How HIV Guts the Immune System
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Although in the absence of treatment, the acquired immunodeficiency syndrome (AIDS) generally develops 8 to 10 years after infection with human immunodeficiency virus (HIV) type 1 (HIV-1), the onslaught on the immune system by HIV-1 begins with the rapid depletion of memory CD4+ T cells, the majority of which reside in the gut. A recent report by Arthos et al. suggests that HIV-1 is able to mediate depletion of gut CD4+ T cells in part by co-opting the molecule that helps direct T cells to the gut: the integrin αβ7.

Although depletion of CD4+ T cells is ultimately reflected (and clinically measured) as a decrease in circulating CD4+ T lymphocytes, analysis of CD4+ T-cell counts in the blood provides an imperfect assessment of the body’s total reservoir of CD4+ T cells, only 1 to 2% of which are found in peripheral blood. As much as 30% or more of all T cells are believed to reside in mucosal sites — most notably, the gut.

Landmark studies conducted in nonhuman primates infected with simian immunodeficiency virus (SIV), and subsequently confirmed in people infected with HIV-1, have shown that primary infection induces a rapid and profound depletion of CD4+ T cells in the gastrointestinal tract. The mechanisms by which this depletion occurs remain controversial. Direct infection appears to have a major role: up to 30 to 60% of CD4+ T cells are infected with SIV by 10 days after infection of the host. However, indirect mechanisms resulting in apoptosis of uninfected cells are also likely to mediate the destruction of CD4+ T cells in the gut.

Several mechanisms appear to account for the distinctive predilection of HIV-1 and SIV for gut CD4+ T cells. Both viruses preferentially replicate in activated memory CD4+ T cells, which make up the majority of CD4+ T cells residing in the gastrointestinal tract. Gut CD4+ T cells also express relatively high levels of the chemokine receptor CCR5, one of the major coreceptors for the entry of HIV-1 and SIV into CD4+ T cells. However, the ability of SIV to infect CD4+ T cells that do not express detectable levels of CCR5 on their surface and to infect cells that do not express typical markers of activation suggests that other factors govern the fondness of HIV-1 for gut T cells.

Arthos et al. describe a series of detailed experiments supporting the hypothesis that HIV-1 is able to bind to the gut homing molecule αβ7. The ability of lymphocytes to migrate to specific areas of the body, such as the skin or the gut, is mediated in part by cell-surface molecules that tether cells to molecular partners expressed on the vascular endothelium. The integrin αβ7 helps direct the trafficking of T cells to the gut by binding to an adhesion molecule expressed on endothelial cells in mesenteric lymph nodes and in the gut lamina propria (Fig. 1).

Initially spurred by the unexpected observation that the HIV envelope can bind to natural killer cells, which lack the principal HIV receptor CD4, the authors demonstrated that αβ7 could serve as an alternative binding partner for the HIV-1 envelope glycoprotein 120 (gp120). CD4-independent binding of gp120 to cells expressing αβ7 could be blocked by antibodies to αβ7. On the basis of existing information on the specific amino acids that mediate binding of ligands to αβ7, the authors were able to identify a region of the variable V2 loop of the HIV envelope that binds to αβ7. Remarkably, the amino acids responsible for binding αβ7 (the leucine–aspartate–valine, or LDV, motif) are highly conserved among HIV-1 strains, despite the fact that the V2 loop is highly variable. Mutation of the LDV motif impaired the ability of HIV to grow in cultured lymphocytes. Finally, binding of HIV-1 to αβ7 was also able to induce activation of another integrin, leukocyte-function-associated antigen 1 (LFA-1), that has a key role in cell-to-cell interactions. LFA-1 facilitates formation of junctions between lymphocytes that are likely to play an important role in the cell-to-cell transmission of HIV. Thus, bind-
Homing of T cells to the gut is facilitated by the integrin α₄β₇ (Panel A). The subsequent binding of the integrin to the mucosal addressin-cell adhesion molecule 1 (MAdCAM-1) mediates tethering of α₄β₇+ lymphocytes to the high endothelial venules (e.g., the lamina propria venule [LPV]) of lymphoid tissue associated with the gut. The integrin α₄β₇ can be co-opted to facilitate the entry and spread of HIV-1 in gut-associated lymphoid tissue (Panel B). Interactions between the V2 loop of the HIV-1 envelope glycoprotein 120 (gp120) and α₄β₇ enhance the binding of the virus to memory CD4+ T cells in the gut and subsequent entry into the cell through mechanisms dependent on CD4 and the chemokine receptor CCR5. Engagement of α₄β₇ by soluble gp120 or gp120 on HIV-1 virions or HIV-1–infect ed cells results in activation of the integrin leukocyte-function-associated antigen 1 (LFA-1), which enhances cellular interactions through interactions of LFA-1 with the intercellular adhesion molecule 1 (ICAM-1) and thereby augments cell-to-cell transmission of HIV-1.

The in vivo significance of the gp120–α₄β₇ interaction. If the importance of this interaction is confirmed, small-molecule antagonists of gp120–α₄β₇ interactions might prove useful in adjunctive therapies. Alternatively, induction of antibody responses against the V2 envelope, which should blunt the ability of the virus to replicate in gut CD4+ T cells, might be a more feasible solution than the generation of broadly neutralizing antibodies against HIV, which have proved frustratingly difficult to generate through vaccination. However, efforts to exploit this new twist to the manifold interactions of HIV with the immune system are likely to be complicated by the variabili-
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