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State-of-the-Art Review

Interleukin-7 and Immunorestoration in HIV: Beyond the Thymus

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ABSTRACT

One of the hallmarks of untreated HIV infection is a progressive loss of effective immunity to both HIV-associated and non-HIV antigens. Combination antiretroviral therapy can frequently control viral replication, resulting in variable levels of immune reconstitution, but has not resulted in restoration of effective immunity to the virus. Understanding the limitations of immune reconstitution following highly active antiretroviral therapy (HAART) and identifying approaches to enhance immunity in this context may not only improve outcome for patients with HIV infection but could also provide insight for immune reconstitution in other conditions associated with T cell depletion.

Following T cell depletion, immune recovery occurs via a dynamic interplay between thymic-dependent and thymic-independent pathways (Fig. 1). Prevailing evidence suggests that in clinical settings wherein thymic function is robust, regeneration of new T cells through the thymus rapidly restores normal T cell numbers and repertoire diversity (1–3). However, due to thymotoxic effects of the virus itself (4) as well as ongoing immune responses directed toward the virus, hosts with less than robust thymic function are more commonly encountered in the setting of HIV infection. When thymic function is limiting, immune reconstitution is dominated by an ongoing expansion of mature T cells and the accumulation of cells bearing an activated phenotype (5). We now know that this peripheral expansion appears to be largely driven by interleukin-7 (IL-7), which is elevated in states of T cell depletion, and results in an enhanced proliferative response to both high-affinity and low-affinity antigens (discussed later). Hosts that depend solely on peripheral expansion not only have chronically reduced T cell numbers, but can, at best, only maintain a repertoire as diverse as that present at the start of the expansion process. Indeed, in HIV infection, there is clinical evidence that the nadir of the CD4 count may be predictive of overall immune competence following HAART-induced immune reconstitution, illustrating that expansion of a very limited repertoire is only of marginal benefit (6,7). These features of thymic-dependent and thymic-independent pathways to T cell regeneration lead to the prediction that the degree of immune competence in a host depends, at least to some degree, on the extent to which of thymic function can be restored (8). As discussed elsewhere in this issue, strategies directed at enhancing immune reconstitution following initiation of highly active antiretroviral therapy (HAART) have been a major area of recent investigation. Ideally, the optimal strategy employed would be capable of restoring thymic function so that repertoire diversity could be normalized. However, although recent evidence has indicated that residual thymic function can persist well into adulthood, there is clearly a decline in the overall degree to which thymic-dependent pathways contribute to T cell regeneration with aging, and this process is further hampered by the direct effects of HIV on the thymus. Furthermore,

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some thymopoietic agents, such as recombinant human interleukin-7 (rhIL-7), also potently modulate thymic-independent peripheral expansion. Emerging studies suggest that the capacity of immunomodulators to facilitate maintenance of repertoire diversity within the context of peripheral expansion might also impact immune competence following T cell depletion.

Despite substantial redundancy in the T cell receptor system in terms of the ability to respond to an individual antigen, it is generally held that the loss of repertoire diversity eventually results in deficiencies in functional immune responses to stringent antigens. At which point responses to an individual antigen are lost following T cell depletion likely varies, depending on the precursor frequency of responding T cells as well as other critical factors (such as the rate of programmed cell death). One potential critical factor pertinent to the immunobiology of HIV infection is the prediction that an extremely skewed immune response could enhance the likelihood of immune escape because HIV is known to have a great capacity for antigenic mutation. Evidence from patients treated during primary HIV infection has shown that, despite similar levels of post-treatment $CD4^+$ T cells when compared to patients initiating therapy after primary infection, there is an enhanced efficiency of the $CD4^+$ response to viral antigens (9) potentially due to a more preserved CD4 repertoire when treatment is initiated early. Indeed, evidence that hosts with homozygosity at the major HLA Class I loci show a diminished capacity to control virus directly illustrates the importance of a broad immune response for immunologic control of HIV infection (10,11). Thus, loss of repertoire related to immune restoration via a dominance of peripheral expansion would be predicted to diminish the breadth of an immune response to the array of antigens expressed by a virus resulting in inferior immunologic control.

IL-7 is a potent T cell active cytokine that may hold promise as an immunorestorative agent. A major reason for the clinical interest in IL-7 in HIV infection is the nonredundant role this cytokine plays in thymopoiesis (12,13). However, IL-7 also has potent effects on mature T cells including an essential role in low-affinity antigen-induced proliferation occurring in T cell-depleted hosts (14,15). Thus, IL-7 can modulate both thymic dependent and thymic-independent pathways of T cell regeneration (Fig. 1). Furthermore, patients with T cell depletion have increased levels of circulating IL-7 (16,17). On the basis of these findings, we have postulated that endogenous IL-7 plays an important role in T cell homeostasis (18).

Using murine models, it has been demonstrated that pharmacologic administration of IL-7 can enhance T cell regeneration following bone marrow transplantation (19,20). This is due to effects on thymopoiesis as well as to enhancement of peripheral expansion in thymic-deficient mice (21). Because an increase in thymic output results in increases in T cell numbers and repertoire diversity it would be predicted that the end result would be an improvement in the ability to respond to antigens. However, given the degree to which thymic function may be limited in clinical situations associated with T cell depletion, an important question is the extent to which the ability for IL-7 to enhance peripheral expansion can restore immune competence. Indeed, in a murine model assessing responses to a stringent antigen following T cell depletion of athymic mice, we have demonstrated that the administration of IL-7 can potently modulate functional immune responses (22). Thus, even in the complete absence of thymic function, potent effects of IL-7 in the periphery can lead to functional immune competence, thus improving the function of an otherwise limited repertoire. Importantly, these results also provide evidence that pharmacologic administration of IL-7 enhances immune reconstitution in hosts with T cell depletion that would be predicted to have physiologic elevations in endogenous IL-7.

The mechanisms through which IL-7 enhances immunity following T cell depletion in athymic hosts may have important implications for the effects of IL-7 therapy in clinical situations associated with T cell depletion. One clear effect of IL-7 on mature peripheral T cells is the inhibition of programmed cell death, which is present at high levels in patients with T cell depletion (22–24). IL-

FIG. 1. IL-7 enhances both thymic-dependent and thymic-independent pathways to T cell reconstitution. Following T cell depletion, new T cells can be regenerated through thymopoietic pathways when thymic function is adequate. However, when thymic function is limited, residual T cell expansion is the primary mechanism through which new T cell are generated. The pharmacologic administration of IL-7 has been shown to enhance both processes.

FIG. 2. IL-7 may broaden the T cell repertoire expanded in response to antigens in thymic-deficient hosts. Following substantial T cell depletion, there is a loss of repertoire diversity. Expansion of residual T cells occurs in response to both high-affinity and low-affinity antigens that are presented during the reconstitution process. In the context of HIV, these antigens may be provided by endogenous virus or as a therapeutic vaccine. As shown in **A**, peripheral expansion may result in further loss of repertoire due to skewing and apoptosis. Pharmacologic dosing of IL-7 (**B**) may preserve repertoire by inhibiting apoptosis and by enhancing expansion in response to lower-affinity antigens. The end result is a potentially broader repertoire with the ability to respond to a larger array of viral antigens.

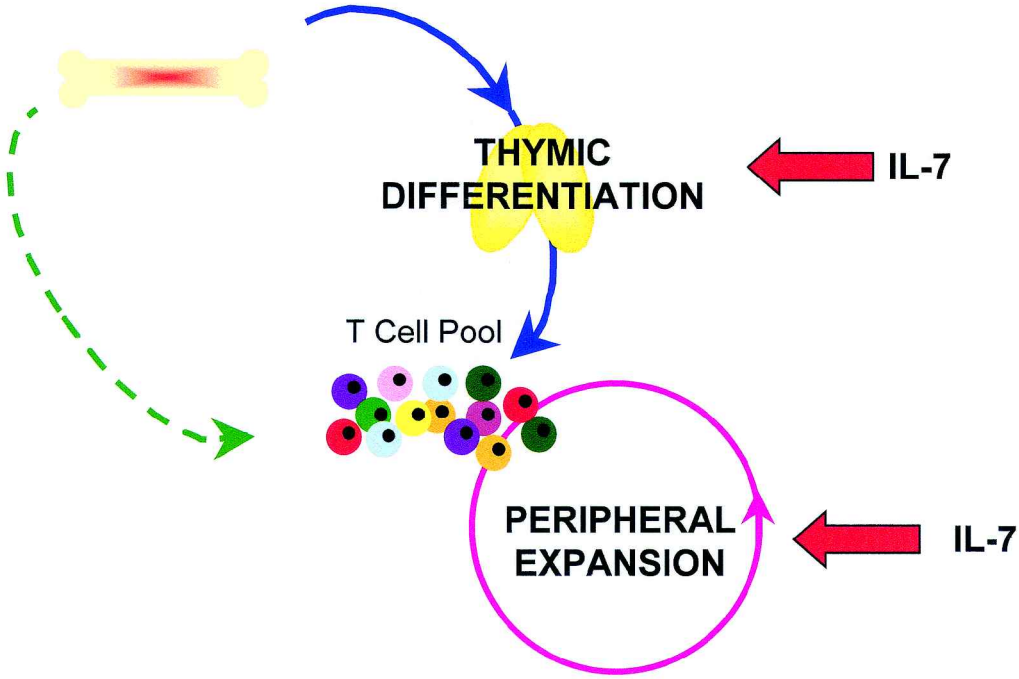
THYMIC
DIFFERENTIATION
IL-7
T Cell Pool
PERIPHERAL
EXPANSION
IL-7

FIG. 1.

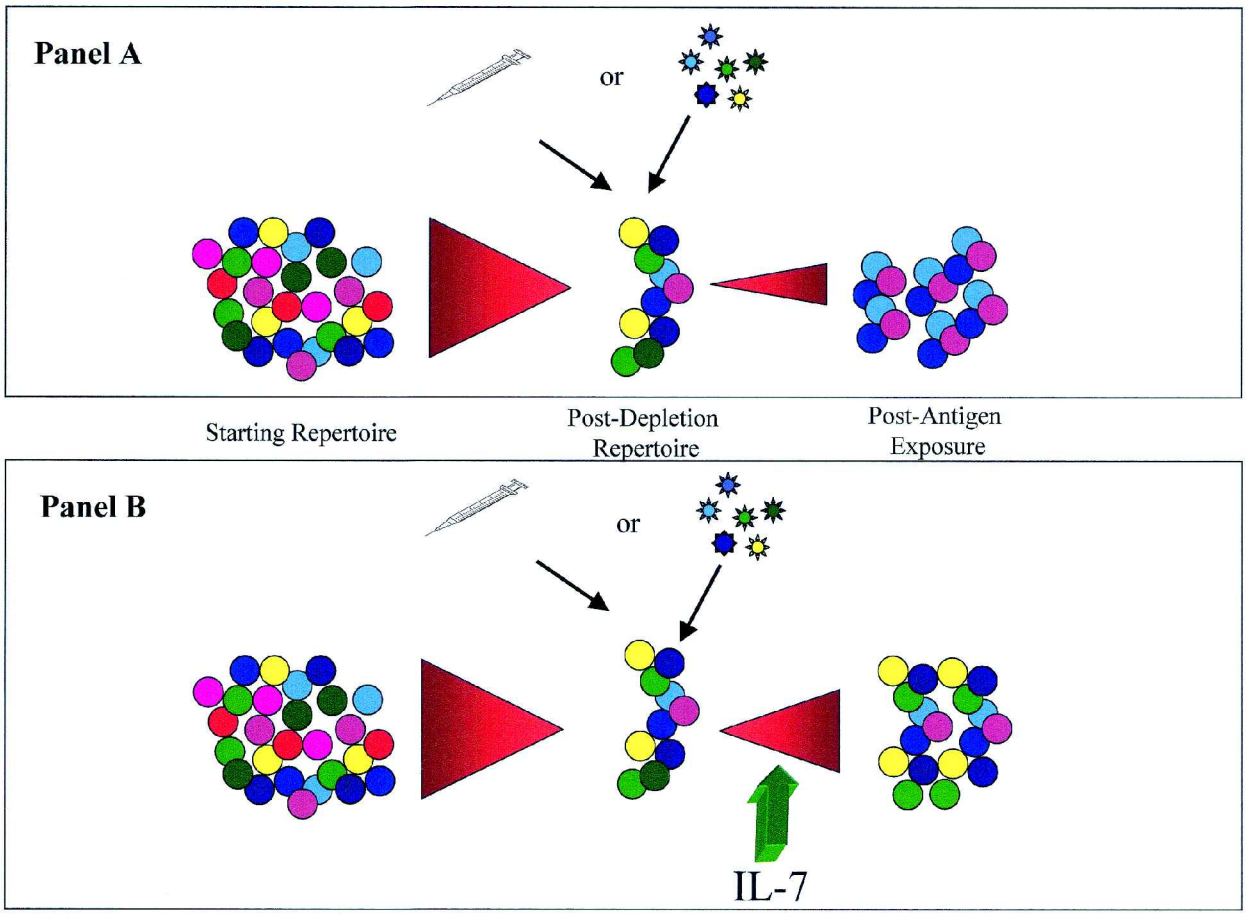
Panel A
or
Starting Repertoire
Post-Depletion
Repertoire
Post-Antigen
Exposure
Panel B
or
IL-7

FIG. 2.

7 may also enhance antigen presentation, thus improving response to nominal antigen. A third, and perhaps most intriguing, mechanism involves modulation of the T cells that are recruited into the expansion process. Peripheral expansion is driven by antigens present in the host milieu during immune reconstitution. Although this can result in repertoire skewing when high-affinity interactions involving viral or other antigens are present, there is now evidence that peripheral expansion also entails proliferative responses toward low- or intermediate-affinity antigens that may be insufficient to induce expansion in T cell-replete environments when IL-7 levels are low. With T cell depletion, as IL-7 levels increase, expansion in response to these antigens may occur as a result of a decreased threshold for activation (25). Pharmacologic doses of IL-7 may further lower the affinity of T cell receptor (TCR) interactions required to induce a proliferative response. Thus, by providing exogenous IL-7, it may be possible to broaden further the array of T cells recruited into the expansion process for any given antigen by enhancing low-affinity responses. Certainly, any simultaneous thymopoietic effects of IL-7 will only help to broaden further the peripheral repertoire.

These predicted effects of IL-7 therapy in HIV infection might be beneficial at multiple levels (Fig. 2). First, in response to the virus itself or to vaccines administered in the context of IL-7 therapy, the prediction is that IL-7 will enhance responses to both high-affinity and low-affinity antigens. Second, by maintaining the repertoire diversity present at the time of initiation of therapy, loss of T cells responding to lower-affinity antigens that occurs during skewing in favor of the highest-affinity antigens might be avoided. Finally, recent evidence has shown that HIV latency in lymphoid tissues represents a real barrier to eradication of the virus despite profound suppression of viral replication by HAART (26) (J. Zack, Personal Communication). If IL-7 can induce both naïve and resting memory cells harboring latent proviral DNA into cycle, then viral replication induced under the cover of antiretroviral therapy may help to purge the latent viral reservoir.

In summary, despite significant progress in the control of viral replication with HAART, many challenges remain. Among these, limitations in overall immune reconstitution, limited restoration of antiviral immune responses, and maintenance of the latent viral pool in lymphoid reservoirs remain central problems. IL-7 therapy may hold promise in these areas by not only enhancing overall immune reconstitution through effects on thymopoiesis but also by potentially broadening the immune response to the virus and/or purging the latent reservoirs in the lymphoid pools through effects on thymic-independent peripheral expansion.

REFERENCES

1. Weinberg K et al. (1993). T lymphocyte ontogeny in adenosine deaminase-deficient severe combined immune deficiency after treatment with polyethylene glycol-modified adenosine deaminase. J Clin Invest 92:596–602.
2. Patel DD et al. (2000). Thymic function after hematopoietic stem-cell transplantation for the treatment of severe combined immunodeficiency. N Engl J Med 342:1325–1332.
3. Mackall CL et al. (1995). Age, thymopoiesis, and $CD4^+$ T-lymphocyte regeneration after intensive chemotherapy. N Engl J Med 332:143–149.
4. Stanley SK et al. (1993). Human immunodeficiency virus infection of the human thymus and disruption of the thymic microenvironment in the SCID-hu mouse. J Exp Med 178:1151–1163.
5. Mackall CL, FT Hakim and RE Gress. (1997). Restoration of T-cell homeostasis after T-cell depletion. Semin Immunol 9:339–346.
6. Blazevic V, N Sahgal, HA Kessler, AL Landay and GM Shearer. (2000). T cell responses to recall antigens, alloantigen, and mitogen of HIV-infected patients receiving long-term combined antiretroviral therapy. AIDS Res Hum Retroviruses 16:1887–1893.
7. Lange CG, H Valdez, K Medvik, R Asaad and MM Lederman. (2002). $CD4^+$ T-lymphocyte nadir and the effect of highly active antiretroviral therapy on phenotypic and functional immune restoration in HIV-1 infection. Clin Immunol 102:154–161.
8. Teixeira L et al. (2001). Poor CD4 T cell restoration after suppression of HIV-1 replication may reflect lower thymic function. AIDS 15:1749–1756.
9. Rosenberg ES et al. (1997). Vigorous HIV-1-specific $CD4^+$ T cell responses associated with control of viremia. Science 278:1447–1450.
10. Kaslow RA et al. (2001). Polymorphisms in HLA class I genes associated with both favorable prognosis of human immunodeficiency virus (HIV) type 1 infection and positive cytotoxic T-lymphocyte responses to ALVAC-HIV recombinant canarypox vaccines. J Virol 75:8681–8689.
11. Tang J et al. (1999). HLA class I homozygosity accelerates disease progression in human immunodeficiency virus type 1 infection. AIDS Res Hum Retroviruses 15:317–324.
12. von Freeden-Jeffry U et al. (1995). Lymphopenia in interleukin (IL)-7 gene-deleted mice identifies IL-7 as a nonredundant cytokine. J Exp Med 181:1519–1526.
13. Peschon JJ et al. (1994). Early lymphocyte expansion is severely impaired in interleukin 7 receptor-deficient mice. J Exp Med 180:1955–1960.
14. Schluns KS, WC Kieper, SC Jameson and L Lefrancois. (2000). Interleukin-7 mediates the homeostasis of naive and memory CD8 T cells in vivo. Nature Immunol 1:426–432.
15. Tan JT et al. (2001). IL-7 is a critical for homeostatic proliferation and survival of naive T cells. Proc Natl Acad Sci USA 98:8732–8737.
16. Fry TJ et al. (2001). A potential role for interleukin-7 in T-cell homeostasis. Blood 97:2983–2990.
17. Napolitano LA et al. (2001). Increased production of IL-7

accompanies HIV-1-mediated T-cell depletion: implications for T-cell homeostasis. Nature Med 7:73–79.
18. Fry TJ and CL Mackall. (2001). Interleukin-7: master regulator of peripheral T-cell homeostasis? Trends Immunol 22:564–571.
19. Abdul-Hai A et al. (1996). Stimulation of immune reconstitution by interleukin-7 after syngeneic bone marrow transplantation in mice. Exp Hematol 24:1416–1422.
20. Bolotin E, M Smogorzewska, S Smith, M Widmer and K Weinberg. (1996). Enhancement of thymopoiesis after bone marrow transplant by in vivo interleukin-7. Blood 88:1887–1894.
21. Mackall CL et al. (2001). IL-7 increases both thymic-dependent and thymic-independent T-cell regeneration after bone marrow transplantation. Blood 97:1491–1497.
22. Fry TJ, BL Christensen, KL Komschlies, RE Gress and CL Mackall. (2001). Interleukin-7 restores immunity in athymic T-cell-depleted hosts. Blood 97:1525–1533.
23. Badley AD, AA Pilon, A Landay and DH Lynch. (2000). Mechanisms of HIV-associated lymphocyte apoptosis. Blood 96:2951–2964.
24. Hakim FT et al. (1997). Constraints on CD4 recovery post chemotherapy in adults: thymic insufficiency and apoptotic decline of expanded peripheral CD4 cells. Blood 90: 3789–3798.
25. Geiselhart LA et al. (2001). IL-7 administration alters the CD4:CD8 ratio, increases T cell numbers, and increases T cell function in the absence of activation. J Immunol 166:3019–3027.
26. Blankson JN, D Persaud and RF Siliciano. (2002). The challenge of viral reservoirs in HIV-1 infection. Annu Rev Med 53:557–593.

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