Viral Escape and the Failure of Cellular Immune Responses

Farci et al. (1) took an important step in understanding host-virus interactions in acute hepatitis C virus (HCV) infection, by demonstrating that increased viral diversity in the hypervariable region of the E2 envelope gene is associated with lack of control of infection. They suggested that, in those who fail to clear the virus, escape mutants arise in the hypervariable region, which leads to loss of immune control.

Recent data from our groups describing the cellular immune responses in acute HCV infection and the interactions between cellular and humoral immune responses in the murine lymphocytic choriomeningitis virus (LCMV) model cast an alternative light on these findings. In LCMV, a noncytopathic RNA virus, CD8+ cytotoxic T lymphocytes (CTLs) are normally responsible for initial antiviral control, without neutralizing antibodies arising later. If CTL responses are absent (through antibody-mediated deletion or in gene-targeted knockout animals), however, antibodies become the principal arm of antiviral defense. In this situation, escape mutations arise rapidly in the envelope glycoprotein GP1 (2). These escape mutations lead to loss of viral control; thus, in this case, immune escape from antibodies has proceeded directly from the failure of cellular immune responses.

Could such a situation arise in HCV? We recently showed that individuals who successfully cleared HCV after acute infection had very large CTL responses against multiple viral epitopes (3). These responses arose early in the infection and showed a peak of activation at the time of maximum alanine aminotransferase (ALT) level—that is, before the significant emergence of antiviral antibodies. Such responses did not occur or were not sustained in all patients, however, and once infection was established, antiviral CTL became scarce (3). Antiviral cellular immune responses were also initially detectable in many patients who failed to eliminate the virus after acute HCV infection, but these responses appeared to be short-lived (4). Antibody pressure without sustained CD8 activity, CD4 activity, or both may thus rapidly select for escape mutants (Fig. 1). Ongoing lack of selective pressure by CTL is manifest by the lack of evolution of viral sequences encoding immunodominant epitopes over time during established infection (5).

Reduction in viral envelope gene diversity is likely to be, as Farci et al. (1) suggest, a feature of more successful immune responses. In our judgment, however, an appropriate balance between cellular and humoral immune responses constitutes another important component of “success” that is often overlooked. Excessive CTL responses against LCMV can lead to death from fulminant hepatitis and/or systemic disease caused by immunopathology (6); inadequate CTL function leads to an exaggerated antibody response and, consequently, to rapid immune escape. If the same basic immunological principles are at play in humans, a holistic approach will need to be taken to studies of HCV and to the design of vaccines against this and other mutable viruses.

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References

Response: We thank Klenerman et al. for the opportunity to discuss further the implications of our recent study (1) on the mechanisms leading to sterilizing immunity in HCV infection. Understanding host-virus interactions is indeed essential for devising preventive strategies against HCV and for unraveling the mechanisms of viral persistence. The correlates of immune protection are still unknown, however. Detailed studies of cellular and humoral immune responses to HCV during the acute phase of HCV infection, performed in parallel with analyses of the genetic evolution of HCV, have not been reported in humans and have only recently been initiated in the chimpanzee model. Thus, most ideas of viral-clearance mechanisms remain hypothetical.

Nonetheless, based on the data so far available, we agree with the main conclusion of Klenerman et al.: that HCV clearance may result from “an appropriate balance between cellular and humoral immune responses.” Indeed, results obtained from both experimental animal models of persistent RNA virus infections and from HCV-infected patients indicate that a reduced effectiveness of CTLs (2), CD4+ helper T cells (3), or antibody-

Fig 1. Influence of interactions between cellular and humoral immune responses on viral escape. Mechanisms that have been shown to influence the generation or maintenance of early cellular immune responses after viral infection include rapid replication kinetics of the virus, high antigen load, poor or improper activation of T1 and T2 helper cells, antigenic sin, interference of the virus with the function of the antigen presenting cells, generation of altered peptide ligands, and genetic factors in the host such as low interferon levels.

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producing B cells (4, 5) is associated with long-term viral persistence. These observations do indeed "cast an alternative light" on the reductionist theories of either CTL dominance or antibody dominance that have hitherto prevailed in studies of sterilizing immunity, and emphasize the need for new concepts that consider both cellular and humoral immune responses, as indicated by Klenerman et al.

Although we concur with the hypothesis that the cellular and humoral components of the immune system together induce definitive viral clearance, resolving that issue will require a comprehensive analysis of cellular and humoral immune responses to HCV in relation to viral quasispecies evolution and to the outcome (i.e., resolution or persistence) of the infection. These studies must be performed early in the course of HCV infection, when the events in the virus-host interaction are likely to determine the outcome of infection. Unfortunately, however, cellular samples are rarely available during that early phase. Until such human samples are prospectively obtained, researchers will likely need to extrapolate from the experimental chimpanzee model. The immunologic basis of HCV clearance will continue to be inferred from associations rather than causal relationships, until the outcome of infection can be altered by specific manipulation of the virus or of separate arms of the host immune response.

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References

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Editor's Summary

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