Introduction

Herpesviruses and T-cell therapy

Herpesviruses establish a lifelong persistent infection in immunocompetent humans, characterized by intermittent episodes of subclinical or clinical reactivation. Host immune responses, especially those mediated by $\alpha/\beta^+$ T cells, are critical for containing primary infection and limiting episodes of reactivation. Thus, individuals with congenital or acquired T-cell immunodeficiencies are susceptible to progressive and potentially life-threatening infections. The immunological defects that permit progression of herpes infection in immunodeficient individuals have now been defined and the adoptive transfer of virus-specific T cells is being pursued as a potential therapy. For example, recipients of an allogeneic bone marrow transplant (BMT) who are cytomegalovirus (CMV)-seropositive, or who receive bone marrow from a CMV-seropositive donor are at considerable risk of reactivating CMV. If these patients are not treated with antiviral drugs, CMV infection may progress to interstitial pneumonia and/or enteritis. The immunological defects that permit progression of herpes infection in immunodeficient individuals have now been defined and the adoptive transfer of virus-specific T cells is being pursued as a potential therapy. For example, recipients of an allogeneic bone marrow transplant (BMT) who are cytomegalovirus (CMV)-seropositive, or who receive bone marrow from a CMV-seropositive donor are at considerable risk of reactivating CMV. If these patients are not treated with antiviral drugs, CMV infection may progress to interstitial pneumonia and/or enteritis. If the bone marrow donor is CMV-seropositive, CMV-specific T-cell clones can be isolated from the donor, expanded in vitro and transferred to the transplant recipient to restore immunity to CMV. Initial studies of T-cell therapy as prophylaxis for CMV disease in allogeneic BMT recipients demonstrate that this approach is safe and may be an effective alternative to antiviral drugs for preventing CMV disease.

HIV and T-cell therapy

In contrast to infection with herpesviruses, which cause severe disease only in immunodeficient hosts, persistent human immunodeficiency virus (HIV) infection is characterized by high levels of virus replication and progressive fatal immunodeficiency in the majority of individuals. The progression of infection may reflect quantitative or qualitative deficiencies in HIV-specific T-cell responses in the HIV-infected host. Treatment with antiretroviral drugs can reduce plasma viral load and improve immune function, but it does not completely abrogate viral replication or eliminate reservoirs of latent virus in most patients. Thus, the adoptive transfer of autologous unmodified and genetically modified HIV-specific T cells expanded to large numbers in vitro is being used to identify and potentially overcome the immunological defects that permit virus replication in individuals with progressive infection, and as an adjunct to drug therapy in patients with low virus loads.

The development of adoptive immunotherapy for CMV and HIV infection is predicated by three factors: (i) the identification of the nature and specificity of effector T cells that exert antiviral activity; (ii) the in vitro isolation and expansion of specific T cells to numbers sufficient to provide an effective response in the recipient after adoptive transfer; and (iii) the ability of transferred T cells to persist in vivo and travel to sites of virus infection.

In this review, the rationale and background data supporting the application of T-cell therapy for CMV and HIV
infection, and the insights derived from the results of the initial studies, are discussed.

**Rationale for adoptive immunotherapy with CMV-specific T cells in allogeneic BMT recipients**

Allogeneic BMT recipients receive chemotherapy and/or radiotherapy in doses sufficient to completely ablate their immune system before transplantation. Reconstitution of immunity from donor cells is delayed, partly as a result of the administration of post-transplant immunosuppressive drugs to prevent graft-versus-host disease (GVHD). A profound deficiency of B- and T-cell immunity exists for several months after transplant in most patients, so these patients are at significant risk of infectious complications. Before the use of ganciclovir as prophylaxis for CMV infection, CMV interstitial pneumonia occurred in 25% of CMV-seropositive BMT recipients in the first 100 days following BMT, and was the leading cause of infectious death in these patients.2 The introduction of ganciclovir therapy has led to a remarkable reduction in the occurrence of early CMV disease in BMT recipients, but its use is limited by toxicity in some patients.7 Moreover, CMV disease still occurs in a significant number of patients when ganciclovir is discontinued after 100 days.8 Consequently, the design of immunotherapeutic strategies to correct B- and T-cell immunodeficiency after BMT may be of clinical benefit.

The passive transfer of immunoglobulin preparations containing CMV-specific antibodies has been examined for the prevention of CMV disease in immunocompromised hosts. In BMT recipients, there was no clear evidence that prophylactic immunoglobulin administration reduced the incidence of CMV disease, although disease outcome was improved by adding immunoglobulin to ganciclovir for the treatment of established CMV interstitial pneumonia.9,10 Studies in a murine model of CMV infection demonstrated that the adoptive transfer of murine CMV-specific CD8+ cytotoxic T cells to immunodeficient mice conferred protection from CMV disease.11 This suggested that prophylaxis of human CMV disease in BMT recipients might also be accomplished by restoring T-cell immunity to the virus. Further support for this approach was derived from an analysis of the recovery of CD4+ and CD8+ CMV-specific T-cell responses in patients receiving allogeneic BMT. This analysis demonstrated a strong correlation between recovery of CMV-specific T-cell immunity and protection from CMV disease.12-14 Indeed, CMV interstitial pneumonia occurred exclusively in the subset of patients who were deficient in CD8+ CMV-specific cytotoxic T cells (Table). These findings encouraged efforts to develop the adoptive transfer of CMV-specific T-cell clones—isolated from the immunocompetent bone marrow donor and expanded in number by *in vitro* culture—as an approach to correct the immune defect and potentially to contain CMV infection.

**Specificity of class I MHC-restricted CD8+ CMV-specific cytotoxic T cells**

Virus-infected cells display class I MHC molecules complexed to short viral peptides on their surface, which serve as the recognition structure for the T-cell receptor on CD8+ T cells. CMV has a large genome and may express more than 200 proteins, which could potentially provide peptides for presentation to T cells. However, the T-cell response to virus infection is usually characterized by the dramatic expansion of one or more clones directed against one or more immunodominant epitopes with lesser contributions from T cells reacting with subdominant epitopes.15 It was essential that the immunodominant responses to CMV in immunocompetent hosts were identified so that T-cell clones representative of this response could be selected for use in therapy. Since CMV expresses its genes in discrete phases, termed the immediate–early, early and late phases, the diagnosis of CMV pneumonia required the presence of CMV in tissue sections or bronchoalveolar lavage with compatible clinical and radiological signs. Statistical analysis was performed using Fisher’s exact test.

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<td>Recovery of CD8 response alone</td>
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<td>Recovery of CD4 response alone</td>
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*aP < 0.01.

CD8+ cytotoxic T lymphocyte and CD4+ T-helper lymphocyte responses were evaluated in samples of peripheral blood lymphocytes obtained at days 30–40, 60–70 and 90–120 after BMT. The responses were assayed and evaluated as described.13,14 The diagnosis of CMV pneumonia required the presence of CMV in tissue sections or bronchoalveolar lavage with compatible clinical and radiological signs. Statistical analysis was performed using Fisher’s exact test.
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Initial experiments were directed at defining the phase of viral gene expression required for cytotoxic T lymphocyte (CTL) recognition, by inducing a metabolic blockade of viral protein or RNA synthesis in target cells. Remarkably, adding an RNA synthesis inhibitor before viral infection of target cells, to block completely the production of newly synthesized viral proteins, did not abolish recognition by CD8+ CMV-specific CTL lines and the majority of CTL clones derived from normal immunocompetent donors. These data indicated that virion proteins, introduced into the cytoplasm of the infected cell after viral entry and uncoating, provided the peptides that were targets of the immunodominant CTL response (Figure 1). Subsequent studies showed that the CD8+ CMV-specific CTLs that recovered after allogeneic BMT and were associated with protection from CMV disease were also specific for structural virion proteins.

Recombinant vaccinia virus vectors encoding individual CMV proteins have been used to characterize further the specificity of CMV-specific CTLs. The matrix protein pp65 is the most frequent target of the immunodominant CTL response, although major responses to a second matrix protein, pp150, are observed in some individuals. Normal CMV-seropositive individuals maintain high levels of CTL specific for pp65 or pp150, suggesting that these effector cells are required to control intermittent episodes of virus reactivation. In vitro, CD8+ pp65- or pp150-specific CTL will lyse CMV-infected cells within 1 h of viral entry. Infected cells remain targets throughout the replicative cycle, despite the expression of viral genes that downregulate class I MHC expression.

Evasion of T-cell immunity by CMV

To facilitate persistence in the host and enhance the probability of transmission to a new host, many viruses have evolved methods to thwart recognition by host effector cells. The CMV genome is particularly well equipped with an arsenal of immune evasion genes. The unique short (US) region of the viral genome encodes four proteins that interfere with different steps in the class I antigen-processing pathway. US3 is expressed in the immediate–early phase and binds to and retains class I MHC in the endoplasmic reticulum. US2 and US11 are early gene products that cause the translocation of class I molecules from the endoplasmic reticulum to the cytosol where they are degraded. US6 is expressed in the early or late phase and blocks the

Figure 1. Presentation of cytomegalovirus antigens to CD8+ cytotoxic T-cell clones. Two classes of viral proteins are available for presentation to cytotoxic T cells, including the virion proteins that enter the cytosol following viral penetration and uncoating, and the newly synthesized immediate–early (IE), early (E) and late (L) proteins. These proteins are processed to peptide fragments by the proteolytic machinery of the proteasome and the peptides transported into the endoplasmic reticulum (ER) by the transporter of antigen presentation (T.A.P.). In the ER the peptides bind to class I MHC and are transported to the cell surface. To distinguish the contribution of virion proteins from that of immediate–early, early and late proteins, the RNA synthesis inhibitor actinomycin D was used to block viral RNA production. This blockade had no effect on CTL recognition, indicating that the peptide epitopes presented by class I MHC were derived from virion proteins.
transport of antigenic peptides into the endoplasmic reticulum. These viral evasion strategies may participate in shaping the host T-cell response, and in part explain the immunodominance of CTL directed at viral antigens that can be presented by infected cells before expression of the US genes.

Virus-specific CD4+ T-helper (T<sub>h</sub>) cells recognize cells expressing class II MHC molecules complexed with viral peptides. In addition to direct effects on infected cells, CD4+ T<sub>h</sub> cells produce cytokines such as interleukin-2 (IL-2), which acts to amplify CD4+ and CD8+ T-cell responses, or IL-4 and IL-5, which promote antibody-producing B cells. CMV also has a strategy to interfere with the presentation of antigens by class II MHC molecules to evade recognition by CD4+ T cells. The US2 gene product induces degradation of the class II DR<sub>α</sub> chain which is required for assembly of the DR<sub>α</sub>β heterodimer and the DM<sub>α</sub> chain which binds to the αβ heterodimer and catalyses the loading of antigenic peptides. Thus, endothelial cells or macrophages that are infected with CMV may fail to activate a CD4+ T<sub>h</sub> response. However, this would only limit direct antiviral activity, since CD4+ T cells could still be activated by uninfected class II<sup>+</sup> antigen-presenting cells that have taken up and processed viral antigens from the extracellular environment.

Adoptive transfer of CD8<sup>+</sup> CMV-specific T-cell clones to BMT recipients

The first study of adoptive immunotherapy with CMV-specific T cells in allogeneic BMT recipients examined the safety of administering CD8<sup>+</sup> CMV-specific CTL clones and determined the ability of the transferred T cells to persist and function in vivo. This phase I study enrolled 14 allogeneic BMT recipients who received bone marrow from a CMV-seropositive donor. The T cells were administered soon after BMT—as prophylaxis for CMV disease rather than as treatment for established CMV pneumo-nia—to limit the potential of CMV for inducing further inflammation in the lungs.

CD8<sup>+</sup> CMV-specific CTL polyclonal lines were generated from the blood of the marrow donor using autologous dermal fibroblasts infected with CMV to stimulate peripheral blood mononuclear cells. T-cell clones were then isolated from the T-cell lines by limiting dilution cultures and were screened for reactivity with CMV structural virion proteins. Expansion of the CTL clones for infusion was accomplished by stimulation with anti-CD3 monoclonal antibody instead of CMV-infected fibroblasts to prevent transfer of the virus. CTL were administered to the BMT recipient by intravenous infusion in escalating doses of 3.3 x 10<sup>7</sup>, 1 x 10<sup>8</sup>, 3.3 x 10<sup>8</sup> and 1 x 10<sup>9</sup> cells/m<sup>2</sup> of body surface area weekly for 4 weeks beginning 28–42 days after BMT. T-cell infusions were well tolerated with only minor toxicities observed in two of the 14 patients.

To assess the efficacy of T-cell infusions for reconstituting T-cell responses, CMV-specific CTL reactivity in peripheral blood was assessed before and during therapy and every 2 weeks after therapy, for up to 12 weeks. Before therapy, three of the 14 patients had reconstituted CD8<sup>+</sup> CTL responses while 11 had no CTL responses. After a 4 week treatment period, all 11 patients exhibited CTL responses equivalent to those in the donor (Figure 2). To distinguish the contribution of infused CTL from endogenous T-cell recovery in the patients, the unique sequences of the rearranged T-cell receptor V<sub>β</sub> gene expressed in infused CTL clones were used as a marker. CMV-specific T-cell clones were isolated from three patients after therapy was completed and the T-cell receptor V<sub>β</sub> gene was sequenced for comparison with the V<sub>β</sub> gene in the infused clones. All of the CTL clones isolated at intervals up to 12 weeks after completion of therapy expressed a T-cell receptor V<sub>β</sub> gene which was identical in sequence to that expressed by the infused clones.

Factors affecting the long-term persistence of transferred CD8<sup>+</sup> CMV-specific CTL

In the recipients of adoptively transferred CD8<sup>+</sup> CMV-specific CTL discussed above, cytolytic responses equivalent to those in the immunocompetent bone marrow donor
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were achieved in all patients immediately after the fourth infusion. However, these cytolytic responses declined over the following weeks in patients who failed to recover endogenous CD4+ CMV-specific T\(_h\) responses.22 This was similar to findings in mice rendered deficient in CD4+ T cells by gene knockout technology where virus-specific CTL may fail to persist or become dysfunctional.24 Although the clinical results are consistent with a requirement for CD4+ CMV-specific T\(_h\) for persistence of CTL, this subset of patients also had GVHD as a consequence of the BMT and required treatment with both cyclosporine and prednisolone. Thus, it was not possible in this study in humans to determine whether a deficiency of CD4+ T\(_h\) or the more intensive immunosuppressive drug therapy was responsible for the decline in transfected CTL.

Virological monitoring of BMT recipients receiving immunotherapy with CD8+ CMV-specific CTL

The 14 patients enrolled in the phase I study (see above) of adoptive immunotherapy as prophylaxis for CMV infection were studied for virus reactivation using weekly cultures of the blood, urine and throat. A positive culture for CMV from the throat was obtained in one patient before therapy and became negative after the first T-cell infusion. Two patients had a positive urine culture during T-cell therapy. No patient had evidence of CMV viraemia and none of the 14 patients developed CMV disease.22 Thus, this study provided sufficiently encouraging evidence of antiviral activity to proceed with a larger phase II study. The phase II study is currently in progress and is evaluating adoptive immunotherapy with both CMV-specific CD8+ CTL and CD4+ T\(_h\) clones as a strategy for preventing CMV disease following allogeneic BMT. It is anticipated that this study will provide an additional insight into the effects of immunosuppression on the persistence and function of transferred T cells.

Rationale for adoptive immunotherapy of HIV infection

HIV differs from persistent human herpesviruses in that the infection is characterized by continuous high levels of virus replication. However, there is substantial evidence that host CD8+ T-cell responses to HIV have antiviral activity and delay disease progression. Early studies of primary infection demonstrated a reduction in plasma viraemia following the development of CD8+ HIV-specific CTL.25 More recently, the development of soluble class I MHC molecules assembled into tetramers and complexed to specific peptides has overcome the low affinity of binding of monomeric class I molecules to T cells, thus permitting the quantification of antigen-reactive CD8+ T cells in peripheral blood using flow cytometry. Studies using tetramers complexed with immunodominant Gag or Pol epitopes to quantify CD8+ HIV-specific T cells in infected individuals have revealed an inverse correlation between the magnitude of the CTL response and viral load.26,27 Individuals termed long-term non-progressors, who have low viral loads and normal numbers of CD4+ T cells, are characterized by having strong CD8+ CTL and CD4+ T\(_h\) responses to HIV Gag.28 These findings suggest that HIV-specific T-cell responses exert considerable antiviral activity, so that boosting these responses by adoptive transfer may be beneficial.

Evasion of T-cell immunity by HIV

Despite the inferential evidence that HIV-specific T-cell responses exert antiviral activity, HIV replication continues in the majority of patients. Several mechanisms have been proposed to explain the failure of the immune response to contain HIV infection and these must be considered in the development of adoptive T-cell therapy. Expression of the HIV Nef protein reduces the surface expression of class I MHC and susceptibility to lysis by HIV-specific CTL in vitro.29 However, the association of HIV-specific CTL responses with lower viral load suggests the protection provided by Nef in vivo must be incomplete and can be overcome with a strong response.26 A more problematic issue may be the error-prone HIV reverse transcriptase, which results in genetic diversification of the initial virus inoculum and provides a source of virus with mutations in CTL epitopes.30 Mutations may promote escape from CTL because the variant peptide either fails to bind to the MHC molecule or T-cell receptor, or because an antagonistic signal is delivered to the T cell, impairing its ability to kill targets expressing the unmutated peptide.31–33 The probability of mutational escape could potentially be diminished in adoptive transfer studies by simultaneously transferring CTL clones specific for multiple epitopes.

Viral reservoirs

Reservoirs of virus pose a problem for both drug- and immune-based therapies. The identification of lymph nodes as reservoirs of ongoing virus replication has led to speculation that CD8+ HIV-specific CTL may accumulate preferentially in the blood rather than the lymphoid tissue.34 Therefore, it is essential to ensure that transferred CTL can migrate to sites of virus replication in lymph nodes. Latent HIV in resting CD4+ T cells represents a reservoir of virus that persists despite drug therapy and, because of the absence of viral protein expression, latently infected cells are also invisible to CTL attack.35 Estimates derived from analysis of the latent pool in patients receiving highly active antiretroviral therapy (HAART) and without detectable plasma virus for more than 2 years, suggest it may take up to 60 years for this reservoir to be eliminated.6 However, therapeutic strategies designed to induce reactivation of
virus from latent sites, such as by the administration of cytokines and/or T-cell-stimulatory antibodies, are being investigated and offer the potential to reduce the latent reservoir. Since HIV-specific T-cell responses decline substantially in patients on HAART, it may be essential simultaneously to boost HIV-specific immunity by adoptive transfer to ensure that cells reactivating HIV are rapidly eliminated by the immune response.

Deficiency in CD4+ HIV-specific T-cell response

A deficiency of CD4+ HIV-specific T-cell responses, which is characteristic of HIV-infected individuals, may underlie many of the limitations of the immune system in containing HIV. Although uninfected CD4+ HIV-specific T cells can be detected at low levels in some patients, if these cells were expanded and reinfused they would be susceptible to infection with HIV. Molecular strategies that rely on expressing proteins or RNA molecules in CD4+ T cells have been developed to block viral replication by selectively inhibiting the function of an essential viral gene and/or to prevent viral entry or integration. Thus, it may be feasible to correct the CD4+ HIV-specific T cells present in the majority of HIV+ patients by isolating and expanding such cells in vitro and introducing genes to protect these cells from infection after reinfusion.

Adoptive transfer of unmodified and LN-modified CD8+ HIV-specific CTL

To begin to address the potential benefits and limitations of T-cell therapy in HIV, we first evaluated the safety and potential antiviral activity of augmenting CD8+ HIV-specific CTL responses. Gag-specific CTL clones were isolated from six HIV-positive patients and some of the clones were transduced with a retroviral vector (LN) encoding the neomycin phosphotransferase (neo) gene to facilitate monitoring of cell persistence and localization to sites of infection. Patients then received three infusions of autologous unmodified CD8+ HIV-specific CTL clones in doses of 3 × 10^6, 1 × 10^6, and 3.3 × 10^6 cells/m^2 at 2 week intervals. This was followed by two infusions of LN-modified CTL at cell doses of 1 × 10^6 and 3.3 × 10^6 cells/m^2 1 week apart. T-cell infusions were tolerated without serious toxicity, although mild-to-moderate flu-like symptoms lasting 24–48 h were observed in patients with a high viral load.

To determine whether the T-cell infusions augmented cytolytic activity in the patient, the ability of peripheral blood lymphocytes (obtained before and after therapy) to kill autologous target cells expressing HIV Gag was assessed. CTL infusion was found to augment Gag-specific lytic activity with the peak activity achieved 1 day after the infusion of the highest cell dose.

Migration of transferred HIV-specific CTL to lymph nodes

Four days after the last infusion of neo-modified CTL, a subset of the patients described above underwent a lymph node biopsy to assess migration of the transferred CTL to lymph nodes. Polymerase chain reaction (PCR) using neo-specific primers followed by in situ hybridization with a neo-specific probe was performed on fixed tissue sections to identify and localize neo-marked cells. Large numbers of neo-positive T cells were detected within the lymph node adjacent to cells actively replicating HIV. This demonstrated that the CTL had homed appropriately to sites of virus replication.

Antiviral activity of adoptive immunotherapy with CD8+ HIV-specific CTL

The antiviral activity of the HIV-specific CTL adoptive immunotherapy was assessed by measuring plasma viral load and the frequency of circulating HIV-infected cells before and after therapy. A transient increase in plasma viral load was observed 1 day after the CTL infusion in some patients; this may reflect the lysis of infected cells and release of the preformed virus. Levels of plasma virus returned to baseline or below within 3 days, although a sustained reduction in plasma virus was not observed. Since cells infected with HIV are the immediate targets of CTL, it was anticipated that changes in this compartment would be the most sensitive assay of antiviral activity. A novel assay for detecting CD4+ T cells actively replicating HIV using direct in situ hybridization with probes to detect HIV RNA in cells was developed, and three of the six patients had measurable levels of these cells in the peripheral blood before therapy. During the 3–4 days after each CTL infusion, the frequency of HIV-infected CD4+ T cells declined dramatically. HIV-infected cells returned to baseline levels in the following days. This resurgence of virus-infected cells did not reflect the selection of variant viruses that escaped CTL recognition but did correlate with a decline in the frequency and lytic activity of adoptively transferred CTL in the blood, suggesting that CTL persistence was the factor limiting antiviral activity.

Strategies to improve persistence of transferred CD8+ HIV-specific CTL

The mechanisms involved in the rapid loss of transferred CD8+ HIV-specific CTL are being investigated. Insights derived from in vitro and animal model studies suggest that a deficiency of IL-2-producing HIV-specific CD4+ T cells may be a critical factor. Studies of lymphocytic choriomeningitis virus (LCMV) infection of CD4+ knockout mice have revealed an essential role for CD4+ T cells in maintaining the persistence and function of CD8+ virus-
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specific CTL. In the hu-PBL-SCID (severe combined immunodeficiency disease) mouse model of HIV infection, in which CD4+ HIV-specific T_h cells are deficient, CD8+ HIV-specific CTL had an antiviral effect in mice challenged with HIV but failed to persist in vivo. Therefore, although CD8+ CTL appear to be important effector cells for controlling HIV, their use as the sole mode of immunotherapy may be limited by the deficiency of CD4+ HIV-specific T_h in most patients.

Several approaches may be used to correct deficient T_h function and improve the persistence and function of adoptively transferred CTL in HIV-infected hosts. The administration of IL-2 with transferred CTL improves CTL persistence and antiviral activity in animal models and is now being evaluated in HIV-infected patients. A more physiological approach to deliver IL-2 to activated CTL may be to engineer genetically the CTL to have a T_h-independent phenotype. One strategy which has evolved from an improved understanding of IL-2 signal transduction utilizes the expression of chimeric cytokine receptors consisting of the extracellular domains of the granulocyte–macrophage colony-stimulating factor (GM-CSF) α and β receptors fused to the intracellular domains of the IL-2 α and β chains, respectively. CD8+ CTL produce GM-CSF after antigen stimulation, and engagement of the chimeric GM-CSF/IL-2 receptor chains by GM-CSF induces heterodimerization of the intracellular IL-2 β and α chains and activates the downstream IL-2 signalling machinery. Finally, it may be possible to restore or augment HIV-specific CD4+ T-cell responses by adoptive transfer. Recent studies have demonstrated that CD4+ T_h responses to HIV antigens can be detected in HIV-infected individuals, and it may be feasible to isolate these cells in vitro, introduce ‘intracellular immunization’ genes to render the cells resistant to HIV and then expand and reinfuse them into the patient to provide an amplified and sustained HIV-specific T_h response.

Conclusions

Substantial progress has been made in our understanding of the role of host T-cell responses in controlling persistent virus infection and the intricate strategies viruses employ to evade complete elimination. For CMV, the balance between host immunity and virus persistence is perturbed in patients undergoing intensive BMT and progressive infection often results. Adoptive transfer of CMV-specific T-cell clones is a novel strategy for restoring protective host immunity and preventing CMV disease in these patients. HIV provides a more formidable challenge for immunotherapy since it progresses in hosts with an initially normal immune system. However, recent studies suggest that the immune defects that contribute to progressive infection can be identified and potentially corrected by adoptive immunotherapy. At present, investigation of the adoptive transfer of virus-specific T cells is primarily restricted to research settings, but the information derived from these studies should assist in the development of therapeutic modalities, such as vaccination, that can be applied more broadly.

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References

S. R. Riddell and P. D. Greenberg


40. Brodie, S. J., Lewinsohn, D. A., Patterson, B. K., Jiyanama, D., Krieger, J., Corey, L. et al. (1999). In vivo migration and function of...
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