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Failure of low-dose recombinant human IL-2 to support the survival of virus-specific CTL clones infused into severe combined immunodeficient foals: Lack of correlation between in vitro activity and in vivo efficacy

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Abstract

Although CTL are important for control of lentiviruses, including equine infectious anemia virus (EIAV), it is not known if CTL can limit lentiviral replication in the absence of CD4 help and neutralizing antibody. Adoptive transfer of EIAV-specific CTL clones into severe combined immunodeficient (SCID) foals could resolve this issue, but it is not known whether exogenous IL-2 administration is sufficient to support the engraftment and proliferation of CTL clones infused into immunodeficient horses. To address this question we adoptively transferred EIAV Rev-specific CTL clones into four EIAV-challenged SCID foals, concurrent with low-dose aldesleukin (180,000 U/m^2), a modified recombinant human IL-2 (rhuIL-2) product. The dose was calculated based on the specific activity on equine PBMC in vitro, and resulted in plasma concentrations considered sufficient to saturate high affinity IL-2 receptors in humans. Despite specific activity on equine PBMC that was equivalent to recombinant equine IL-2 and another form of rhuIL-2, aldesleukin did not support the engraftment and expansion of infused CTL clones, and control of viral load and clinical disease did not occur. It was concluded that survival of Rev-specific CTL clones infused into EIAV-challenged SCID foals was not enhanced by aldesleukin at the doses used in this study, and that in vitro specific activity did not correlate with in vivo efficacy. Successful adoptive immunotherapy with CTL clones in immunodeficient horses will likely require higher doses of rhuIL-2, co-infusion of CD4+ T lymphocytes, or administration of equine IL-2.
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1. Introduction

Significant progress has been made toward defining the mechanisms of immune control of lentiviral infections, and it is evident that viral specific CTL and CD4+ helper T lymphocytes are critically important in limiting lentiviral replication. Nonetheless lentiviruses persist, and in HIV-1 infection, T cell responses ultimately fail to control virus replication and progression to AIDS results. Protective vaccines will undoubtedly need to induce CTL and CD4+ T cell responses, but development of such vaccines is hampered because the correlates of T cell-mediated protection are still not known. Specific knowledge gaps include how to induce and support a protective CTL response in the face of CD4+ T lymphocyte deficiency, the specific epitopes that must be recognized by CTL to control lentivirus

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replication, and the qualitative characteristics (i.e. functional avidity) of protective CTL.

A growing body of evidence indicates that CD8+ CTL are critical in containing lentiviral replication. The appearance of virus-specific CTL in the peripheral blood is temporally associated with the decline of primary viremia in acutely HIV-1-infected patients, and occurs well before serum neutralizing antibody activity is detected (Borrow et al., 1994; Koup et al., 1994). High levels of HIV-1-specific CTL are detected in HIV-1-infected clinical long-term nonprogressors (Rinaldo et al., 1995), and CTL activity is inversely correlated with viral load (Betts et al., 1999). Moreover, loss of HIV-1-specific CTL activity is associated with rapid clinical progression to AIDS (Klein et al., 1995). In addition, high numbers of tetramer-positive CD8+ T lymphocytes coincide with control of primary viremia in acutely HIV-1-infected patients (Wilson et al., 2000), and an inverse association between circulating tetramer-positive CD8+ T lymphocytes and viral load has been reported (Ogg et al., 1998). In the SIV system, emergence of CTL in rhesus monkeys coincides with virus clearance during primary infection (Kuroda et al., 1999). Moreover, depletion of CD8+ T lymphocytes in infected monkeys is associated with a rapid increase in viremia (Jin et al., 1999; Schmitz et al., 1999). Vaccines that induce high frequency SHIV-specific CTL responses in rhesus monkeys result in reduced viral loads and prevention of clinical AIDS following homologous SHIV challenge (Barouch et al., 2000; Barouch et al., 2001a,b).

Deficient CD4+ T lymphocyte help in HIV-1-infected individuals is likely the main determinant of the functional impairment and decline of virus-specific CD8+ CTL, leading to loss of immune control of viremia and clinical progression to AIDS. One mechanism by which CD4+ T cells support CTL proliferation and survival is by secretion of IL-2 (Altfeld and Rosenberg, 2000; Cheng et al., 2002; Lanzavecchia and Sallusto, 2000). In an effort to enhance T lymphocyte responses in HIV-1-infected patients, recombinant human IL-2 (rhuIL-2) administration has been used. In these patients, rhuIL-2 can augment immune responses and increase CD4+ T lymphocyte counts (Aladdin et al., 2000; Davey et al., 1997; Jacobson et al., 1996). Recombinant huIL-2 has also been administered to HIV-1-infected individuals to support adoptively transferred HIV-1-specific lymphocytes and CTL (Klimas et al., 1994; Koenig et al., 1995; Tsoukas et al., 2001). In addition, low-dose aldesleukin, a modified form of rhuIL-2, has been used successfully to support adoptively transferred MART-1 specific CTL clones in metastatic melanoma patients (Yee et al., 2002).

Equine infectious anemia virus (EIAV) is a macrophage-tropic lentivirus that causes persistent infection in horses. Specific immune responses are required for EIAV control, since severe combined immunodeficient (SCID) foals fail to eliminate the initial viremia following challenge with EIAV, as compared to normal foals (Perryman et al., 1988). SCID in Arabian foals is caused by a frame-shift mutation in the gene encoding the catalytic subunit of DNA-dependent protein kinase (Shin et al., 1997; Wiler et al., 1995), and has an autosomal recessive mode of inheritance (Perryman and Torbeck, 1980). The equine SCID defect is more severe than its murine counterpart in that SCID foals are incapable of forming either coding or signal joints (Shin et al., 1997). Adoptive transfer of EIAV-specific T and B lymphocytes to a SCID foal results in functional CTL and neutralizing antibody activity, and is protective against EIAV challenge (Mealey et al., 2001). The specific contribution of infused CTL to the protective effects observed in this study was difficult to determine due to the neutralizing antibody response (Mealey et al., 2001).

As in HIV-1 and SIV, virus-specific CTL are critically important in EIAV control. The initial plasma viremia in acute EIAV infection is terminated prior to the appearance of neutralizing antibody, but concurrent with the appearance of CTL (Hammond et al., 1997; McGuire et al., 1994). CTL epitopes have been identified in Gag, Pol, Env, Rev, and in the protein encoded by the S2 open reading frame (Lonning et al., 1999; McGuire et al., 2000; Mealey et al., 2003; Zhang et al., 1998). Indirect evidence for CTL-mediated control of EIAV replication was provided by the observation that plasma viral variants escaped recognition of Env-specific CTL in an infected horse (Mealey et al., 2003).

The functional avidity of the interaction between CTL and their target cells determines the efficiency with which CTL recognize and kill their specific targets (Gallimore et al., 1998). In comparison to low avidity CTL, high avidity CTL of the same specificity recognize target cells expressing lower antigen density, and initiate lysis of targets more rapidly at any given antigen density (Derby et al., 2001). Adoptive transfer experiments in mice infected with LCMV as well as in mice infected with vaccinia virus constructs expressing HIV-1 proteins indicate that the in vivo protective effects of CTL correlate with their avidity (Alexander-Miller et al., 1996; Derby et al., 2001; Gallimore et al., 1998), but such studies have not been performed in a

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