Comment on Jansen et al, page 1427

Are HIV-specific CD4+ T cells useless?

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In this issue, Jansen and colleagues challenge the hypothesis that early HIV-specific CD4+ T cell responses might protect against disease progression. Their data suggest that neither HIV Gag-induced IL-2 nor IFN-γ production by CD4+ T cells is predictive of the clinical evolution.

The authors first showed that HIV-specific IL-2 and/or IFN-γ responses at 1 year after seroconversion were similar in 7 rapid progressors and 6 long-term asymptomatics (LTAs); hence, this parameter was not predictive of the different clinical evolution. More importantly, in a large cohort study of 96 patients, Gag-specific responses at 1 year also failed to predict evolution toward AIDS. In the smaller longitudinal study, CD4+ T-cell responses were analyzed again at a later time, when the progressors had already evolved to AIDS, while the LTAs were still disease-free. Gag-specific cytokine responses were preserved in LTAs but were largely lost in progressors, whose viral load was much higher from the outset. From this impressive set of data, the authors conclude ". . .viral load [determines] the nature and magnitude of HIV-specific CD4+ T-cell responses, rather than HIV-specific CD4+ T-cell responses controlling HIV plasma viral load."

Do the data by Jansen et al imply that the adaptive immune system is useless in preventing HIV progression? Is it even futile to try and induce protective immunity by immunization? Maybe it is too early for such desperate conclusions. Earlier studies have suggested that a preserved CD4+ T-cell function, probably by "helping" effector CD8 T cells, could protect against rising viral load and disease progression.[1] Although many previous studies were rather small and/or cross-sectional, some were also prospective.[2]

Although well done, the present study suffers from some conceptual and technical limitations. First, CD4+ T-cell responses were evaluated 1 year after seroconversion, a time when the viral load has reached a set point that already reflects the equilibrium between "fitness" of the virus and all the patient's defense systems. One can argue that immune mechanisms around the time of seroconversion, including CD4+ and CD8+ T-cell responses, might determine the viral set point at 12 months. Moreover, a pool of "consensus" subtype B peptides together with anti-CD28 and anti-CD49 were used as the stimulus. This acceptable and convenient set-up has a few disadvantages. The consensus most probably differs from the patient's virus and therefore obscures possible isolate-specific responses.[3] In addition, a response of a similar magnitude may represent a vigorous response to a narrow set of epitopes, resulting in immune escape and increasing viral load, or an equilibrated response to a broad range of epitopes, effectively controlling the virus. Moreover, it was recently suggested that not just IL-2 and IFN-γ, but more complex cytokine patterns need to be considered as correlates of protection.[4] Finally, potential differences in antigen-presenting cell (APC) function may go unnoticed, since the set-up chosen largely circumvents the APC function.

In their final sentence, the authors cast some doubt on vaccination, based on their observations in infected, treatment-naive patients. However, even if we accept that HIV at relatively low copy numbers can undermine the protective potential of CD4+ T-cell responses in these patients, it is still quite possible that prophylactic or therapeutic vaccination will induce protective CD4+ T-cell responses in subjects that are either uninfected or in whom the virus is completely suppressed by highly active antiretroviral therapy (HAART).

In conclusion, these provocative data will undoubtedly stimulate the scientific discussion and inspire new studies to investigate which immune responses are protective and ultimately important to design efficient HIV vaccines and immunotherapies. ■

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