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Will chronic rejection ever respond to treatment?

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In *acute* allograft rejection, the end-point is irreversible damage of the graft (microvascular) endothelium by inflammatory cells and antibodies, and thrombosis and necrosis of the graft. In *chronic* rejection a prime manifestation, common to all transplants, is persistant perivascular inflammation and concentric longitudinal allograft arteriosclerosis [1] affecting particularly the first and second order intragraft branches of transplant arteries (Table 1). Thus, to understand the molecular mechanism of chronic rejection, we should know how the immune inflammation regulates vascular smooth muscle cell (SMC) proliferation.

Key words: Chronic rejection – Allograft – Arteriosclerosis

Regulation of vascular smooth muscle cell proliferation

Vascular smooth muscle cells have two phenotypes, contractile phenotype relevant in adult organisms, and synthetic phenotype, relevant during embryogenesis. During arteriosclerosis, there is a gradual transition from the contractile to the synthetic phenotype [2], the phenotype that is capable to cell division.

In vitro studies have relevated a variety of molecules, including polypeptide mitogens (such as platelet-derived growth factor, insulin-like growth factor, epidermal growth factor, and fibroblast growth factor), interleukins (such as IL-1, and -6), vasoactive hormones (such as endothelin) and eicosanoids, which may induce vascular smooth muscle cell proliferation.

Aortic allografts: a model for transplant arteriosclerosis

In order to investigate which of these molecules may be operative in chronic vascular changes of an organ allograft, we have developed an in vivo model: aortic allotransplantation across histoincompatible rat strains [3]. Non-immunosuppressed allografts undergo an acute adventitial inflammatory episode after transplantation, with CD25 positive (blast) cells and oedema, which spontaneously subsides. This is followed by more a chronic type of inflammation in the adventitia, induction of smooth muscle cell proliferation in the media, focal fragmentation of the internal elastic lamina and appearance of proliferating smooth muscle cells in the intima. This process leads to concentric intimal thickening and gradual occlusion of the graft. Applications of proper antibody and immunofluorescence demonstrates increased expression of class II antigens in the allograft endothelium, and depositions of IgG and complement on the vascular wall. These alterations observed in aortic allografts, are virtually indistinguishable from those seen in human allograft vasculature during chronic rejection.

Role of eicosanoids

Out of the various regulatory molecules listed above and being possibly of significance in the induction of allograft arteriosclerosis, we have investigated the role of eicosanoids [4]. During the chronic stage there is an increased synthesis of thromboxane B2 in an aortic allograft which is lacking in syngeneic grafts, but only a small (compensatory?) increase in 6-keto-PGF1alpha and no change in LTB4. These observations are compatible with human studies, demonstrating increased levels of thromboxane in the urine of chronically-rejecting transplant recipients.

Modtification of allograft arteriosclerosis by extraneous factors

Of particular interest is whether and how this process may be modified by extraneous factors, particularly if the process is reversible; and what is the role of diet and the impact of CMV infection. Our preliminary studies indicate, so far, that retransplantation of an allograft back to the syngeneic host 1 month after transplantation, inhibited the progression of the intimal changes. On the other hand,

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Table 1. Manifestations of chronic rejection in different organs

Heart[a]	Kidney[b]	Liver[c]
Inflammation	Inflammation	Inflammation
Arteriosclerosis	Arteriosclerosis	Arteriosclerosis
Fibrosis	BM thickening	Vanishing bile ducts &
	Glomerular sclerosis	portal arteries
	Tubular atrophy	Fibrosis
	Fibrosis	

[a] Rose and Uys, Pathology of graft atherosclerosis (chronic rejection), in Cooper and Novitsky, Transplantation and replacement of thoracic organs, Kluwer Academic Publ., Dordrecht 1990 [6]
[b] Croker and Salomon, Pathology of renal allograft, in Tisher and Brenner, Renal Pathology, L. B. Lippincott, Phila, 1989 [7]
[c] Oguma et al. Hepatology, 1989: 9: 204 [8]

transplantation to the allogeneic host definitely continued the process. Feeding the recipient rat with cholesterol and cholic acid induced hypercholesterolemia in the recipients, with increased levels of both VLDL and LDL, but with no change in HDL cholesterol. There was no alteration in the levels of triglycerides, either. This diet did not enhance the arteriosclerotic process in our animals, which might indicate that increased levels of cholesterol may not, per se, be enhancing to the process. It should be also noted that in man, a better correlation has usually been obtained between accelerated arteriosclerosis and triglycerides rather than with cholesterol.

Pharmacological interference with allograft arteriosclerosis

Drugs known to inhibit the immune response, such as cyclosporine (at the level of 5 mg/kg/day), azathioprine (2 mg/kg/day), or steroids (methyl prednisolone, 0.5 mg/kg/day), although anti-inflammatory for adventitial inflammation, did not inhibit allograft arteriosclerosis and the increase in intimal thickeness. In fact, at this dose level, the administration of CyA significantly enhances arteriosclerosis [5].

The separate application of two inhibitors for lipid mediators of inflammation, i.e., GR32191B (a thromboxane A2 receptor blocker), and WEB2170 (a PAF receptor blocker), significantly reduced the rate of smooth muscle proliferation in the allograft, but delayed the arteriosclerotic process by only 1–3 months (to be published). The application of BIM23401 (angiopeptin), a somatostatin analogue, also reduced the level of smooth muscle cell proliferation, but was able to delay the generation of arteriosclerosis by 3 months, at the most.

Discussion and conclusions

In order to understand chronic rejection, we should understand allograft arteriosclerosis. In particular, we should know how the immune inflammation regulates arterial smooth muscle proliferation. Allograft arteriosclerosis seems to be under the control of the immune response, and may be reversible (at least) at very early stages post transplantation. In our hands, hypercholesterlemia did not enhance it, but we do not know the role of triglycerides. Conventional immunosuppressive drugs do not inhibit the process at levels capable of reducing the allograft immune response in the rat. In fact, cyclosporine may enhance it. Instead, the application of certain antagonists to lipid mediators of inflammation, or certain octapeptide analogues of somatostatin may inhibit the rate of proliferation of arterial smooth muscle cells and the induction of allograft arteriosclerosis.

We consider it likely that this condition will become treatable. Before the treatment format materializes one should, however, know in more detail the structure of the molecular cascade leading to smooth muscle cell proliferation in the allograft vascular wall. At present it is not possible to judge whether the treatment should be prophylactic, and directed particularly to the perioperative period (when the allograft seems to be most vulnerable to damage contributing to the process), or whether an effective treatment may be established when the process is already underway.

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References

1. Demetris AJ, Zerbe T, Banner B (1989) Morphology of solid organ allograft arteriopathy: identification of proliferating intimal cell populations. Transplant Proc 21: 3667–3669
2. Thyberg J, Hedin U, Sjölund M, Palmberg L, Bottger BA (1990) Regulation of differentiated properties and proliferation of arterial smooth muscle cells. Arteriosclerosis 10: 966–990
3. Mennander A, Tiisala S, Halttunen J, Yilmaz S, Paavonen T, Häyry P (1991) Chronic rejection in rat aortic allografts. An experimental model for transplant arteriosclerosis. Arteriosclerosis Thromb 11: 671–680
4. Mennander A, Tiisala S, Ustinov J, Paavonen T, Häyry P (1991) Chronic rejection of rat aortic allografts. III. Synthesis of the major eicosanoids by the vascular wall components, and the effect of inhibition of the thromboxane cascade. Submitted
5. Mennander A, Tiisala S, Paavonen T, Halttunen J, Häyry P (1991) Chronic rejection of rat aortic allografts. II. Administration of cyclosporine induces acclerated allograft arteriosclerosis. Transplant Int 4: 173–179
6. Rose AG, Uys CJ (1990) Pathology of graft atherosclerosis (chronic rejection). In: Cooper DKC, Novitsky D (eds) The Transplantation and replacement of thoracic organs. Kluwer Academic Publishers, Dordrecht, Boston, London, pp 161–182
7. Croker BC, Salomon DR (1989) Pathology of the renal allograft. In: Tisher CC, Brenner BM (eds) Renal Pathology. LB Lippincott, Philadelphia, pp 1518–1554
8. Oguma S, Belle S, Starzl TE, Demetris AJ (1989) A histometric analysis of chronically rejected human liver allografts: insights into the mechanisms of bile duct loss: direct immunologic and ischemic factors. Hepatology 9: 204–209