Immunoglobulin G2 Antibodies and HIV-Infected Long-Term Nonprogressors: What Is the Mechanism?

To the Editor—The article by Martinez et al. demonstrating that CD4 Th1 cell frequencies and IgG2 antibody titers correlated with the persistence of long-term nonprogression during HIV infection was of considerable interest [1]. Their data provide both prognostic and potentially mechanistic information that may become very valuable to clinicians and basic immunologists. However, a word of caution is warranted with respect to the interpretation of IgG2 antibody titers. The authors may overstate matters when they indicate that human IgG2 antibodies are induced by interferon (IFN)-γ and that human IgG2 antibody titers, therefore, can be used as a biomarker of Th1 cell activity in vivo.

The studies cited by Martinez et al. indicating that IFN-γ induces IgG2 antibodies are all of murine antibodies. Unfortunately, there is no direct correlation between the structure, function, activities, and/or cytokine induction of the 4 murine IgG subtypes (IgG1, IgG2a, IgG2b, and IgG3) and the 4 human IgG subtypes (IgG1, IgG2, IgG3, and IgG4) [2, 3]. Furthermore, in contrast to mice, the role played by IFN-γ in the induction of IgG subtypes in humans is not well established. With respect to functional activity, of the human IgG subtypes, it is IgG3, not IgG2, that most strongly supports the cell-mediated phagocytic activities induced by IFN-γ [4]. Specifically, IgG3 antibodies fix complement significantly more efficiently and bind significantly more avidly to phagocytic Fcγ receptors than do IgG2 antibodies [2, 3].

In light of observations made in patients with selective IgG2 deficiency, this antibody subtype appears to be particularly important for human antibody responses to carbohydrate antigens [5–9]. How this relates to the progression of HIV infection is not immediately apparent. However, it is interesting to speculate that Martinez et al.’s impressive findings on IgG2 may suggest a mechanistic link between titers of antibodies to specific, but unknown, carbohydrate epitopes and prevention of the progression of HIV infection.

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References

Reply to Spellberg

To the Editor—We are grateful to Spellberg for his comments [1] regarding our article [2] demonstrating that the presence of IgG2 antibodies directed against the gp41 fraction of the HIV-1 envelope, together with high frequencies of interferon (IFN)–γ–producing CD4 Th1 cells specific for the HIV-1 p24 capsid protein, was the best predictor for the persistence of long-term nonprogression. We first reported the importance of anti-HIV-1 IgG2 antibodies for long-term nonprogression in 2001 [3]. In our recent article in the Journal, we showed that, although IgG1 antibodies are the major component of the humoral immune response to HIV-1 infection, the presence of IgG2 antibodies against various HIV-1 proteins, including gp41 and p24, was negatively correlated with viral loads and was positively correlated with levels of IFN-γ produced by HIV-1–specific CD4 Th1 cells. The presence of these anti–HIV-1 IgG2 antibodies at study entry was also strongly associated with the persistence of low plasma and cell-associated viral loads (C.R., unpublished data).

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