The immune response to HIV
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Breaching the mucosal barrier
The main drivers of HIV infection in the genital mucosa are CD4+ memory T cells, but CC-chemokine receptor 5 (CCR5)+ macrophages have been implicated as well. How HIV reaches these cells is less clear, but dendritic cells (DCs) probably have an important role. HIV can enter DCs not only using CD4 and CCR5, but also using C-type lectin receptors, such as DC-specific ICAM3-grabbing non-integrin (DC-SIGN) and langerin. DCs form a network within squamous epithelia, such as those covering the vagina, ectocervix and foreskin, extending their dendrites higher towards the epithelial surface than do T cells. In columnar epithelia, such as those covering the endocervix and rectum, DCs can stretch their dendrites through epithelial tight junctions towards the luminal surface. It is thus plausible to assume that DCs are frequently the first leukocyte type encountered by HIV in the mucosa. HIV might also cross columnar epithelial cells by transcytosis, a process whereby virions are taken up on the luminal side of the epithelial cell into a coated vesicle. The vesicle is then transported to the basal side of the cell, where its contents are released into the extracellular space of the stroma.

CD1a+ DCs residing within squamous epithelia are called Langerhans cells. Langerhans cells have been shown to endocytose HIV-1 virions very efficiently, and pass HIV-1 to susceptible CD4+ T cells and to stromal DCs without being themselves productively infected. To reach Langerhans cells, HIV seems to be able to breach the mucus layer and then move through the interstitial spaces between differentiated squamous epithelial cells to depths of 40 μm. In the ectocervix and vagina, the outer epithelial layers do not contain classical cell–cell tight junctions, and this might facilitate HIV entry. By contrast, endocervical columnar epithelial cells are joined by impermeable tight junctions. This indicates that the vagina and ectocervix might in fact be quite vulnerable to HIV penetration and infection, even without microabrasions and tears.

Amplification in draining lymph nodes
In most cases, mucosal HIV infection occurs with a single founder virus, indicating that the infection probably arises from a single focus of infected CD4+ T cells. At the end of the initial phase of localized viral replication, after approximately 10 days, HIV virions and/or virus-bearing cells reach local lymph nodes, where the infection strongly amplifies and systemic spread takes off. At this time, DCs in lymph nodes begin to present processed HIV antigens to naive B cells and T cells, thereby initiating the adaptive response to the infection. Subcapsular sinus macrophages might contribute to the establishment of HIV-specific humoral immunity by displaying captured virions to follicular B cells.

The DC response to HIV
Conventional DCs are responsible for initiating antiviral adaptive immunity in the draining lymph node. Furthermore, they activate natural killer (NK) cells through the secretion of interleukin-12 (IL-12), IL-15 and IL-18. Conventional DCs have not been shown to be directly activated by HIV, possibly owing to the blockade of effective HIV-1 replication in conventional DCs by the nucleoside hydrolase SAM domain- and HD domain-containing protein 1 (SAMHD1) and potentially other restriction factors, such as apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G (APOBEC3G). However, some HIV strains circumvent SAMHD1-mediated restriction and in these cases, interaction of the HIV capsid with cyclophilin A (CYP A) in conventional DCs has been shown to induce antiviral type I interferons (IFNs) through a cryptic cytoplasmic sensor. Tripartite motif-containing protein 5 (TRIM5) also recognizes the HIV capsid lattice to induce innate immune signalling. The function of conventional DCs is also impaired during HIV-1 infection. Dysfunction can be a consequence of direct viral interactions with conventional DCs (for example, through the interaction with DC-SIGN) or a result of indirect mechanisms, such as the production of IL-10 by monocytes during infection. This DC dysfunction could contribute to a lack of effective antiviral adaptive immunity and a lack of adequate NK cell activation.

Plasmacytoid DCs (pDCs) are mediators of innate immunity. pDCs activated by HIV-1 produce type I IFNs, which, in addition to inhibiting viral replication, may contribute to nonspecific CD8+ T cell proliferation. Furthermore, evidence shows that pDCs produce T cell-attracting chemokines, which may facilitate viral spread by providing a source of new CD4+ T cells for HIV to infect. However, HIV-exposed pDCs also upregulate TNF-related apoptosis-inducing ligand (TRAIL), which can lead to T cell apoptosis. Finally, HIV-exposed pDCs prime regulatory T (Treg) cells, which could impair the function of conventional DCs through secreted IL-10 or cell-bound cytotoxic T lymphocyte antigen 4 (CTLA4), further blunting adaptive immunity by promoting ‘immunoregulatory’ conventional DCs. Thus, pDCs can promote deleterious immunopathology during HIV-1 infection.

The T cell response to HIV
It takes up to 30 days before HIV-specific CD8+ T cells begin to measurably curtail viral replication, through the direct cytolytic effects of perforin and granzymes on infected CD4+ T cells and through the indirect effects of cytokines and other soluble factors. At the same time, HIV starts to mutate epitopes recognized by CD8+ T cells, in particular those present in the founder virus. The earliest T cell responses are often specific for Env and Nef, whereas Gag-specific and Pol-specific responses tend to arise later. Epitope changes are rapidly optimized for the fittest variants and occur through three main mechanisms: mutations that affect HLA allele binding; mutations that affect TCR recognition; and mutations that affect epitope processing, which can also occur in sequences flanking the actual T cell epitope.

During the initial months of HIV infection, CD8+ T cells are the strongest contributors to viral control. Once a balance has been reached between the adaptive T cell response and the ability of HIV to escape, the initial viral set point is reached. Immunodominant responses to more conserved virus epitopes probably result in a lower set point viraemia. The HLA type of the infected individual seems to be important in determining which CD8+ T cell epitopes become immunodominant; patients with HLA types associated with CD8+ T cell recognition of more conserved HIV regions (such as HLA-B27+ patients and HLA-B57+ patients) have a better clinical outcome.

The earliest and strongest immune dysfunction in HIV disease is that of CD4+ T cells. Owing to the massive killing of these cells by HIV-1, T helper cell functions are increasingly compromised during the course of infection. The relative inefficiency of CD8+ T cell responses against escape mutants, compared with the initially strong responses against founder virus sequences, might be a direct
consequence of waning T helper cell function. Over time, CD8+ T cells also become exhausted owing to persistent antigen exposure and repeated activation. Whereas recently activated T cells give rise to central memory T cells with high proliferative capacity and effector memory T cells with potent cytotoxic and cytokine-producing abilities, exhausted T cells lose proliferative capacity and effector functions. Negative regulatory molecules of immune activation, in particular T cell immunoglobulin domain- and mucin domain-containing protein 3 (TIM3), programmed cell death protein 1 (PD1) and CTLA4, are upregulated on T cells during HIV infection. Treg cells express the TIM3 ligand galectin 9, through which they exert an immunosuppressive effect on CD8+ T cells. CD8+ T cells restricted by the protective HLA alleles HLA-B27 and HLA-B57 express less TIM3 following activation and are therefore less prone to Treg cell-mediated inhibition and exhaustion, probably contributing to the improved viral control and clinical outcomes in patients with these haplotypes.

The B cell response to HIV

HIV does not replicate in B cells, although infectious virions on the surface of B cells may facilitate the early events of infection by mediating the more efficient passage of the virus to target cells, as has been proposed for DCs and follicular DCs. Early after infection, a high viral burden and the presence of high levels of pro-inflammatory factors lead to rapid dysregulation of B cells in various tissues, starting with intestinal mucosal tissues and followed by other secondary lymphoid tissues as the virus disseminates. These alterations in B cells probably contribute to the inadequacy of the HIV-specific B cell and antibody responses. Although most of our understanding of B cell immunopathogenesis in HIV infection is derived from the analysis of B cells and antibodies that circulate in the blood, there have been important insights gained from direct analyses of lymphoid tissues, sites where most of the body’s B cells reside. In early HIV infection, the intestinal mucosa undergoes numerous changes that cause polyclonal B cell activation but also a loss of germinal centres, which is associated with increased follicular lysis and B cell apoptosis. In the chronic phase of HIV infection, when patients are clinically asymptomatic, follicular hyperplasia is observed in secondary lymph nodes, and these changes reflect increased activation and differentiation of germinal centre B cells. In late-stage HIV infection, when patients become symptomatic, secondary lymphoid tissues become involuted and fibrotic with increased deposition of collagen. These changes are associated with the loss of homeostasis and the reversal of immune-activating effects on B cells, culminating in a generalized loss of immune function.

Further reading