Suppressing the suppressor

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In this issue of Blood, Brockman and colleagues demonstrate that active HIV replication rapidly triggers production of the immunosuppressive cytokine IL-10 and that IL-10 reversibly inhibits HIV-directed T-cell activity. Application of these findings may ultimately lead to therapies that restore immune function to fight HIV infection.

The correlation between effective T-cell responses and control of HIV infection suggests therapies that restore HIV-directed T-cell activity may successfully establish long-term, immune-mediated control of HIV infection. What hinders immune-restorative therapies is the lack of understanding of the mechanisms underlying T-cell suppression and the failure to control HIV infection. Studies in the lymphocytic choriomeningitis virus (LCMV) model of chronic viral infection have revealed that multiple host-based immunosuppressive factors inhibit T-cell responses, prevented virus clearance. Extension of these studies to human chronic infections, such as HIV and hepatitis B and C viruses, demonstrated that the same suppressive factors can also inhibit human T-cell responses, suggesting that conserved host mechanisms are invoked during chronic infections. Recent findings in the LCMV system identified the dominant role of the cytokine IL-10 in suppressing antiviral T-cell responses and leading to viral persistence. Antibody blockade of IL-10 effectively restored T-cell activity, eliminating an otherwise chronic LCMV infection. The finding that IL-10 is also elevated during HIV infection suggests that similar immunosuppressive mechanisms may be employed to subvert HIV-specific immunity and that blockade of IL-10 may effectively restore antiviral T-cell activity to control virus replication.

To test this hypothesis, Brockman et al isolated cells from HIV-infected patients and stimulated the T cells with HIV peptide to mimic the in vivo interaction of HIV-specific T cells with infected or antigen-presenting cells. Consistent with the immunosuppressive state prevalent during infection, HIV-specific T cells responded poorly to HIV stimulation, failing to proliferate or produce antiviral effector molecules. However, when an IL-10 receptor-blocking antibody was included in the stimulation, immunosuppression was alleviated and HIV-specific CD4 and CD8 T cells rapidly proliferated in response to viral antigen. In the presence of IL-10 blockade, HIV-specific CD4 T cells produced elevated levels of the antiviral and immunostimulatory cytokines IFN-γ and IL-2, indicating functional immunity was restored by blocking IL-10-mediated immunosuppression. Although previous studies have identified the role of IL-10 in suppressing HIV-specific CD4 T-cell responses, the authors now establish that IL-10 inhibits CD8 T-cell function and thus, further reveal the extent of IL-10-mediated immunosuppression during HIV infection. Interestingly, the authors’ work indicates that the de novo expression of IL-10 actively and constantly suppresses T cells that are otherwise ready to respond to infection. This exciting prospect suggests that the threshold between exhausted and productive T-cell responses is maintained on a fine line. Based on LCMV studies in mice and, more recently, SIV infection in nonhuman primates, therapies that propel T cells across that line may substantially enhance control of HIV infection in vivo.

Although previous studies have clearly defined increased IL-10 expression during HIV infection, conflicting reports exist. To clarify this discrepancy and to further examine how IL-10 mediates immunosuppression, the authors measured IL-10 expression during multiple stages of HIV infection and observed that IL-10 levels directly correlated with virus replication, the highest being in viremic individuals and nearly absent in aviremic patients and elite controllers (ie, those that control HIV in the absence of antiviral therapy). In documenting this correlation the authors potentially clarify previous discrepancies but more importantly define the relationship between active virus replication and IL-10–mediated immunosuppression. Mechanistically, whether the virus itself induces IL-10 or whether “sensors” of HIV trigger IL-10 to dampen the immune response is unclear. In turn, by suppressing the immune response, elevated IL-10 may further facilitate virus replication, thereby potentiating the cycle. Clinically, this study clearly defines a timetable for the implementation of IL-10 blocking therapies to be effective.

Determination of the mechanisms that inhibit T-cell activity may ultimately enable the development of therapeutic approaches to reverse the suppressive factors and allow T-cell responses to effectively fight infection. However, the same negative immunoregulatory pathways that prevent T-cell function during chronic viral infection are also integrally involved in preventing autoimmunity. As the authors note, the restoration of desired immune responses while preventing undesired ones is a delicate balance, and thus potential detrimental side effects should be considered when implementing therapies that disrupt the IL-10 (or any immunoregulatory) pathway. Importantly, IL-10 is one of multiple immunoregulatory factors that have recently been identified to negatively modulate T-cell activity during HIV infection and that hold the potential as therapeutic targets. Future studies to determine how these factors work individually and in combination may ultimately lead to the development of therapies to restore antiviral immunity while maintaining the negative regulation required to prevent immunopathology or autoimmunity.

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REFERENCES


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