Immune Responses to Human Immunodeficiency Virus Type 1 in Exposed but Uninfected Individuals: Protection or Chance?

Editorial

In this issue of *The Journal,* Langlade-DeMoyen et al. (1) present evidence that higher frequencies of cytotoxic T lymphocyte (CTL) precursors directed against the HIV-1 *nef* protein are found in uninfected sexual partners of HIV-1-seropositive individuals than are seen in normal donors. This "at risk" population lacks evidence of infection with HIV-1, as assessed by PCR, culture, or serology. In accord with previous reports (2), moderate CTL precursor frequencies for *env* and *gag* were seen in normal donors as well, but few precursors for *nef* were detected. The data as presented are less than totally convincing, and some nagging questions remain. For example, the sex of the normal donors and six seronegative partners surveyed is not stated, and greater alloreactivity in parous women might cloud the conclusions. Note that of the two seropositive partners studied, the female had markedly higher precursor frequencies than did the male. In contrast to the greater CTL frequency seen in this sole serconverting female, 6 of 15 female partners seroconverted during the study while only 1 of 8 male partners seroconverted.

Nonetheless, the general observation that immune responses to HIV-1 might be detected in "at risk" individuals is not unexpected, and the *nef* protein is not an unlikely target for protective immunity. The observations of Langlade-DeMoyen et al. (1) on *nef* precursor frequencies join a growing body of evidence that exposure to HIV-1 can produce detectable immune responses in the absence of sustained infection. The presence of antibodies to *nef* protein in HIV-exposed individuals has been described by several investigators (3–5) and denied by equally as many others (6–8). Cytotoxic responses have also been described in uninfected infants born to infected mothers (9, 10), although these reports do not delineate the target proteins of the CTL activity detected. Recently, a good deal of attention has been attracted by reports that lymphocytes from seronegative partners of homosexual men with sexual exposure to HIV-1 exhibit proliferation and elaboration of IL-2 and IFN-γ in response to stimulation with HIV-1 envelope protein (11). Also, the concept of "compartmentalized" transient infection has been advanced (12), with the finding of cell-mediated responses as well as antibody in the urine of similar populations.

Accepting that these observations are accurate and will be confirmed by other investigators, one is still left with the quandary of how to interpret these results. Perhaps the simplest possibility, and the one that would tell us the least if verified, is that *nef* is simply an immunogenic protein capable of eliciting CTL in humans when presented in a favorable manner to exposed individuals. It is also possible, as hypothesized in the current article, that the immune response detected is protective, at least against challenge through natural routes of exposure in some hosts, preventing, aborting, or clearing infectious virus. The possibility that *nef*-reactive CTL activity represents a cross-reactive allogeneic response, or even autoimmunity, is also worthy of consideration. It is also quite possible that the natural history of HIV infection includes abortive or transient infections in individuals who are less susceptible genetically, or who are exposed to small inocula of virus, or to defective or avirulent virus. This latter possibility seems to be suggested by recent animal experiments, where vaginal inoculation with less virulent simian immunodeficiency virus (SIV) appeared to result (repeatedly) in transient detection of virus without persistent infection, and the development of low but detectable immune responses (13). Unfortunately, these animals were not protected from challenge with virulent SIV.

Is it protection, or is it chance? Additional studies will no doubt soon tell the tale.

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