Promethean thymus?

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Editorial

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The advent of highly active antiretroviral therapy (HAART)[1] has engendered much hope for individuals with HIV infection. Such treatment often substantially reduces viral burden with a resulting increase in peripheral CD4$^+$ T cell counts (1). However, it remains unclear whether this increase in circulating T cells represents a functional reconstitution of the damaged immune system. The thymus is central to this issue.

In T cell ontogeny, progenitor cells from the bone marrow migrate to the thymus where they mature and are selected for release into the periphery as naive (CD45RA$^+$CD62L$^+$) cells. In humans, this thymus-dependent pathway of T cell generation is most active during the first few years of life creating the immunological arsenal that will be used to recognize and respond to new antigens, particularly microbial invaders, throughout the lifetime of the individual (2). As these naive cells encounter their specific antigen, they become activated, divide, and expand into variable numbers of progeny cells. Most cells will die in this process; however, some will revert to a resting state as memory cells, primed to respond quickly should the invaders return. Based on considerable evidence in animal models and humans, it is widely believed that over time thymic function markedly decreases (and in many individuals eventually ceases) so that de novo naive cells are no longer generated and peripheral T cells are largely restricted to the memory population (3). Thus, when there is a significant loss of T cells later in life, such as may result from toxic insults from chemotherapy or irradiation, or from infections such as HIV, regeneration of a functional immune system via the thymic-dependent pathway may be limited, and thymic-independent expansion may account for the vast majority of restored cells (3). In HIV infection, this may be compounded further by a direct viral effect on the thymus. HIV can infect cells during several stages of thymopoiesis and may also directly infect thymic epithelial cells, possibly disrupting the microenvironment that is critical for T cell differentiation (2). Therefore, even if there were no age-dependent loss of thymic function, HIV could inhibit thymus-dependent regeneration of immune-competent cells consequent to its direct detrimental effect on thymopoiesis.

Several investigators have considered the possibility of immune reconstitution in HIV by evaluating phenotypic markers on T cells, functional parameters, and the T cell receptor Vβ repertoire following HAART. Phenotypic markers indicate that, reminiscent of what is seen after intensive chemotherapy in oncology patients (4, 5), there is a two-stage recovery of CD4$^+$ T cells. During the initial 6 mo after therapy, the increase in CD4$^+$ T cells is almost entirely within the memory pool, indicating thymic-independent peripheral expansion. However, between months 6 and 12 one finds a growing pool of phenotypically naive cells, suggesting the possibility of a

contribution by a thymic-dependent pathway to immune reconstitution (6, 7). Interestingly, these reports did not address the naive CD8$^+$ T cell population. In addition, Autran et al. (6) evaluated reactivity to recall antigens and found enhanced activity at 3 and 6 mo. If there is thymus-dependent reconstitution following HAART, one would expect to find a more diverse Vβ repertoire. Several investigators have addressed this issue with differing results. In one report, Connors et al. (7) failed to note a rebuilding of the CD4$^+$ T cell repertoire 3 mo after HAART, but Autran et al. (6) found significant restoration at 6 mo. In the latter report, there was no corresponding enhancement of the CD8$^+$ T cell repertoire. While these studies have proven to be important it remains unclear whether immune reconstitution is in fact possible in HIV disease.

In this context, McCune et al. (9) present their study in this issue of *The Journal*. Although they did not address the question of the effect of therapy on thymopoiesis, the data are relevant to the question of whether thymus-dependent T cell generation occurs in persons with HIV infection. CT scans of HIV-infected individuals were reviewed for thymus mass. Biopsies were not done; however, there was a statistically significant correlation between thymic mass and the presence of circulating CD45RA$^+$CD62L$^+$ CD4$^+$ T cells. Interestingly, there was no such correlation with regard to the CD8$^+$ T cell subset. There was also a correspondence between increased thymus tissue mass and younger age and lower CD4$^+$ T cell count regardless of age. These data are similar to those in oncology patients who had increases in thymus size after cytoreduction with chemotherapy. Such increases correlated with patient age and return of naive T cells (4). McCune et al. (9) suggest that the enhanced tissue mass with lower CD4$^+$ T cell counts in HIV infected individuals could be a consequence of a system that is turned on in response to a significant insult. The authors argue that thymic-dependent regeneration of T cell pools may be possible in some individuals with HIV, perhaps offering hope for at least partial reconstitution of the immune system after HAART.

Several interesting questions are raised by the McCune et al. (9) report. As the authors note, there may be some uncertainty regarding the thymic derivation of T cells based on currently available phenotypic markers. In this regard, it is noteworthy that there was no correlation between increased thymic mass and phenotypic naive CD8$^+$ T cells. These data are consistent with previous reports of CD8$^+$ T cell expansion after cytoreductive therapy as well as with the lack of enhancement of the CD8$^+$ T cell Vβ repertoire following HAART. It is possible that differential production or selection by the thymus of CD8$^+$ versus CD4$^+$ T cell subsets, or differential peripheral apoptosis and/or anergy of regenerated CD4$^+$ and CD8$^+$ T cells could account for the lack of regeneration of naive CD8$^+$ T cells. McCune et al. (9) also comment that thymus mass on CT scan does not necessarily indicate functional thymus tissue. In this regard, Haynes et al. (Haynes, B.F., L.P. Hale, K.J. Weinhold, D.D. Patel, H. Liao, P.B. Bressler, D.M. Jones, J.F. Demarest, K. Geghard-Mitchell, A.T. Haase, and J.A. Bartlett, manuscript submitted for publication) have found that, in HIV-positive individuals examined at autopsy, CT shadows consistent with thymus were actually lymphocytic

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infiltrations. Furthermore, individuals who underwent thymectomy before contracting HIV infection had increases in phenotypically naive CD4^{+} T cells after HAART in the absence of a diversified Vβ repertoire. This observation raises the possibility of thymus-independent reconstitution of phenotypically naive T cells after HAART. Further delineation of potential sources of these cells is required. It is possible that peripheral expansion of naive T cells may occur with appropriate cytokine induction. In this regard, it has been demonstrated recently that peripheral lymphoid tissue may provide the microenvironment necessary for T cell generation and this can be enhanced with cytokines (10, 11). It will be important to evaluate de novo naive T cell regeneration for functional parameters, including neoantigen responses.

Time may prove to be important to fully appreciate the potential for immunological reconstitution of HIV-infected individuals, given that substantial immunological reconstitution of oncology patients may require upwards of 2 yr (5). Finally, the role of virologic factors and the effect of HAART may need further consideration. The evidence taken together lend support to the concept of early treatment of HIV to prevent damage to the thymus and a skewing of the lymphocyte populations. In conclusion, the potential for immunological reconstitution of HIV-infected individuals remains uncertain. Further delineation of the role of thymic versus extrathymic pathways in this reconstitution will be critical not only to our understanding of the ability of the immune system, like Prometheus' liver, to spontaneously repair itself, but also to our ability to therapeutically enhance this process.

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