HOT TOPICS

IL-15 in HIV infection: pathogenic or therapeutic potential?

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ABSTRACT. Recent studies have shown that interleukin-15 (IL-15) is produced during acute HIV and SIV infection, and may impact viremia and viral set point. This is further supported by the findings that administration of IL-15 during acute SIV infection dramatically increases viral set point. Although the role of intrinsic IL-15 during chronic infection is much less defined, *in vivo* administration of IL-15 does not increase viral replication in SIV-infected animals. Recent data also suggest that IL-15 acts, not only on CD8+ T cells and natural killer cells, but also on effector memory CD4+ T cells. IL-15 clearly expands very different CD4+ T cell subpopulations than IL-2 in SIV-infected animals, and may be useful for the restoration of effector memory CD4+ T cells that are depleted early in HIV and SIV infection. Understanding IL-15's role in SIV infection may help us to design novel therapeutic approaches to HIV infection.

Keywords: IL-15, HIV, AIDS, T cells

Interleukin-15 (IL-15) is a pleiotropic cytokine that enhances innate and adaptive immunity, primarily by acting on CD8+ T cells and natural killer (NK) cells (reviewed in [1, 2]). In recent years, evidence has emerged as to the possible role IL-15 may play in HIV and SIV infection. Several *in vitro* studies had indicated that IL-15 may enhance function and survival of HIV- and SIV-specific CD8+ T cells [3-10], and this suggested a possible vaccine adjuvant or therapeutic application for IL-15. However, IL-15 treatment of non-human primates has revealed some unexpected results that could not be fully anticipated from the *in vitro* studies. We will present here what is known about IL-15 in acute and chronic HIV/SIV infection, concentrating on results from *in vivo* studies of IL-15 administration, and discuss the implications of these findings for the possible role of IL-15 in pathogenesis, and also its application as a therapeutic cytokine.

IL-15 IN ACUTE HIV AND SIV INFECTION

Although the exact mechanism by which viral set point is determined is not understood, events during the initial stages of HIV and SIV infection are believed to determine viral set point later in the chronic phase, and therefore contribute to disease pathogenesis. Recent studies have indicated that IL-15 may play a role during acute HIV/SIV infection. A study comparing the plasma cytokine and chemokine profiles of humans acutely infected with HIV, hepatitis B virus or hepatitis C virus demonstrated that only in HIV infection is a substantial increase in several proinflammatory cytokines, including IL-15, observed within the first 7 days of infection [11]. Similarly, in the acute phase of pathogenic SIV infection of rhesus macaques, anti-inflammatory cytokines such as IL-10 and TGF-β are induced much later [12], whereas IL-15 is increased transiently during the first weeks of infection [13]. In contrast, during non-pathogenic SIVagm infections of African green monkeys, mostly immunosuppressive cytokines are detected, including IL-10 and TGF-β [12]. Administration of IL-15 increases SIV-specific CD8+ T cell and NK cell numbers in acutely SIV-infected animals [14], and this is associated with reduced numbers of infected cells in lymph nodes. Although this may suggest that IL-15 has a protective effect during acute infection, other observations suggest a pathogenic role. The potentially detrimental effect of IL-15 during acute SIV infection was shown in two recent studies [14, 15], in which IL-15 administration during acute infection led to 1,000-fold increases of viral set point months later. This increased viral replication is associated with enhanced activation and proliferation of effector memory CD4+ T cells, the target population of HIV and SIV infection, and loss of anti-SIV antibodies [14]. Furthermore, serum IL-15 levels in acutely SIV-infected rhesus macaques correlate with viral loads [13]. There are several mechanisms which could explain how IL-15 affects viral replication at set point, including altering immune control or the numbers or types of infected cells. From the above it is apparent that more studies are needed to determine whether IL-15 plays a protective or detrimental role in acute HIV/SIV infection.

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IL-15 IN CHRONIC HIV AND SIV INFECTION

Much less is known about IL-15 in chronic HIV and SIV infection. A study examining the plasma IL-15 level in patients during structured treatment interruption (STI) indicated that patients with higher IL-15 levels were able to control viral replication even in the absence of highly active anti-retroviral therapy (HAART) [16]. Involvement of IL-15 in the SIV-mediated CNS pathology was suggested recently as increased IL-15 mRNA was found in the brains of SIV-infected macaques [17] and this may contribute to the enrichment and persistence of brain CD8+ T cells in SIV-infected macaques. In a study examining the plasma IL-15 level in chronically HIV-infected individuals, no difference in IL-15 was found when aviremic, viremic, slow-progressing and uninfected individuals were compared [18]. From the above, it is not clear if IL-15 provides any protection during chronic infection. Administration of IL-15 during chronic SIV infection induces a more than 2-fold increase in blood CD8+ T cells and NK cells [19]. In the absence of anti-retroviral therapy, however, it does not affect viral replication [19, 20], indicating that the environment during chronic infection is very different from that during acute infection where IL-15 alters viral set point. These findings suggest that IL-15 during chronic infection does not contribute to viral replication.

One of the hallmarks of HIV and SIV infection is the massive depletion of CD4+ T cells from the gut, which starts early during acute SIV and HIV infection (summarized in [21]). This massive depletion, specifically of effector memory CD4+ T cells, predetermines the outcome of infection as it results in an insurmountable stress of replenishment on the immune system (reviewed in [22]). IL-15 has been shown to induce homeostatic proliferation of peripheral effector memory CD4+ and CD8+ T cells in healthy rhesus macaques and in chronically SIV-infected macaques with anti-retroviral therapy-induced suppression of viral replication, but not in animals with uncontrolled viral replication [19, 20]. We have also found that effector memory CD4+ T cells rapidly expand when viremia is suppressed in IL-15-treated, chronically SIV-infected macaques (Y. Mueller and P. Katsikis, unpublished observation). Further support of IL-15's ability to induce CD4+ T cell homeostatic proliferation was shown in CD8+ cell-depleted, SIV-infected animals [15]. These studies raise the prospect of IL-15 as a therapeutic adjuvant to increase effector memory CD4+ T cells that are known to be depleted in HIV infection.

IL-15 AS A THERAPEUTIC CYTOKINE

IL-15 is a cytokine which may be involved in inflammatory diseases [23]. This raises the question as to whether IL-15 administration may be associated with toxicity. However, although in one study, transient side effects such as reduced neutrophils and weight loss were found in healthy rhesus macaques treated daily for up to 14 days with human recombinant IL-15 produced in mammalian cells [24], species-specific rhesus macaque IL-15 produced in bacteria and given daily [25] or intermittently [14, 19, 24] up to 100 μg/kg, twice weekly for four weeks, did not produce any toxicity in healthy and SIV-infected rhesus macaques. IL-15 is less toxic than IL-2 when tested for the induction of vascular leak syndrome in mice [26], one of the toxic side effects of IL-2 therapy (reviewed in [27]). These findings indicate that species-specific IL-15 can be used safely without the side effects reported for IL-2.

Based on its effect on memory CD8+ T cells, IL-15 is being explored as an adjuvant for vaccines (see [28]). IL-15 could also prove to be beneficial as a adjuvant cytokine therapy in patients with chronic HIV infection under HAART. Although HAART improves the life span and quality of life for most patients, CD4+ T cells in these patients are still lower than in uninfected individuals [29], and a group of HAART-treated, HIV-infected individuals showed no improvement in the CD4+ T cell numbers (immunological non-responder) [30]. Since the depletion of memory CD4+ T cells during acute and chronic HIV infection may determine disease progression, restoring memory CD4+ T cell numbers could slow down disease progression and prevent opportunistic infections. The most promising candidates for immune restoration are the common gamma-chain cytokine family members IL-2, IL-7 and IL-15 owing to their T cell survival and growth factor properties. These cytokines have some overlapping, but not identical, immune modulating effects as a result of their shared signaling pathway through the common gamma-chain receptor (reviewed in [31]). IL-2 has been extensively tested for immune reconstitution; however, IL-2 clinical trials have yielded little clinical benefit [32]. This could be due to the CD4+ T cell subpopulations that IL-2 expands in patients, in particular naïve CD4+ T cells and transitional memory CD25+ CD45RA+CD45RO+ CD4+ T cells [33-35], which are probably generated from the naïve pool and may therefore not restore or enhance immunity. IL-2 also induces FoxP3+ cells with weak suppressive activity [34, 35]. Similarly, in uninfected rhesus macaques IL-2 increases transitional memory cells, but not effector memory CD4+ T cells [20]. Although IL-15 expands CD8+ T cells and NK cells, recent data suggest that IL-15 can also be used to restore CD4+ T cell numbers in virally-suppressed, SIV-infected macaques ([20] and Y. Mueller and P. Katsikis, unpublished observation). If these cells originate from the diminished memory pool in the patients, then they could potentially increase host immunity. More studies are necessary to investigate the immune-restoring effect of IL-15 in HIV/SIV infection in the presence of anti-retroviral therapy, with a specific emphasis on effector memory CD4+ T cell populations and their specificity. The use of IL-15 as a vaccine adjuvant has not yielded significant benefit to vaccine efficacy. Clearly, IL-15 treatment of chronic SIV infection has not lived up to its promise, however, the therapeutic potential of using IL-15 in combination with antiretrovirals as an immune reconstitution strategy merits more attention. The failure of IL-2 in clinical trials should not discourage further investigation of IL-15.

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