Interactions between Viruses in Transplant Recipients

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Viral coinfections may modulate disease expression, enhance pathogenicity, and lead to greater cumulative immunosuppression in the host. The pathophysiological basis of these may be direct virus-virus interactions, effect of cohabitating viruses on host cell function, or impaired host immune responses. The interrelationship between viral pathogens has become increasingly more relevant and its scope wider as new or previously unrecognized viruses continue to emerge as pathogens in transplant recipients. The pathways and mediators that modulate biological activity represent potential targets for immunomodulatory interventions as adjunctive therapies for transplant recipients.

It has long been recognized that viral infections—particularly those due to herpesviruses—in transplant recipients may be followed by a cascade of complex interactions with the host defense system that can facilitate infections due to other viruses or enhance their pathogenicity (table 1). A landmark study 2 decades ago showed that herpesvirus infections in renal transplant recipients were followed by alterations in T lymphocyte subsets that persisted for up to 100 days after transplantation [1]. Sequelae of coinfection of viruses may also result from direct interactions between the viruses—for example, via regulatory genes with the ability to transactivate or repress the expression of the genes of cohabitating virus, or from yet unknown factors [2]. Discernment of their clinical relevance continues to be of interest as new viruses or new roles for known viruses emerge in transplant recipients. Significant strides have also been made in elucidating the mechanisms of virus-virus or virus-host interactions.

Here, I discuss the current state of knowledge regarding interactions between viruses in transplant recipients, the pathophysiological basis and clinical sequelae of these interactions, and their implications for antiviral management with use of either antiviral agents or immunomodulatory approaches.
Table 1. Interactions between viruses in transplant recipients, the clinical consequences of infection, and likely mechanisms.

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NOTE. CMV, cytomegalovirus; EBV, Epstein-Barr virus; HCV, hepatitis C virus.

which can enhance production of virus in an autocrine manner [8] and may have a role in attenuating the antiviral effects of IFN-α [9]. CMV can lead to activation of nuclear factor–κB, a transcription factor involved in stimulating a broad array of genes, including those that may have a role in inflammatory responses [10]. Finally, neutrophil migration, chemotaxis, and respiratory burst activity of phagocytic cells have been shown to be decreased during acute CMV infection [11, 12].

**Human herpesvirus–6 (HHV-6).** The primary target cells of HHV-6 are CD4+ T lymphocytes [13]. Although this characteristic is shared with HIV, CD46 and not CD4 is the receptor for HHV-6. HHV-6 preferentially replicates in CD4+ T cells, causing cytopathic effects and cell death [14]. Infection of PBMCs with HHV-6 results in suppression of T lymphocyte function, as shown by reduced IL-2 synthesis and cellular proliferation [15, 16]. Although HHV-6 most efficiently replicates in CD4+ T cells, its cellular host range is wide and includes CD8+ T cells, macrophages, NK cells, megakaryocytes, and possibly epithelial cells [9, 17]. Besides directly infecting cells, HHV-6 is a potent inducer of cytokines, such as TNF-α, IFN-γ, and IL-1β [15, 18]. Immunomodulatory effects of HHV-6 may in large part be due to the production of these cytokines [15, 18].

**INTERACTIONS AMONG HERPESVIRUSES**

**β-Herpesviruses.** A body of evidence obtained from transplant recipients has shown that the interactions between CMV and the 2 other β-herpesviruses, HHV-6 and human herpesvirus–7 (HHV-7), have an impact on the pathogenicity of these viruses. HHV-6 shares 67% DNA homology with CMV. Apart from the overall immunosuppressive effects of these viruses, in vivo biological interactions between them during cellular coinfection may affect infectivity of virions and disease progression. Formation of complexes between the glycoproteins gH and gL of CMV and HHV-6 [19] play a role in virus-induced cell fusion and syncytium formation and, ultimately, in the spread of virus from cell to cell [9, 19, 20].

That coinfection with HHV-6 and CMV occurs frequently and modulates the expression of disease due to either virus has been shown in a number of studies in transplant recipients [21–26]. The incidence of symptomatic CMV infection and peak CMV load was significantly higher in liver transplant re-
cipients with HHV-6 infection than in those without it [27]. HHV-6 antigen was detected histopathologically in biopsy samples obtained from 6 liver transplant recipients with allograft dysfunction; 4 of 6 patients also had CMV in the same biopsy samples [25]. Of 19 liver transplant recipients with CMV infection, 17 (89%) had concomitant HHV-6 and/or HHV-7 infection. CMV disease was documented in 14 of 19 patients with coinfections [28].

Despite the fact that HHV-6 and HHV-7 are closely related, with 46.6%-84.9% homology in their genomes, the 2 viruses differ in certain biological effects, such as rate of replication and capacity to induce apoptosis and cell differentiation [29]. Whereas CD4 receptor expression was more pronounced in HHV-6-infected persons than for HHV-7-infected persons, HHV-7 was less active in inducing apoptosis, thus favoring continued cell proliferation [29].

Although HHV-7 has been less extensively studied than HHV-6, several studies, particularly among renal transplant recipients, have suggested an important role of HHV-7 in the pathogenicity of CMV [28, 30–32]. The risk of developing CMV disease for renal transplant recipients was increased in patients with concurrent infection due to HHV-7, whereas the association between CMV and HHV-6 was less conclusive [30]. Patients with CMV and HHV-7 coinfection were more likely to have CMV disease than were those with CMV infection only [30]. In the same study, detection of HHV-7 but not HHV-6 was associated with more episodes of cellular rejection [30]. It is plausible that a beneficial effect of antiviral prophylaxis on allograft rejection may in part be mediated via its effect on herpesviruses other than CMV [33].

**HHV-6 and Epstein-Barr virus (EBV).** CMV and HHV-6 can modulate disease progression due to EBV. One of the earliest observations with regard to HHV-6 was that human B cells appeared to be particularly susceptible to HHV-6 infection in vitro only if they had been previously infected with EBV [34]. Infection of EBV genome-positive cells by HHV-6 leads to reactivation of EBV [35]. HHV-6 up-regulated, by up to 10-fold, the expression of an immediate-early transactivator called ZEBRA protein (shown to be critical for switching from latency to the lytic cycle), as well as diffuse and restricted early antigens, in EBV-producer and -nonproducer cell lines [35]. Expression of late EBV gene products, such as the viral capsid antigen and viral membrane glycoprotein, in EBV-producer cells was also increased after infection with HHV-6 [35]. HHV-6 causes receptor protein CR2 for EBV to be expressed on immature or prethymic CD38+ stem cells, which have the capacity to acquire T and B cell markers [36]. By inducing EBV, HHV-6 may therefore contribute to an increase in the B cell pool infected with EBV.

EBV-seropositive patients with primary CMV infection demonstrated antibody profiles of EBV recurrence [37]. Most of these patients also showed diagnostic increases in HHV-6 antibody [37]. Primary infections with EBV did not induce immune reactivations of CMV infection [37]. EBV seronegativity and primary EBV infection have been recognized as major risk factors for lymphoproliferative disorder after transplantation [38]. Use of OKT3 as an antirejection treatment and CMV seromismatch (recipient-negative/donor-positive serostatus) increased this risk by 4- to 6-fold. The 3 risk factors synergistically enhanced the rate of fatal infection and/or CNS involvement 654 times more than when none of these risk factors were present [38].

**INTERACTION BETWEEN HERPESVIRUSES AND HEPATITIS C VIRUS**

At least 3 studies have shown that CMV infection significantly increased the risk of fibrosis and allograft cirrhosis in liver transplant recipients undergoing transplantation because of hepatitis C virus (HCV) [39–41]. CMV viremia was associated with significantly diminished cirrhosis-free actuarial survival in patients with hepatitis due to HCV [39]. Fibrosis scores were higher and fibrosis of stage ≥2, as determined by liver biopsy 4 months after transplantation, was more common in patients with CMV infection (P = .01 for each) [41]. Graft failure, defined as cirrhosis, relisting for liver transplantation, retransplantation, or death, was significantly more common among CMV-infected patients [41]. Donor age, CMV infection, receipt of mycophenolate mofetil, and year of transplantation each independently predicted graft failure [41]. The mean time of fibrosis-free survival in patients with hepatitis C in another study was also significantly lower among those with CMV infection [40].

Notably, however, in 2 studies in which preemptive therapy for CMV disease was instituted on detection of viremia by sensitive assays (PCR or antigenemia), a correlation between CMV infection and progression of hepatitis C could not be shown [42, 43]. It is therefore plausible that early subclinical infection that is aborted by preemptive therapy has a lesser impact on the rate of recurrence of hepatitis C or its severity than does otherwise ongoing viremia.

HHV-6 infection has also been shown to have a contributory role in the pathogenesis of hepatitis C. Although HHV-6 viremia did not affect the overall rate of recurrence of hepatitis C, it was associated with a more severe form of recurrence. The development of severe recurrence, that is, a fibrosis score of ≥2, was significantly more common in patients with HHV-6 infection in 1 study [44]. In another report, patients with HHV-6 viremia tended to have an earlier recurrence and significantly higher fibrosis scores on recurrence than did those without HHV-6 viremia [43]. Other variables that may influ-
ence the outcome of hepatitis C recurrence, such as HCV genotype, alcohol use, CMV infection, and augmented immunosuppression, did not differ for patients who did and did not have HHV-6 viremia [43]. Of note, patients who received ganciclovir as preemptive therapy for CMV infection had lower total Knodell scores and a trend toward lower fibrosis scores than those of patients who did not receive ganciclovir [43]. A protective effect of ganciclovir on the severity of hepatitis C recurrence was proposed to be mediated via its mitigating effect on HHV-6 infection.

Although the pathophysiological basis of the association between HHV-6 infection and severity of hepatitis C, particularly the progression of fibrosis, remains to be determined, a number of biological plausibilities exist. Effective T cell–mediated immunity is believed to be important in clearing or neutralizing HCV infection [45]. HHV-6 inhibits cell-mediated immune function—that is, the mitogen-driven proliferative response of T lymphocytes. HHV-6 is also a potent inducer of cytokines, such as TNF-α, that play a role in the development of hepatic fibrosis. It has been proposed that TNF-α leads to activation of Kupffer’s cells in the liver, a key component in the cascade of hepatic fibrogenesis [46]. Production of TNF-α can also lead to the induction of transforming growth factor-β1. The latter is a fibrogenic cytokine and a potent stimulus for hepatic stellate cells to increase the production of extracellular matrix protein, which is the initial step in hepatic fibrosis [47]. Finally, HHV-6 preferentially infects and destroys CD4+ T lymphocytes. Although CD4+ T cells secrete a number of soluble mediators of immune function, the primary cytokines produced by these cells are IFN-γ and IL-2. IFN-γ is antifibrogenic and down-regulates the activation of hepatic stellate cells [43]. Thus, enhanced fibrosis with HHV-6 may be mediated via its effect on CD4+ T cells.

INTERACTION OF CMV WITH OTHER VIRUSES

**BK virus.** Experimental studies have shown that CMV induces gene expression and replication of primate polyomaviruses [2, 48]. BK virus may also have a modulatory effect on CMV. In dually infected semipermissive cells, the expression of CMV immediate-early protein was enhanced by heterologous transcriptional transactivation by the BK virus large T antigen [2]. In hematopoietic stem cell transplant recipients, CMV infection has been shown to coexist with hemorrhagic cystitis due to BK virus [49]. In renal transplant recipients, CMV infection conferred a significantly higher risk for nephropathy due to BK virus [50].

**Respiratory viruses.** Seasonal differences in prevalence have been noted for many medical illnesses, including viral infections. In temperate regions of the world, infections due to respiratory viruses occur with a greater frequency in the winter. Outbreaks of infection due to influenza virus, respiratory syncytial viruses, and rhinoviruses are associated with an increase in wintertime frequency of respiratory tract infections. Patients undergoing liver transplantation in the fall had a higher incidence of CMV disease in 1 report [51]. In renal transplant recipients, transplantation in October and November was associated with a 5-fold–greater risk for CMV disease than was transplantation in other months [52]. Whether the seasonal pattern of CMV is triggered by respiratory viruses or yet unrecognized viruses or factors and the mechanism by which this may occur remain to be determined. However, influenza virus infections have been shown to be associated with a significant increase in levels of cytokines, such as IL-6 and TNF-α [53]. These proinflammatory cytokines could potentially modulate CMV replication.

INTERACTIONS OF HERPESVIRUSES AND HCV WITH HIV

Transplantation is increasingly being considered a therapeutic option for patients with HIV infection and end-stage organ failure. A number of DNA viruses—in particular, herpesviruses—may modulate HIV replication by transactivating the HIV long terminal repeat sequences [54–56]. HHV-6 can upregulate CD4 expression and induce CD4 receptors and CD8+ T cells, NK cells, thus rendering them susceptible to infection with HIV. Indeed, HHV-6 has been proposed to be a cofactor in the acceleration of HIV infection [18]. More recently, HHV-8 has also been shown to induce HIV replication in vivo and in vitro [57]. Viral coinfections may not always have a deleterious effect. For example, competition for CD4 by HHV-7 and HIV may interfere with receptor binding and subsequent HIV replication [13].

Coinfection with HCV and HIV has been shown to lead to higher HCV loads, accelerated course of HCV infection, and progression to cirrhosis [58–60]. The precise basis for these observations has not been fully discerned. However, extrahepatic sources of replication of HCV in coininfected patients, such as peripheral blood monocytes/macrophages and lymphocytes [61], may account for greater overall virus loads in these patients.

As many as 30% of persons with HIV in the United States are coinfected with HCV [62]. In HIV-infected patients undergoing liver transplantation, survival was significantly lower among those coinfected with HCV than among those without HCV infection [62]. However, the survival rate among HIV- and HCV-positive transplant recipients was similar to that among those in undergoing transplantation because of HCV infection but who were not HIV-infected. Intolerance to antiretrovirals and adverse drug interactions in coinfected patients...
after posttransplantation initiation of antiviral therapy for HCV poses a significant management challenge [62].

IMPACT OF THERAPY WITH ANTIVIRAL AGENTS ON COINFECTING VIRUSES

Efficacy of antiviral agents in the clinical setting may result from an additional salutary effect on 1 or more co-infecting viruses. This is particularly relevant in the case of herpesvirus. In vitro susceptibilities to antivirals of HHV-6 are similar to those of CMV; both ganciclovir and foscarnet are active against HHV-6, whereas acyclovir is not. Ganciclovir prophylaxis for CMV infection in allogeneic stem cell transplant recipients has been shown to be effective against HHV-6 reactivation as well [63, 64]. In hematopoietic stem cell transplant recipients with encephalitis due to HHV-6 infection, HHV-6 loads in serum decreased from 2.0 to 0 copies/mL after initiation of antiviral therapy, and those in CSF decreased from 4.4 to 2.0 copies/mL [65]. HHV-6 viremia correlated with abnormal mental status in liver transplant recipients, and the use of ganciclovir as CMV prophylaxis was protective against this effect [66].

The clinical and virological response of HHV-6 infections to ganciclovir, however, may be erratic or not always predictable. In liver transplant recipients, CMV DNA levels decreased with 2 weeks of ganciclovir treatment, and the symptoms resolved in 42 liver transplant recipients who received ganciclovir, whereas the effect on HHV-6 infection was less predictable [28]. In allogeneic stem cell transplant recipients, HHV-6 encephalitis developed in 2 of 5 patients receiving intravenous ganciclovir therapy [67]. CMV antigenemia and symptoms resolved in 42 liver transplant recipients who received ganciclovir, whereas the effect on HHV-6 infection was less clear [67]. In allogeneic stem cell transplant recipients, HHV-6 encephalitis developed in 2 of 5 patients receiving intravenous ganciclovir [68]. It has been shown that HHV-6 U69, a homologue of human CMV UL-97-encoded kinase, has an ∼10-fold lower capacity to phosphorylate ganciclovir, compared with UL-97 of CMV, and it may account for the erratic response of HHV-6 to ganciclovir [69].

Limited data are available on the impact of ganciclovir on herpesviruses other than β-herpesviruses. Although HHV-8 and varicella-zoster virus DNA were not detected during treatment with oral ganciclovir or valganciclovir, EBV DNA in the blood was common during the receipt of these drugs [70]. Adenovirus DNA was detected in 7.2% and 4.6% of the patients who received oral ganciclovir and valganciclovir, respectively, as CMV prophylaxis [71]. The clinical relevance of this observation remains to be determined. In vitro studies, however, have shown that adenovirus regulator protein E1A 13 S up-regulates the CMV major immediate-early promoter [72].

SUMMARY

This review highlights the fact that the intensity of immunosuppression of transplant recipients may be heightened and/or the pathogenicity of the viruses may be enhanced by concurrent infection with ≥1 virus. The basis of these may be virus-virus interaction involving regulatory genes and gene products or virus-host interactions resulting from modulation of the host cell functions, production of suppressive cytokines, or secondary effects on host immune responses. These pathways or mediators represent potential targets for immunomodulatory interventions. Approaches directed toward modulating disease progression by neutralization of suppressive cytokines, augmentation of cellular immunity (e.g., by adoptive transfer of cellular immunotherapy), or administration of specific antibodies that may inhibit the targets of molecular interactions implicated in viral propagation [73–76] warrant investigation as adjunctive therapeutic modalities for viral infections in transplant recipients.

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