Allograft Arteriosclerosis and Immune-Driven Angiogenesis

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During most of the last century, the concept of atherosclerosis as a cholesterol storage disease prevailed.1 By the mid-1980s, it had become clear that in addition to lipid-engorged macrophage foam cells, cells of the adaptive immune response, particularly T lymphocytes, localized in atheromatous lesions.2 These observations raised the possibility that immune and inflammatory processes might participate in atherogenesis. However, it remained unclear whether the immune response in atherosclerosis simply followed cholesterol-inflicted damage or could possibly play a more primary role in arterial disease.

As can happen when the experimentalist maintains clinical contact, observation of the patient afforded a perspective on this puzzle. The adoption of cardiac transplantation created a new disease: accelerated coronary arteriosclerosis.3 Even in recipients with nonischemic cardiomyopathy and normal lipids, an aggressive form of intimal disease could narrow epicardial and intramyocardial coronary branches and all too often threaten graft survival. We have preferred the term arteriosclerosis (hardening of the arteries) to atherosclerosis (gruel in the arteries) because the allograft coronary artery lesions often lack a lipid-rich core typical of atheroma.

This iatrogenic disease provided a strong indication that immune activation could induce explosive intimal disease even in the absence of a strong lipid stimulus. Most cases of atherosclerosis depend at least in part on dyslipidemia. At one end of the spectrum, a child whose only risk factor is elevated low-density lipoprotein (LDL) due to homozygous familial hypercholesterolemia can develop severe atherosclerosis in the first decade of life (Figure).4 However, allograft coronary disease taught us that at the other extreme, immune factors themselves could lead to arteriopathy even in the absence of classical lipid risk factors (Figure). Just as study of familial hypercholesterolemia led to epochoval advances in our understanding of lipid-driven atherosclerosis, we reasoned that close scrutiny of allograft arterial disease could furnish new insight into immune and inflammatory mechanisms of arterial disease.

An early scheme of the pathogenesis of allograft arteriopathy posited a pivotal role for an immune response directed against foreign transplantation antigens as the trigger to a cytokine cascade that wrought the arterial damage.5 Renal transplanters recognized graft arteriopathy as “chronic rejection.” Hypothesizing that the mechanism of allograft arteriopathy differs fundamentally from myocardial rejection, we rejected that term (Table).6 Myocytolysis characterizes parenchymal rejection. Cytolytic T cells, the effector arm of the cellular immune response, mediate this lethal damage to cardiac myocytes. These killer T cells usually bear the CD8 marker and recognize their target cells by an interaction that involves class I transplantation antigens. In stark contrast, a fibroproliferative, not cytolytic, reaction typifies allograft arteriopathy. Much evidence points to a helper T cell–dependent and cytokine- and growth factor–mediated mechanism for development of this type of arterial lesion. The helper T cells usually bear the CD4 marker and recognize their target cells by an interaction that involves class II transplantation antigens (a reaction termed the allogeneic response). This postulated pathogenic pathway for allograft arteriopathy, first proposed in 1989,7 has withstood the test of time. Experiments in genetically altered mice increasingly support this model.7,8 Moreover, such experiments often show disparity in the effects of various mutations on parenchymal versus arterial disease, supporting the fundamental mechanistic differences noted above.8,9

If immune-mediated reactions cause allograft arteriopathy, why don’t the immunosuppressants taken by transplantation recipients prevent the disease? The usual menu of drugs currently used actually succeeds in preventing parenchymal rejection for the most part. However, cyclosporin poorly suppressed the ability of foreign endothelial cells to engender a cellular immune response in vitro.10

How then can we combat allograft arteriopathy in the clinic? This disease still represents a major limitation to the long-term success of cardiac transplantation and remains a pressing clinical problem. Perhaps more effective immunosuppressive regimens will prove better able to inhibit this process. Indeed, rapamycin may inhibit the immune response to foreign endothelial cells more effectively than cyclosporin. Statin treatment seems to limit the disease, perhaps in part because of effects independent of lipid lowering.11,12 Allograft arteriopathy, however, has far from disappeared and thus requires new therapies.

The recognition of the inflammatory nature of graft coronary disease suggests that antiinflammatory strategies might help. In this issue of Circulation, Nykänen et al13 show that angiopoietin-1 can protect against the development of arteriosclerosis in allografted rat hearts. Their previous work14 showed that vascular endothelial growth factor (VEGF) enhanced formation of these lesions. In their current article,13...
they show that its endogenous antagonist, angiopoietin-1, can forestall lesion formation. These observations draw attention to the role of microvessels in this disease.

Microvessels populate many human atheroma and the arterial lesions in some lipid-driven models of atherosclerosis as well. Anti-angiogenic strategies can limit experimental atherogenesis, and the results of Nykänen et al extend this concept to allograft vasculopathy. However, the story of the microvasculature in allografts is even more complex than in usual atherosclerosis. Experiments performed a decade ago showed more exuberant angiogenesis in allografted arteries than in native arteries. We compared arterial lesions in heterotopic cardiac allografts and the native heart in hypercholesterolemic rabbits. Both hearts experienced the identical lipid milieu, yet the expanded intima in the allografted arteries contained many more microvessels and T lymphocytes than those in the recipients’ own arteries. These observations suggested that the allogenic immune response accentuated angiogenesis during atherogenesis. Later studies showed that during the atherogenic response in vitro, T lymphocytes produce angiogenic growth factors including VEGF. Thus, the observations of Nykänen et al may have particular relevance to this special form of arteriosclerosis. In addition to angiopoietin, transplanted hearts can overexpress another endogenous modulator of angiogenesis. Human cardiac allografts overexpress thrombospondin-1 (TSP-1), an extracellular matrix glycoprotein that inhibits angiogenesis and facilitates smooth muscle cell proliferation. Significant elevation of TSP-1 in cardiac allografts associates with the severity of cardiac allograft arteriosclerosis. Smooth muscle cells from the luminal (inner) layer of the expanded intima intensely express TSP-1, whereas the greatest VEGF expression occurs in infiltrating inflammatory cells in the abluminal (outer) layers of the intima. Neovascularization co-localizes with VEGF-producing cells and is sparse in areas with intense TSP-1 expression. These data suggest that angiogenesis modulators, such as TSP-1, inhibit angiogenesis and promote smooth muscle cell proliferation, processes that promote transplantation arteriopathy.

What lessons can we draw from the tale of transplantation arteriopathy? First, the life-saving procedure of cardiac transplantation comes with a biological cost — a risk of obliterative arteriopathy that too often replaces one disease with another.

Second, by studying the rarer but extreme forms of disease, we can gain insight into the pathogenesis of the more common but often multifactorial afflictions. Indeed, most cases of “usual” atherosclerosis likely lie between the two poles of strictly immune-dependent allograft arteriopathy and the solely lipid-driven lesions in the young familial hypercholesterolemic patient (Figure). In most atherosclerotic patients, a mix of lipid disorders and immune and inflammatory factors conspire to promote the disease.

Third, we must remember that angiogenesis can cut both ways in arteriosclerosis. Formation of neovessels in the lesion may sustain its growth and provide a portal for entry of inflammatory cells. These potential adverse actions of angiogenic therapy for atherosclerosis merit thoughtful consideration.

Fourth, opposing forces are the norm in biology; in this case, the actions of anti-angiogenic and antiinflammatory

### Cardiac Allograft Parenchymal Rejection Versus Arteriopathy

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<td>Histological hallmark:</td>
<td>Myocytolysis</td>
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<td>Major effector cell:</td>
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factors can countervail the heightened angiogenic response in the transplanted artery.

Finally, by picking apart the fundamental details of disease pathogenesis, we may identify new therapeutic targets that will aid us in treating patients. When we really understand myocardial failure and atherosclerosis, we won’t need to transplant hearts. Until then, we must strive to understand and overcome allograft arterial disease.

Acknowledgments
Dr Libby is supported in part by a grant from the National Heart, Lung and Blood Institute (HL-43364).

References

Key Words: Editorials angiogenesis arteriosclerosis transplantation inflammation