Correspondence

Significance of Early Secreted Antigenic Target 6–Specific T Cell Depletion after HIV-1 Infection

To the Editor—I read with the interest the article by Geldmacher et al. [1] reporting the early effects of human immunodeficiency virus (HIV)–1 infection on the frequencies of interferon (IFN)–γ–producing CD4+ T cells that recognize the Mycobacterium tuberculosis–specific region of difference (RD) 1 antigens early secreted antigenic target (ESAT)–6 and culture filtrate protein 10. Geldmacher and colleagues observed disproportionate effects of HIV-1 on these cells and speculated that their depletion might account for the large increase in the risk of tuberculosis (TB) during this period. Although the risk of TB may indeed increase immediately after HIV-1 seroconversion, neither of the 2 cited references support this concept [2, 3]. It would be important to know whether such data have been collected and published.

Furthermore, it is difficult to understand how the study’s findings might illuminate the cellular basis of such risk. No incident TB cases occurred among the 4 individuals whose M. tuberculosis–specific T cell frequencies declined acutely because of HIV-1 infection. All had latent M. tuberculosis infection on entry, as best as can be determined presently. One may argue that current tests to detect latent M. tuberculosis infection do not adequately differentiate between true M. tuberculosis persistence and immunologic memory of resolved infection. Indeed, the proportion of persons with latent M. tuberculosis infection that can be reactivated by antitumor necrosis factor therapy is orders of magnitude lower than that identified by skin testing [4]. The same may be true for HIV-1 infection.

However, the one incident case of TB reported in the article by Geldmacher and colleagues occurred in a subject whose RD1–specific T cell counts rose progressively before the diagnosis of TB, rather than falling. I do not believe that these observations should be dismissed as chance events in a small population, given that several natural history studies of non–HIV–1–infected TB household contacts have similarly observed an association between high-level ESAT–6–induced IFN–γ production and an increased risk of TB (rather than protection from the disease) [5–7]. The same relationship has been reported for large tuberculin skin test reactions [8]. These observations suggest that high-level M. tuberculosis–specific T cell production of IFN–γ is a biomarker of incipient TB, regardless of HIV–1 status. Other unmeasured T cell populations may play a greater role in protection. Future studies of the effects of HIV–1 on these poorly characterized cells will be very informative.

Robert S. Wallis
Pfizer

References

Potential conflicts of interest: none reported.
Financial support: none reported.

Reply to Wallis

To the Editor—We agree with Dr. Wallis [1] that it is not completely clear whether detected Mycobacterium tuberculosis–specific CD4+ T cell responses are associated with true latent M. tuberculosis infection that has the potential to relapse or whether these are “real” memory cells that persist despite complete clearance or irreversible sealing of the infectious agent [2]. Both scenarios could occur in different patients. However, the rapid depletion of M. tuberculosis–specific CD4+ T cells after human immunodeficiency virus (HIV)–1 infection is likely to generally affect the antimycobacterium efficiency of the immune system, even in the case of reinfection.

There is consensus in the scientific community that M. tuberculosis–specific CD4+ T cell responses are important for the control of M. tuberculosis infection. A
recent article [3] describing the adoptive transfer of transgenic M. tuberculosis–specific CD4+ T cells in the mouse model provides conclusive evidence to support this hypothesis. Because conventional memory CD4+ T cells are the main cell subset lost during HIV-1 infection, the dramatically increased frequency of active cases of tuberculosis (TB) among HIV-1–infected humans living in areas in which TB is endemic suggests that CD4+ T cells play an important role in protection against M. tuberculosis infection. The observation of reactivation of latent M. tuberculosis infection as a major complication of anti-tumor necrosis factor–α therapy provides further support for this position, because such treatment significantly decreases the functionality of conventional M. tuberculosis–specific CD4+ T cells [4]. These facts and our findings support our hypothesis that the depletion of M. tuberculosis–specific CD4+ T cells is associated with decreased immunity to M. tuberculosis [5], which increases the risk for active TB after HIV-1 infection. An increased risk of TB during the first year of HIV-1 infection has been demonstrated by Sonnenberg et al. [6]. However, their study did not discriminate between M. tuberculosis reinfection and reactivation.

The increase in M. tuberculosis–specific CD4+ T cell responses in HIV-1–infected subjects with active TB does not argue against their role in the control of M. tuberculosis infection. Apparently, the notion that the presence of large numbers of M. tuberculosis–specific CD4+ T cells in the blood equates to protection from active TB in the lungs is too simple. Once control is lost and active TB develops, the presence of increasing amounts of M. tuberculosis antigen is likely to drive the expansion of this population of cells, and simultaneous negative regulation by regulatory T cells [7] and possibly by inhibitory receptors (such as programmed death 1) [8] is likely to decrease the antimicrobial efficiency of M. tuberculosis–specific T cell responses. Independent of the underlying pathomechanism of coinfection with M. tuberculous and HIV-1, our observations help to interpret IFN-γ release assay results for HIV-1–infected individuals.

We agree that further proof is needed to support the hypothesis that reactivation of latent M. tuberculosis infection occurs via HIV-1–induced depletion of M. tuberculosis–specific CD4+ T cells. Larger longitudinal studies of individuals with and without detectable M. tuberculosis–specific CD4+ T cells who subsequently become infected with HIV-1 will be necessary to elucidate the relationships between detectable M. tuberculosis T cell responses before HIV-1 infection, their depletion, and their sporadic reappearance after HIV-1 infection and progression to active TB.

Christof Geldmacher,1 Norbert Heinrich,1 Richard A. Koup,2 and Michael Hoelscher2

1Department of Infectious Diseases and Tropical Medicine, Klinikum of the Ludwig-Maximilians-University of Munich, Munich, Germany; 2Immunology Laboratory, Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

References

3. Gallegos AM, Pamer EG, Glickman MS. De-pletion, and without detectable M. tuberculosis– specific CD4+ T cells who subsequently become infected with HIV-1 will be necessary to elucidate the relationships between detectable M. tuberculosis T cell responses before HIV-1 infection, their depletion, and their sporadic reappearance after HIV-1 infection and progression to active TB.

Christof Geldmacher, Norbert Heinrich, Richard A. Koup, and Michael Hoelscher

1Department of Infectious Diseases and Tropical Medicine, Klinikum of the Ludwig-Maximilians-University of Munich, Munich, Germany; 2Immunology Laboratory, Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

References

3. Gallegos AM, Pamer EG, Glickman MS. De-pletion, and without detectable M. tuberculosis– specific CD4+ T cells who subsequently become infected with HIV-1 will be necessary to elucidate the relationships between detectable M. tuberculosis T cell responses before HIV-1 infection, their depletion, and their sporadic reappearance after HIV-1 infection and progression to active TB.

Christof Geldmacher, Norbert Heinrich, Richard A. Koup, and Michael Hoelscher

1Department of Infectious Diseases and Tropical Medicine, Klinikum of the Ludwig-Maximilians-University of Munich, Munich, Germany; 2Immunology Laboratory, Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

References

3. Gallegos AM, Pamer EG, Glickman MS. De-pletion, and without detectable M. tuberculosis– specific CD4+ T cells who subsequently become infected with HIV-1 will be necessary to elucidate the relationships between detectable M. tuberculosis T cell responses before HIV-1 infection, their depletion, and their sporadic reappearance after HIV-1 infection and progression to active TB.