Review

Microbial translocation, immune activation, and HIV disease

Nichole R. Klatt[1], Nicholas T. Funderburg[2], and Jason M. Brenchley[1]

[1] Laboratory of Molecular Microbiology, Program in Barrier Immunity and Repair, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health, Bethesda, MD, USA
[2] Division of Infectious Diseases, Center for AIDS Research, Case Western Reserve University/University Hospitals Case Medical Center, Cleveland, OH, USA

The advent of combination antiretroviral therapy (cART) has significantly improved the prognosis of human immunodeficiency virus (HIV)-infected individuals. However, individuals treated long-term with cART still manifest increased mortality compared to HIV-uninfected individuals. This increased mortality is closely associated with inflammation, which persists in cART-treated HIV-infected individuals despite levels of plasma viremia below detection limits. Chronic, pathological immune activation is a key factor in progression to acquired immunodeficiency syndrome (AIDS) in untreated HIV-infected individuals. One contributor to immune activation is microbial translocation, which occurs when microbial products traverse the tight epithelial barrier of the gastrointestinal tract. Here we review the mechanisms underlying microbial translocation and its role in contributing to immune activation and disease progression in HIV infection.

Persistent immune activation and microbial translocation during HIV infection

The pathology of disease caused by HIV infection is complex and multifaceted. In addition to high levels of systemic viral replication, HIV infection results in chronic immune activation and overall immunological dysfunction, which are closely associated with progression to AIDS [1–3]. Furthermore, even in HIV-infected individuals who are successfully treated with cART, persistent immune activation is associated with increased morbidity and mortality [4–6]. Several lines of evidence indicate that a key contributor to immune activation and disease progression during HIV infection is microbial translocation [6–51]. During HIV infection and pathogenic simian immunodeficiency virus (SIV) infection of nonhuman primates, several factors underlie microbial translocation, including breakdown of the tight epithelial barrier of the gastrointestinal (GI) tract and mucosal immune dysfunction [8,16,17,24,42]. A more complete understanding of the mechanisms underlying microbial translocation may provide insight into the development of novel therapeutic interventions aimed at decreasing microbial translocation and subsequent immune activation, thus decreasing morbidity and mortality in HIV infection.

Immunological abnormalities in progressive infection

One of the earliest insults to the immune system after infection with HIV is direct infection and depletion of CD4 T cells [52]. This depletion first occurs rapidly in mucosal tissues, where high numbers of activated memory CD4 T cells (the preferred target of HIV) reside. A slower, and progressive, depletion of CD4 T cells in peripheral tissues and blood ensues [53]. Given that the majority of CD4 T cells reside within mucosal tissues, early loss of mucosal CD4 T cells represents loss of the majority of these cells within the body [52]. Although this depletion probably induces homeostatic pressure to restore mucosal CD4 T cells, low levels of mucosal CD4 T cells are insufficient to cause progression to AIDS [53]. Indeed, during non-progressive SIV infection of natural hosts, who do not progress to AIDS, moderate depletion of mucosal CD4 T cells is observed, but does not result in disease progression [54,55].

Although CD4 T cells represent the most drastically affected lymphocyte cell type after HIV infection [56], other leukocyte subsets are also altered. Indeed, increased turnover, cell cycle perturbations, apoptosis, immune senescence, and altered functionality among CD8 T cells, B cells, and innate immune cells are also observed [57,58]. Among both CD4 and CD8 T cells, loss of essential naïve and central memory cell populations occurs, resulting in an increased frequency of short-lived effector cells [53,59]. Among natural killer (NK) cells, altered functionality, including decreased cytokine production, increased cytotoxicity, and dysfunctional homing have been observed [60,61]. Defective B cell responses have also been reported in HIV infection, including hyperactivation of B cells and dysregulation of B cell subsets, leading to altered antibody production [62]. Dendritic cell (DC) subsets are also significantly altered, including abnormal levels of plasmacytoid and myeloid DCs, and loss of mucosal $CD103^+$ DCs [42,63,64]. Macrophages are also dysfunctional during HIV infection, with a reduced capability for phagocytosing bacterial products in mucosal tissues and, in addition, may be targets for HIV infection [16,29]. High plasma levels of proinflammatory cytokines such as interferon-α (IFN-α), interleukin-1 (IL-1), IL-6, IL-18 and tumor necrosis factor-α (TNF-α) are also thought to result from innate cell activation [63,65]. Finally, lymphoid tissue fibrosis, manifested by collagen deposition in lymphoid tissues and associated with expression of transforming growth factor-β (TGF-β), limits immunological responses and CD4 T cell restoration, even after initiation of cART [66].

These cumulative immunological abnormalities of both the innate and adaptive arms of the immune system have

Corresponding author: Brenchley, J.M. (jbrenchl@mail.nih.gov)
Keywords: HIV; microbial translocation; immune activation; mucosal immunity.

been referred to as immune activation, given that they seem to result from the immune system being overtly activated [1]. The degree to which the immune system is activated is of extreme importance to HIV-infected individuals considering that it represents the strongest correlate of disease progression, morbidity, and mortality [1–5,67]. Thus, chronic and generalized immune activation is far-reaching, and it is really no surprise that untreated individuals eventually succumb to opportunistic infections, given the vast dysfunction of the immune system during progressive HIV disease.

The mechanisms which underlie immune activation during HIV infection are multifaceted and complex, and are likely to be both direct and indirect. One factor which can directly contribute to immune activation is viral replication [68]. Direct stimulation of the immune system by HIV can occur via at least two mechanisms: stimulation of HIV-specific T and B cells and stimulation of innate cells via viral RNA binding to Toll-like receptor 7 (TLR7) and TLR8 [69]. However, the extent to which the immune system is activated during chronic HIV infection cannot solely be attributed to the virus itself. Indeed, the immunocompromised state associated with chronic HIV infection can lead to reactivation of viruses normally controlled by the immune system, including Epstein–Barr virus (EBV) and cytomegalovirus (CMV) [68]. Replication of these viruses can also contribute to immune activation via recognition of virus-infected cells by antigen-specific T and B cells and by viral products binding to pattern recognition receptors. One of the direct consequences of activation of the immune system is secretion of proinflammatory cytokines, such as IFN-α, TNF-α, IL-1, IL-6, and IL-18, which can contribute to additional immune activation and apoptosis of immune cells [63,65,70]. High levels of systemic proinflammatory cytokines can also decrease the ability of the immune system to maintain healthy levels of lymphocytes that normally produce homeostatic effector cytokines such as IL-17 and IL-22 [19,42]. This skewing away from IL-17/IL-22^{+} lymphocytes probably contributes to immune activation, particularly in mucosal tissues where cells producing effector cytokines such as IL-17 and IL-22 are crucial for maintaining the integrity of the epithelial barrier [19,42]. Indeed, an inability to maintain immunological and epithelial integrity of the GI tract results in translocation of luminal antigens, including microbial products, into the peripheral circulation. Microbial products, which can directly stimulate the immune system, in peripheral circulation and other anatomical sites have been shown to contribute to immune activation in HIV-infected individuals and in progressively SIV-infected Asian macaques [6–10,12,14–19,21,22,25,29,31,32,35,36,38,40,41,44,48–50,71].

Evidence for microbial translocation

The human GI tract is colonized with approximately 10^{14} normal flora bacteria, which live in symbiosis with the host and can enhance immune function [72]. These organisms are essential for efficient metabolic function and digestion, and the human body has coevolved with microbiota leading to a symbiotic relationship that promotes a healthy GI tract [72]. Given the crucial importance for these bacteria to avoid direct contact with the systemic immune system, several structural and immunological host factors exist to prevent microbial products from translocating from the lumen of the intestine. These include a physical barrier of epithelial cells [16], intestinal IgA [73], and a network of immune cells such as macrophages, DCs, T cells, and innate lymphoid cells [42,72]. However, during HIV infection there is an assault to several of these protective mechanisms, and microbial products translocate into the lamina propria of the GI tract and, eventually, into systemic circulation.

Microbial translocation during HIV infection was first described in 2006, when it was demonstrated that bioactive microbial products were significantly elevated in plasma from HIV-infected individuals and from progressively SIV-infected Asian macaques [7]. Furthermore, the levels of lipopolysaccharide (LPS) in these individuals directly correlated with activation of both the adaptive and innate arms of the immune system [7]. These data provided insights into an underlying cause of immune activation observed during HIV infection. In the six years since these data were published, microbial translocation during pathogenic HIV or SIV infections has been corroborated by several groups, with at least 44 reports of microbial translocation occurring during progressive HIV or SIV infection [6–51]. Microbial translocation is not a phenomena restricted to HIV infection. Indeed, microbial translocation has been reported in several diseases including inflammatory bowel diseases (IBD), infection by hepatitis C virus (HCV), alcoholism, and cardiovascular disease [74].

Microbial translocation and immune activation

Although the degree to which microbial translocation, viral replication (e.g., by HIV, CMV, and EBV), and proinflammatory cytokines cause immune activation in progressively HIV or SIV-infected individuals is unclear, several specific effects of microbial product-mediated immune activation can be considered. Indeed, chronic TLR activation in HIV disease, through recognition of translocated bacterial products and/or viral products, can cause dysregulation of immune responses [30,75] and has been potentially linked to a number of comorbidities, including dementia in AIDS patients [8].

Monocytes and macrophages express a variety of pattern recognition antigen receptors, and stimulation of these cells via these receptors can contribute to inflammation and cardiovascular disease [76]. Specifically, increased levels of activated monocyte subsets are observed in progressively HIV- or SIV-infected individuals and are probably being activated by a variety of microbial products [8,77]. Moreover, elevated plasma levels of soluble markers of monocyte and macrophage activation (sCD14 and sCD163) have been reported in HIV infection [38,78]. Furthermore, plasma levels of sCD14 (a bacterial LPS receptor) independently predict mortality in cART-treated HIV-infected individuals, and plasma levels of sCD163 (a scavenger receptor) are associated with unstable non-calcified coronary plaques in cART-treated HIV-infected individuals [38,78]. Thus, chronic innate immune activation may directly contribute to the increased thrombosis risk observed in HIV-infected individuals. Indeed,