Cooling Off the Host Immune Response to Acute Simian Immunodeficiency Virus Infection—Is Less More?

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(See the major article by Tabb et al on pages 880–92.)

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Infectious diseases clinicians have long known that intervention with appropriate antimicrobial therapy is often insufficient to successfully treat infections, because the cumulative effects of the host inflammatory response can lead to a systemic inflammatory response syndrome, often with devastating short-term and long-term clinical consequences. Many research models have attempted to guide the development of adjunctive immunomodulatory approaches in a wide variety of infectious diseases. In this issue of the Journal, Tabb and colleagues take a step in this direction for lentiviral infection, using the clinically available anti-tumor necrosis factor alpha (TNF) monoclonal antibody adalimumab (Humira) in rhesus macaques with acute infection with a pathogenic variant of simian immunodeficiency virus (SIV).

During the pathogenesis of human immunodeficiency virus (HIV) infection, the virus targets HIV-specific T cells [1] and preferentially replicates in the setting of generalized immune activation [2]. The loss of CCR5-expressing lymphocytes results in reduced gut integrity and ongoing inflammation [3]. The cumulative and persistent effects of immune activation and inflammation have negative long-term consequences for HIV-infected individuals [2], even under conditions of durable suppression of HIV replication obtained by use of current combination antiretroviral therapy (cART) regimens [4, 5]. Tabb et al have previously shown in the SIV model that the integrity of the lymph node architecture is vital to maintaining effective antiviral responses, is degraded in early infection by dysregulated release of inflammatory cytokines, and culminates in fibrosis and functional degradation of the affected lymph tissues [6]. Recently published work in the SIV model has further implicated the early loss of CD4+ T cells in the destruction of the follicular dendritic cell network in lymph nodes, which is vital to lymph node function, through the reduction of CD4+ T cell–elaborated lymphotoxin B involved in the maintenance of the follicular dendritic cell architecture [7, 8]. Thus, the case for the nonsalutary impact of an uncontrolled host inflammatory response to lentiviral infection is clear—more is not better.

Tabb and colleagues examine the impact of anti-TNF immunotherapy administered to rhesus macaques shortly before and for 12 weeks after intravenous exposure to a pathogenic strain of SIV on the basis of the knowledge that it is an early inflammatory marker of acute SIV infection in lymphoid tissue. Although they observed no effect on the dynamics of plasma viremia or the activation status of circulating T cells, they noted reductions in CD163+ macrophage and neutrophil infiltration into the paracortical T-cell zone, TGF-β expression in the T-cell zone, and overall lymphoid tissue fibrosis. Limitation in lymphoid tissue fibrosis was associated with increased tissue T-cell preservation. Thus, the authors concluded that there might be a rationale to initiate anti-inflammatory therapy in patients with acute HIV infection in the hope of limiting disease progression.

This work is very timely, given the explosion in information regarding the nature of acute SIV and HIV infection, the understanding that prolonged cART alone is unlikely to cure HIV infection, and the growing attempts to harness host gene expression mechanisms to reduce the size of...
the latent HIV reservoir as a next step toward the elimination of HIV in an infected individual [9]. However, like most cutting-edge research, Tabb and colleagues generate a host of new questions for the field as we ponder a way forward from their research results. Treatment with anti-TNF prior to SIV exposure makes this model difficult to translate into the clinic, where it would be ethically impossible to justify pretreatment of at-risk individuals with this immunotherapy. Rather, one would have to identify individuals in the earliest stages of acute HIV infection and then assess the impact of anti-TNF. This approach is best guided by additional preclinical studies in nonhuman primates to gauge the effect of anti-TNF at short intervals after SIV exposure and when circulating SIV RNA is detectable. A clinical study would be most relevant if fresh lymph node tissue could be examined, which, while feasible, would add considerable logistical complexities and cost. Finally, how should one balance the merits of an anti-TNF study in acute HIV infections as compared to the merits other approaches, such as the use of anti-HIV monoclonal antibodies, therapeutic vaccination, statins, or angiotensin-receptor blockade?

What is clear from the study by Tabb and colleagues is that a greater understanding of the similarities and differences in the immunopathogenesis of early events during SIV and HIV infection present a powerful rationale and opportunity for next steps toward modulating the host response to lentiviral infection, with a view to mitigating the impact of HIV infection and, ultimately, to pointing the way toward both a cure and an effective vaccine.

Notes

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References