T cell development in human cytomegalovirus infection
Gamadia, L.E.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
INTRODUCTION
Throughout life, the human body encounters viruses, which are dealt with by the immune system. Some viruses enter the body to be cleared completely, whereas others enter the body to remain there for life, rendered harmless through immune control mechanisms. Once controlled, immunity is established, protecting the organism from disease upon reencounter with the same virus.

In organ transplantation, prevention of graft-rejection is achieved by administration of immunosuppressive drugs, which target the immune system in an aspecific, general manner. Whereas the efficacy of immunosuppressive drugs in the prevention of graft rejection is clearly established, protective immunity against micro-organisms (viruses and bacteria) and tumor surveillance are compromised under immunosuppressive drug regimens, resulting in an increase in incidence of malignancies and infectious complications. In renal transplant recipients, post-transplant infectious disease by persistent herpesviruses as Epstein Bar Virus (EBV), Varicella Zoster Virus (VZV), Human Herpesvirus 6,7, and 8 (HHV-6,7,8) and Cytomegalovirus (CMV) is common. These viruses are asymptomatically present in the host before transplantation and subsequent start of immunosuppressive therapy. Immunosuppression disrupts the balance between persistent virus and immune system, leading to active viral infection. The virus most commonly associated with severe disease symptoms after transplantation is CMV. Furthermore, apart from CMV-induced visceral disease, CMV-infection is associated with an increase in acute and chronic graft rejection. The exact mechanism by which cytomegalovirus precipitates graft rejection is as yet unclear.

Cytomegalovirus
Cytomegalovirus is a β-herpesvirus, which, once acquired, establishes lifelong infection. In the western Caucasian population, the prevalence of latent CMV infection is estimated to be 50%. CMV-infection is acquired by intimate contact, and iatrogenically by unfiltered blood transfusion and solid organ transplantation. In healthy individuals, CMV-infection is usually asymptomatic, but in transplant recipients receiving immunosuppressive drug therapy CMV-infection can cause severe morbidity involving many organ systems. Given the fact that the prevalence of CMV in the general western population is 50%, and in hemodialysis patients anticipating kidney transplantation was reported to be 60%, incidence of primary CMV-infection after transplantation can be calculated to be approximately 20-25%.
up of CMV-seronegative recipients of a CMV-seropositive donor by quantitative CMV-PCR shows that virtually in all patients CMV-replication can be detected in the peripheral blood[16]. However, CMV-infection does not lead to clinical disease symptoms in all patients, i.e. in some patients viral replication and spread occur yet no disease symptoms develop.

Immunity

Protective immunity to herpesviruses such as CMV is based on the development of B and T cells with specialized effector functions; B-cells secrete high affinity neutralizing antibodies, whereas CD8⁺ T cells can kill infected cells and/or produce cytokines that inhibit the replication of the pathogen. CD4⁺ T cells provide "help" for B and CD8⁺ T cells by producing cytokines and by activation of antigen presenting cells. After the initial infection is cleared, long-lived T and B cells exist, leading to protective immune memory responses upon reencounter with the same pathogen, preventing reinfection or greatly reducing severity of disease[17]. CD8⁺ T cells are thought to be one of the main effector arms in the immune response, determining successful clearance of primary viral infection and protection during renewed encounters. However, in allo-reactive immune responses, the same cells play a major role in rejecting the allograft[18; 19]. Elucidating the precise differentiation pathways of virus-specific cells therefore could also provide insight into the generation of alloreactive T cell responses.

Human post thymic CD8⁺ T cell differentiation consists of the generation of effector cells upon antigenic triggering and generation of memory cells ensuring protection upon renewed contact with the antigen. Currently, many models of CD8⁺ memory-cell formation are in use, based on mainly two models; the linear model, where memory cells directly descend from effector cells, and the divergent model, where a naive cell, upon antigenic stimulation, develops into either a memory or effector cell[20]. The first model infers that memory T cell development only occurs after removal or at least severe reduction of antigen, and is entirely stochastic, whereas in the second model certain naive cells bypass the effector stage and develop directly into memory cells, but the direct instructional mechanism is largely unknown. In both models however, memory cells are able of rapid proliferation upon renewed antigenic challenge, whereas effector cells are end-stage differentiated cells with high cytotoxic potential but no proliferative capacity, and are thought to become redundant after
the antigen is successfully combated. The divergent pathway model has been proposed to play a role in insufficient protective anti-viral immune responses, where only memory (-effector) cells and no effector cells are generated during primary or secondary infection, leading to persistent viral infection and impaired immune control. In both models, the determinants of becoming a long-lived memory cell are as yet unclear.

New technologies

Formerly, virus-specific cellular immune responses could not be assessed in an antigen-specific manner directly ex-vivo without prior expansion. The aid of new techniques, like intracellular cytokine staining upon short-term antigenic stimulation and HLA/peptide tetrameric complexes, make it possible to study virus-specific T cells in a specific manner directly ex vivo. Antigen specific CD4 and CD8+ T cell responses can be meticulously studied qualitatively and quantitatively. The identification of CMV-specific CD8+ T cells with a known specificity makes it possible to assess cross-reactive potential of these cells to alloantigens.

Scope of this thesis

This thesis focuses on anti-CMV T cell responses in kidney transplant recipients. The occurrence of primary CMV-infection after kidney transplantation provides us with a model to monitor the development of anti-viral cellular immune responses from the time point of infection. First, the adaptations of CMV-specific T cell responses in reaction to immunosuppression were studied, as were the correlates of protective vs. impaired immunity determined. Second, the availability of CMV-peptide specific tetramers opened the opportunity to directly investigate the relation between virus-specific repertoires and allo-specific repertoires.

References


