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Prompt treatment of initial acute rejection episodes may improve long-term graft outcome

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Abstract Acute rejection episodes have been cited as a major immunological risk factor for the development of chronic rejection. To examine the influence of a single rejection event on ultimate graft outcome, acutely rejection rat kidney grafts were retransplanted sequentially into syngeneic rats and their functional and structural behavior assessed over time. Early structural changes (days 3 and 4) were completely reversible, while signs of chronic rejection did become obvious during the long-term follow up. More advanced deteriorated grafts (days 5 and 7) were irreversibly damaged and the rats died shortly after retransplantation. Those results indicate the critical impact of acute rejection episodes on chronic graft rejection. Immediate and aggressive treatment of acute rejection episodes may remove this event as a risk factor for late deteriorating changes.

Key words Chronic rejection · Acute rejection episodes · Retransplantation

Introduction

Chronic rejection is the most important cause of late graft loss. Its mechanisms remain ill understood; no established therapy is currently available. Potential risk factors include alloantigen-dependent factors, such as acute rejection, and several alloantigen-independent events. The single role of those risk factors and their potential mechanistic interactions are unknown [1, 2, 4, 6].

We examined the contribution of a single acute rejection episode on the development of chronic graft rejection by retransplanting acutely rejected rat renal allografts sequentially into donor strain recipients and following those long term.

Materials and methods

Male rats (200–250 g) were used throughout the experiment. Principles of laboratory animal care as stated in the NIH publication 86–23, revised 1985, in addition to permission by the local authorities were followed. LEW × BNF_1 → LEW renal allografts (n = 20) demonstrating characteristic signs of acute rejection and LEW → LEW isografts (n = 12) as controls were used. To test the impact of a single acute rejection episode. LEW × BNF_1 allografts and LEW isografts were removed from their LEW recipients after 3, 4, 5, and 7 days (n = 12/group) and retransplanted into donor strain hosts. The grafts were followed functionally and harvested 4, 8, and 32 weeks after retransplantation. Urinary protein excretion was measured weekly. Kidney grafts were examined morphologically (hematoxylin/eosin and periodic acid – Schiff stains, quantitated by a glomerulo- and arteriosclerosis index) and immunohistologically using monoclonal antibodies (mAbs) against monocytes/macrophages (ED-1), T cells, and their subsets (CD5, CD4, CD8; mAbs obtained from Serotec, Wiesbaden, Germany) using the alkaline phosphatase – anti-alkaline phosphatase method. Positive cell counts were expressed as mean ± SD of cells/field of view (c/FV; > 20 FV/section were evaluated at 400 ×).

Results

LEW ↘ BNF1 → LEW allografts demonstrated a medium survival time of 14.5÷2 days; LEW → LEW isografts functioned indefinitely. At 5 and 7 days after transplantation, acutely rejecting allografts showed severe cellular infiltrates (ED-1, 54÷7 and 42÷6 c/FV; CD-4, 28÷4 and 20÷6 c/FV; CD-8, 42÷8 and 36÷5 c/FV, respectively), associated with extensive necrosis; these changes could not be reversed by retransplantation in donor strain animals. In contrast, most allografts recovered completely when retransplanted after 3 (12/12) and 4 (9/12) days. Monocytes/macrophages and T-lymphocytes infiltrating increasingly by 3 and 4 days after transplantation (ED-1, 12÷6 and 18÷5 c/FV; CD-4, 10÷5 and 18÷7 c/FV; CD-8, 15÷4 and 19÷8 c/FV, respectively) decreased in number when examined 32 weeks after retransplantation (ED-1, 6÷3 and 8÷2 c/FV; CD-4, 8÷3 and 11÷4 c/FV; CD-8, 6÷3 and 5÷2 c/FV, respectively. Only a few sclerosed glomeruli (approx. 10% focal sclerosis) and mild arterial changes similar to those seen in retransplanted isografts were observed; characteristic signs of chronic allograft rejection did not become obvious.

Discussion

To examine the impact of acute rejection episodes on chronic graft rejection, we retransplanted acutely rejecting rat renal allografts sequentially into donor strain animals, thus removing the ongoing host immunological influence. When retransplantation was performed at early stages (by 3 and 4 days) most grafts recovered completely, while characteristic signs of chronic graft rejection were not observed. The low grade cellular infiltration and the development of minor signs of glomerulosclerosis observed both in retransplanted allo- and isografts (3 and 4 days) over the long term may represent an expression of ischemic damage and reperfusion injury during engraftment [7]. However, advanced stages of acute rejection (days 5 and 7) could not be reversed by retransplantation and the recipients began to die shortly thereafter.

Both early and late acute rejection episodes have been cited as critical for the development of chronic graft rejection [1, 5]. Completely reversed acute rejection episodes had no impact on the development of chronic graft dysfunction [3]. Additionally, morphological characteristics, severity, and success of treatment seem important. Delayed diagnosis, particularly of late acute rejection episodes and more advanced stages secondary to inadequate follow-up, may, in addition, be influential. Different mechanisms may also apply for early and late acute rejection episodes.

Both retransplanted allo- and isografts demonstrated minor cellular infiltrates with minor signs of glomerulosclerosis over time. Alloantigen-independent factors such as as ischemia and reperfusion injury, and their interaction with alloantigen-dependent factors may play a role in this context and are currently being investigated [7].

In summary, our results demonstrate that early acute rejection episodes are completely reversible after retransplantation and do not progress to chronic graft deterioration. Adequate and prompt treatment might remove acute rejection episodes as a risk factor for chronic graft rejection.

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