ABSTRACT

Human Immunodeficiency Virus-1 (HIV-1) infection is characterized by chronic immune activation and progressive loss of CD4\(^+\) T cells leading to a wide array of immune dysfunction particularly involving immune response directed against viral antigens. HIV-1 encodes for fifteen proteins for e.g. tat, rev, nef, gp120, gag etc, any of which might serve as a target for immune recognition. Immune response to the envelope proteins have been studied a lot due to their presence on the surface of the virus. The Tat protein has also been focus of immunization studies because of its potent regulatory activity. The Tat protein although being nuclear in localization, is also released from infected cells and acts on uninfected cells. Furthermore, a correlation between anti-Tat immune response and slow progression of the disease exists in the literature. Several investigators have used Tat as a potential candidate for vaccination with encouraging results Although Tat has been found to be a successful candidate; few reports imply that Tat acts as an immunosuppresor for the co-immunized viral antigens. The mechanism by which Tat mediates its immunosuppression remains to be elucidated. In order to identify unambiguously the role of Tat in immune response of a co-immunized antigen, we have constructed a bicistronic vector expressing Tat and gp120 from CMV promoter with an internal ribosome entry site and analyzed the role of Tat in elicitation of gp-120 specific immune response. The T cell responses to gp120 were greatly diminished in mice co-immunized with Tat as compared to mice immunized with gp120 alone. This immunosuppressive activity of Tat was not confined to viral antigen only as it also suppressed the immune response of an unrelated antigen. Analysis of cytokine profile suggests that Tat induces IL-10 and since IL-10 has been demonstrated to have appreciable T cell inhibitory activity, it is plausible that IL-10 could be responsible for Tat mediated immunosuppresion. The immunosuppressive effect of Tat was not observed in IL-10 deficient mice confirming the role of IL-10 in Tat mediated immunosuppression. Thus our results demonstrate that the immunosuppressive effect of Tat is mediated through IL-10 and suggests that Tat induced IL-10 mediated immune suppression seems to cripple immune surveillance during HIV-1 infection.
The nature of the interaction between HIV and the immune system is complex and the mechanism of T cell response and cytokine induction to restrict the infection is not well understood. HIV infected individuals have high frequency of HIV-1 specific CTLs, however, the immune system is unable to clear the infection and eventually virus production continues. There seems to be several reasons for CTL dysfunction. Dysregulation of cytokines that are induced due to interaction of HIV-1 specific T cells with antigen presenting cells is one of the possible causes of CTL dysfunction. IL-12 is a hetero-dimer, which is secreted from antigen presenting cells and act on T cells and NKT cells to induce IFNγ from T cells. Interleukin12 (IL-12) production is believed to be impaired in individuals with HIV infection and this impairment manifests early in disease. We have studied the role of IL-12 in CTL dysfunction by using HIV-1 gp120 antigen DNA as a model in murine system. We have immunized wild type (WT) and IL-12 deficient mice with gp120 and observed CTL response was impaired in IL-12 deficient mice as compared to WT mice. Our results further demonstrate that co-immunization with IL-12 vector restores the impaired CTL response in IL-12 deficient mice immunized with gp120. However, immunization with IL-12 vector fails to rescue the CTL response in IFNγ deficient mice. This finding suggests a phase specific role of IL-12 in CTL response, specifically in priming of CD4+ T cells that provide help to CD8+ T cells. Our results also suggest that IL-12 is vital for priming of antigen specific T cells and plays an essential role in induction of IFNγ from T cells.