The Adventitia
A Dynamic Interface Containing Resident Progenitor Cells

Mark W. Majesky, Xiu Rong Dong, Virginia Hoglund, William M. Mahoney, Jr., Guenter Daum

Abstract—Conventional views of the tunica adventitia as a poorly organized layer of vessel wall composed of fibroblasts, connective tissue, and perivascular nerves are undergoing revision. Recent studies suggest that the adventitia has properties of a stem/progenitor cell niche in the artery wall that may be poised to respond to arterial injury. It is also a major site of immune surveillance and inflammatory cell trafficking and harbors a dynamic microvasculature, the vasa vasorum, that maintains the medial layer and provides an important gateway for macrophage and leukocyte migration into the intima. In addition, the adventitia is in contact with tissue that surrounds the vessel and may actively participate in exchange of signals and cells between the vessel wall and the tissue in which it resides. This brief review highlights recent advances in our understanding of the adventitia and its resident progenitor cells and discusses progress toward an integrated view of adventitial function in vascular development, repair, and disease. (Arterioscler Thromb Vasc Biol. 2011;31:1530-1539.)

Key Words: aortic diseases • growth factors • morphogenesis • vascular biology

For many years, the tunica adventitia has been regarded as a collagen-rich connective tissue containing fibroblasts and perivascular nerves (Figure 1A). We now know that that definition is far too limiting. Recent studies show that the adventitia functions as a dynamic compartment for cell trafficking into and out of the artery wall, it participates in growth and repair of the vessel wall, and it mediates communication between vascular endothelial cells and smooth muscle cells (SMCs) and their local tissue environment (Figure 1B).1–3 The adventitia is also where formation and regression of microvessels that penetrate and nourish the intimal and medial layers are controlled.4–5 The adventitia contains lymphatic vessels and autonomic nerves, and it plays a critical role in control of lumen size by regulation of medial smooth muscle tone and control of inward (negative) and outward (positive) wall remodeling responses.9–13 Moreover, the adventitia contains resident populations of macrophages, T-cells, B-cells, mast cells, and dendritic cells that carry out important surveillance and innate immune functions in response to foreign antigens.14–17 Of particular interest is the accumulating evidence that the adventitia functions as a stem/progenitor cell niche in the artery wall that maintains both endothelial and mural cell progenitors that may be poised to respond to arterial injury.18–22 Therefore, the adventitia consists of a complex community of interacting cell types, and abundant evidence now indicates that a better understanding of molecular mechanisms for homeostasis, repair, and disease of the vessel wall will require a greater appreciation of the integrated role of the adventitia with the intimal and medial layers. Toward this goal, we review the current literature and highlight recent findings on this important but understudied tissue layer.

Development of the Adventitia
Major advances have been made in our understanding of the molecular and genetic pathways that control vascular development.23,24 Most of those advances have come from studies focused on the early steps including vasculogenesis, vascular patterning, and formation of venous and lymphatic endothelial cells. However, we still know very little about later stages of vascular development, and particularly lacking are studies on formation of the adventitia. In broad outlines, development of the vessel wall begins with the formation of angioblasts and their self-assembly into a primitive vascular plexus.25 The vascular plexus then undergoes a complex remodeling process to yield a network of large and small arteries, veins, and lymphatic vessels that constitute a functional embryonic circulatory system.26–28 Vascular plexus remodeling is closely followed by investment of nascent vessel walls with SMCs and pericytes.29–32 The interaction of endothelial cells with mural cells initiates maturation responses in both cell types32–34 that are coupled with inputs from biomechanical forces acting on these cells to shape continued development of the vessel wall.35–37
mechanisms act to terminate the iterative layering process that drives formation of the tunica media? The answer to that question provides an important starting point to understand how the adventitia is formed. A recent analysis of tunica media formation in mice hypomorphic for elastin sheds some light on this question.\(^\text{38}\) In elastin (Eln)-deficient mice, development of the aortic media is not significantly different from wild-type until embryonic day (E) 18.5, well after the time that the characteristic number of layers of SMCs is laid down (E15.5).\(^\text{38,45}\) Beginning at E18.5, Eln\(^{+/−}\) embryos exhibit elevated rates of SMC proliferation leading to formation of dramatically elongated and tortuous arteries with thickened walls that rapidly progress to vascular occlusion and perinatal death.\(^\text{46}\) In Eln\(^{+/−}\) embryos, the aorta develops normally until E18.5, after which additional layers of SMC and elastin are produced ectopically in the inner adventitial layer, whereas lumen diameter is preserved.\(^\text{38,45,47}\) The elastic lamellae that do form in these mice are thinner than those in wild-type mice. As Eln\(^{+/−}\) mice have a normal life span, the adaptations in arterial wall structure during the late fetal period appear to have distributed wall tension per SMC layer to approximately normal values and to restore arterial compliance to within the physiological range.\(^\text{38,47,48}\) These studies indicate that the characteristic number of SMC layers in the mouse thoracic aorta is established by E15.5, thus signaling the initiation of development of the aortic adventitia.\(^\text{38,45}\) What then is the cellular basis of compensatory wall structural changes that occur later in arterial development (E18.5 to birth) in elastin-deficient mice? Is this adaptive mechanism retained in at least some adult vessels, and on injury or pathological activation could it explain, for example, the dramatic wall remodeling responses described in pulmonary hypertension?\(^\text{49}\) Interest in these questions has been amplified by recent reports suggesting that the inner adventitia has properties of a progenitor cell niche in the artery wall, characterized by a restricted domain of sonic hedgehog (Shh) signaling (Figure 2).\(^\text{18–22}\) As discussed further below, resident progenitor cells expressing the stem cell antigen-1 marker (Sca1, also called Ly6A/E) have been isolated from the aortic adventitia that exhibit potentials to differentiate to vascular SMCs and pericytes in primary explant culture. Considering the clustering of these resident progenitor cells near the media-adventitia border (Figure 3) and their differentiation to SMCs in vitro,\(^\text{18,20,21}\) it is possible that the ectopic layers of SMC and elastin that appear in the inner adventitia of elastin hypomorph mice\(^\text{38,45,47}\) are derived from these resident progenitor cells. It will be of interest, therefore, to determine the number, localization, and fate of adventitial progenitor cells in elastin-deficient mice.

**Response of the Adventitia to Arterial Injury**

At this point, it is instructive to look back in time to see that these intriguing observations of resident progenitor cells in the adventitia may have been anticipated by earlier reports describing a role for the adventitia in arterial wound healing. The vessel wall has a substantial intrinsic capacity for wound repair. Under normal conditions, the artery wall in adult animals has very low to undetectable rates of endothelial cell or SMC proliferation. When subjected to overstretch injury,
However, proliferation rates in all layers of artery wall can increase more than 100-fold. Most animal models of intimal hyperplasia rely on injury to rodent arteries that lack the preexisting subendothelial intimal cells that are commonly present in human arteries. In rodent vessels, migration of medial SMCs to the intima is, therefore, thought to be essential to form a neointima during repair of arterial injury. Observations that medial cell proliferation precedes accumulation of intimal cells and that intimal cells express SMC marker proteins, including smooth muscle myosin heavy chain at undiminished levels. Of interest, neointimal SMCs from balloon-injured canine carotid arteries were morphologically and immunologically identical to type 2 cells.

Direct evidence for the capability of adventitial cells to migrate through the media and into the intima has been obtained by transplanting cells onto the adventitial side of an artery and monitoring movement of these cells following arterial injury. For example, adenoviral vectors expressing β-galactosidase were used to label adventitial cells before balloon catheter injury of rat common carotid arteries. β-Galactosidase-positive cells were observed within the medial layer at 3 days and in the neointima at 7 and 14 days after injury. Adenoviral-mediated delivery of Smad7, an inhibitory Smad that blocks transforming growth factor-β signaling, to the adventitia before balloon injury resulted in significant reductions in the number of β-galactosidase-positive cells in the neointima concomitant with reduced neointimal thickening. These findings suggest that cells originating in the adventitia migrate to the neointima and contribute to intimal thickening after arterial injury, at least in rodent arteries, and that transforming growth factor-β signaling plays an important role in one or more steps in this process. One adventitial cell type that may respond to arterial injury in this way is the adventitial fibroblast, based on many observations that these cells undergo phenotypic conversion to SMC-like myofibroblasts. In addition, an intriguing possibility is that Adventitia-derived Sca1+ cells from genetically marked donor mice and then transplanted those cells onto the outside of a vein graft placed into the arterial circulation. Adventitia-derived Sca1+ cells were found in the media at 2 weeks and in the intima at 4 weeks, where they no longer expressed Sca1 antigen and became immunopositive for SMC marker proteins. An early event observed following many forms of arterial injury is adventitial inflammation and an accumulation of monocytes and activated macrophages in the adventitia. This local inflammatory response may be necessary for downregulation of the ongoing adventitial niche signaling that maintains Sca1+ cells as progenitors, thus resulting in the “release” of these progenitor cells to adopt other cell fates. Inhibition of early leukocyte recruitment decreases injury-induced neointimal formation consistent with this possibility. Recent studies using inducible SMC-specific cre recombinase-mediated fate mapping approaches show that a majority of neointimal SMCs do indeed arise from medial SMCs in a femoral artery wire injury model in adult mice. However, important paracrine contributions to neointimal lesion growth can be made by numerically small or transient cell populations in vivo. Moreover, the adventitia is a rich source of reactive oxygen species and nitric oxide (NO). Reactive oxygen species production has been associated with...
increased adventitial fibroblast migration, extracellular matrix production, medial smooth muscle hypertrophy, and neointimal hyperplasia after arterial injury. Taken together, the adventitia may have 2 roles in neointimal lesion formation that are not mutually exclusive: (1) as a hub for recruitment of inflammatory cells that may directly stimulate medial SMC migration and proliferation, as well as disrupting ongoing adventitial niche signaling to enable the differentiation of resident progenitor cells toward a SMC-like fate; and (2) as a source of neointimal precursor cells that contribute to the cellular mass of developing neointimal lesions.

The Adventitia as a Stem/Progenitor Cell Niche in the Artery Wall

As mentioned above, in 2004, Hu et al reported that adult ApoE−/− mice harbor progenitor cell populations in the aortic root adventitia that differentiate to SMCs when exposed to platelet-derived growth factor-BB in vitro. These cells have the surface marker profile Sca1+, CD34+, c-kit+, Flk1− but are negative for the embryonic stem cell marker stage-specific embryonic antigen-1. When obtained from genetically marked Rosa26 donor mice and transferred onto the outside of an experimental vein graft that was then placed into the arterial circulation, adventitial Sca1-positive cells migrated through the media and were found in the graft neointima at 4 weeks, where they had downregulated Sca1 expression and were now SMC marker positive. By comparison, when genetically marked adventitial Sca1-negative cells (Sca1−, mostly fibroblasts) were grafted instead of adventitial Sca1+ cells, the majority of Sca1− cells remained clustered in the graft adventitia after 4 weeks, and they were only rarely found in the neointima. Thus, in this model, adventitial Sca1+ cells with a potential to form SMCs could migrate from the adventitia to vein graft neointima, differentiate to SMCs, and promote neointimal lesion growth. In 2006, Zengin et al reported a “vasculogenic zone” in adult human arteries that contains CD34+ progenitor cells capable of forming vascular structures in arterial ring explant cultures in vitro and promoting the formation of microvessels in transplantable tumor models in vivo. This “vasculogenic zone” is localized to a region between the media and the adventitia in human blood vessels that is reminiscent of the location in which Sca1+ cells were found in the aortic root of wild-type and ApoE−/− mice. Pasquonelli et al also reported finding CD34+ cells located between the media and the adventitia in human thoracic aortas and femoral arteries. Hoshino et al (2008) identified progenitor cells in the adventitia of human pulmonary arteries that express mesenchymal stem/progenitor cell markers but are negative for endothelial and hematopoietic cell markers. These progenitor cells differentiate to SMCs, osteogenic cells, and adipogenic cells in selective culture media in vitro. Campagnolo et al isolated CD34+/CD31− cells from human saphenous veins that express the stem cell marker Sox2 and display clonogenic and multilineage differentiation potential in vitro (discussed further below). Finally, Zorzi et al demonstrated that rat thoracic aorta contains adventitial macrophage-like cells, which function to support angiogenesis in an aortic ring assay, presumably by releasing vascular endothelial growth factor. A subset of these cells acquire an endothelial cell phenotype when cultured in the presence of vascular endothelial growth factor and formed capillary-like structures in a matrigel assay in vitro. These studies raise the possibility that adventitial progenitor cells may play a role in formation and maintenance of a microvascular network in the adventitia called the vasa vasorum (discussed further below).

In 2008, Passman et al reported that CD34+, Sca1+, c-kit−, Flk1−, CD140b+ cells cluster in a domain of Shh signaling...
that is restricted to the adventitial layer of artery wall (Figure 3). In E18.5 Shh−/− embryos, the number of adventitial Sca1+ cells (AdvSca1) in the aortic root is greatly diminished. Treatment of AdvSca1 cells in primary explant culture with Shh or the hedgehog (Hh) signaling antagonist cyclopamine provided evidence that Hh signaling mediates mitogenic and survival responses in these progenitor cells. Mouse aortic AdvSca1 cells appear to be a heterogeneous population with different potentials for cell differentiation. When freshly isolated from mouse thoracic aorta and placed into serum-containing culture medium, roughly 50% of the isolated AdvSca1 cells differentiate to SMC-like cells and form pericytes in matrigel assays in vivo. ≈25% proliferate and maintain a progenitor cell phenotype (ie, self-renewal), and the remaining 25% lose expression of Sca1 but do not acquire detectable levels of SMC marker proteins. A small percentage of AdvSca1 cells form osteogenic cells in the presence of BMP2 or adipogenic cells in the presence of dexamethasone, insulin, and isobutylmethylxanthine. Similarly, Campagnolo et al isolated a population of CD34+/CD31− cells from the perivascular zone of adventitial vasa vasorum in human saphenous veins from patients undergoing coronary artery bypass surgery. These cells could be cloned in vitro and were found to possess multilineage potential to form osteoblasts, adipocytes, pericytes, and SMCs under selective differentiation-promoting conditions in vitro. When transplanted into ischemic hindlimbs of immunodeficient mice, human saphenous vein-derived progenitor cells adopt a pericyte-like phenotype, form N-cadherin-mediated physical contacts with endothelial cells, improve hindlimb angiogenesis, and enhance blood flow recovery. In summary, these data suggest that the adventitia harbors multiple types of progenitor cells that appear to act in concert as part of a healing response to vascular injury.

### Microvascular Networks in the Adventitia: Vasa Vasorum

The studies described above demonstrate that the adventitia supports a unique progenitor niche-like environment that contains cells that have the potential to self-renew and contribute to arterial wound repair and neointimal growth. Both progenitor cells and niche-like support cells in the adventitia may communicate with medial SMCs and luminal endothelial cells via soluble factors produced within the media and intima and carried by transmural bulk fluid flow driven by steep pressure gradients from the lumen to the adventitia. In addition, the adventitia supports angiogenesis of the vasa vasorum and contributes to the progression of atherosclerotic plaques. The vasa vasorum ("vessels of the vessels") forms a microvascular network in the adventitia of large arteries (>0.5 mm thick) that supplies oxygen and nutrients to the outer layers of the vessel wall. For example, when intercostal arteries, the source of vasa vasa- rum in the descending aorta, are ligated in dogs, the tunica media undergoes necrosis. These studies show that whereas proximal SMC layers nearest the lumen are nourished by diffusion from the circulation, the middle and outer layers of the descending aorta are supplied by vessels originating from the adventitia.

Many studies have correlated the presence of atherosclerotic plaque lesions with segments of the vessel wall supplied by vasa vasorum. Similar to its role of providing oxygen and nutrients to the outer artery wall, the vasa vasorum also extends into the intima and nourishes developing atherosclerotic plaques. Moreover, as the principal route for leukocyte trafficking into the lesion, modulating the number vasa vasorum microvessels may affect plaque growth. For example, treatment with 2 angiogenesis inhibitors, endostatin and the fumagillin analog TNP-470, inhibits atherosclerotic plaque progression. Likewise, angiotatin, an inhibitor of endothelial cell migration and proliferation that promotes endothelial apoptosis, was also found to inhibit plaque neovascularization and plaque growth.

The role of hypoxia in mediating angiogenesis in the adventitia is not limited to the descending aorta. For example, the pulmonary artery undergoes adventitial neovascularization in response to hypoxia. Davie et al examined the effect of cytokines released by adventitial fibroblasts on the proliferation, migration, and tubulogenesis of vasa vasorum endothelial cells. In culture, exposure to conditioned media from adventitial fibroblasts cultured under hypoxic conditions increases the proliferation of vasa vasorum endothelial cells and potentiates the formation of tubular endothelial structures. The authors went on to highlight the proangiogenic effects of endothelin-1 produced by hypoxic adventitial fibroblasts and signaling through ETB receptors in vasa vasorum endothelial cells in vitro. Therefore, in the cases described above, adventitial progenitor cells may serve as a local source of pericytes de novo that stabilize nascent microvessels and thereby promote angiogenesis in the outer layers of artery wall.

### Role of Adventitial Inflammation in Vascular Wall Remodeling

Vascular remodeling in response to chronic changes in blood flow depends on interactions of the endothelium with cells of the medial and adventitial layers. Using a mouse carotid flow reduction model, Zhou et al showed that inward remodeling required early adventitial accumulation of CXCR3-positive macrophages. In this model, the chemokine receptor CXCR3 and its ligands IP10 and Mig are required to
recruit monocytes to the adventitia. Both IP10 and Mig transcripts rapidly increase to reach peak levels within 6 hours of carotid flow reduction surgeries. The authors found evidence for a unique subset of macrophages accumulating in the adventitia of vessels undergoing inward remodeling responses, suggesting either amplification of a preexisting subset of adventitial macrophages or homing of monocytes with particularly high levels of CXCR3 expression to the adventitia, or both. Likewise, Tang et al showed that macrophage depletion prevents flow-dependent inward remodeling in mouse carotid artery. Inward remodeling is associated with transient adventitial macrophage activation and superoxide-stimulated cytokine production (interleukin-1β, interleukin-6, IP10, and Mig). Both cytokine production and inward remodeling were dependent on expression of MyD88, an adapter protein that is critical for activation of the transcription factor nuclear factor-κB by factors regulating immune responses and inflammation. This mechanism is consistent with multiple studies implicating Toll-like receptor-dependent signaling in the development of intimal hyperplasia and atherosclerosis.

Another example of a role for the adventitia in vessel wall remodeling comes from an analysis of the blunted response to angiotensin II–mediated hypertension in RAG1−/− mice lacking B and T lymphocytes. In this model, adoptive transfer of T cells, but not B-cells, restores the angiotensin II–induced hypertensive response. Infusion of low doses of angiotensin II stimulate vessel wall cells to produce RANTES and other chemokines that recruit T cells to the aortic adventitia and adjacent periadventitial adipose tissues. In these adventitial and periadventitial sites, T cells become activated to produce tumor necrosis factor-α, interferon-γ, and p47phox. Increased T cell p47phox activity stimulates superoxide production that scavenges locally produced NO in the vessel wall. Adipocytes then release tumor necrosis factor-α and other cytokines that stimulate NADPH oxidase activity in SMCs, further reducing NO levels and increasing vascular smooth muscle contractile tone. These studies highlight the important roles played by the adventitia as a site for T cell homing, activation, and superoxide production. They also point to coordinated signaling interactions between adventitial cells and periadventitial adipose tissue as mediators of effector T cell activation, cytokine production, and blood pressure regulation. Infusion of angiotensin II also stimulates the production of interleukin-6 and monocyte chemotactic protein-1 by adventitial cells. Production of these factors is correlated with adventitial thickening, monocyte recruitment, macrophage differentiation, and aortic wall remodeling. When monocytes and aortic adventitial fibroblasts are cocultured in vitro, increased levels of IL6 and monocyte chemotactic protein-1 are found in conditioned medium. This conditioned medium promotes the differentiation of monocytes into macrophages, enhanced monocyte chemotactic protein-1 production, and matrix metalloproteinase-9 expression by adventitial fibroblasts. These findings provide further support for the important role of the arterial adventitia as a mediator of inflammatory cell interactions that can initiate physiological flow-dependent remodeling responses, as well as predisposing the artery wall to vasospasm and pathogenic remodeling of the medial layer.

**Figure 4.** Adventitia interacts with surrounding tissues. The adventitia is positioned between the vessel wall (top) and the surrounding tissues in which the vessel is located (bottom; Tissue). From this position, adventitial cells could participate in development, repair, and disease processes in either of these adjacent tissues. In this example, Shh signaling maintains Sca1+ adventitial progenitor cells (green) that can differentiate to SMC-like cells to replace lost or damaged myocytes in the media (solid arrow pointing up). Under other conditions, resident adventitial cells, including Sca1+ progenitors, could respond to injury or disease of surrounding tissues and participate along with cells of the adjacent tissues to repair tissue damage (solid arrow pointing down). Dashed arrows indicate hypothetical roles of adventitial cells or adjacent tissue cells in the processes indicated.

**Interactions of the Adventitia With Surrounding Tissues**

Because of its location between the vessel wall and the surrounding tissues in which the vessel is located, adventitial cells could, in principle, participate in tissue repair or disease processes in either the vessel wall itself or in surrounding nonvascular tissues (Figure 4). For example, in an experiment designed to produce pancreatic adenocarcinomas, Tian et al used Pdx-cre to activate expression in pancreatic epithelial cells of a constitutively active form of the Shh signaling protein smoothened (Smo-W535L, also called SmoM2) in transgenic mice. Surprisingly, although they could demonstrate expression of the SmoM2 transgene in pancreatic epithelium and localization of SmoM2 protein to primary cilia, a requirement for Hh signal pathway activation in vertebrates, there was no signaling response detectable in the epithelium, and no adenocarcinomas were found. However, expression of Pdx-cre is known to leak into the stromal compartment and activate signaling responses in pancreatic mesenchymal cells. In fact, careful examination of Pdx-cre mice crossed with a cre-activated reporter strain (R26R) revealed that in addition to reporter expression in pancreatic epithelium, rare β-galactosidase-positive cells are also detected in the adventitia of pancreatic blood ves-
Indeed, large mesenchymal tumors are formed in Pdx-Cre/SmoM2 transgenic mice that originate from the adventitial layer of arteries within the pancreas and projected into pancreatic stroma. These mesenchymal tumors are smooth muscle marker positive, suggesting that they arise either from adventitial myofibroblasts or from the resident pool of AdvSca1. These results raise the possibility that the adventitial progenitor cell niche may be a substrate not only for wound repair or disease processes in the artery wall but also for hyperplastic or neoplastic changes in adjacent tissues as well.108

Perivascular adipose tissue (PVAT) is often found associated with large arteries, and important signaling interactions are thought to occur between PVAT cells and cells of the artery wall. For example, PVAT is a source of mesenchymal progenitor cells that can produce pericyte-like cells and participate in the formation and regression of microvascular networks in the adventitia and perivascular space.110 PVAT is also a source of paracrine factors that affect short-term contractile responses of vascular SMCs to vasoactive agonists, as well as influencing long-term regulation of blood pressure.111 These effects may be at least partly dependent on the ratio of brown to white adipocytes that comprise thoracic PVAT.111 PVAT may also signal to adventitial cells, in addition to medial SMCs. Using liquid chromatography-tandem mass spectrometry, the secretome of PVAT was investigated in rats.112 Among the secretory proteins identified was complement 3, which was subsequently shown to stimulate adventitial fibroblast migration and myofibroblast transition in vitro.112 Moreover, increased expression of complement 3 in PVAT was found to be tightly associated with adventitial thickening and myofibroblast clustering around PVAT in deoxycorticosterone acetate-salt hypertensive rats.112 Finally, inflammation and oxidative stress in PVAT may play important roles in the vascular dysfunction associated with metabolic syndrome.113

Summary and New Perspectives

Going forward, the studies described above raise a number of important new questions to be addressed. We still do not know what mechanisms act in developing arteries to terminate tunica media formation at the characteristic number of layers of smooth muscle and elastic fibers identified by Wolinsky and Glagov.44 Does the onset of Shh signaling in the adventitia around E16.5 in the mouse20 reflect formation of a media-adventitia border during vascular development? If so, what is the molecular identity of such a border-forming mechanism? What is the origin of adventitial progenitor cells in the embryo? Hu et al18 showed that these cells do not arise from bone marrow, Passman et al20 reported that they are not derived from cardiac neural crest, and Wasteson et al114 showed that they do not originate from somites. What roles do the individual adventitial cell types, including resident tissue macrophages, play in morphogenesis of the adventitia? In adult arteries, it is now well documented that adventitial cells respond rapidly to vascular injury.59,115 Also, inflammation of the adventitia is common in arteries undergoing wound repair, atheroma formation, or flow-induced wall remodeling.12,14–16,115,116 What secreted factors recruit monocytes and T cell subsets to the adventitia, and what resident cell types in the adventitia produce those factors? Recent reports suggest that the adventitia has properties of a stem/progenitor cell niche in the artery wall.18–21 What functions do adventitial progenitor cells have in maintenance and repair of the artery wall? What cell types interact with resident progenitor cells to produce a progenitor niche-like signaling environment in the adventitia? In addition to Shh, what other secreted factors and extracellular matrix components are critical elements of the adventitial progenitor niche?117,118 What mechanisms act to maintain adequate pool sizes of adventitial progenitor cells in adult vessels? Is depletion of this progenitor pool with age a contributing factor to the degenerative changes in artery walls seen in the elderly or in rapid aging syndromes?119,120 Do arterial injury and the accompanying inflammation disrupt signaling interactions that maintain progenitor cells and lead to depletion of endogenous progenitor pools in the adventitia or in perivascular niches found in other tissues?115,116,121–123 Finally, how do adventitial cells contribute to formation of intimal lesions, and do adventitial cells have a role in tissue repair or disease pathogenesis in tissues and organs that normally surround individual arteries? Answers to these and other important questions about the adventitial layer of blood vessels will provide for a better understanding of how all 3 layers of vessel wall interact to form, maintain, and repair a functioning vascular system.

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Disclosures

None.

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