The adventitia: The outs and ins of vascular disease

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Long before it was established that the adventitia is a major source of vasoactive factors and a pivotal participant in vascular remodeling, it was noted that the changes occurring in the adventitia could be a signal of impending vascular disease, among them marked hypercellularity, increased connective tissue production, and clear signs of inflammation. Various forms of hypertension, atherosclerosis, and vascular injury are characterized by adventitial cell proliferation and increased leukocyte levels in the perivascular space. In 1915, Albutt[1] reported finding inflammatory cells in the perivascular adventitia of atherosclerotic arteries. Almost half a century later, Schwartz and Mitchell[2] showed a positive correlation between the magnitude of adventitial inflammation and the severity of atherosclerosis. However, for more than 30 years, these observations remained a curious, yet peculiar phenomenon that was largely ignored and generally considered irrelevant to homeostasis of the vessel wall. Until recently, doubts persisted that this outer segment of the blood vessel could have far-reaching effects on the vascular wall, including profound changes affecting medial smooth muscle and endothelial cell biology.

Over the past decade, however, a few landmark studies illustrated a highly important role for the adventitia in dysfunction, ranging from interference in endothelium-dependent responses to a direct contribution of adventitial myofibroblasts to restenosis. It is our expectation and hope that the reviews and original publications in this issue will shed important new light on an important role for the adventitia in vascular physiology and pathophysiology.

Maiellaro and Taylor[3] highlight the emerging new paradigm of vascular inflammation, describing an inward progression of inflammation from the adventitia toward the intima. Major strides have been made in revealing the identity of the adventitial cell population, which we now know includes monocytes, macrophages and T-cells together with increased differentiation of resident fibroblasts into myofibroblasts. Moreover, these changes were shown to coincide with local production of more obvious pro-inflammatory mediators (cytokines and growth factors) as well as connective tissue production. Of particular importance to this discussion has been the observation that after vascular injury but prior to neointimal hyperplasia, the adventitia is highly populated with these cell types[4–6]. While this overview does not pinpoint the initiating factor in adventitial inflammation, numerous studies by the Taylor group and others suggest that systemic and local angiotensin II potently elicits release of a variety of chemoattractant proteins for leukocytes and lymphocytes.

A major conduit for leukocytes, progenitor cells and oxygen permeating the vascular wall, the adventitial vasa vasorum almost certainly plays a critical role in inflammation and remodeling. Ritman and Lerman[7] review the role of the vasa vasorum in vascular health and disease. They emphasize that the vasa vasorum is present in large arteries (thicker than 0.5 mm) that supplements diffusion-limited exchange of nutrients and waste clearance with the vascular lumen. Sharp increases in vasa vasorum density are observed in a variety of vascular disease states, often in response to decreased oxygen tension in the vascular media. A potentially harmful consequence of the increased vasa vasorum density is facilitation of plaque rupture as the result of enhanced delivery of instigating inflammatory cells and their secreted cytokines[8,9]. Interestingly, the impaired function of endothelial conduit arteries that often precedes atherosclerosis could also be...
expected to occur in the vasa vasorum, which is enriched in endothelium. The consequence of such dysfunction would likely serve to exacerbate the inflammatory process in the adventitia and media. In this stimulating review, the hemodynamic foundation for altered diffusion and clearance of compounds circulating in the vasa vasorum is discussed. Importantly, changes in transmural arterial pressure affect both perfusion and transvascular flux of circulating compounds such as lipids. The authors put forth the intriguing hypothesis that intravascular lipid and inflammatory cell transport is amplified in vessels that contain vasa vasorum, now expanding to include both the conduit artery lumen and abluminally through the vasa vasorum. Thus, there are several mechanisms by which the adventitial vasa vasorum may contribute to atherosclerotic development and subsequent events.

From a practical standpoint, the adventitia is well suited for delivery of various agents as well as gene transfer techniques aimed at promoting or disrupting inflammation and remodeling. Numerous laboratories have taken advantage of the ease of application of such agents as well as the relatively controlled and sustained local delivery afforded by the adventitia, in comparison to the intima where constant flow limits effective delivery. Using an “outside-in” approach, Siow and Churchman [10] review their studies, taking aim at the limits effective delivery. Using an controlled and sustained local delivery afforded by the adventitia, in comparison to the intima where constant flow limits effective delivery. Using an “outside-in” approach, Siow and Churchman [10] review their studies, taking aim at the limits effective delivery.

The effects of TGF-β1 and PDGF-BB, that have been strongly implicated in smooth muscle cell and fibroblast migration in atherogenesis as well as the vascular response to injury [11,12]. The effects of TGF-β1 or PDGF-BB are cleverly antagonized by expressing all or part of the growth factor receptor locally in the adventitia by adenoviral means [13,14]. The authors also did a thorough job of surveying a variety of studies utilizing adventitial adenoviral gene transfer to modulate growth factors in a way that will prevent adventitial cell migration and even neo-vascularization. However, limitations in the ability to target specific cell types in many of these studies leave questions regarding the role of individual adventitial cell types in these processes. Further studies aimed at targeting growth factor receptors or signaling molecules to specific cell types will be necessary in order to answer these questions.

Until recently, methods to study the interactive role of the vascular adventitia and media in a controlled environment with reduced complexity (in vitro) were not available. Of late, vascular engineering, an advanced technical method for modeling key aspects of blood vessels, has shown the potential for gaining further mechanistic insight into vascular function as well as therapeutic advances. A variety of studies focused on constructing arteries by replicating only the media and intima [15–17]. However, given the increasingly evident role of the adventitia in modulating vascular physiology and pathology, these models do not provide a complete representation of vascular biology. In the review by Auger et al. [18], studies aimed at completing a 3-dimensional functional model by generating a tissue-engineered adventitial layer are described in detail. Clearly, adventitial engineering cannot replicate all of the complexities of the adventitial wall, including the vasa vasorum, an external elastic lamina, integrated mast cells, and innervation; nevertheless, the value of vascular tissue engineering derives from a reductionist approach that limits model complexity, focusing on specific elements and characteristics. A major advantage of adventitial engineering is its ability to directly test the effect of exogenous or paracrine factors on adventitial function, separate from effects on the media or intima, since engineered vessels (with or without adventitia) can be generated [18,19], obviating the need to mechanically strip the adventitia of native vessels, a procedure that is plagued by being either incomplete or causing inadvertent trauma to the vessel wall.

In their review, Auger et al. describe a self-assembled vascular structure (i.e., no artificial scaffolds or templates were used) that includes medial and adventitial layers [18,19]. This tissue-engineered vessel compares well with native vessels in terms of structure, receptor expression, and physiological responsiveness, although research in this area is still in its infancy. Novel findings using reconstructed arteries include the observation that the adventitia contributes to vessel wall contractility in response to endothelin-1; this might be important in pathological states characterized by heightened vasomotor tone, or even alter vascular stiffness in various vascular diseases or with aging [19–21]. Until vascular engineering can replicate a considerably more complex environment with multiple adventitial cell types and functioning vasa vasorum, caution should be taken to avoid broad interpretation of the results.

Endothelin-1 (ET-1) expression in the adventitia and its functional consequences are extended in the original study by An et al. [22]. A critical pathway is identified, linking angiotensin II, ET-1, adventitial fibroblasts, superoxide production by NADPH oxidase, and collagen matrix generation. It was previously shown that both angiotensin II (through reactive oxygen species generation) and ET-1 (through activation of ETa receptors) stimulate fibroblasts to produce collagen. The current study links these two observations through their critical intermediaries NADPH oxidase. Using both pharmacological and molecular blockade of NADPH oxidase (nox2), An et al. demonstrate that application of angiotensin II to adventitial fibroblasts stimulates secretion of collagen matrix via activation of NADPH oxidase and production of superoxide anion. The specificity of apocynin as an inhibitor of NADPH oxidase has recently been called into question [23], and thus part of the effect ascribed to this compound may involve other oxidases besides NADPH oxidase. Nonetheless, in combination with the findings made in nox2 knockout mice, this study helps elucidate a role for adventitial fibroblast NADPH oxidase in downstream pathways leading to the enhanced vascular stiffness and fibrosis that accompany hypertension and heart failure.

The review by Haurani and Pagano [24] summarizes the direct and paracrine role of the adventitia in medial hypertrophy during vascular remodeling. Evidence is presented that changes in the adventitia may induce medial hypertrophy...
during hypertension or atherosclerosis. In one cited study, adventitial cells in the basilar artery increased 3 weeks after a NO synthase (NOS) inhibitor was administered to induce hypertension in rats, prior to the development of medial or intimal thickening [25]. Moreover, in hypercholesterolemia adventitial remodeling precedes coronary endothelial dysfunction [26]. These findings suggest that adventitial remodeling is a precursor of pathological changes in the media and/or intima. In particular, after vascular injury the ensuing intimal hyperplasia presumably results from infiltration of migrating adventitial myofibroblasts as well as transformed medial cells affected by paracrine influences deriving from the adventitia. The authors propose that this paracrine effect is primarily the result of hydrogen peroxide formation by NADPH oxidase in adventitial fibroblasts (and possibly macrophages). Targeting adventitial cells with a gp91-phox-based inhibitor had a profound blocking effect on neointimal growth. These findings are corroborated and expanded upon by Chan et al. [27], who show that adventitial application of the NADPH oxidase inhibitor apocynin attenuated hypoxia-induced neointimal hyperplasia as well as endothelial dysfunction. Their study is unique because it supports a role for the adventitia in neointimal hyperplasia in intact blood vessels exposed to hypoxia, i.e., even in the absence of vessel fissures caused by injury, which may facilitate the movement of adventitial myofibroblasts inward toward the intima. Aside from the concerns raised earlier in this editorial about the specificity of apocynin as an inhibitor of NADPH oxidase, the data are consistent with previous demonstrations that adventitial reactive oxygen species (ROS) play a critical role in neointimal growth.

Because NADPH oxidase is the adventitial enzyme responsible for initiating ROS-generated vascular proliferation, it is important to examine the variety of stimuli that activate NADPH oxidase. Clearly, angiotensin II has been considered a prototype stimulus for NADPH oxidase in the peripheral vasculature. In addition, Haurani and Pagano [24] review the numerous humoral stimuli that may elicit ROS generation from NADPH oxidase in the systemic and pulmonary circulations. Their review clarifies the connection among adventitial NADPH oxidase and vascular inflammation (MCP-1 and IL-6 expression), vascular signaling, medial hypertrophy, and heightened vasoconstriction with reduced NO bioavailability [28,29], although this latter feature remains somewhat controversial. There is a balance between adventitial ROS generation and endogenous antioxidant systems. A shift in the balance toward excess ROS generation launches a series of pathological growth signals that result in intimal and medial hypertrophy and vascular dysfunction. Further examination of the proximal signaling pathways should provide additional therapeutic targets to prevent or slow the development of atherosclerosis.

The involvement of the adventitia in vascular homeostasis would not be complete without an understanding of the contribution of circumferential adipose tissue. Thalmann and Meier [30] comprehensively review a wide array of secretory factors released from perivascular white adipose tissue (pWAT), which they describe as a “depot” for a multitude of vasoactive factors. They posit a role for a multitude of cytokines, including IL-1, TNF-α, IL-6 and MCP-1, in the vascular processes that control inflammation and insulin sensitivity. Other pWAT secretory factors include VEGF and leptin, which are believed to evoke an angiogenic response and thus have the potential to play a notable role in vasa vasorum expansion. However, although a correlation is drawn between secretion of cytokines from pWAT and obesity-induced hypertension, no direct evidence is cited to show that the balance of pro-constrictor vs. dilator cytokines is tipped in favor of increased vascular tone. Aside from a thorough review of the manifold effects of pWAT-derived factors, the review offers little explanation for how increased perivascular adiposity results in obesity-related hypertension or proximal vascular atherogenesis. The effect of TNF-α to inhibit NOS and thus vasodilator NO may be one explanation for decreased vasorelaxation and hence increased tone [31]. Such an overall constrictor effect could suggest that relative TNF-α levels are elevated with obesity, but such a singular increase in this cytokine is unlikely. Thus it appears more likely that with increased perivascular fat deposition, the balance of pro-constrictor growth factors and cytokines prevails.

In this context, it is important to consider the role of the major pWAT-derived protein adiponectin, reportedly the most abundant adipose-derived protein in the circulation [32,33]. One very intriguing study by Fésis et al. [34], also in this issue, demonstrates a delayed rectifier potassium channel-mediated, anti-contractile effect of adiponectin. However, deletion of the adiponectin gene (Apn−/−) in mice is ineffective at attenuating the anti-contractile effect of perivascular fat on mesenteric vasodilatation. The authors ascribe the persistent anti-contractile effect of perivascular fat in Apn−/−/mice to a transferable “adipocyte-derived relaxing factor” (ADRF) as previously described in the rat but do not clarify the nature of this factor. At this juncture, it is noteworthy to point out that obesity is associated with an increase in adipocyte-derived superoxide anion, previously shown to enhance arterial constriction in response to perivascular nerve stimulation. The latter findings highlight the importance of studies characterizing the chemical nature of ADRF and its interplay with ROS.

Original descriptions of vascular wall biology focused on the obvious histological components, including the intima, media, and adventitia. Intense investigation over the past 25 years has shown that these anatomically distinct regions have markedly different physiological and biochemical properties as well, acting in concert to define vascular physiology and instigate vascular pathology. This Review Focus Issue highlights the contribution of the outermost layer of this vascular triad, demonstrating a critical role of the adventitia in vasomotion, vascular proliferation, hypertrophy, and atherosclerosis. It is anticipated that the adventitia will become a major site for therapeutic intervention because of its accessibility and because drug delivery via the adventitia can be both sustained and regionally targeted.
References


