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Microbial translocation: translating SIV to HIV

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Abstract

Purpose of Review—This article describes recent advances in understanding the causes and consequences of microbial translocation in HIV and SIV infections.

Recent findings—Persistent microbial translocation contributes to aberrant immune activation in immunodeficiency lentiviral infections and thereby, pathogenesis and mortality. Efforts to delineate the circumstances surrounding translocation have benefited from use of Simian Immunodeficiency Virus (SIV)-infected nonhuman primates and highlight the overwhelming immunologic diversion caused by translocating microbes. The use of therapeutics aimed at reducing microbial translocation show promise and will benefit from continued research into the mechanisms that promote systemic microbial dissemination in treated and untreated infections.

Summary—Insights into the source and identity of translocating microbes in lentiviral infections continue to enhance the development of adjunct therapeutics.

Keywords

HIV; SIV; AIDS; microbial translocation; microbiome

INTRODUCTION

SIV infection of rhesus macaques (RMs) is the leading model for studying mechanisms of HIV-1 disease progression, recapitulating most of the salient aspects of infection, including viral kinetics, immune dysfunction, and responses to therapeutic interventions [1]. Like other non-human primate HIV-1 models, RMs exhibit a persistent immune activation that is modestly reduced with the initiation of antiretroviral therapy (ART). Although immune activation in treated infection may in part stem from residual antigen presentation [2, 3] microbial translocation has emerged as a significant contributor.

Microbial translocation broadly describes the passage of microbes or microbial products from the lumen of the gastrointestinal (GI) tract into systemic circulation, absent of overt bacterial infection. As first described by Brenchley et. al [4], microbial translocation was detected through increased levels of plasma lipopolysaccharide (LPS), LPS-binding protein

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Conflicts of Interest
None.

(LPB), and soluble CD14 (sCD14). In both HIV and SIV infections, LPS levels correlate with a number of immune activation parameters including monocyte TNF α expression, plasma IFN α , and CD8+ T-cell activation. In RMs, treatment with a broad spectrum antibiotic regimen was associated with reduced fecal gram-negative bacterial loads concomitant with decreased plasma LPS, indicating that the gastrointestinal tract may be the primary source of translocating bacterial products in SIV-infected RMs and by inference, HIV-infected individuals.

Since this publication, many groups have validated and expanded upon these findings. Here, we will cover recent evidence for and contributors to microbial translocation in lentiviral infections, mechanisms by which translocation contributes to immune activation, and therapeutics aimed at mitigating lingering translocation.

SYSTEMIC DISSEMINATION OF MICROBIAL PRODUCTS

In HIV and SIV infections, microbial translocation has been described predominantly by identifying bacterial products in circulation. Recently, high throughput sequencing of DNA in circulation has allowed for the identification of systemically disseminated bacterial taxa. In rhesus and cynomolgous macaques (CM; a species of Asian macaques often used for SIV studies), Ericson et. al. observed that plasma 16S rDNA was dramatically elevated during hyperacute SIVmac239 infection [5]. Both before and shortly after infection, translocating bacterial populations in Asian macaques (RM and CM) are composed predominantly of Proteobacteria, with a modest relative expansion throughout infection. In CMs, hyperacute infection is characterized by a rapid increase in plasma levels of Bacteroidetes and Spirochetes at the expense of the remaining phyla. In CM followed longitudinally, hyperacute expansion is rapidly controlled but falters with the onset of late chronic disease. It is unknown whether plasma 16S rDNA remains elevated in RMs; however, 16S rDNA recovered from the mesenteric lymph nodes (MLN) and livers of chronically infected RM has previously revealed an enrichment for Proteobacteria, suggesting that the taxa of translocating bacteria remains altered [6]. In HIV-infected patients, sequencing of circulating bacteria products has not been as thorough as in RMs. Although there are significant increases in 16S rDNA during untreated, chronic infection [7], a longitudinal analysis is wanting [8, 9].

The GI tract is presumed to be the most significant contributor to microbial translocation given it has the largest anatomic bacterial load and the extent of damage incurred to the GI tract during untreated HIV/SIV infection. Whereas few bacteria are located within the intestinal lamina propria in health, translocating bacteria are increasingly observed post-infection and have been identified as predominantly Proteobacteria in RMs [6, 10]. In CMs, Ericson et. al. additionally demonstrated that overlap between taxa in the plasma and stool increases after SIV infection [5]. Whether Proteobacterial enrichment among translocating species is preferential or due to an alteration in site of translocation post-infection is unknown. [6]. Proteobacterial frequencies are similarly enriched in the oral and respiratory mucosa and though these sites show signs of luminal dysbiosis [11–16], a systemic survey for sites of microbial translocation (bacteria and other) has not been executed during HIV or SIV infection. However, a comparison of bacteria from adjacently collected luminal and

lamina propria-isolated colonic samples reveals that a preference for Proteobacterial translocation at the intestinal tract is certainly a contributor [6]. A thorough characterization of systemically disseminated microbial products is essential for identifying the origin of these microbes and for designing targeted therapeutics.

MICROBIAL DYSBIOSIS: INSTIGATOR OR BYSTANDER?

Intestinal microbial dysbiosis – an imbalance in the composition of the intestinal microbiome – has been well-described in North American, HIV-infected patients, with many studies further showing a correlation between expansion of particular bacterial taxa, systemic immune activation, and microbial translocation [17–20]. These studies broadly describe increases in Proteobacteria at the expense of Firmicutes and particular alterations within the Bacteroidetes phylum with an inversion of *Bacteroides* to *Prevotella* ratio. With the acknowledgement that different populations have unique genetic and lifestyle factors, Monaco et. al [21] and Ling et. al. [22] recently characterized the fecal microbiome of Ugandan and Chinese cohorts, respectively. In both cohorts, HIV infection was associated with relative increases in Proteobacteria and Firmicutes and declines in Bacteroidetes; however, there were notable differences in sub-taxa. Whereas the most significant differences described by Monaco et. al. pertained to changes in Bacilli, Gammaproteobacteria and Actinobacteria taxa, Ling et. al. described differences primarily in Bacteroidales, Clostridiales, and Negativicutes, with both groups describing increased *Enterobacteriaceae* post-infection. Only Ling et. al. described a significant post-infection difference in *Prevotella*. Monaco et. al further described correlations between several operational taxa units (OTU) and sCD14 whereas Ling et. al. described correlations with pro-inflammatory cytokines and IL-22.

Intriguingly, evidence for overt microbial dysbiosis in SIV-infected macaques remains scant. As summarized in Table 1, although we and others have demonstrated a lack of intestinal dysbiosis in macaque cohorts [6, 15, 23], some have described pointed disruptions [24–26]. Although intestinal dysbiosis is a known detriment to health, observed dysbiosis in untreated HIV-infected humans may be coincidental or irrelevant, overshadowed by viral-mediated pathogenesis. Noguera-Julian et. al [27] demonstrated that stratification by sexual practice removes evidence for infection-associated fecal dysbiosis. In a cohort of over 200 men, the authors demonstrated that men who have sex with men displayed a *Prevotella*- and Proteobacteria-enriched enterotype whereas heterosexual males had a *Bacteroides*-rich enterotype, independent of infection. Furthermore, although HIV-infected individuals displayed reduced bacterial richness, neither richness nor dysbiosis correlated with microbial translocation or systemic inflammation when sexual preference was considered.

Notwithstanding a role for intestinal bacterial dysbiosis, there is recent evidence for a role of viral dysbiosis in lentiviral disease progression. Building upon a previous report describing an expansion of adenoviridae in RMs with advanced AIDS [23], Handley et. al. [26] assessed the fecal metagenome of RMs vaccinated against SIV and observed that vaccinated-unprotected animals displayed stark increases in adenoviridae and saploviruses as compared to either unchallenged or vaccine-protected animals. Among animals with GI tract complications, there was evidence for significantly increased enteroviruses, adeonoviridae

and adeno-associated virus; however, frequencies of these viruses did not correlate with serum LBP, suggesting that viral dysbiosis is tied to neither bacterial dysbiosis - absent in this study - or translocation. Corroborating this data, Monoco et. al. similarly demonstrated that HIV-infected individuals exhibited an expansion of fecal adenoviridae and anelloviridae, which correlated with CD4+ T-cell counts [21]. Although this publication noted that fecal bacterial dysbiosis was evident, no correlations between viral dysbiosis and microbial translocation were noted.

Fecal bacterial populations resemble those isolated from mucosa [18, 20, 21]; however, the intestinal microbiome shows notable compositional differences longitudinally and cross-sectionally [28, 29], and it is unlikely that similar microhabitats exist at all mucosal domains. It is worth noting that despite extensive care, intestinal biopsy samples cannot be thoroughly rid of fecal material and thus capture luminal, adherent and translocating species alike. Disentangling dysbiosis from sub-mucosal microbial translocation (bacterial and other) will require a precise analysis of microbial microhabitats in order to properly ascribe the effects of dysbiosis on disease progression [30].

BREAKDOWN OF MUCOSAL BARRIER FUNCTION

Damage to the intestinal epithelial barrier resulting from viral-dependent inflammation [31] is augmented by the loss of T_H17 cells, which are preferentially depleted among mucosal CD4+ T-cells in both progressive HIV and SIV infections [32–34]. T_H17 cells secrete a number of cytokines - including IL-17, IL-21 and IL-22 - necessary for promoting epithelial cell regeneration, tight junction formation, chemokine induction, neutrophil recruitment, and the production of microbial-regulatory factors [35]. These factors shape the microbiome immediately adjacent to the epithelial barrier and form the first line of immunological defense against bacterial and fungal antigens.

The mechanisms governing preferential T_H17 depletion are unclear. Although many publications implicate preferential infection, these results have not been not uniformly replicated, perhaps owing to differences in T_H17 phenotyping and measures of “preference” [33, 34, 36–41]. To address infection during viral transmission, Stieh et. al. vaginally challenged female RMs with SIVmac239 and SIVmac766 and characterized SIV-infected cells within the reproductive tract 48 hours post-infection [41]. These authors observed by fluorescence microscopy that although T_H17 cells (here, CCR6+CD3+ T-cells) made up 19% of all CD4+ T-cells, they made up 84% of SIV-infected T-cells. Supporting previous reports in GI tract tissues, T_H17 cells in the female reproductive tract did not express higher levels of CCR5 and were not cycling at a higher frequency, leading to uncertainty as to why these cells might be preferentially infected. Following HIV and SIV infection, the epithelial barrier itself releases chemokines that recruit a wave of innate immune cells, including dendritic cells which form aggregates at the epithelial barrier [42, 43]. As T_H17 cells routinely sample antigen from intestinal dendritic cells [44, 45], this initial influx may seed early T_H17 infection. Indeed, Stieh et. al. observed aggregates of SIV-harboring T_H17 and non-CD3+ cells directly under the vaginal epithelium.

Importantly, the loss of IL-17 producing cells extends beyond Th17 cells to include IL-17-expressing CD8+ T-cells and innate lymphoid cells (ILCs) [46, 47] – a cell type similarly responsible for regulation of microbial containment but do not express CD4 and are incapable of being infected by HIV or SIV. In SIV, depletion of ILCs was most severe in the IL-17-expressing ILC3 subset, with profound decreases observed in both jejunal and colonic tissue [48]. Prolonged depletion in RMs appears limited to intestinal tissues and is attributable to both increases in ILC3 apoptosis and progressive ILC1 polarization. In contrast, Kloverpris et. al. [49] recently demonstrated that HIV-infected patients exhibit circulating - but not intestinal - losses of all ILC subsets throughout infection. In these patients, ILC2s and ILC3s exhibited a downregulation of cell proliferation and viability transcripts limited to acute infection, coupled with increases in CD69 expression. Despite intestinal ILC preservation, circulating ILC levels correlated with plasma levels of intestinal fatty acid binding protein (released by GI tract epithelial cells into circulation upon death), suggesting a relationship with reduced intestinal integrity. Although the mechanisms for ILC losses are still under investigation, it is reasonable to speculate that as with T_H17 cells, there may be a role for altered intestinal tryptophan catabolism [17, 24, 50] and the loss of mucosal CD103+ DCs [51]. Alternatively, the loss of ILCs may instigate Th17 losses by permitting dysregulation among translocating species [24, 52]. The collective loss of IL-17 signaling and damage to the epithelial barrier thus form a self-perpetuating avenue for microbial translocation in progressive SIV infection and likely, HIV-1 infection.

TRANSLOCATION AT THE INTERSECTION OF IMMUNE ACTIVATION

Microbial translocation has emerged as a leading contributor to immune activation in lentiviral disease progression. To be sure, ongoing viral replication plays a role in immune activation; however, in non-progressor hosts of SIV infection, microbial translocation and immune activation are restricted to acute infection [53–55]. Recently, a renewed appreciation for the plasticity of the immune system [56, 57] has led to the consideration that prolonged immune activation and dysfunction may be directly influenced by the taxa of translocating microbes [58–60].

Myeloid cell dysregulation has been extensively documented in HIV infection but until recently, focused largely on circulating cell subsets and their potential contributions to lentiviral replication and latency [61, 62]. To broadly assess anti-microbial intestinal innate responses, Glavan et. al. measured longitudinally expression of pattern recognition receptors and levels pro-inflammatory cytokines in the jejunum of SIVmac251-infected RMs [25]. Here, the authors observed that there was a robust increase in MDA5 and TLR 2, 5, 6, 7, 9, and 10 transcripts during acute infection – increases that exceeded what was seen in the blood – and that these responses dampened with progression into chronic infection.

Hypergammaglobulinemia is common in progressive lentiviral infection. Although this expansion was previously considered non-specific, translocation may induce a specific anti-microbial humoral response. Hel et. al. [63] characterized immunoglobulin responses in both the plasma and intestinal tissues of HIV-infected individuals and observed that while circulating IgA and IgG concentrations were elevated after infection, IgM showed stark increases in rectal washes. Using a custom protein microarray that included proteins from

varied human gut microbes, the authors observed that circulating IgM and IgG from infected patients displayed significantly reduced responses to Proteobacteria and Firmicutes, but not Bacteroidetes antigens. In contrast, rectal IgM responses were significantly elevated against both bacterial and food antigens in infected patients, with variable responsiveness by IgA and IgG. Intriguingly, these authors further observed an inverse correlation between rectal IgA concentrations – both bulk and anti-microbial– and plasma levels of sCD14, suggesting that low intestinal IgA may permit systemic microbial dissemination.

To determine the effect translocating bacteria may have on infected CD4+ T-cell function, Yoder et. al. [64], used a lamina propria aggregate culture model to infect CD4+ T-cells with an HIV-1 clone in the presence and absence of bacterial exposure. In non-exposed CD4+ T-cells, the authors reported 1000 differentially regulated transcripts and predicted disruption to a number of pathways, including OX40, PPAR and FOXO3. When the authors carried out the same infection in the presence of *Prevotella* sp., disruptions to these pathways were absent and instead, infection most strongly promoted increases in granzymes and type I interferon stimulated genes. Although the contribution of *Prevotella* to disease progression remains uncertain [27], this study proposes a useful methodology by which to evaluate the effect of translocating microbes on immune activation.

These studies are part of a larger shift in focus in the HIV field, towards a more holistic assessment of the collective anti-microbial response. A full account of how translocation and lentiviral replication shape each other is necessary for the development of appropriate and durable therapeutics.

THERAPEUTICS

The entwined relationship between the microbiome, epithelial integrity, and intestinal immunity has led researchers to consider that targeting any one of these facets may reduce inflammation in antiretroviral-treated (ART) HIV-infected individuals. Several recent publications have detailed anti-microbial therapeutics in two categories – those that aim to neutralize circulating microbial products and those that seek to restore the intestinal microbiome.

In both HIV-infected individuals and SIV-infected macaques, anti-microbial therapeutics have shown promising results [65, 66]. Building on the previous observation that phosphate and LPS-binding drug sevelamer reduced immune activation and non-AIDS related co-morbidities in SIV-infected RMs [66], Pandrea et. al. dually targeted microbial translocation and mucosal inflammation by co-treatment of SIVsabBH66-infected PTM with the nonabsorbed antibiotic rifaximin and anti-inflammatory drug sulfasalazine [67]. Treatment during acute infection was associated with lower plasma LPS and sCD14, T-cell activation, markers of hypercoagulation and viremia with subsequent improved mucosal CD4+ T-cell frequencies. However, these results did not persist into chronic infection, complimenting previous reports suggesting that microbial translocation is only treatable in the presence of ART [65, 66, 68, 69].

Although the contribution of dysiosis to untreated disease progression remains contentious, probiotic administration to ART-treated HIV-infected individuals [69] and SIV-infected macaques [68] demonstrates a clear immunological benefit. Considering a report demonstrating that ART and IL-21 co-treatment improved intestinal T_H17 recovery independent of improved translocation [70], Ortiz et. al. recently demonstrated that combining ART, probiotics and IL-21 enhanced immune reconstitution and lowered microbial translocation in SIVmac239-infected PTMs [71]. The mechanisms for reduced translocation in this trivalent approach remain unknown; however, the synergistic benefits of this regimen may indicate that a basal threshold of stasis (viral suppression, commensal restoration, and T_H17 presence) is required to sustain physical and immunological mucosal repair.

Fecal microbial transplantation (FMT) has been proposed as an added treatment for ART-treated, HIV infected individuals. FMT has the benefit of introducing a presumably balanced microbiome, including under-characterized microbes with essential roles [72]. To address the feasibility of this treatment for HIV-infected individuals, Hensley-McBain et. al. [73] gave SIVmac239-infected, ART-treated macaques antibiotics followed by FMT from donor uninfected macaques. Here, antibiotics were used to clear the host microbiome [74]. Successful engraftment of the donor microbiome led to significant improvements in peripheral T_H17 and T_H22 compared to pre-FMT, as well as decreased intestinal T-cell activation. No increases in circulating LBP or IL-6R were noted; however, there were persistent increases in sCD14 out to 6 weeks post-FMT, indicating that microbial translocation *per se* does not preclude immune reconstitution. Vujkovic-Cvijin et. al [75] similarly attempted FMT in ART-treated, HIV-infected individuals but here, in the absence of antibiotic pre-treatment. Although FMT was well-tolerated, no changes in inflammatory profiles were noted and an examination of the host fecal microbiome revealed only partial engraftment. These studies indicate that although FMT may serve a potential immunological benefit, extensive studies are needed to tailor this treatment to HIV-infected individuals.

CONCLUSION

Microbial translocation remains a strong contributor to inflammation in both untreated and treated lentiviral infections. The identification of translocating species in SIV-infected RMs has revealed an enrichment for Proteobacteria [5, 6] and led to a realization that specific deficits in anti-microbial immunity likely contribute to translocation and subsequently, disease progression. The continued, detailed categorization of translocating species at potential sites of transmission is necessary for the identification of the most immunostimulatory moieties. The encouraging results of probiotic and FMT as ART-adjuncts highlight the benefits of anti-microbial therapy in treated lentiviral infections and suggest that targeted anti-microbials may further improve immune reconstitution in infected patients.

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Key Points

- Microbial translocation in SIV infection includes the preferential migration of pro-inflammatory bacterial taxa.
- Viral and bacterial dysbiosis are independent of one another. Recent evidence in non-human primates calls into question the role of bacterial dysbiosis on microbial translocation.
- Immune activation in lentiviral infections includes anti-microbial deficits, further contributing to microbial translocation.
- Anti-microbial translocation therapeutics enhance immune reconstitution in treated lentiviral infections.

Table 1

Publications assessing dysbiosis in the SIV macaque model

Publication	Cohort	Source	Taxa Increased	Taxa Decreased	Key Observations
McKenna Plos Pathogens 2008 [15]	Longitudinal	Stool	None	None	No SIV-induced dysbiosis, but dysbiosis present in colitic animals
Klase Mucosal Immunol 2015 [6]	Longitudinal	Stool	None	None	Proteobacterial species preferentially translocate
Handley Cell 2012 [23]	Cross-sectional	Stool	None	None	Viral dysbiosis in SIV
Vujkovic-Cvijin Cell Rep 2015 [24]	Longitudinal	Stool	Isolated during acute infection	<i>Lactobacillus</i> and <i>Streptococcus</i>	Lactobacillus levels associated with tryptophan metabolism and Th17 cells in the host
Glavan Mucosal Immunol 2016 [25]	Cross-sectional	Jejunal biopsy	Proteobacteria genera during acute infection	Several Firmicutes during chronic infection	Altered taxa associate with pattern recognition receptor expression in host
Handley Cell Host Microbe 2016 [26]	Longitudinal	Stool	<i>Enterobacteriaceae</i> and <i>Moraxellaceae</i> in animals with low CD4 counts	None	Viral dysbiosis in SIV