Chronic Rejection in Rat Aortic Allografts
An Experimental Model for Transplant Arteriosclerosis

Ari Mennander, Sinikka Tiisala, Jorma Halttunen, Serdar Yilmaz, Timo Paavonen, and Pekka Häyry

Chronic rejection has several histological appearances, depending on the type of organ graft. Common to all of them is transplant arteriosclerosis associated with an ongoing inflammatory response in the transplanted graft. To the contrary of classical atherosclerosis, in which the manifestations are mostly focal, proximal, and asymmetric, transplant arteriosclerosis is generalized, and the intimal thickening is concentric. In this article, we describe an experimental animal model whereby transplant arteriosclerosis may be investigated in the inbred rat. Aortic allografts were transplanted from DA (RT1+) to major histocompatibility complex-incompatible WF (RT1-) rats or, for control, to rats of the DA strain. Transplantation was followed by an acute inflammation episode in the aortic adventitia of the allograft, largely lacking in the syngeneic graft, with a prominence of lymphoid activation markers (CD25) in the cells of the inflammatory infiltrate. The inflammation episode peaked at 2 months after transplantation, became attenuated, and was followed by a proliferative response of myocytes in the allograft media. An increase in the migration of myocytes to the subendothelial space (presumably through small breaks generated in the internal elastic lamina) was observed thereafter, and myocyte proliferation continued in the intima with some intermingled macrophages. Finally, necrosis and disappearance of myocytes and their replacement by fibrous tissue were observed in the media. These alterations are virtually identical with the vascular lesion of chronically rejecting parenchymal organ transplants in human subjects. We suggest that aortic allografts exchanged between histoincompatible rat strains may be used as an experimental model for transplant arteriosclerosis. (Arteriosclerosis and Thrombosis 1991;11:671–680)

Only 15 years ago, most cadaveric allografts were lost to acute rejection. During recent years, very significant progress has been made in documenting the various molecular and cellular pathways of acute rejection. This, in turn, has led to improvements in the immunosuppression, diagnosis, and treatment of acute rejection episodes. Currently, most centers report an approximate 85% cadaveric allograft survival of most organs at 1 year, with the exception of the pancreas. Instead, a different problem, chronic rejection, has emerged, becoming a prime obstacle of long-term allograft survival.

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arteriosclerosis in the inbred rat. Moreover, we document for the first time the sequence of events in the development of these histopathological lesions in experimental animals.

**Methods**

**Animals**

WF (AG-B2, RT1<sup>+</sup>) and DA (AG-B4, RT1<sup>+</sup>) rat strains were used for transplantation. The WF nucleus was originally obtained from H.O. Sjögren, University of Lund, Sweden, and the nucleus for the DA strain from J.L. Gowans, Dunn School of Pathology, Oxford, U.K. Later, all animals were purchased from the Versuchstierzucht, Hannover, F.R.G. Male rats weighing 200–300 g that were 2–4 months old were used as donors and recipients.

**Transplantations**

A segment of descending thoracic aorta approximately 1.5 cm long was removed, thoroughly perfused with saline, and used as a transplant. All animals received 1–2.5 ml chloral hydrate as an anesthetic agent. The graft was transplanted into a heterotopic position below the renal arteries and above the bifurcation. The cranial suture line was made as close to the renal arteries as technically possible to minimize the difference in diameter. An end-to-end anastomosis was performed with a 9-0 continuous nylon suture. In our experience, the frequency of technical failures was about one in 100 operations. The total ischemic time was approximately 60 minutes, during which the graft was kept in an ice bath for 15 minutes. No single graft was lost to thrombosis. The morphological changes were quantified according to standard morphometric principles<sup>12</sup> and expressed as point score units (PSUs), that is, the mean number of points on a given anatomic area using straight cross-sectional lines and a 0.02-mm grid. The following variables were evaluated: the number of nuclei and the thickness of the different layers of the aorta, that is, the adventitia, media, and intima, separated from each other by the external and internal elastic laminae, respectively. A minimum of five technically successful transplantations were made for each time point, and their means were used as final scores.

**Histological Specimens and Staining**

For evaluation of morphological changes, paraffin sections were stained with hematoxylin and eosin, Masson trichrome, or elastin. Longitudinal sections were prepared so that the vessel wall on both the graft and the host sides of the suture line could be observed, as well as cross sections for evaluation of circular changes in the graft. These specimens were compared with the thoracic aorta of the recipient as the normal control. The cross sections were prepared from the center of the graft to avoid the effects of the suture line.

**Immunohistochemistry**

For immunohistochemistry, 3–4-μm-thick frozen cross sections were stained by the immunoperoxidase technique with the following monoclonal antibodies (ascites fluid; Sera-lab, Sussex, England): W3/25 to Cd4; OX8 to Cd8; OX42 to macrophages, granulocytes, and dendritic cells; OX39 to interleukin-2 receptor (Cd25); and OX4 to class II common determinant. Monoclonal anti-α-smooth muscle actin was obtained from Bio-Makor, Rehovot, Israel. The cryosections were labeled by a two-layer indirect peroxidase technique described in detail elsewhere.<sup>11</sup> Briefly, the sections were incubated with appropriately diluted monoclonal antibody (usually 1:20; anti-actin in 1:10,000), washed, and incubated consecutively with peroxidase-conjugated rabbit anti-mouse immunoglobulin and goat anti-rabbit immunoglobulin (Dako Immunoglobulins a/s, Glostrup, Denmark), followed by treatment with the substrate solution containing the chromogen 3-amino-9-ethylcarbazole. Hydrogen peroxide was added to the 3-amino-9-ethylcarbazole solution immediately before use. The samples were counterstained with Mayer’s hemalum solution and then mounted.

**Evaluation of Histology and Immunohistochemistry**

The morphological changes were quantified according to standard morphometric principles<sup>12</sup> and expressed as point score units (PSUs), that is, the mean number of points on a given anatomic area using straight cross-sectional lines and a 0.02-mm grid. The following variables were evaluated: the number of nuclei and the thickness of the different layers of the aorta, that is, the adventitia, media, and intima, separated from each other by the external and internal elastic laminae, respectively. A minimum of five technically successful transplantations were made for each time point, and their means were used as final scores.

For immunohistochemistry, only one to four samples per time point were stained. The samples were evaluated by examining the entire cross section.

**In Vivo Labeling and Autoradiography**

In some allografts, the recipient rat received 250 μCi of tritium-labeled thymidine (H-TdR, NEN, Boston, Mass.) by injection into the dorsal penis vein 30 minutes before the rat was killed. The histology samples were processed from paraffin sections, stripping-film autoradiography (Kodak AR-10, Eastman Kodak, Rochester, N.Y.) was performed, and labeling of the nuclei in the transplanted aortic wall was compared with the labeling index in the recipient aorta.

**Results**

**Morphological Changes**

At least five technically successful allografts were examined for each time point: at 0, 10, and 20 days and at 1, 2, 3, and 6 months after transplantation; the 1-year time point represents three transplantations only. Correspondingly syngeneic controls were made at 20 days and at 1 and 3 months. For each graft, the thickness and number of nuclei in the three layers of the vessel wall were determined from cross sections.
Adventitia/cells

psu

SYN △ ALLO

TIME/MONTHS

Adventitia/thickness

psu

SYN △ ALLO

TIME/MONTHS

The effect of the suture line was examined from longitudinal sections.

Adventitia.

NUCLEI. Very few nuclei, which were mainly fibroblasts (on average, 0.5±0.5 PSU per cross-sectional line), were detected in a normal aortic adventitia. In the allografts, there was a rapid infiltration of inflammatory cells into the adventitia, with a peak of 8.9±5.0 PSUs at 2 months, after which the inflammation declined. The number of nuclei decreased thereafter and reached nearly normal values at 1 year after the operation (Figure 1, upper panel).

The adventitia of the syngeneic grafts was also infiltrated by some inflammatory cells, as detected by the increase in the number of nuclei in the adventitia. Nevertheless, the inflammatory response was weaker than that in the allografts. A peak value of 3.8 PSUs was reached at 20 days; the nuclear density remained slightly elevated compared with that of normal adventitia thereafter.

THICKNESS. The thickness of the adventitia of a nontransplanted rat aorta was 2.7±0.7 PSUs. The thickness increased postoperatively in the allografts, reaching a peak of 5.9±0.6 PSUs at 1 month. The increase in thickness was mostly due to edema associated with or caused by the inflammation. Thereafter, the thickness decreased steadily, reaching normal values by 6 months, when fibrotic changes become evident.

The response in the syngeneic grafts was more modest (Figure 1, lower panel).

Media.

NUCLEI. The number of nuclei in the media of a normal rat aorta was 3.1±1 PSUs. In the allografts, the number of nuclei remained normal until 1 month after transplant, after which a sharp drop, indicating medial necrosis, was observed. The minimum values were reached by 6 months. Thereafter, the allograft media was essentially acellular. In the syngeneic grafts, the nuclear density of the media remained at pretransplant control levels throughout the observed time (Figure 2, upper panel).

THICKNESS. The thickness of the medial layer of a nontransplanted rat aorta was 5.0±0.4 PSUs. In the allografts, the thickness of the media decreased steadily during the time range observed. At one year, a minimum value of 3.2±0.2 PSUs was observed, showing a 40% decrease compared with the nontransplanted control value. Weakening of the medial layer is a likely reason for the occasional aneurysms observed in the allografts, mostly close to the suture line (not shown). In the syngeneic grafts, the thickness of the medial layer remained at control levels throughout the observed time range (Figure 2, lower panel).

Intima.

NUCLEI. The number of nuclei in the normal rat aortic intima was 0.5±0.5 PSU, consisting of the
endothelial monolayer only. The number of nuclei in the intima of allografts increased after transplantation, reaching a peak of 3.3±0.5 PSUs at 1 year. No significant changes were observed in the syngeneic grafts compared with nontransplanted controls (Figure 3, upper panel).

**Thickness.** The intima of a normal rat aorta consists of a monolayer of endothelial cells, with a thickness of approximately 0.1±0.1 PSU. In the allografts, there was a steady increase of intimal thickness to 2.7±1.1 PSUs at 1 month, to 3.8±0.8 PSUs at 3 months, and up to 5.1±0.6 PSUs at the end of the observation period of 12 months. In the syngeneic controls, the thickness remained at normal control levels during the observed time (Figure 3, lower panel).

*Photomicrographs of histology.* Characteristic changes in the aortic allograft and in the syngeneic controls are shown in Figures 4 and 5.

**Immunohistochemistry**

The subclasses of infiltrating leukocytes in the grafts were examined by immunoperoxidase staining. Also, the expression of the major histocompatibility complex class II antigen and of the interleukin-2 receptor was determined.

In the allograft adventitia and in the syngeneic grafts, nearly all cells, which were mostly inflammatory, expressed class II antigens throughout the observation period (not shown).

Very few cells expressing the interleukin-2 receptor were detected in syngeneic controls. In allografts, the expression of interleukin-2 receptor was somewhat higher shortly after transplantation, when positive cells were found in the adventitia only (Table 1). Thereafter, the amount of interleukin-2 receptor–expressing cells declined in the adventitia (not shown).

No consistent differences were seen between the amount of Cd4- and Cd8-positive cells until 1 year (Table 1).

Cells reacting with monoclonal antibody OX42 to monocytes and macrophages were frequent in the allograft adventitia (Table 1), but positive cells were also detected in the media and intima from 20 days to 3 months onward (see below).

**Intimal Response**

The origin and type of proliferating cells in the intima were determined by autoradiography in combination with immunohistochemical staining with monoclonal antibodies.

In the intima, most cells were smooth muscle cells as detected by an antibody directed to smooth muscle cell actin (Figure 6). Some T lymphocytes, but par-
particularly macrophages, were also detected in the intima (Figure 7).

Autoradiography of the histological sections performed at 1 and 2 months after transplantation demonstrated \( ^3 \)H-TdR-incorporating cells in the adventitia, media, and intima (Table 2). Most of the proliferating cells in the adventitia were inflammatory cells, whereas most of the proliferating cells in the media and intima were actin-positive cells, as judged by comparison between the autoradiographs and immunohistochemical staining. Occasional \( ^3 \)H-TdR-incorporating cells were also seen in the endothelial lining, particularly 2 weeks after transplantation.

**Table 1.** Immunohistochemistry of Adventitial Inflammation

<table>
<thead>
<tr>
<th>Type of graft</th>
<th>Time (mo)</th>
<th>Intensity of inflammation (PSU)</th>
<th>Cd4</th>
<th>Cd8</th>
<th>IL-2 R</th>
<th>Mo/Mp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allograft</td>
<td>0.3</td>
<td>4.5</td>
<td>2+</td>
<td>3+</td>
<td>2+</td>
<td>2+</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>6.2</td>
<td>2+</td>
<td>3+</td>
<td>2+</td>
<td>2+</td>
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<tr>
<td></td>
<td>2</td>
<td>8.8</td>
<td>2+</td>
<td>3+</td>
<td>1+</td>
<td>3+</td>
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<td>3</td>
<td>4.6</td>
<td>2+</td>
<td>3+</td>
<td>1+</td>
<td>3+</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>3.2</td>
<td>2+</td>
<td>2+</td>
<td>1+</td>
<td>3+</td>
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<tr>
<td></td>
<td>12</td>
<td>1.7</td>
<td>2+</td>
<td>1+</td>
<td>1+</td>
<td>2+</td>
</tr>
<tr>
<td>Syngeneic graft</td>
<td>0.6</td>
<td>3.8</td>
<td>2+</td>
<td>2+</td>
<td>-</td>
<td>3+</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2.6</td>
<td>2+</td>
<td>1+</td>
<td>-</td>
<td>3+</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.8</td>
<td>2+</td>
<td>1+</td>
<td>-</td>
<td>2+</td>
</tr>
<tr>
<td>Nontransplanted</td>
<td></td>
<td>0.5†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Arbitrary scale from – through 3+.
†Monoclonal antibodies used included the following: W3/25 to Cd4; OX8 to Cd8; OX39 to interleukin-2 (IL-2) receptor (R); monocytes/macrophages (Mo/Mp) to OX42.
‡The adventitia contained only occasional nuclei of connective tissue cells.
FIGURE 4. Photomicrographs of longitudinal sections of syngeneic graft (panel A) and an allograft (panel B) 6 months after transplantation. Lower-case letters indicate major anatomic structures of the aortic wall: a, adventitia; m, media, separated by external and internal elastic laminas (arrows); i (in the allograft), intima; and e (in both types of grafts), endothelial lining. Note inflammation in the adventitia, complete loss of nuclei, narrowing of the media, and intimal proliferative response in the allograft, which are lacking in the syngeneic graft. Hematoxylin and eosin stain, ×96.

Internal and External Elastic Laminas

The integrity of the internal and external elastic laminas was determined by staining for elastin. After 3–12 months after transplantation, both the internal and external laminas of syngeneic grafts were intact (not shown). In the allograft, the external elastic lamina was essentially intact, whereas the internal elastic lamina displayed occasional small breaks (Figure 8).

Discussion

Histopathological lesions of chronic organ allograft rejection carry a variety of manifestations depending on the type of organ allograft. A manifestation common to all of these is obliterative transplant arteriopathy, affecting first the small- and medium-sized (<50-μm external diameter) intra-organ muscular arteries. The areas of predilection include interlobar, arcuate, and interlobular muscular arteries of the kidney,13 large and small epicardial and penetrating intramyocardial arteries branching from the epicardial coronaries of the heart,14 and second- and third-order branch arteries of the hepatic hilus.15 Gross histological alterations in the transplant such as glomerular sclerosis, interstitial fibrosis, tubular atrophy, and eventual infarcts in the kidney; fibrosis and infarcts in the heart; and fibrosis and vanishing bile ducts in the liver may be considered secondary to the obliterative arteriopathy and hypoxia.

An excellent description of obliterative arteriopathy in various parenchymal organ transplants has been given by Demetris et al.15 The most prominent feature is concentric intimal hyperplasia intermixed with some degree of inflammation and the dominance of actin-stained irregular and spindle-shaped cells between the endothelium and the internal elastic lamina in cardiac and renal allografts, but to a lesser extent, in liver allografts. Occasional macrophages are also present. The internal elastic lamina is grossly intact but usually focally disrupted, the media may appear thinned, and individual myocyte vacuolization and pyknosis is detected. The adventitia of most affected vessels is expanded, edematous, and infiltrated by varying degrees of inflammatory macrophages and lymphocytes. Proliferation of both inflammatory and spindle-shaped actin-positive cells in the intima was a characteristic finding when an antibody reactive in phases other than G0 of the cell cycle was used.15

Thus, the obliterative arteriopathy of human transplants is strikingly different from atherosclerotic ar-
teriopathy of human subjects, which is usually focal and asymmetric, particularly involves major vessels and the proximal part of the coronaries, and results in atherosclerotic calcifications and plaques, usually with an entirely disrupted internal elastic lamina. The nonimmunosuppressed aortic transplant model, described for the first time in this article, carries striking morphological similarities to the vascular lesions of parenchymal organ transplants in human subjects. The intimal response, including endothelial cell hypertrophy and smooth muscle cell proliferation in the intima and minor breaks in the internal elastic lamina, is virtually identical to corresponding alterations in human heart and kidney transplants.

Also, the rat aortic allografts biochemically resemble chronically rejecting human transplants. In chronic renal transplant rejection, an increase in thromboxane synthesis and in plasma levels of thromboxane has been demonstrated. In contrast, plasma levels of prostacyclin were not increased or, rather, tended to be reduced. Similarly in our model, there was a sharply increased synthesis of thromboxane B$_2$ (A. Mennander, unpublished observations), but no increase in the synthesis of 6-keto-prostaglandin F$_{1\alpha}$, when rat aortic allograft rings were incubated in vitro.

The intimal response was associated with ongoing inflammation in the adventitia, and concomitantly, myocyte necrosis was observed in the media. As in human transplants, the process is slow: Distinct changes are recorded first between the first and third month after transplantation, and extreme alterations are recorded between 6 months and 1 year.

The first recorded alteration was inflammation in the aortic allografts, particularly in the adventitia. Inflammation was timewise linked, and it preceded induction of the intimal proliferative response. As the activated cell forms displaying interleukin-2 receptors were recorded during the inflammatory episode mostly in the allograft but not in the syngeneic graft, an acute rejection episode appeared to be a prerequisite for the development of intimal hyperplasia. Increases in intimal cell number and in the thickness of the intima begin shortly after initiation of an acute episode of rejection and initially follow the inflammatory response in the adventitia. However, the intimal response may later become independent of adventitial inflammation, as the increase

**Figure 5.** Higher-magnification photomicrographs of cellular response in the intima (panel A) and of inflammation in the allograft adventitia (panel B). In panel A, letters iel and the arrow indicate internal elastic lamina and internal border of the media, respectively; e indicates endothelial lining. In panel B, letters eel and the arrow indicate external elastic lamina and outer border of the media, respectively. Hematoxylin and eosin stain, ×240.
**Figure 6.** Photomicrographs of smooth muscle α-actin staining in syngeneic graft (panel A) and in allograft (panel B). Note intense staining of media (m) in the syngeneic graft, indicating preservation of myocytes, and a nearly complete loss of staining in media of the allograft, indicating medial smooth muscle cell degeneration and fibrosis. Instead, in the allograft intimal cells stain strongly for smooth muscle α-actin. Inflammatory cell nuclei in adventitia (in panel B) counterstain black. e, endothelial lining. Immunoperoxidase and hemalum stain, ×96.

**Figure 7.** Photomicrographs showing staining of allograft intimal cells with antibody to macrophages (OX42, panel A) and with antibody to smooth muscle α-actin (panel B). A series of five OX42-positive macrophages is shown in panel A, whereas most of the intimal cells display cytoplasmic reactivity to α-actin (panel B). Letters iel and the arrow indicate internal elastic lamina. Immunoperoxidase and hemalum stain, ×240.
TABLE 2. Proliferative Response in Three Layers of Aortic Allograft at the Peak of Adventitial Inflammation, 2 Weeks and 1 Month After Transplantation*

<table>
<thead>
<tr>
<th>Time after transplantation</th>
<th>Tritium-labeled thymidine-incorporating nuclei/500 nuclei</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adventitia</td>
</tr>
<tr>
<td>2 weeks</td>
<td>21</td>
</tr>
<tr>
<td>1 month</td>
<td>23</td>
</tr>
</tbody>
</table>

*Two determinations only. In the recipient thoracic aorta, <1 tritium-labeled thymidine-incorporating nuclei per 500 nuclei was present in any one of the layers of the vascular wall.

in intimal thickness continues while the inflammation in the adventitia subsides.

In the past, some attempts have been made to develop animal models for chronic rejection, particularly in a genetically defined background: A group of investigators in Uppsala, Sweden, has been using rat heart allografts acutely immunosuppressed with antithymocyte globulin or cyclosporine. Craemer et al in Pittsburgh have employed rat heart allografts exchanged between strains with selected histocompatibility differences with compatibility in the class II locus of the major histocompatibility complex. Finally, Foegh et al have transplanted heart allografts between normocholesterolemic or hypercholesterolemic random-bred rabbit strains, immunosuppressed with cyclosporine, as originally suggested by Alonso et al. Our own experience with rat kidney allografts transplanted between major- and minor-histoincompatible rat strains and initiated with a short course of cyclosporine is also promising (S. Yilmaz, unpublished observations). Why, then, develop a model employing an aortic allograft?

There are important reasons for developing this model. The immune response generated by the aortic allograft is sufficient to induce chronic alterations in the transplant but is insufficient to induce an acute irreversible rejection. No initial immunosuppression is thus needed, and no transplants were lost to acute rejection. Thus, this model offers a possible way to investigate the effects of individual drugs, including immunosuppressive drugs, on obliterator arteriopathy without employing any unwanted prophylactic immunosuppressive treatment.

At the present, very little is known about the immunogenetic basis and molecular biology of allograft arteriosclerosis. It is known from animal models that both major and minor histocompatibility differences may produce chronic rejection of rat cardiac allografts. Our preliminary results (A. Mennander, unpublished observations) suggest that retransplantation of an allograft back to the syngeneic donor strain may obliterate the progression of intimal proliferation. The role of antibodies, previously taken for granted, is becoming controversial. Neither do we consider it conceivable that cytotoxic T cells can directly induce endothelial or smooth muscle damage, as the majority of inflammation is located in the adventitia.

In addition to the inflammatory cells within and in the vicinity of the vessel wall, the components of the wall itself and the endothelial and smooth muscle cells are also important. Both cell types are capable of producing a variety of cytokines and growth factors, which can potentially induce morphological changes.

Mediators of inflammatory leukocytes, cytokines, comprise one group of molecules that are likely involved in the pathogenesis of transplant arteriosclerosis. In addition to inflammatory cells, these molecules are secreted by many cell types, including the cell types of the vascular wall. Interleukin-1 acts as a mitogen for smooth muscle cells and fibroblasts, whereas endogenous prostaglandin production inhibits the interleukin-1-stimulating proliferative response. We do not know of any documented effects of interleukin-2 and interleukin-6 on the proliferation of smooth muscle cells. Instead, another leukocyte-derived cytokine, γ-interferon, inhibits smooth muscle proliferation, at least in response to growth factors, such as platelet-derived growth factor, or stimulatory lymphokines, such as interleukin-1.

Another group of molecules most likely active in the pathogenesis of chronic transplant arteriosclerosis includes arachidonic acid metabolites, eicosanoids, and platelet-activating factor. Increased levels of thrombox-

![Figure 8](http://atvb.ahajournals.org/)

**Figure 8. Photomicrograph showing elastin staining of allograft wall, demonstrating occasional breaks (arrows) in the internal elastic lamina (iel). e, endothelial lining. ×240.**
ane, but not of prostacyclin or prostaglandins, has been reported in patients with chronic rejection.16

A third group of molecules of large potential interest in the generation of this lesion is the growth factors. Growth factors are produced by endothelial and smooth muscle cells as well as by cells that have invaded the vessel wall, including monocytes, platelets, and leukocytes. The effects of growth factors on smooth muscle cell proliferation are most likely complex, as the same peptide may have both stimulatory and inhibitory activities on a single cell line, at least in vitro.27 Platelet-derived growth factor, particularly the β-chain containing heterodimers or homodimers, are stimulatory to smooth muscle cells, and an upregulation of the platelet-derived growth factor β-receptor has been observed in rat heart and renal tissue undergoing chronic vascular rejection (Reference 28 and N.A. Higgy and L.C. Paul, personal communication). Other growth factors including epidermal growth factor and basic fibroblast growth factor and cytokines such as interleukin-1 and tumor necrosis factor may regulate the expression of platelet-derived growth factor mRNA,29 in addition to having potential direct effects on smooth muscle cell proliferation.

It is most important to realize how these interactions are regulated. This model will make this type of study possible. The aortic transplant is the simplest possible model to investigate actual alterations of various molecular pathways within the vascular wall, independently of the rest of the transplanted organ. Thus, the model makes it possible to quantify the biochemical and molecular alterations during the arteriosclerotic process within the vascular wall, separately in its three compartments. These possibilities will be explored in later communications.

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References


Key Words • chronic rejection • allograft • arteriosclerosis
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