolemia is associated with an increase in vasa vasorum density, whereas hypertension is marked more by an increase in adventitial matrix,\(^6\) and diabetes mellitus may in fact impair vasa vasorum growth.\(^6\) Furthermore, the absence of increased neovascularization in diabetic animal models contrasts with findings in patients with diabetes mellitus, whose plaques demonstrate elevated microvessel density, inflammatory cell content, and intra-plaque hemorrhage.\(^6\) The latter is thought to be the major driver for atherosclerosis progression because of an increase in a hemoglobin-haptoglobin complex, which impairs hemoglobin clearance and amplifies oxidative stress and endothelial cell dysfunction.\(^6\)

**Vasa Vasorum and Vascular Inflammation**

As summarized 6 years ago, there is an “outside-in” theory whereby vascular inflammation begins in the adventitia and advances to the media and intima\(^6\) (Figure 1). This theory opposes the long-held “inside-out” concept that monocytes infiltrate the vessel wall from the luminal side. Among the arguments favoring the outside-in theory are the presence of resident immune cells in the adventitia and the homing of macrophages to that site.\(^1\) Additionally, balloon angioplasty experiments in pig coronary arteries demonstrate that the adventitia is the primary site for acute inflammation after mechanical vascular injury.\(^1\) These results are consistent with reports from human studies that show inflammatory cell infiltration from the adventitia to plaque and formation of adventitial lymph follicles that contain plasma cells.\(^6\) P-selectin and vascular cell adhesion molecule 1 are upregulated in vasa vasorum endothelial cells very soon after balloon angioplasty.

![Figure 1. Depiction of inside-out and outside-in theories of vascular inflammation.](http://circ.ahajournals.org/)

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**Mulligan-Kehoe and Simons**

**Arterial V asa Vasorum**

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injury, which provides a means for inflammatory cells trafficking in and out of the adventitia.17

The outside-in concept is further demonstrated in a model of aortic transplantation between histocompatible rat strains.71 Thirty days after transplantation, the vasa vasorum in the adventitia of aortic allografts mount a robust angiogenic response. Electron microscopy was used to detect leukocytes infiltrating the adventitial vasa vasorum of the rejected graft, thus indicating that the vasa vasorum serve as a conduit for inflammatory cell entry into the graft during the rejection process.

Data in humans also support this scenario. A study of coronary artery segments from 99 patients with and without atherosclerotic plaque demonstrated expression of the leukocyte adhesion molecules vascular cell adhesion molecule 1, intercellular adhesion molecule 1, and E-selectin predominantly on the intimal vasa vasorum rather than the arterial luminal endothelium.22 The presence of T cells, B cells, macrophages, and dendritic cells in the adventitia has also been documented in humans,2,70,73 mouse models of atherosclerosis,1,16,74 and pigs after coronary artery angioplasty.17 Aortas of children, who have not developed atherosclerosis, have leukocytes surrounding the adventitial vasa vasorum.75 Studies in mice show that adventitial immune cells are present in noninflamed wild-type mice, and their numbers increase in hypercholesterolemic ApoE−/− mice, with T cells being the most predominant over the course of plaque development,1,16 whereas at the same time, such accumulation is not reflected in the intima. The adventitial T-cell dominance in mice is consistent with human studies.76 Clustered immune cells in the mouse adventitia structurally organize into aortic tertiary lymphoid structures,1,2,16,76 found predominantly at sites that border the elastic lamina adjacent to atherosclerotic plaque.76 Although the function of aortic tertiary lymphoid structures has not been identified clearly, there is some evidence that the aggregates are sites for selection of specific subsets of B cells.2

The inside-out theory has stimulated numerous investigations into the role of resident adventitial immune cells and the growth of the vasa vasorum in relationship to atherosclerosis. The studies indicate that they play an important role in disease progression and require ongoing investigations to determine their relevance in human atherosclerosis.

**Vasa Vasorum and Neointima Formation**

Neointima formation after mechanical vascular injury such as balloon angioplasty or in the setting of vessel wall disease such as atherosclerosis is the key event responsible for much of the morbidity and mortality. Neointima in these settings is composed of proliferating SMCs and extracellular matrix (ECM). The key event has long been held to be the proliferation of medial SMCs.77 Recent studies suggest additional possibilities for the origin of neointimal SMCs and the factors that control it.

Although expansion of vasa vasorum has been linked to neointima formation, the detailed molecular link between these events has been elusive.78 Studies in normal rabbit and rat carotid arteries showed that the addition of angiogenic growth factors to the vessel adventitia resulted in expansion of adventitial vasculature and neointima formation even in the absence of any endovascular trauma. Conversely, inhibition of growth factor signaling reduced it.79–80 Microcomputed tomography imaging further demonstrates a direct correlation between the computed tomography–determined extent of adventitial angiogenesis and the extent of neointima.9,81 Thus, there is a strong correlation between the extent of the adventitial vasculature and the extent of neointima formation. Overall, the entire process appears to be composed of 2 parts: angiogenesis-independent growth, likely driven by SMC proliferation in the media, and angiogenesis-dependent growth (Figure 2).

The latter, characterized by the appearance of extensive adventitial vasculature (and, by extension, vasa vasorum) correlates with the influx of blood mononuclear cells and local inflammation. One of the consequences of inflammation is the development of endothelial-to-mesenchymal transition (EndMT). During EndMT, normal endothelial cells acquire mesenchymal characteristics that include changes in cell shape and polarity; expression of mesenchymal markers such as α-smooth muscle actin, calponin, and vimentin; and decline or outright loss of endothelial marker expression. As a result, endothelial cells transform into cells of mesenchymal lineages, including SMCs and fibroblasts, and begin producing large amounts of ECM, including collagen.82,83

This sequence of events occurs during normal embryonic development, in which EndMT plays a crucial role in formation of cardiac valves.84–86 However, it also occurs in a number of pathological settings in adult tissues, including myocardial infarction,87 fibrosis,88–90 portal hypertension,91 vascular malformations,92 and transplant rejection.92 The final common event leading to EndMT is activation of transforming growth

![Figure 2. Angiogenesis-dependent and -independent development of neointima. Correlation between the extent of neointima formation that occurs after vessel injury in the presence and absence of adventitial angiogenesis. Note formation of some neointima even when adventitial angiogenesis is fully suppressed and a linear relationship between the growth of neointima and the extent of adventitial angiogenesis once it starts. I/M indicates intima/media. Adapted with permission from Khurana et al.45](http://circ.ahajournals.org/doi/10.1161/CIRCULATIONAHA.114.014237)
factor (TGF-β) signaling, which plays a central role in driving endothelial cells to mesenchymal fate.88,94 Subsequent intracellular events are less clear but probably involve both canonical (SMAD2)82,91 and noncanonical TGF signaling pathways, changes in microRNA (miRNA) expression,94,95 and activation of expression of the Snail gene.96 Events leading to endothelial TGF-β signaling activation are less clear. A number of processes have been implicated, including shear stress,97–99 stimulation with endothelin-1,100 Notch,100 and caveolin deficiency,101 among others.

One of the recently identified mechanisms regulating TGF-β signaling in the endothelium involves fibroblast growth factor (FGF)–mediated suppression of TGF receptor expression. Baseline FGF signaling is responsible for the maintenance of let-7 miRNA expression in normal endothelial cells. Let-7 miRNAs target expression of a number of TGF family members, including FGFR1; in the absence of FGF input, let-7 levels decline and FGFR1 levels increase, thus enabling activation of TGF-β signaling.82 The importance of this FGF/TGF signaling link lies in the fact that the continuous FGF signaling input needed to suppress TGF-β signaling activation depends on expression of the key endothelial FGF receptor, FGFR1.82 Interestingly, certain inflammatory conditions associated with production of tumor necrosis factor-α, interleukin 1β, or interferon-γ result in a profound decline of FGFR1, activation of TGF-β signaling, and the onset of EndMT (Figure 3). Thus, this mechanism likely explains the previously reported link between inflammation and Endo-MT.83,102–104 Atherosclerosis, a chronic inflammatory disease potentiated by tumor necrosis factor-α1 and interferon-γ,106 is associated with infiltration of T cells and macrophages into diseased blood vessel wall; thus, EndMT may well be an important contributor to altered cellular and ECM composition in the vessel wall that promotes atherosclerotic disease progression.

With these considerations in mind, it is reasonable to suggest that expansion of adventitial vasculature, including vasa vasorum, in inflammatory settings provides the endothelial substrate and the milieu needed for EndMT. Functionally, induction of EndMT contributes to accumulation of SMCs, which leads to formation of neointima, extensive deposition of collagen, and other ECM proteins that lead to fibrosis and a potential for greater accumulation of white blood cells and platelets because of increased expression of various adhesion molecules (Figure 3).

**Vasa Vasorum and the Atherosclerotic Plaque**

**Vessel Permeability**

Increased permeability is an early indicator of vascular integrity breakdown, which is controlled by endothelial cell junction stability. Early in the angiogenic process, vessels become

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**Figure 3.** Endothelial to mesenchymal transition and neointima development. Fibroblast growth factor (FGF) signaling input via FGF receptor(s) maintains expression of let-7 microRNAs that suppress expression of transforming growth factor (TGF)-β and its receptors. Initiation of TGF signaling leads to endothelial-to-mesenchymal transition (EndMT), which is manifested by expression of mesenchymal markers, deposition of extracellular matrix, and increased expression of endothelial adhesion molecules, which leads to neointima formation. ECM indicates extracellular matrix; ERK, extracellular signal-regulated kinase; FGF-R, fibroblast growth factor receptor; FRS2, fibroblast growth factor receptor substrate 2; ICAM-1, intercellular adhesion molecule 1; IFN-γ, interferon-γ; IL-1β, interleukin 1β; SMCs, smooth muscle cells; TGFβR1, TGF-β receptor 1; TNF-α, tumor necrosis factor-α; and VCAM-1, vascular cell adhesion molecule 1. Reprinted with permission from Chen et al.82

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**Figure 4.** Intraplaque vasa vasorum in human coronary artery. The vasa vasorum identified with endothelial marker *Ulex europaeus I* are shown in (A) the adventitia and extending through the media and into the intima (magnification, ×20) and (B) the border area of the necrotic core (magnification, ×40). Note the multiple branches of the vasa vasorum in panel B. Reprinted with permission from Virmani et al.110
permeable, and this increase in permeability enables deposition of serum proteins that are key factors in establishing a provisional matrix to facilitate proangiogenic growth factor and inflammatory cell adhesion and migration. Local and systemic inflammation increase vascular permeability. In the case of vasa vasorum, increased permeability enables entry of inflammatory cells, red blood cells, and lipoproteins during their angiogenic expansion phase.\textsuperscript{107,108} Examination of atherosclerotic coronary arteries from human autopsy donors shows that vasa vasorum microvessels invading the media from the adventitia lack mural cell coverage.\textsuperscript{109} Furthermore, the interendothelial contact at endothelial junctions is either incomplete or absent in 76% of the vessels. These factors make vasa vasorum inherently more permeable.

Analysis of serial sections of coronary lesions from victims of sudden death with plaque rupture demonstrates that an increase in intraplaque microvessel density is associated with plaque hemorrhage, a characteristic of unstable plaque\textsuperscript{110} (Figure 4). The immature, fragile vasa vasorum found in the plaque are leaky and highly susceptible to hemorrhage. Extravasated erythrocytes and their membranes are a source of free cholesterol and hemoglobin iron, which may put the plaque at high risk of rupture because of their ability to elicit an influx of macrophages, which would normally remove the red blood cells.\textsuperscript{111} However, relative influx and efflux of phagocytic macrophages and clearance of apoptotic macrophages in advanced atherosclerotic plaque are defective. As a result, apoptotic macrophages, which are also a source of free cholesterol, accumulate in the necrotic core along with free cholesterol from erythrocytes. This promotes a proinflammatory response, increased infiltration of macrophages that release proteases, which causes damage to surrounding cells.

Additionally, extravasated red blood cells exposed to plaque lipid undergo hemolysis followed by oxidation of released hemoglobin, which leads to release of free heme or iron. The interaction of hemoglobin with plaque lipid causes further lipid oxidation, which results in endothelial upregulation of heme oxygenase-1, which opens the heme porphyrin ring, producing redox active iron that further stimulates plaque lipid and endothelial toxicity.\textsuperscript{112} These events, in combination with the enlarged necrotic core, create stress on the fibrous cap, making it prone to rupture.\textsuperscript{113} This concept is supported by serial magnetic resonance imaging in patients showing that intraplaque hemorrhage is correlated with a growth of plaque and lipid-rich necrotic core volumes.\textsuperscript{114}

Plaque regression is an elusive goal that has defied the efforts of many investigators. Although a variety of approaches have been tried, none have been uniformly successful. Inhibition of plaque neovascularization, for instance, reduction in the number of vasa vasorum feeding the plaque, is high on the list of potential targets. One unanswered question is when such treatment should be administered. Vasa vasorum in the media are more mature than the microvessels in the intimal plaque, which lack an SMC layer, tight junctions, and a continuous basement membrane\textsuperscript{110} and are susceptible to rupture and hemorrhage.\textsuperscript{110} Antiangiogenic molecules would be expected to induce involution of the unstable vessels lacking pericytes and SMCs before affecting more mature vasculature.

Although there are no studies that directly demonstrate that inhibition of the vasa vasorum reduces plaque volume (primarily because of resolution limitations of noninvasive imaging modalities), there are correlative data that suggest that inhibition of the angiogenic vasa vasorum limits the infiltration of inflammatory cells into the plaque.\textsuperscript{31} Such a reduction in plaque macrophage content would have multiple plaque-stabilizing effects.\textsuperscript{115}

If inhibition of neovascularization is the goal, a critical consideration is delivery of a therapeutic agent that restores abnormal vasa vasorum to normal, mature vessels. Recent studies in cancer patients have shown that antiangiogenic therapy can
prune and regress the angiogenic vessels, reverting the remainder to normal maturation. In particular, normalization of tumor vasculature reduces microvessel density and vascular diameter, whereas perivascular cell coverage increases. This results in decreased vascular permeability and interstitial fluid pressure, thereby improving tumor oxygenation and reducing its growth. The same phenomena have been observed in cancer patients treated with antiangiogenic molecules. This concept also applies to the vasa vasorum. Studies with an antiangiogenic protein, rPAI-1, demonstrated that it significantly reduces plaque area and volume, inflammatory cell number, and necrotic core size while increasing vascular lumen diameter. Of note, rPAI-1 treatment only inhibits the microvasculature, whereas the larger first-order vasa vasorum are left intact (Figure 5).

Potential Therapeutic Approaches Based on Inhibition of Vasa Vasorum Growth

The discovery of angiogenesis inhibitors and development of genetically modified mice have enabled testing of the effects of these inhibitors on vasa vasorum neovascularization and corresponding plaque growth. Many of these inhibitors are cleavage products of an extracellular protein, several of which have been shown to inhibit vasa vasorum neovascularization. Endostatin, a cleavage product of type XVIII collagen, inhibits plaque growth and vasa vasorum density in atherogenic ApoE−/− mice by blocking macrophage uptake of low-density lipoprotein, a primary cause of atherosclerosis. Angiostatin, a plasminogen cleavage product, inhibits vasa vasorum density in atherogenic ApoE−/− mice, which correlates with reduced infiltration of mononuclear cells into the plaque. A truncated isoform of plasminogen activator inhibitor 1, rPAI-1, inhibits angiogenic vasa vasorum and promotes plaque regression in atherogenic LDLR−/−/ApoB100/100 by altering the basement membrane/ECM composition in favor of vasa vasorum collapse. The rPAI-1 protein opposes native angiogenic vasa vasorum stability by disrupting the FGF2/perlecan interactions that are required for trafficking of resident inflammatory and progenitor cells to the media and intima; then serve as a source of endothelial cells for Endo-MT, thus fueling the neointima expansion. This emerging biology suggests that interventions aimed at regression of the vasa vasorum and restoration to its normal architecture will likely have a therapeutic effect and may potentially alter the natural history of diseases such as atherosclerosis and restenosis.

Conclusions

The accumulating data link the expansion of the adventitial vasa vasorum to neointima formation and atherosclerotic plaque development and growth, whereas their regression is accompanied by a reduction in neointima and plaque growth, yet the precise mechanism linking these processes remains elusive. This is in part because both vascular diseases and the adventitial response to injury are multifactorial, and hence, vasa vasorum can affect a variety of events. They can facilitate blood and oxygen delivery to the vessel wall, thereby setting the milieu for growth and expansion; function as highways for trafficking of resident inflammatory and progenitor cells to the media and intima; then serve as a source of endothelial cells for Endo-MT, thus fueling the neointima expansion. This emerging biology suggests that interventions aimed at regression of the vasa vasorum and restoration to its normal architecture will likely have a therapeutic effect and may potentially alter the natural history of diseases such as atherosclerosis and restenosis.

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Disclosures

None.

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dependent mechanism.


