Transpl Int (1996) 9 [Suppl 1]: S3–S4

Petri K. Koskinen
Serdar Yilmaz
Erkki Kallio
Cathrien A. Bruggeman
Pekka J. Häyry
Karl Lemström

Rat cytomegalovirus infection and chronic kidney allograft rejection

P. K. Koskinen (✉) · S. Yilmaz · E. Kallio · P. J. Häyry · K. Lemström
Transplantation Laboratory, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland

C. A. Bruggeman
Department of Medical Microbiology, University of Limburg, Maastricht, The Netherlands

Abstract To investigate the effect of cytomegalovirus (CMV) infection on the development of experimental chronic kidney allograft rejection, orthotopic kidney allografts from DA donors (Ag-B4, $RT1^{a1}$) to WF (Ag-B2, $RT1^{u}$) recipients were used. The rats received cyclosporine A (CsA) for 12 weeks. A group of recipients was infected with 10^5 plaque-forming units of rat CMV (RCMV), and another group was left non-infected and used as controls. The grafts were removed 12 weeks after transplantation. RCMV infection significantly enhanced the development of chronic kidney allograft rejection as follows: the intensity of interstitial inflammation ($P < 0.025$), particularly the degree of pyroninophilic cells in the inflammatory infiltrate ($P < 0.025$); the glomeruli mesangial matrix increase ($P < 0.05$) and capillary basement membrane thickening ($P < 0.01$); the extent of endothelial cell swelling ($P < 0.025$) and intimal proliferation ($P < 0.025$) in the graft vasculature; and the extent of tubular epithelial atrophy ($P < 0.025$). The chronic allograft damage index (CADI) was significantly increased to 4.2 ± 0.9 in RCMV-infected allografts, compared with 0.8 ± 0.4 in non-infected ($P < 0.02$). At the molecular level, RCMV infection significantly increased vascular endothelial ($P < 0.05$) and tubular epithelial ($P < 0.01$) ICAM-1 expression. Viral antigens were detected in tubular epithelial cells and in some inflammatory cells.

Key words Kidney transplantation · CMV infection · Chronic rejection · ICAM-1

Introduction

Chronic rejection, characterised by interstitial fibrosis, glomerulosclerosis, tubular atrophy and arterial narrowing, is the major reason for loss of renal allografts after the first posttransplant year [1]. Acute rejection episodes, low cyclosporine doses, and infections, especially cytomegalovirus (CMV) infection, have been recognised as most important risk factors for the development of this disorder [2].

Materials and methods

To investigate the effect of CMV infection on the development of chronic kidney allograft rejection, orthotopic kidney allografts from DA donors (Ag-B4, $RT1^{a1}$) to WF (Ag-B2, $RT1^{u}$) recipients were used. The kidney and 1 cm of ureter were removed en bloc, including the renal artery and the renal vein. The recipient right kidney was removed, leaving the ureter as long as possible. The donor kidney was transplanted to the recipient's abdominal aorta and inferior vena cava below the left renal artery. The rats received cyclosporine A (CsA), 5 mg/kg per day s.c. for 12 weeks. At 7 days after transplantation, left nephrectomy was performed to remove the recipient's own kidney. A group of recipients was infected with 10^5 plaque-forming units of rat CMV (RCMV) [3] 9 days after transplantation, and another group was left non-infected and used as controls. The rats were monitored twice a week for serum creat-

Table 1 Effect of rat cytomegalovirus (RCMV) infection on chronic kidney allograft changes (*CADI* chronic allograft damage index, *BM* basement membrane)

	DA → WF	DA → WF + RCMV	*P*
CADI	4.2 ± 0.9	0.8 ± 0.4	< 0.02
Interstitium			
Inflammation	0.1 ± 0.1	0.9 ± 0.2	< 0.025
Pyroninophilic cells (%)	0 ± 0	18 ± 7	< 0.025
Glomeruli			
Mesangial matrix increase	0.4 ± 0.1	0.9 ± 0.2	< 0.05
Capillary BM thickening	0 ± 0	0.7 ± 0.1	< 0.01
Vessels			
Endothelial swelling	0 ± 0	0.6 ± 0.2	< 0.025
Intimal proliferation	0 ± 0	0.6 ± 0.2	< 0.025
Tubuli			
Epithelial atrophy	0 ± 0	0.6 ± 0.2	< 0.025
Endothelial ICAM-1	0.6 ± 0.2	1.8 ± 0.2	< 0.05
Tubular cell ICAM-1	0.2 ± 0.2	1.4 ± 0.4	< 0.01

inine and the diagnosis of acute rejection was made if there was an unexplained rise in serum creatinine > 200 μmol/l. The grafts were removed for histology 12 weeks after transplantation. The presence of RCMV early and late antigens in kidney allografts was demonstrated using a mixture of mouse monoclonal antibodies against early (#8) and late (#35) antigens of RCMV [4]. The expression of ICAM-1 was demonstrated using a mouse IgG_1 monoclonal antibody to rat intercellular adhesion molecule-1 (ICAM-1; CD54, 1A29, Seikagaku Co., Tokyo, Japan).

Results

RCMV significantly enhanced the chronic allograft damage index (CADI) (Table 1), which is the sum of interstitial inflammation and fibrosis, mesangial matrix increase and sclerosis of glomeruli, intimal proliferation of arteries, and tubular atrophy. The CADI was significantly increased to 4.2 ± 0.9 in RCMV-infected allografts, compared with 0.8 ± 0.4 in non-infected ($P < 0.02$). The vascular wall changes of RCMV infected allografts were associated with a significantly increased ICAM-1 expression in the tubular cells ($P < 0.01$) and in endothelial cells ($P < 0.05$) compared with the controls. RCMV early and late antigens could be detected in tubular epithelial cells and in some inflammatory cells of the infected allografts.

Discussion

To conclude, our results provide experimental evidence that RCMV infection is associated with enhanced chronic allograft changes reflecting the chronic kidney allograft damage index. At the molecular level, these RCMV-induced chronic changes are linked with increased vascular endothelial and tubular epithelial ICAM-1 expression. Supporting the concept that CMV is able to infect various kidney cell types, we found early and late RCMV antigen expression in tubular epithelial cells and in some interstitial inflammatory cells.

References

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