Ateries are composite muscular, fibroelastic tubes that function to convey blood to the body from the heart at high pressure. The arterial wall consists of 3 tunicae that differ somewhat in structure depending on vessel size and vessel bed. The tunica intima (inner coat or intima) consists of a layer of luminal endothelial cells supported by basement membrane and, in conduit arteries of humans and other large animals, an underlying stroma containing at least several layers of vascular smooth muscle cells (VSMCs). The tunica externa (outer coat or adventitia) consists mostly of collagen fibers and fibroblasts with occasional microvessels and nerve endings. The tunica media (middle coat or media) consists of multiple layers of VSMCs intercalated between elastic and collagen fibers. The elastic laminae are equally prominent in large elastic arteries and, besides the well-developed internal elastic lamina which separates the media from intima, are less prominent in medium and small muscular arteries. Fenestrations are found in the internal elastic lamina of elastic and muscular arteries and may play a role in direct intercellular communications, the passage of diffusible substances, and perhaps...
for cellular migration.² The medial compartment of arteries is normally avascular unless it consists of ≥29 lamina, for example, in the thoracic aorta, or the intima is abnormally thickened >0.35 to 0.5 mm.³⁴ In thickened or pathological arterial walls, medial-penetrating microvessels may arise from adventitial parent vessels or even from the central lumen.⁵ Except in the special circumstances associated with penetrating microvessels, VSMCs are the exclusive cell type of the media and have both contractile functions, for example, regulating vessel diameter, as well as synthetic functions, for example, maintaining the extracellular matrix (ECM), including elastic and collagen fibers.⁶ VSMC contractile functions and regulation of blood flow are more apparent in medium and small arteries, whereas regulation of structural ECM molecules is more critical in large arteries. The media is characterized by low proliferative rates of VSMCs, long-lived elastic fibers, and more rapid turnover of collagen fibers.

Inflammatory reactions of both innate and adaptive immunity are shaped by the local microenvironment in which they occur. Because the vessel media is comprised almost exclusively of VSMCs, it is likely that these cells and their products determine the nature of the medial microenvironment. VSMCs in the media of different regions of the vasculature are of distinct embryological origins. For example, VSMCs of the aortic root are derived from the second heart field, those of the ascending aorta and aortic arch from neural crest, those of the root are from local somites expressing distinct Hox genes, those of the coronary arteries from angioblasts/endothelial cells, and those in many peripheral sites from local mesenchyme.⁷ Later in life, medial VSMCs may arise from committed progenitor cells that are located in the medial-adventitial border. This degree of heterogeneity may imply that the medial microenvironment is different in different parts of the arterial tree. However, there is little information to support or refute this surmise. Phenotypic alterations of VSMCs may result in a proinflammatory state, although it is thought that medial VSMCs throughout the arterial tree are of a similar contractile, nonproliferative phenotype. In normal and atherosclerotic arteries, the media is generally spared of resident and infiltrating leukocytes.⁸–¹⁰ In contrast, medial inflammation is typical in certain aortic aneurysms and large-vessel vasculitides.¹¹–¹² We think that a balance between the pro- and antibacterial effects of medial VSMCs and their ECM versus the relative strength of effector immune responses determines the occurrence and outcome of medial inflammation. The role that medial VSMCs play in shaping inflammatory responses is the subject of this review.

**Stress-Induced Inflammatory Responses of VSMCs**

Under homeostatic conditions, quiescent VSMCs maintain arterial tone and a bland vessel wall microenvironment. In addition to products of infectious agents and damaged cells, the deviation of numerous physiological variables from homeostatic values may initiate stress responses and, if severe or unresolved, may lead to proinflammatory responses.¹³ Like most other cell types, VSMCs produce numerous cytokines and chemokines in response to diverse systemic and cellular stresses, such as genotoxic stress, ER (endoplasmic reticulum) stress, hypoxia, and so on, enumeration of which is beyond the scope of this review. In addition to such common perturbations, vascular cells uniquely sense stressors in the form of abnormal hemodynamic forces. Specifically, changes in blood flow and pressure are sensed by endothelial cells and VSMCs, respectively, resulting in orchestrated structural changes that maintain mechanical homeostasis.⁹ Adaptations in vessel size and wall mass are broadly described as vascular remodeling and accrue from changes in each of the arterial compartments, including that of the media (Figure 1).

Endothelial inflammatory responses that lead to the preferential development of atherosclerosis at sites of disturbed blood flow have been extensively characterized.¹⁴ The role of medial VSMCs in initiating or amplifying stress-induced inflammation in arterial remodeling and disease is less appreciated. It was long thought that arterial enlargement or shrinkage in response to chronic changes in blood flow was an intrinsic property of the vessel wall, although it is now known that macrophages play an essential role.¹⁵–¹⁸ Sensing of blood flow changes by luminal endothelial cells results in superoxide-initiated inflammation that extends into the media with multiple cytokines and chemokines, for example, inter-leukin (IL)-1, IL-6, CCL2, and CXCL10, being produced by VSMCs.¹⁵ These proinflammatory responses recruit macrophages specifically to the adventitia, which in turn lead to structural vessel diameter changes by turnover in medial cells and reorganization of ECM. In flow-mediated vascular remodeling, the perivascular infiltrate generally resolves without pathological sequelae after the adaptive structural changes restore normal hemodynamic stresses, an example of a homeostatic role for vascular inflammation. Inflammatory responses in medial VSMCs also occur in conduit arteries subjected to hypertension induced by aortic constriction.¹⁹ Despite marked cytokine and chemokine production by medial VSMCs, an accompanying macrophage infiltrate is largely confined to the adventitia. In contrast, persistent hypertension leads to pathological medial thickening. The proinflammatory factors produced by medial VSMCs in response to changes in blood pressure overlap with those induced by flow alterations, including IL-6, CCL2, and CXCL10.¹⁸,¹⁹ These studies demonstrate stereotypic inflammatory responses of VSMCs to sterile stimuli that recruit leukocytes to the vessel wall, but sparing the media. Vascular cells that are tethered to the arterial ECM likely play a primary role in mechanical stress–induced vascular inflammation because it is doubtful that immunocytes can directly sense changes in hemodynamic forces once they have exited from the bloodstream.
Initiation and Amplification of Innate Immune Responses by VSMCs

Almost all cell types have the ability to sense potent inflammatory stimuli of pathogens and tissue damage, but generally at much higher thresholds than specialized myeloid cells, such as dendritic cells and macrophages. Isolated VSMCs constitutively express several pattern-recognition receptors, including toll-like receptor (TLR)3 and TLR4 with robust responses to their corresponding ligands of ds-RNA and lipopolysaccharide, molecular markers of viruses and bacteria, respectively. The expression and activity of TLR3 and TLR4 in VSMCs is enhanced by immune-derived cytokines, such as interferon (IFN)-γ and IFN-α. Other TLRs typically expressed by myeloid cells, such as TLR2, which recognizes a repertoire of microbial cell wall components, are absent in VSMCs under basal conditions, but are inducible by microbial infections. Similarly, the expression of non-TLR cytoplasmic pattern-recognition receptors, such as MDA5 and RIG-I, are highly induced in VSMCs by IFN-γ, and this induction results in enhanced responses to their specific ligand of ds-RNA. Although the NOD and NLRP families of intracellular sensors have been less extensively studied in human VSMCs, there are confirmatory data for a role of NOD2 and NLRP3 in these cells. In addition to pathogen-derived molecules, pattern-recognition receptors may also be stimulated by diverse endogenous molecules released by cellular injury and, notably, VSMCs can be activated by self-RNA via IFN-γ-inducible MDA5. Despite the considerable evidence for innate defense responses by VSMCs in vitro, analyses of clinical specimens of vascular inflammation demonstrate minimal TLR and NOD2 expression by VSMCs in situ as compared with endothelial cells, macrophages, and dendritic cells. An exception is the in vivo demonstration of robust responses to ds-RNA by TLR3/MDA5/RIG-I expressing human coronary artery segments interposed into the aorta of immunodeficient mouse hosts in which resident leukocytes are absent after early emigration from the graft. Remarkably, this study also showed greater responses of isolated VSMCs to ds-RNA than 10-fold larger numbers (but equivalent total surface areas) of peripheral blood mononuclear cells; similar observations of more substantial TLR3-induced signaling are seen in other human primary cell types, such as endothelial cells and fibroblasts compared with macrophages and dendritic cells. However, even VSMC innate immune responses that are less vigorous than those of leukocytes may still play a significant role in the medial compartment as an initial trigger for inflammation.

Pattern-recognition receptor signaling in VSMCs results in the production of many proinflammatory molecules. These include cytokines that may activate macrophages (eg, TNF-α, IFN-α, and IFN-β) or skew T cell differentiation (eg, IL-1, IL-6, and transforming growth factor [TGF]-β), adhesion molecules that may support leukocyte trafficking (eg, VCAM-1 and ICAM-1), and chemokines that may recruit macrophages (eg, CCL2) or T cells (eg, CCL5 and CXCL10). As mentioned above, the interpretation of VSMC inflammatory responses are more meaningful when compared with those of other vascular cells and leukocytes, taking into consideration cell density. It is notable that VSMCs and endothelial cells are 10- to 100-fold more potent producers of CXCL10 than leukocytes, whereas the reverse pattern is seen for the production of TNF-α in response to a variety of pathogen-derived molecules or analogues. The different capacity in synthesis of proinflammatory factors between vascular cells and leukocytes has been confirmed by cellular activation with phorbol ester/calcium ionophore or cytokines in which VSMCs, endothelial cells, and fibroblasts produce 10- to 100-fold more IL-6, IL-8, and CXCL10, whereas leukocytes are exclusive.
producers of IFN-γ, VSMCs, but not endothelial cells, are capable of producing low amounts of TNF-α. Immune responses may also differ because of phenotypic modulation of VSMCs with 10-fold greater responses to ds-RNA seen in cells derived from carotid artery intima than aorta media. In addition to proinflammatory factors, TLR signaling may also induce the expression of anti-inflammatory genes. It is of interest that in murine models of arteriosclerosis, TLR2 and TLR4 generally aggravate the disease phenotype, whereas TLR3 and TLR7 may, under certain circumstances, ameliorate pathogenic manifestations. The relevance of these latter findings to human disease is uncertain, with conflicting findings of increased versus decreased inflammatory effects in clinical samples of atherosclerotic vessels treated with their synthetic ligands.

For the most part, the aforementioned studies reveal that VSMCs can initiate both proinflammatory and protective gene transcription programs in response to diverse stimuli of microbial infection and cellular injury. The responses of VSMCs may predominate for certain stimuli (eg, dsRNA), are characterized by the production of particular proinflammatory factors (eg, IL-6 and CXCL10), and are enhanced after activation with immune-derived factors (ie, IFN-γ) from artery-infiltrating leukocytes. This bidirectional relationship underscores the shaping and amplification of inflammatory responses between different cell types within the vessel wall. Thus, sentinel resident leukocytes or infiltrates of innate immunocytes early in the immune response can further stimulate VSMC (or endothelial cell) inflammatory responses, which recruit additional leukocytes from the circulation.

Modulation of Adaptive Immune Responses by VSMCs

T cell activation is dependent on 3 types of signals: recognition of cognate antigen bound to major histocompatibility complex (MHC) antigens (or direct recognition of nonself MHC molecules bound with antigen), antigen-independent positive and negative costimulators expressed by the antigen-presenting cell, and the milieu of cytokines in the local environment in which T cells proliferate and differentiate. The activation of naïve T cells requires the specific signals expressed by professional antigen presenting cells, such as macrophages and dendritic cells, within lymphoid organs. Memory T cells, which have previously encountered their cognate antigen, may preferentially respond to costimulators expressed by nonprofessional antigen presenting cells, such as vascular cells, in peripheral tissues. Endothelial cells readily activate memory T cells in reductionist coculture systems and in more complex in vivo models. In contrast, VSMCs do not lead to the proliferation and production of cytokines by resting memory T cells under the same experimental conditions. It should be noted that significant species discrepancies have been reported for T cell responses to vascular cells. For instance, murine VSMCs, but not endothelial cells, can activate T cell proliferation and cytokine production.

Like most other somatic cell types, VSMCs display constitutive expression of class I MHC molecules (recognized by CD8 cytotoxic T cells) and inducible expression of class II MHC molecules (recognized by CD4 helper T cells). Basal expression of MHC molecules by vascular cells in vivo is dependent on low level production of IFN-γ by T cells and innate immunocytes. Thus, administration of immunosuppressive agents to healthy dogs or the equivalence of endocrine ablation experiments in normal porcine or human coronary arteries (by transplantation to severe combined immunodeficient mice where they cannot respond to murine IFN-γ because of receptor species-specificities) leads to diminished basal expression of class I MHC antigens by endothelial cells and VSMCs and loss of class II MHC antigens by endothelial cells in vivo. On the other hand, increased production of IFN-γ by local immune responses can increase the expression of MHC antigens by vascular cells and even lead to detectable expression of class II MHC antigens by medial VSMCs. Isolation and propagation of vascular cells in vitro causes diminished expression of class I MHC antigens by endothelial cells and VSMCs and abrogation of class II MHC antigen expression by endothelial cells because of absent sources for IFN-γ. Curiously, treatment with IFN-γ induces equivalent expression of class II MHC antigens by cultured endothelial cells and VSMCs. The marked difference in sensitivity of MHC class II antigen expression by VSMCs compared with endothelial cells in situ, despite comparable responses in cell culture, has not been explained, but may relate to phenotypic alterations of the cells under culture conditions. Importantly, MHC antigen expression by VSMCs is recognized by the T cell receptor. Activated CD4 T cells, induced by initial coculture with allogeneic endothelial cells, will proliferate in a class II MHC antigen-dependent fashion when subsequently transferred onto cultures of VSMCs that are syngeneic to the endothelial cells. This observation may be of pathological relevance as T cells infiltrating the arterial wall must first come into contact with endothelial cells before encountering VSMCs. Furthermore, there are limited early responses of resting T cells to VSMCs as evidenced by upregulation of CD25 expression.

Because both vascular cell types express MHC antigens, their distinctive immune functions may relate to differences in the expression of costimulator molecules. Unlike professional antigen-presenting cells, endothelial cells and VSMCs do not express B7 molecules (CD80 and CD86) that are required for the costimulation of naïve T cells. Instead, endothelial cells and VSMCs have comparable expression for a plethora of positive and negative costimulators, including LFA-3 (CD58), ICAM-1 (CD54), CD44, PD-L1 (CD274), and PD-L2 (CD273). A major difference between the vascular cell types is that endothelial cells but not VSMCs basally express OX40-L (CD252) and upregulate ICOS-L (CD275) in response to proinflammatory cytokines. Transduction of VSMCs with OX40-L induces the capacity to stimulate allogeneic memory T cell proliferation and cytokine production, albeit only in the presence of essential amino acid repletion (as discussed further below).

The milieu of inflammatory factors is not necessary for T cell activation, but intensifies and skews the adaptive immune response to produce characteristic effector cytokines. As previously mentioned, both VSMCs and endothelial cells are vigorous producers of cytokines in response to cellular stress and injury, including IL-1, IL-6, and TGF-β. Although it is not possible to dissect the modulation of T helper cell responses by vascular cells directly in humans, we have used humanized
mice to address the question. In this experimental system, segments of human coronary arteries are interposed into the aorta of severe combined immunodeficient mice, which are subsequently reconstituted with allogeneic (to the artery donor) human peripheral blood mononuclear cells that leads to infiltration and injury of the artery graft by activated memory T cells. Administration of biological antagonists in this model does not differentiate between VSMC versus endothelial sources of cytokine (though VSMC effects may predominate because they constitute the most frequent cell type of the vessel wall), and T cells are minor producers of the cytokines tested. Blocking IL-1 selectively inhibits IL-17 production by artery-infiltrating T cells, neutralization of IL-6 leads to the emergence of a regulatory T cell subset, whereas inhibition of TGF-β increases IFN-γ production by alloreactive T cells. These data support the concept that early nonimmune injury of organ grafts, for example, by ischemia–reperfusion, can influence the later process of immune-mediated arteriosclerosis.

In comparing the effects of VSMCs to that of endothelial cells on adaptive immune responses, it was found that IFN-γ–treated VSMCs inhibit the activation of T cells by endothelial cells across a semipermeable membrane. A search for soluble anti-inflammatory mediators produced by VSMCs was not successful. Instead, VSMCs exhibit an exquisite sensitivity to IFN-γ–inducible production of indoleamine 2,3-dioxygenase (IDO), the rate limiting enzyme for catabolism of the essential amino acid, tryptophan. IDO has potent effects on innate and adaptive immune responses, it was found that IFN-γ may have endocrine effects on VSMCs from circulating sources and other cytokines, such as IFN-α, IFN-β, and TNF-α may also induce IDO production. IDO catalyzes the essential amino acid, tryptophan (TRP) along the kynurenine (KYN) pathway. Tryptophan depletion and kynurenine accumulation in the microenvironment has immunosuppressive effects on T cells by preventing clonal proliferation, promoting apoptosis, inducing ignorance or anergy, and generating regulatory T cells (Tregs). The avascular structure of the media may enable significant tryptophan gradients to persist locally without replenishment from circulating amino acids. Medial VSMCs may be less sensitive to the detrimental effects of tryptophan depletion because their lower rate of cell division likely requires lower rates of protein synthesis and IFN-γ may also preferentially induces the tryptophan incorporating amino-acyl-tRNA synthetase (TrpRS) in this cell type.

Unlike the classical definition of immune privileged sites using tissue transplantation, immunoprivilege of the arterial media was first described in the context of host defense to infectious agents. It was noted that infection of mice with certain viruses resulted in large vessel arteritis and that the pathological manifestations are more severe and persistent in the absence of IFN-γ. These murine models of chronic viral vasculitis are characterized by striking inflammation of the intima and adventitia of elastic arteries with sparing of the media, despite productive infection of VSMCs. Further studies revealed that viral tropism for the media of large arteries was as a result of a failure to effectively clear the virus from VSMCs, even though virus was effectively cleared from other vascular sites and other organs. The inability of effector T cells and macrophages to enter the virus-infected arterial media was interpreted as evidence of immune privilege for this site, resulting in persistent antigen expression. Of note, under experimental conditions associated with increased severity of virus infection in this animal model, the media demonstrated signs of neutrophilic infiltrates and VSMC necrosis. The relevance of these experimental findings to human disease has been questioned because of issues of species-specificity regarding viral tropism and the absence of an etiologic role for the γ-herpesvirus studied in human vasculitis. Although viral infection of large arteries in humans is rare, cerebral vasculopathy caused by infection with varicella zoster α-herpesvirus is similarly distinguished by viral antigen expression without inflammation of the media accompanied by accumulation of leukocytes in the intima and adventitia.

We have interpreted the medial sparing of leukocytic infiltrates in arteriosclerosis as consistent with immunoprivilege of this vascular compartment in noninfectious human diseases. Most atherosclerotic and transplant vasculopathy lesions
display a paucity of infiltrating leukocytes and viable VSMCs within the media, although these benign features are overshadowed by the more impressive pathology of adjacent vascular compartments. We have further characterized medial immunoprivilege in our humanized mouse model. Human T cells progressively infiltrate the intima and adventitia, but initially spare the media of allogeneic coronary artery grafts. The number of VSMCs remains unchanged until late stages and VSMC-dependent vasomotor responses persist longer than those of the endothelium. The loss of VSMC function and survival at later time points is associated with inadequate compensatory outward vascular remodeling that fails to maintain lumen size. We have not noted differences in medial inflammation and injury between visceral (coronary) and somatic (internal mammary or inferior epigastric) arteries using this model. A relative sparing of the media is also found in murine aortic transplantation models where differences in immunogenetics can be used to regulate the strength of the immune response. Although grafting between fully mismatched strains results in intense inflammation and loss of medial VSMCs within 2 weeks, grafting between single minor histocompatibility antigen mismatched strains leads to sparing of medial infiltration and survival of medial VCMCs greater than 2 to 4 weeks. These studies reinforce the concept for an immunoregulatory environment created by the intrinsic cells of the arterial media or the ECM that they produce.

Mechanisms of Medial Immunoprivilege
The mechanisms contributing to medial immunoprivilege are incompletely understood. It is likely that both passive (mechanical) and active (biological) mechanisms play a role as in other immunoprivileged sites (Table). The classical notion of absent vascularity preventing afferent and efferent arms of immune responses does apply to the arterial media. The lack of endothelial cells within the media of most arteries denotes an absence of both lymphatic and blood vessels. An exception is the microvessels normally found in the outer media of the thoracic aorta. The finding of resident leukocytes in the outer but not inner media of nondiseased thoracic aortas implies that leukocyte trafficking is facilitated by direct vascular access under homeostatic conditions. Furthermore, neovascularization of the inner media is seen in aneurysmal and atherosclerotic thoracic aortas that is associated with increased leukocyte infiltration. Similarly, medial and intimal neovascularization correlates with greater inflammation of atherosclerotic coronary arteries, although intimal rather than medial leukocytes were quantified in this study. In these observational human studies, it cannot be determined whether the development of new mural vessels is a cause or consequence of inflammation. A proinflammatory role for medial neovascularization has been demonstrated in murine models. However, medial neovascularization is not a prerequisite for medial inflammation, and leukocyte infiltration into the media can readily occur in the context of robust immune responses. Even though lymphatic channels are not found in the media of normal and atherosclerotic coronary arteries, it does not exclude soluble antigen or even rare antigen-presenting cells from extravasation into the adventitia where they may collect into perivascular lymphatic vessels. It has not been determined whether direct infiltration of foreign antigens into the arterial media can immunize the recipient, although antigen expression in other avascular immunoprivileged tissues can succeed or fail to activate immunity depending on the experimental conditions.

A reasonable assumption for medial immunoprivilege is an elastin barrier to cellular traffic. However, there is little experimental evidence to support this concept beyond the basic observation that leukocyte infiltrates may spare the medial compartment whose inner and outer borders consist of elastic laminae. The hypothesis does not account for the fenestrations of elastic laminae, or the prominent internal elastic lamina of medium and small muscular arteries, the elastic laminae breaks often seen in atherosclerotic arteries, or no apparent increase of inflammatory vascular disease in individuals with elastin haploinsufficiency syndromes. Perfusion of the rodent aorta with elastase results in elastin fiber fragmentation and marked medial inflammation, although this may be accounted for by tissue damage and the chemotactic activity of elastin-derived peptides. Further work is required to determine whether elastic fibers, or even the associated collagen fibers, prevent leukocyte migration, whether leukocytes are capable of migrating through elastic lamina fenestrations, whether

<table>
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<tr>
<td>i. Elastic laminae—barrier to leukocyte trafficking or macromolecule diffusion</td>
<td></td>
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<td>B. Active</td>
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<tr>
<td>1. IDO</td>
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<td>i. Prevent T cell proliferation</td>
<td></td>
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<td>ii. Promote T cell apoptosis</td>
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<td>iii. Induce ignorance or anergy of effector T cells</td>
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<td>i. Inhibit leukocyte activation</td>
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<td>5. Coinhibitory molecules</td>
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<td>i. Presence of PD-L1</td>
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IDO indicates indoleamine 2,3-dioxygenase; MHC, major histocompatibility complex; and TGF-β, transforming growth factor-β.

*The level of evidence varies from largely observational studies for passive mechanisms to loss/gain of function studies for active mechanisms and relevant references (Ref) are listed.
T cells or macrophages possess the full complement of proteases necessary to digest medial ECM, and whether leukocyte migration predominates in axial and circumferential directions within a lamina versus a radial direction across laminae. Besides leukocytes, the media may also present a barrier to the diffusion of macromolecules required to initiate and amplify inflammation. Although little work has been performed on the transport of proinflammatory cytokines and chemokines across the arterial media, numerous studies have examined this issue for several plasma proteins. Convection-diffusion of fluid and molecules between lumen and perivascular space occurs along pressure and concentration gradients and against sequential barriers of vascular cells and ECM. Early studies in which excised human arteries were perfused with serum revealed the media to be almost freely permeable to small molecules (eg, inorganic compounds), almost impermeable to large molecules (eg, lipoproteins), and relatively permeable to intermediate size molecules (eg, albumin). The greater distribution of albumin versus lipoprotein across the human aortic wall supports the filtration data. More sophisticated studies in rabbit aortas confirm relatively rapid diffusion of albumin through the media with more gradual accumulation of albumin bound to elastin fibers. A simple assessment of cytokine and chemokine expression profiles across the arterial wall is not informative of their diffusion properties. For example, low expression of leukotriene B4 in the media of abdominal aortic aneurysms is caused by neutrophil and macrophage production in both intraluminal thrombus and adventitial boundaries. Simultaneous transcript measurements show a more complex pattern for CXCL10 in arteriosclerotic coronary arteries where protein expression largely localizes to intimal and adventitial CXCR3-expressing T cells, despite predominant production by medial VSMCs, which lack the cognate receptor. CXCL10, like many proinflammatory molecules, is also positively charged and binds with low affinity to acidic glycosaminoglycan moieties on endothelial cells, and this pool can be rapidly mobilized by negatively charged agents in patients with atherosclerosis. Thus, specific and nonspecific binding to vascular cells and ECM may limit cytokine diffusion and activity. This sequestration effect is perhaps best documented for latent complex of TGF-β in the vessel wall. Our group has investigated whether the production of anti-inflammatory factors by VSMCs may result in medial immunoprivilege. TGF-β, known to inhibit T cell and macrophage activation, is highly expressed by medial VSMCs and, to a lesser extent, by intimal VSMCs of nondiseased human coronary arteries. The VSMC expression of TGF-β is decreased in atherosclerotic vessels and after cellular activation in vitro. Serological neutralization of TGF-β in humanized mice led to heavier medial infiltration by allogeneic T cells, increased production of the proinflammatory cytokine IFN-γ, and greater loss of medial VSMCs in coronary arteriosclerosis. The expression of TGF-β by medial VSMCs progressively decreased with ongoing allograft rejection, and this immune-related reduction may limit its protective effects. Then again, we found that VSMCs synthesized large amounts of IDO in response to IFN-γ that is produced by infiltrating leukocytes. IDO catalyzes the rate-limiting step in catabolism of the amino acid, tryptophan, that is essential for T cell proliferation; thus, contributing to placental immune privilege. It is likely that tryptophan depletion is more effective in an avascular microenvironment with an impediment to substrate repletion, such as the arterial media. Pharmacological inhibition of IDO in humanized mice increased medial infiltration by allogeneic T cells and accelerated the loss of medial VSMCs in coronary artery grafts. Thus, IFN-γ-inducible expression of IDO complements immune-mediated loss of basal TGF-β expression by VSMCs to maintain medial immunoprivilege because inflammatory conditions develop from homeostatic states. In support of the experimental data using human arteries, TGF-β and IDO also have antiatherosclerotic effects in mouse models. 

**Operational and Failed Medial Immunoprivilege in Arterial Disease**

The trafficking of leukocytes from the circulation to sites of peripheral inflammation is generally through the wall of postcapillary venules and does not involve larger blood vessels. However, the arterial wall, like any tissue, can be a target of inflammatory responses in which case leukocytes may be recruited either directly from the arterial lumen or via mural microvessels. In chronic inflammatory conditions, the extent of leukocyte infiltration can differ markedly between arterial compartments. Atherosclerotic vessels typically demonstrate a medial-sparing pattern of mononuclear cellular infiltrates with preferential accumulation of leukocytes within the intima and adventitia. This phenomenon in atherosclerotic plaques or transplant vasculopathy is usually not explicitly described in histological reports (but is evident in accompanying photomicrographs) or is only mentioned in passing. Similarly, resident leukocytes that may engage in immune surveillance are specifically identified in the intima of nondiseased human aortas and coronary arteries of young subjects dying of trauma, but are not apparent in the adjacent media. A few immunohistological studies have quantified the differences in leukocyte numbers between the layers of the arterial wall. In human, ascending thoracic aortas, T cells, and macrophages predominate in the adventitia, are 5- to 10-fold less in the intima, and are consistently absent from the inner media of nonaneurysmal specimens. Scattered leukocytes are found in the outer media in association with microvessels, particularly in a subset of aneurysmal specimens. The sparse medial infiltrates in arteriosclerotic arteries are generally associated with a preservation of VSMCs in that compartment, despite evidence of cellular injury elsewhere in the vessel wall. It is therefore not unexpected that VSMCs may remain functional even in the presence of endothelial dysfunction. Coronary arteries in patients with atherosclerosis or transplant vasculopathy demonstrate intact responses to the direct smooth muscle dilator, nitroglycerin, but absent dilator or even contractile responses to the endothelial-dependent dilator, ace-tylcholine. Temporal studies in humanized mice confirm that VSMC vasoreponses remain intact at 1 week after immune reconstitution, a time after endothelial dilator production function has already been lost as a result of cytokines produced by allogeneic T cells. Preserved medial vasomotion is not necessarily...
beneficial because it can result in paradoxical vasoconstriction in response to dysfunctional endothelial signals. On the other hand, a functional media may be of great importance in allowing for the active outward remodeling changes that are crucial in compensating against lumen loss in the early stages of coronary atherosclerosis and transplant vasculopathy.\(^{56,97}\)

Sparing of medial infiltrates and injury is not invariably in arteriosclerotic vessels, and transmural inflammation and medial destruction may be seen with severe pathology. Unlike chronic rejection that develops under cover of adequate immunosuppression, acute rejection of allografts may be characterized by panarteritis in addition to parenchymal leukocytic infiltrates and cellular injury.\(^{8,98}\) In advanced atherosclerotic lesions with intense inflammation of the plaque and adventitia, attenuation of the contiguous media with associated infiltrates and loss of VSMCs is observed.\(^{89}\) Leukocytic infiltrates of all vascular compartments is more common in certain inflammatory arterial diseases, such as abdominal aortic aneurysms and large- or medium-vessel vasculitides. Although the abdominal aorta, unlike the thoracic aorta, is not normally supplied with vasa vasorum, it is more prone to heavy transmural infiltrates associated with medial neovascularization, marked loss of VSMCs, and destruction of ECM architecture.\(^{11,100}\) It is an interesting but unexplored possibility that the extension of the inflammatory process into the media involves a change in the nature of the inflammatory process. Specifically, it has been observed that patients with COPD develop a more aggressive form of the disease when they develop autoimmune responses to fragmented elastin\(^{101}\); perhaps, something similar occurs in inflammatory aneurysms. In giant cell arteritis, infiltrating T cells and macrophages may be found in all arterial compartments and are associated with medial scarring and breaks in the elastic laminae.\(^{102,103}\)

Similarly, panarteritis and medial injury is also a feature of Takayasu’s disease and Kawasaki disease.\(^{12,104}\) Characteristic fibrinoid necrosis of the media is observed in settings in which antibodies, for example, acute vascular rejection, or immune complexes, for example, polyarteritis nodosa, lead to activation of complement. These lesions are often accompanied by neutrophilic infiltrates. The failure of medial immunoprivilege under these circumstances may arise as a result of the more robust nature of the elicited inflammatory or immune responses. However, even in these arterial diseases with more extensive inflammation, subtle or fleeting signs of medial immunoprivilege may be seen. For instance, inflammatory abdominal aortic aneurysms have predominantly adventitial compared with medial infiltrates\(^{11,100}\); IFN-γ, iNOS-, and TGF-β producing leukocytes localize to the intima or adventitia, but not media in giant cell arteritis.\(^{102,103}\) and leukocyte infiltrates, including neutrophils, start in the intima and adventitia before rapidly spreading to the media in Kawasaki disease.\(^{104}\)

### Conclusion

The arterial media is often spared from the consequences of inflammatory processes affecting the vessel wall. Immune privilege of the arterial media, as in other privileged sites, is not an absolute phenomenon. Sparing of medial infiltrates and injury is characteristic of chronic, inflammatory disorders, such as atherosclerosis and transplant vasculopathy. It likely arises when the anti-inflammatory effects of medial VSMCs and the ECM that they produce exceed their proinflammatory functions. Medial immunoprivilege may be overwhelmed in the context of robust immune responses. It is possible that medial immunoprivilege may represent a disadvantage if sustained, as in viral evasion of the immune system. We view medial immunoprivilege as a natural protective measure in the pathogenesis of arteriosclerosis; earlier destruction and dysfunction of the media is likely to result in more severe forms of disease. That is, in the absence of medial immunoprivilege, coronary atherosclerosis and transplant vasculopathy would result in more rapid progression and earlier complications than the natural history of these diseases. It is possible that pharmacological enhancement of these protective responses may represent a novel therapeutic strategy in advanced arteriosclerosis or other more vigorous forms of arteritis in which medial immunoprivilege is lost.

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### Disclosures

None.

### References


