Recent Highlights of ATVB

Adventitia and Perivascular Cells

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The past few years have seen significant advances in our understanding of the multiple and dynamic roles of the adventitia and its companion perivascular tissues for vessel wall homeostasis and disease. It is now becoming clear that signals originating from within the adventitia and from perivascular cells play essential roles in regulation of vascular development, physiology, artery wall remodeling, immune surveillance, and vascular disease. The adventitia is in contact with and completely surrounds the media and is the interface between the vessel wall and its neighboring tissues. It contains many different interacting cell types including fibroblasts, microvascular endothelium, nerves, resident macrophages, T cells, B cells, mast cells, and dendritic cells. The adventitia is also home to resident vascular progenitor cells whose formation and maintenance depend, in part, on sonic hedgehog signaling. Perivascular cells are in close contact with the adventitia, particularly for the aorta and coronary arteries. Perivascular tissue includes adipocytes, lymphatic vessels, perivascular nerves, and stromal cells exhibiting mesenchymal stem cell–like properties. The adventitia and periadventitial cells function in concert. They are linked by microvessels, nerves, and migratory cells to regulate vascular physiology, homeostasis, structural remodeling, and exert major influences on the progression or regression of vascular disease. Crosstalk between intima, media, and adventitia further links the adventitia-periadventitial unit to the rest of the vessel wall. Much of the work advancing our concepts of the adventitia and periadventitial tissues has been published in ATVB, and some of those key studies are discussed in this highlights article. In the following summary, areas that have attracted the most interest over the past 2 years in ATVB are reviewed including the multiple roles of perivascular adipose tissue (PVAT) on control of vascular physiology and remodeling, adventitial progenitor cells and their contribution to neointimal formation, and the perivascular space as a target for local delivery of therapeutics.

Perivascular Control of Arterial Physiology

Control of peripheral resistance through contraction and relaxation of constituent vascular smooth muscle is a critical function of muscular arteries and arterioles in vivo. There are many known factors that stimulate or inhibit smooth muscle cell (SMC) contraction in intact blood vessels. Many of these factors are derived from endothelial flow–responsive pathways on the intimal side of the vessel wall, and others arise from vasoactive nerves that penetrate the tunica media of these vessels from the adventitial side. Less well known, however, are the factors that originate from perivascular cell types surrounding the outside of the artery wall. For example, one candidate linking PVAT to arterial contractile tone is the adipokine chemerin, a 14-kDa protein that is secreted from adipocytes as prochemerin and then released by serine protease activity. Chemerin stimulates chemotaxis of macrophages and dendritic cells. Chemerin receptors are also found on SMCs in the tunica media where they mediate smooth muscle contraction. Obesity and hypertension are well-known comorbidities, and arteries from obese animals and humans were found to exhibit amplified contractile responses to chemerin receptor agonists.

On the other hand, production of vasorelaxing or anti-contractile activity by PVAT has been described for many years. One important component of this adipose tissue–derived anti-contractile activity is adiponectin. Adiponectin is an adipocyte-derived 244 amino acid long peptide hormone that regulates metabolic processes, including fatty acid oxidation, and also mediates vasorelaxation. Adiponectin receptors on vascular SMCs activate calcium-sensitive potassium channels (BKca) leading to stimulation of endothelial nitric oxide synthase activity and production of nitric oxide. A similar pathway exists in endothelial cells. Together, the production of nitric oxide from endothelial cells and SMCs mediates the anticontractile effects of PVAT-derived adiponectin. In obesity, there is a loss of PVAT-mediated anti-contractile activity that is correlated with reduced bioavailability of adiponectin. Another feature characteristic of PVAT in obesity is local inflammation. Mammalian target of rapamycin complex 2 is reported to control inflammation and is expressed in PVAT. When rictor, an essential mammalian target of rapamycin component 2 in mammalian target of rapamycin complex 2, was deleted in mouse adipose tissue, gene expression and protein release of interleukin 6, macrophage inflammatory protein–1α, and tumor necrosis factor–α, were increased and dilations of aortic rings were impaired. Moreover, a high-fat diet alone was sufficient to induce down-regulation of rictor gene expression in PVAT and epididymal adipose depot. These studies suggest that controlling mammalian target of rapamycin complex 2 activity in PVATs may offer a therapeutic avenue for inflammation-driven cardiovascular damage frequently observed in obesity.

Adventitial/Perivascular Control of Wall Structure

Vascular SMCs are recruited from multiple types of progenitor cells in the embryo to form the tunica media. The
Adventitial/Perivascular Cells in Vascular Disease

The adventitia has long been known to accumulate inflammatory cells in atherosclerotic arteries. More recent studies have shown that leukocytes are also present in the adventitia in normal, nondiseased artery wall. With the development of atherosclerotic plaques on the luminal side, adventitial leukocytes increase in number and organize into germinal center-like structures suggesting local antigen presentation and antibody production. Perivascular cells in adipose tissue surrounding atherosclerotic human coronary arteries exhibit a heightened proinflammatory phenotype and contribute to leukocyte accumulation in the adventitia of these vessels. Coronary PVAT may also produce factors that contribute to life-threatening coronary vasospasm in addition to the progression of atherosclerosis.

To directly test the role of PVAT tissue on arterial responses to injury, Manka et al transplanted a small amount (2–3 mg) of PVAT from donor mice fed a high-fat diet to recipient low-density lipoprotein receptor–deficient mice also fed a high-fat diet. Inguinal subcutaneous adipose tissue was transplanted as controls. Two weeks after transplant, mice were given wire injuries to the carotid artery and examined 2 weeks later. Transplanted PVAT tissue was associated with increased neointimal thickening, greater numbers of adventitial macrophages, and pronounced increases in the density of vasa vasorum microvessels in the injured adventitia. This effect of accelerated neointimal hyperplasia may be due, in part, to elevated perivascular leptin production in diet-induced obese PVAT tissue. Studies in leptin-deficient (ob/ob) mice or in leptin receptor–deficient (db/db) mice showed that enhanced neointimal formation after carotid wire injury in high-fat diet–induced obese mice depended on leptin receptor signaling. Thus, current evidence suggests that adipokines, including leptin, produced by PVAT in obesity play important roles in the enhanced risk for cardiovascular disease in obese patients. Adventitia and PVAT tissues also are involved in the pathogenesis of abdominal aortic aneurysms. For example, in transgenic mice overexpressing endothelin-1 selectively in the endothelium of apoE−/− mice (eET1/aapoE−/−), development of abdominal aortic aneurysms correlated with increased reactive oxygen species production, macrophage infiltration, and CD4(+)/T-cell accumulation in PVAT compared with apoE−/− alone or eET mice alone.
Adventitial Progenitor Cells

Not long ago, it was common to read descriptions of the adventitia as loosely organized connective tissue containing fibroblasts and perivascular nerves. In contrast, today, we recognize that the adventitia is a hub of complex and dynamic interactions between many different types of leukocytes, microvessels, nerves, lymphatics, and progenitor cells. The known progenitor cells in the adventitia are heterogeneous in their potentials for cell differentiation, and current evidence suggests 2 types of progenitors coexist in the AdvSca1 population; one that differentiates into mural cells and another that differentiates into macrophage-like cells. AdvSca1 progenitor cells with smooth muscle differentiation potentials have been shown to migrate into the developing neointima in vein graft models and contribute to ≈30% of intimal SMCs in atherosclerotic lesions from ApoE-deficient mice. Similar findings were reported for a rat model of transplant arteriosclerosis. Grudzinska et al transplanted labeled adventitial tissues in rat aortic allograft experiments to show that the major source of intimal cells originated from the adventitia (79±20.6% of intimal cells originated in the adventitia). The movement of cells from the adventitia to the intima in this model was dependent on monocyte chemoattractant factor-1/chemokine (C-C motif) ligand 2. Moreover, despite the phenotypic conversion of medial SMCs from a contractile to a synthetic phenotype, few, if any, medial SMCs migrated into the intima in this model. Using ex vivo decellularized aortic segments in a bioreactor, Wong et al showed that sirolimus stimulated adventitial progenitor cells that were seeded on the outside of the vessel scaffold to migrate in a CXCR4-dependent manner to the intimal side and form neointimal lesion–like accumulations of SM22α- and calponin-positive cells. In addition, sirolimus stimulated differentiation of AdvSca1 progenitor cells into SMCs but not endothelial cells. The above models are in contrast to the movement of labeled medial SMCs to the intima observed in a carotid wire injury model of arterial injury in the rat. It will be interesting to determine why the 2 models exhibit such differences in the origin of neointimal cells. It may be related to the degree of medial SMC death, which is usually robust in transplant models, or to differences in the extent of activation of innate immune responses in the 2 types of injury.

In the late fetal and early neonatal period, the adventitia exhibits strong expression of sonic hedgehog signaling reporters (patched-1, patched-2, and gli-1) that are colocalized with AdvSca1 progenitor cells. In a study investigating the role of hedgehog signaling in a transgenic mouse model of pancreatic cancer, Tian et al reported finding stromal tumors arising from the adventitia of blood vessels within the pancreas and suggested an origin from AdvSca1 progenitor cells. These findings indicate that the adventitia-periadventitia unit is a site for pathological changes in vivo and that these tissues on the outer layer of artery walls can also communicate with organ-specific cell types surrounding the blood vessel in native tissues. Although there is much to learn about the potentials for adventitial and periadventitial stem/prorogenitor cells for vascular therapy and vascular disease, the possibility of harnessing their potential for vascular repair is an attractive therapeutic objective.

Perivascular Drug Delivery

Introduction of therapeutics into the vascular lumen leads to rapid distribution throughout the body and systemic effects. To target therapy to specific vessels or vascular beds, more precise delivery methods have been developed that involve local administration to perivascular tissues. For example, Katare et al reported direct application of alginate microbeads encapsulated with mesenchymal stem cells into the perivascular space surrounding the femoral artery in CD1 mice after unilateral hindlimb ischemia. In this particular example, the mesenchymal stem cells were engineered to express glucagon-like peptide-1 (glucagon-like peptide-1 mesenchymal stem cells), a factor with proangiogenic, antiapoptotic, and cardioprotective effects. Increased capillary and arteriolar density in hindlimb muscles with increased foot salvage was observed after perivascular, but not intramuscular, administration of glucagon-like peptide-1 mesenchymal stem cells. In another study, this time targeting SMC proliferation in a murine carotid artery ligation model, Redmond et al reported that administration of the hedgehog signaling inhibitor Ptc1 small interfering RNA markedly reduced smooth muscle proliferation and pathological vascular remodeling. The Ptc1 siRNA was incorporated into a pluronic gel preparation and applied to the adventitial side of the carotid artery. In addition to localizing delivery of a therapeutic compound directly to the site of arterial injury, the perivascular route of administration might recruit perivascular and adventitial cells to participate in signaling to the intima and media to achieve desired clinical outcomes.

Summary

The multiple roles of adventitia and its companion perivascular tissue in vascular homeostasis and disease are active areas of current interest as reflected in this ATVB highlights article. Interactions between the adventitia and perivascular cells with the rest of the artery wall are extensive. These interactions extend to both resident and infiltrating leukocytes and further emphasize the dynamic interface that the adventitia and perivascular cells function within to regulate vessel wall growth, maintenance, and disease.

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References


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