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The interplay between antiviral immunity and allo-immune reactivity after renal transplantation
Consortium between the Centres Amsterdam, Leiden and Nijmegen (ALLOVIR)

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ABSTRACT

In the consortium "ALLOVIR" we aim to characterize the effect of CMV and BKV infections on the innate immune responses to viral and alloantigens. Furthermore, we want to characterize the interplay between adaptive immune responses to viral and alloantigens with emphasis on the role of heterologous immunity. Thirdly, we will characterize the manifestations of these immune responses in the allograft, as reflected in tissue and urine, and their correlation with graft function. Finally, we will assess how immunosuppressive drugs interfere with these cross-reactive immune responses.

1. Introduction

Current immunosuppressive treatment has improved kidney-allograft survival, albeit at the expense of reduced immunosurveillance to pathogenic microorganisms. Consequently, viral infections are increasingly observed in renal transplant recipients. Cytomegalovirus (CMV) is the most frequent cause of viral infection after renal transplantation. In the last decade also BK virus (BKV)-infection has been recognized as a major cause of morbidity after renal transplantation. For the defence against viral infections, initiation of the innate immune response is critical. NK cells are activated, and sensing of viral RNA and DNA induces the production of type I interferons and NFκB-activation, which subsequently results in increased production of pro-inflammatory cytokines. Next, activated dendritic cells (DCs) initiate the adaptive immune response. Antigen-specific naïve T-lymphocytes undergo clonal proliferation and differentiate into effector cells which will eliminate virus-infected cells. After the viral load has become very low, most of the effector cells die in the contraction phase of the immune response, but a small population of antigen-specific memory T-cells remains. During latency, the cellular effector compartment steadily increases in size and a persistent systemic cytokine-type-I pro-inflammatory reaction is induced. During each phase of the antiviral response, major effects on the allo-immune-response can be expected, varying from non-specific activation of the immune system to modulation of NK cells, and induction of memory T-cells with cross-reactivity to allo-antigens, known as heterologous immunity. Thus, both previous and current viral infections in a renal transplant candidate will have major impact on his innate and allo-immune responsiveness. This holds especially true for infections that elicit a long-lasting T cell response, i.e. persistent viral infections. In view of the impact of these infections on the building of an individual's memory compartment and the well known relative insensitivity of this compartment to immunosuppressive drug regimens, we hypothesize that a better understanding of the interplay between viral pathogens and the allo-immune response and of the influence that currently used immunosuppressive drugs exert on this interplay, will improve donor selection and use of immunosuppressive drug regimens.

We established a consortium of six research groups from three Dutch University Medical Centres. The aim of this consortium is to characterize the effect of CMV and BKV infections on the innate immune responses to viral and alloantigens. Furthermore, we want to characterize the

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interplay between adaptive immune responses to viral and alloantigens with emphasis on the role of heterologous immunity. Thirdly, we will characterize the manifestations of these immune responses in the allograft, as reflected in tissue and urine, and their correlation with graft function. Finally, we will assess how immunosuppressive drugs interfere with these cross-reactive immune responses (Figs. 1–2).

2. General approach

2.1 . Characterization of the effect of CMV and BKV infections on the innate immune responses to viral and allo-antigens

In groups of patients with different serological CMV status of recipient and donor, we study how primary CMV infection and reactivation or reinfection affects the function of both plasmacytoid DC (pDC) and NK cells in allo-immune responses. In a later stage, similar experiments will be done in relation to BKV infection. The presence of pDC in relation to other DC subsets, their activation status and their capacity to induce either direct or indirect allopresentation will be studied. The NK cell's KIR genotype will be related to the risk of viral infection and/or disease. Next, phenotypical and functional changes in the NK cell repertoire upon viral infection and their implications for the alloresponse will be determined. Finally, the influence of immunosuppressive drugs on the function of each cell type will be studied.

2.2 . Characterization of the interplay between adaptive immune responses to viral and alloantigens with emphasis on the role of heterologous immunity

In the same patient groups, cross-reactivity of virus-specific effector and memory cells against a panel of HLA typed target-cells and target-cells transduced with single HLA molecules, and against the specific graft-donor will be measured before and at several time points after transplantation. We hypothesize that heterologous immunity is at least in part responsible for the resistance against induction of transplant tolerance. Therefore, it is of great importance to obtain more insight in the characteristics of antiviral and cross-reactive allo-immune responses and their sensitivity to immunosuppressive drugs.

2.3 . Characterization of the manifestations of anti-viral and allo-immune responses in the allograft, as reflected in tissue and urine, and their correlation with graft function

Allograft biopsies obtained according to protocol or upon clinical indication from patients with CMV or BKV infection will be compared for the presence of markers of innate immunity and alloreactivity. The phenotype of graft-infiltrating cells (GICs) will be analysed and GIC will be eluted to detect virus- and allo-specific cells. We will search for urinary markers reflecting the outcome of innate and/or adaptive immune responses against CMV, BKV, or the allograft. All data will be related to the clinical course after transplantation.

3. Preliminary results

3.1 . Characterization of the effect of CMV and BKV infections on the innate immune responses to viral and alloantigens

Association of NK cell KIR/HLA genotypes with risk of primary or secondary viral infection, CMV disease and rejection episodes after renal transplantation.

To ascertain the association of NK cell KIR/HLA genotype with risk of CMV infection/disease, we analysed 90 CMV negative recipients of a first kidney transplant from a CMV positive donor. They were treated with triple immunosuppressive therapy consisting of prednisone, tacrolimus and mycophenolate mofetil. All recipients received prophylactic treatment with valganciclovir for 3 months after transplantation. Clinical endpoints were time from transplant to first sign of laboratory proven CMV disease and time of transplant to time of first rejection, with a one-year follow-up. In this group, we observed a 43.3% and 30% incidence rate of CMV disease, respectively rejection. Of the 27 recipients who experienced a rejection episode, 14 got CMV disease during the first year after transplantation. Of these, 12 had a rejection episode preceding the development of CMV disease, suggesting that in this group, CMV disease was not a risk factor for rejection. The KIR gene distribution and the compiled genotypes observed in our cohort were comparable to those found in previous studies and KIR typing results revealed a similar gene distribution between the groups with and without CMV disease. On the basis of KIR genotypes AA and BX (BA and BB), recipients were categorized into two groups. Twenty-seven out of ninety (30%) recipients carried the genotype AA, of which 9 (33%) had CMV disease. Of the remaining 63 (70%) recipients with the KIR genotype-BX, 30 (48%) had CMV disease. There was no significant difference between the two genotyped groups regarding occurrence of CMV disease, although there was a trend towards a lower incidence of CMV disease in recipients carrying the KIR AA genotype. Neither did we find a significant risk associated with either the number of activating or inhibitory KIRs. Missing KIR ligand (combined HLA-C and -B) was not associated with a different rate of CMV disease either [1].

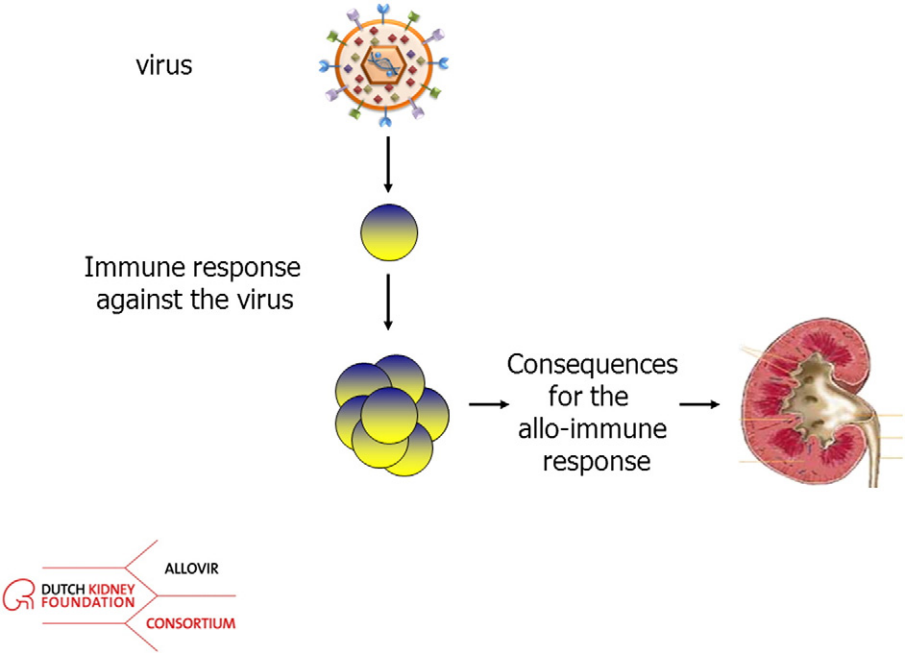

Fig. 1. Interplay between persistent viral infection and alloreactivity in man.