Beyond the Adventitia
Exploring the Outer Limits of the Blood Vessel Wall
Scott T. Robinson, W. Robert Taylor

The anatomy of the arterial wall has traditionally been divided into 3 distinct regions, forming concentric layers surrounding the blood vessel lumen. The intima, consisting of a single layer of endothelial cells in direct contact with the lumen; the media, containing layers of smooth muscle cells and extracellular elastin fibers; and the adventitia, composed largely of collagen and other extracellular matrix protein but also containing fibroblasts, inflammatory cells, and a separate microvasculature. The earliest studies on the role of inflammation in the pathogenesis of atherosclerosis focused on the role of endothelial and smooth muscle cells in disease progression; ie, the cell types that reside within the inner arterial layers. Some of the earliest observations demonstrated that an upregulation of adhesion molecules on the endothelial surface initiates the disease process, resulting in the recruitment of monocytes into the vessel wall. More advanced lesions are characterized by the migration and proliferation of the smooth muscle cells, which further contribute to the remodeling of the arterial microstructure. The accumulation of cells and matrix proteins within the developing plaque leads to a lumen narrowing and an altered intimal microenvironment. The adventitia, on the other hand, has historically been regarded as a minor participant in the disease process, and its functional role in plaque formation and development have largely been overlooked. However, the inflammatory response that occurs in the setting of atherosclerosis clearly involves adventitia. Contributions of adventitia-derived inflammatory cells, cytokines, and microvasculature likely contribute significantly in many different vascular disease states. The involvement of the adventitia in vascular pathology suggest that there is an “outside-in” component to atherosclerosis that is synergistic with the traditional “inside-out” view of atherogenesis.

However, arteries are obviously contained within surrounding tissue which, in the case of most vascular beds, is adipose tissue. If extramedial elements can play a role in cardiovascular disease, what about the involvement of components beyond the adventitia? White adipose tissue (WAT) represents a potentially important and understudied element of vascular inflammation. What was once viewed as an inert reservoir of energy storage is, in actuality, an active and dynamic tissue. The cellular constituents of WAT include the adipocytes, endothelial cells forming the microvasculature, inflammatory cells, and a host of potential stem or progenitor cells. Adipocytes are capable of generating a variety of adipokines, and, although WAT as a whole has also been shown to produce a number of inflammatory cytokines, it is unclear from which cells the cytokines are secreted. The fact that perivascular adipose tissue surrounds many of the arteries that are prone to atherosclerosis suggests an interaction with additional components of the vessel wall. In fact, adipocytes migrating from the perivascular fat have been detected within the adventitia. The ability of WAT to promote an inflammatory environment, and the proximity of perivascular adipose tissue to the artery wall raises the possibility that WAT may play a prominent role in vascular pathophysiology.

In this issue of Circulation Research, Chatterjee et al characterize the gene expression profile of perivascular adipose tissue, demonstrating an unique proinflammatory environment that could potentially influence vascular disease. In this study, the gene expression profile from nondiseased human perivascular adipose tissue samples was compared to samples derived from subcutaneous and visceral depots. Genes indicative of adipocytic differentiation were found to be dramatically lower in perivascular adipose tissue than in subcutaneous and visceral regions, suggesting that perivascular adipocytes exist in a more primitive adipocytic state. This idea was further supported by the morphological appearance of perivascular adipocytes, which were, on average, less than half the diameter of their subcutaneous and visceral counterparts. Interestingly, a comparable reduced state of differentiation was observed in vitro differentiated preadipocytes derived from the perivascular tissue, but not from preadipocytes isolated from other regions. This suggests that the change in gene expression seen between depots was exclusively attributable to phenotypic differences in adipocytes and not the contributions of other, potentially confounding cell types. It was further observed that inflammatory gene expression was significantly higher in perivascular adipose tissue, a result that was again corroborated by the in vitro differentiation assay. Antiinflammatory adipokines, on the other hand, were markedly reduced.

The authors then explored this same phenomenon in a simple but elegant mouse model. As was seen in humans, gene expression in perivascular adipose tissue showed a reduced state of adipocytic differentiation and a heightened inflammatory environment. After just 2 weeks of a high-fat diet, the perivascular adipose tissue appeared to take on an...
even less differentiated status, whereas the inflammatory state was exacerbated above and beyond that of the other adipose depots. This data not only demonstrate the dynamic nature and sensitivity of perivascular adipose tissue but they also implicate the perivascular adipocyte as a potential key mediator in the initiation of atherosclerosis.

These data clearly support the idea of a responsive proinflammatory perivascular milieu. However, a mechanism for these observations has yet to be determined. As a potential explanation, Chatterjee et al8 present the intriguing notion that the functional differences observed in perivascular adipose tissue and in vitro differentiated adipocytes arise because they are derived from a precursor that is distinct from that found in subcutaneous and visceral depots. However, the cellular composition of the various depots was not extensively studied. Although the idea of a novel, phenotypically distinct, adipocyte progenitor is certainly an exciting possibility, the cellular composition of the perivascular adipose tissue must be thoroughly resolved and the functional contributions of all cell types must be examined to resolve the complexity of the periadventitial niche.

In addition to adipocyte progenitors, the presence of inflammatory cells within the adipose tissue, such as macrophages and T cells, may strongly influence the local perivascular environment. Macrophages, the primary infiltrate of the vessel wall in the progression of atherosclerosis, are a veritable cytokine factory and undergo a phenotypic transformation once resident within the vessel wall. Although there were no observable differences in macrophage number within the tissues examined in this study, the presence of the cell type was noted. Therefore, the possibility of differences in local macrophage function remains. An increase in T-cell infiltration, on the other hand, was observed by Chatterjee et al8 in all adipose tissue of mice fed a high-fat diet. No differences were observed between the different depots, but this was not extensively investigated. An increase in obesity-induced T-cell infiltration in both visceral9 and perivascular adipose tissue has been previously reported; however, comparisons between the different depots was not explored. The possibility that different T-cell subsets persist within each depot could also influence the inflammatory state of each particular adipose region. T cells have recently been implicated in the development of hypertension,10 with hypertensive mice showing a high infiltration of T cells in the periadventitial fat. In the setting of hypertension, the periaortic T-cell population appears to contain a higher percentage of CD8+/CD4− (double negative) regulatory T cells, which are capable of inducing a proinflammatory environment. It may be that the type of T cell is more important than the number of T cells. The presence of a particular subset of T cells may regulate the inflammatory environment of the perivascular adipose tissue, thus making it more responsive to changes in diet.

The observation by Chatterjee et al8 that each adipose depot maintains adipocytes in an apparent altered state of differentiation presents an intriguing possibility of the role of progenitor cells in adipose tissue function. Both the number and function of recently identified adipocyte progenitor cells11 can be explored in a depot specific manner, to better understand the differences observed in this study. In addition to a lineage-specific adipocyte progenitor, the role of adipose derived stem cells (ADSCs), highly touted as an available and accessible adult stem cell source, should be further explored. These ADSCs have demonstrated a regenerative capacity in osteogenesis,12 cartilage repair,13 skeletal muscle,14 and cardiomyocyte formation,15 as well as in the setting of neovascularization.16,17 The interaction between perivascular adipose tissue and the blood vessel may include the involvement of ADSCs in endogenous vascular repair processes. Conversely, the ADSCs may contribute to atherosclerosis via local mobilization of proangiogenic cells in plaque neovascularization. Perivascular adipose tissue thus represents a stem cell niche easily accessible to the blood vessel which could play a significant role in both vascular homeostasis and inflammation.

The novel work by Chatterjee et al,8 demonstrates that the perivascular adipose tissue is a unique microenvironment in a hyperinflammatory state that is highly susceptible to changes in diet. The inflammatory contribution of WAT likely reflects just one component of the complex environment of the perivascular compartment that also includes progenitor/stem cells and inflammatory cells. The potential interaction of cells from beyond the adventitia with the blood vessel adds a new level of complexity to the current paradigm of the pathogenesis of atherosclerosis and may represent a novel target for therapeutic strategies.

Sources of Funding
Supported by NIH grants R01HL070531, and R01HL090584 and Veterans Affairs Merit Review Funding.

Disclosures
None.

References


**Key Words:** obesity ■ growth factors/cytokines ■ other vascular biology
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Circ Res. 2009;104:416-418
doi: 10.1161/CIRCRESAHA.109.194225
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/104/4/416

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