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Alloantigen-independent factors lead to signs of chronic rejection in long-term kidney isografts

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Abstract Chronic rejection is the most important cause of graft failure after the first year of transplantation. In addition to the effects of host immunological injury, antigen-independent factors may gain in importance over the long term. We therefore assessed the influence of such factors on rat kidney isografts functioning for prolonged periods and compared our findings with those observed in naive control rats and in allograft recipients. Functional, morphological, and immunohistological changes in the isografts became obvious 32 weeks after engraftment, and by 52 weeks the findings mimicked those of chronic allograft rejection. As allografted kidneys sustained these changes earlier on and more intensely, both alloantigen-independent and -dependent factors are thought to be implicated in this process.

Key words Chronic rejection
Isografts · Alloantigen-independent influences

Introduction

Although chronic allograft rejection is the predominant reason for late allograft loss, regardless of organ type, the pathophysiology underlying this enigmatic phenomenon is not understood [1]. Progressive morphological changes of renal transplants include proliferative vascular changes, glomerulosclerosis, interstitial fibrosis, and tubular atrophy occurring in parallel with deteriorating function. Early acute rejection episodes may influence the later course of the graft, as may antigen-independent factors which include the duration of ischemia and the ratio of functioning kidney mass to body weight [2].

In the present study, we attempted to assess the impact of alloantigen-independent factors on chronic changes in kidney isografts functioning for prolonged periods by comparing functional, morphological, and immunohistological alterations with those occurring in allografts and in naive controls.

Materials and methods

Lewis (LEW, $RT1^l$) recipients of orthotopic LEW kidney isografts were either untreated or received an initial low dose of cyclosporin A (CsA, 5 mg/kg daily × 10 days; $n = 24$). CsA (5 mg/kg daily × 10 days)-treated LEW recipients of Fisher 344 (F-344, $RT1^{lv1}$) kidney allografts ($n = 50$) were use as controls; this strain combination represents an established model of chronic rejection in which functional and morphological changes occur progressively [3]. Additional controls included age-matched uninephrectomized and non-nephrectomized naive LEW rats ($n = 24$/group). Urinary protein excretion was determined serially. Kidneys were removed at serial intervals and sections stained with hematoxylin and eosin and periodicacid-Schiff. Immunohistology in allografts, isografts, and naive LEW kidneys was performed for macrophages (ED-1), T cells (OX-19), CD4+ T helper cells (OX-4), CD8+ T cytotoxic/suppressor cells (OX-8), MHC class II (OX3), ICAM-1 (IA29), sev-

eral cytokines including TNF-α, TGF-β, EGF, IL-2, IL-6, and PDGF, and the deposition of immunoglobulins, C3, and fibrin. Functional, morphological, and immunohistological evaluations were obtained serially at 2, 4, 8, 12, 16, 24, 32, 48, and 52 weeks after engraftment.

Results

By week 52, isograft recipients, regardless of CsA treatment, excreted >40 mg of protein per 24 h, significantly ($P < 0.01$) more than unilateral nephrectomized rats which excreted 14 mg/24 h. Allograft recipients demonstrated functional deterioration earlier and more intensely, excreting > 65 mg/24 h by week 24.

By 32 weeks after engraftment, cellular infiltration in the periglomerular and perivascular areas had become marked in the isografts; tubular atrophy was obvious, and significant thickening had occurred in the vascular walls. At the same time, the intima of vessels demonstrated vacuolization and infiltration by macrophages; large amounts of TNF-α, PDGF, and TGF-β were expressed. By 52 weeks, almost all vessels demonstrated marked to severe luminal narrowing, while glomeruli demonstrated focal and segmental collapse. Macrophages infiltrated the glomeruli in considerable numbers, while TNF-α was expressed strongly. T cells infiltrated periglomerular and peritubular areas, while ICAM-1 and MHC-II were expressed on endothelial and infiltrating cells.

Chronic lesions similar to those developing in isografts by 32–52 weeks had occurred in kidney allografts by 16–24 weeks, when partial collapse and sclerosis of glomeruli, marked interstitial fibrosis with tubular atrophy, and varying degrees of intimal proliferation and sclerosis of vessels were seen. By 32 weeks, graft arteriosclerosis had become generalized in the allografts, while glomerulosclerosis and interstitial fibrosis were widespread. Control kidneys in non-nephrectomized or uninephrectomized rats remained unchanged throughout this period.

Discussion

Although the progression of chronic rejection of organ allografts is well recognized both clinically and in experimental systems, the factors responsible for its etiology remain obscure. Both alloantigen-dependent and -independent factors have been thought to influence the process. We therefore evaluated kidney isografts over prolonged periods and found progressive functional and morphological changes similar to those observed in chronically rejected allografts, although occurring considerably later and less intensely, at least by 52 weeks. The effects of CsA treatment were inconsequential.

As the progressive morphologic alterations noted in the present experiments are similar to those described in human isografts, the effects of alloantigen-independent influences apart from recurrence of the original disease, initially thought to be responsible for those findings, are emphasized [4]. These may include host immune-independent responses such as a prolonged ischemic time, reperfusion injury, and the long-term effects of a diminished ratio of functioning kidney mass to body weight [2, 5]. Thus, alloantigen-dependent factors in addition to the initial damage caused by as yet poorly defined factors may lead to the long-term destruction of organ grafts.

References

1. Tilney NL, Whitley WD, Diamond JR, Kupiec-Weglinski JW, Adams DH (1991) Chronic rejection – an undefined conundrum. Transplantation 52:389
2. Yilmaz S, Paavonen T, Häyry P (1992) Chronic rejection of rat kidney allografts. II. The impact of prolonged ischemia on transplant histology. Transplantation 53:823–827
3. Hancock WW, Whitley WD, Tullius SG et al (1994) Cytokines, adhesion molecules and the pathogensis of chronic rejection of rat renal allografts. Transplantation (in press)
4. Glassock RJ, Feldman D, Reynolds EG, Dammin GJ, Merrill JP (1968) Human renal isografts: a clinical and pathological analysis. Medicine 47:411–454
5. Almond PS, Matas A, Gillingham K, Dunn DL, Payne WD, Gores P, Gruessner R, Najarian JS (1993) Risk factors for chronic rejection in renal allograft recipients. Transplantation 55:752