

Can We Control the Progression of HIV by Monitor Markers of Microbial Translocation?

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Abstract

This review summarizes microbial translocation in HIV infection. Microbial translocation can be measured by bacterial products in plasma, such as LPS and bacterial DNA or RNA fragments, or indirectly by LBP, sCD14, EndoCAB, and anti-flagellin antibodies. In some study, these markers had contrary results. May be microbial translocation is not the sole driver of HIV progression. Several lines of research indicated that a major contributor to immune activation and disease progression during HIV infection was microbial translocation. Although successful treatment with ART increased GALT CD4⁺ T cells and suppresses HIV RNA, the numbers of these cells did not return to prior levels. There is a negative effect of mucosal immune dysfunction and microbial translocation on HIV disease progression in the presence of ART. The topic of microbial translocation and immune activation in HIV infection still is a research focus.

Keywords Microbial translocation; HIV-1; Immune activation; ART

Introduction

Human immunodeficiency virus (HIV) infection is a chronic illness characterized by progressive CD4⁺ T cell loss and immune system destroys. HIV infection is now controlled by anti-retroviral therapy (ART), resulting in reduced death from opportunistic infections. However, despite successful viral suppression, many HIV patients still have persistent immune activation [1,2].

In fact, the mechanism of immune activation in HIV infected patients is not fully understood in nowadays. Although their viral load is successfully suppressed by ART, some immune activation phenomenon appears at the same time. Several studies suggest that immune activation could be a consequence of gut-triggered systemic inflammation and microbial translocation [3]. Microbial translocation and chronic activation of the immune system are major driving forces of HIV disease progression [6]. It was found that the magnitude of HIV-associated chronic immune activation could predict disease progression [3-5]. Low levels of immune activation were observed in chronically infected natural hosts of simian immunodeficiency virus (SIV), who do not progress to diseases despite high levels of virus replication [6-8]. One study showed that early *in vivo* blockade of microbial translocation in SIV-infected pigtailed macaques would result in the control of chronic immune activation [9]. However, the relationship of microbial translocation, immune activation and HIV infection has not been completely understood. If we can control the extent of microbial translocation in HIV infected patients, it may be helpful for controlling the progression of HIV infection, especially in ART accepted patients.

Microbial translocation is caused by depletion of CD4⁺T cells in the gut mucosa and the gut's increased permeability; it is also observed in idiopathic CD4 lymphocytopenia [10]. Infection with HIV-1 leads to

the depletion of CD4⁺T cells in gut-associated lymphoid tissues (GALT), which is associated with the translocation of microbial products, such as lipopolysaccharide (LPS), across the mucosa of the gastrointestinal tract [11,12]. CD4⁺T cell depletion in GALT occurs within 4-6 weeks of primary HIV infection [13]. In gut, the expression of genes associated with inflammation increased but the expression of genes regulating epithelial barrier and digestive functions decreased [13]. Increased levels of LPS that occurred in patients with chronic progressive HIV infection decreased after 48 weeks of effective ART but this level did not normalize [11]. These increased levels of LPS are associated with persistent immune activation [11]. So study the phenomenon of microbial translocation in HIV infected patients will help to understand persistent immune activation with HIV.

In this review, we discuss microbial translocation markers, immune active and microbial translocation under ART. Some new results show in this paper and we want to illuminate these work in itself aspect.

Microbial translocation markers in HIV infection

The extent of microbial translocation can be assessed either directly through the measurement of bacterial products in plasma, such as LPS and bacterial DNA or RNA fragments, or indirectly by soluble CD14 (sCD14), LBP and EndoCAB [6]. In recent studies, plasma levels of intestinal fatty acid binding protein (IFABP), as a marker of enterocyte damage, have also been used to correlate intestinal impairment and microbial translocation [2,14,15].

sCD14 is secreted by monocytes, dendritic cells and hepatocytes; it binds both LPS and peptidoglycan of Gram positive bacteria. sCD14 is a receptor molecule produced primarily by macrophages and hepatocytes as part of the innate immune response to LPS [16-18]. sCD14 functions as a co-factor along with LBP to mediate LPS recognition and response by Toll-like receptor 4 (TLR-4) [18]. So sCD14 is accepted as a marker of immune activation. LPS is a potent

immunogenic component of Gram-negative bacterial cell membranes, and the presence of LPS in the blood stream is a marker of the breakdown in gut-mucosal immune barrier [11,18,20]. Nevertheless, in fact each marker has limitations: sCD14 can be induced by different factors other than LPS in unsuppressed HIV-1 infection [21]; LPS is only present in Gram-negative bacteria and plasmas have to handle with care to prevent contamination. On the other hand, although 16S rDNA is present in both Gram-negative and Gram-positive bacteria, it has been technically hampered due to DNA contamination [4].

sCD14, EndoCab and LBP are measured in the plasma or serum by enzyme-linked immunosorbent assay (ELISA) in the majority of published studies [22]. In particular, sCD14 has been given the relatively easy standardization of its measurement between different laboratories [6]. It must be noted that sCD14 serves as a biomarker of monocyte activation [23], and although it correlates with LPS, it is not a direct and specific marker of microbial translocation per se. Conversely, the commercial *Limulus* amoebocyte lysate (LAL) assay allows for the quantitative determination of LPS in reference to known endotoxin concentrations and is therefore a direct measure of endotoxemia [6]. In a new study, Shive demonstrated that inflammatory cytokines can induce the release of sCD14 in peripheral blood mononuclear cell cultures from healthy donors. So sCD14 is a marker of monocyte activation, not restricted to activation by LPS [24]. An alternative method to assess microbial translocation is the detection and quantification of the universally conserved microbial 16S rRNA gene in plasma by PCR [25,26].

However, contradictory results have been published that link microbial translocation and HIV disease. Recent studies of microbial translocation have also reported consistent associations with sCD14, but inconsistent associations across LPS, LBP, and EndoCab [2,18]. This inconsistent associations across markers of microbial translocation suggested that markers of LPS bio reactivity as opposed to LPS exposure were perhaps more reliable measures for microbial translocation-related outcomes [2,18]. Redd et al. [27] demonstrated no correlation between LPS levels and counts of sCD14, a co-receptor in the recognition of bacterial LPS in systemic circulation. In another study, increased levels of LPS were associated with HIV infection in late stages [36,63]. These contrary findings indicate that microbial translocation is not the sole driver of HIV progression [28]. On the other hand, incongruence among these studies may also result from differences in experimental approaches in determining the levels of LPS and sCD14 [29]. These results told us the markers of microbial translocation in HIV-associated patients may have special situation.

Microbial translocation and immune active in HIV/SIV infection

HIV infection results in chronic immune activation, which is closely associated with progression to acquired immunodeficiency syndrome (AIDS) [30]. Several studies illustrate that a key contributor to immune activation and disease progression during HIV infection is microbial translocation [31-37]. During HIV infection and pathogenic SIV infection of non-human primates, several factors underlie microbial translocation, including injury of the epithelial barrier of the gastrointestinal tract and mucosal immune dysfunction [33,38,39].

In our previous study indicated that complex interactions occur between diverse types of enteroendocrine cells and various immune cells through paracrine mechanisms or via mechanisms dependent on cell-to-cell contact; such interactions might play key roles in

maintaining the gut mucosal barrier integrity of rhesus macaques [40]. Then our another new study revealed that acute simian/human immunodeficiency viruses (SHIV), and by extension HIV infection could affect the expression of gastrointestinal tract epithelial tight junction associated genes, probably through IL-17A and other immune alterations [41]. These two studies talked about integrity of the gut mucosal barrier, which had effect on microbial translocation. Then we will research the relationship between Th17 cell and microbial translocation in HIV-1 infected patients.

In recent years, several researches have focused on the hypothesis that translocation of gut microbe antigens across an injured intestinal epithelial barrier. This phenomenon plays an important role in the chronic immune activation. Brenchley et al. [11] first reported increased circulating LPS in both HIV-infected humans and SIV-infected rhesus macaques during chronic infection. More recently, clinical investigations [42,43] have confirmed that microbial translocation is also a major source of immune activation and may contribute to the rapid disease progression in HIV infected children [44]. But, in another study, Wittkop et al. illuminated that autoimmune response and microbial translocation were not associated with immune activation [45]. So, we should deeply understand the relationship between microbial translocation and immune activation in HIV.

Indeed, many of these investigations have demonstrated that the persistence in translocation was associated with chronic inflammation [46,47] and impaired reconstitution of intestinal CD4⁺T cells [31,48]. Interesting, investigations of nonhuman primates demonstrated that microbial translocation did not occur in nonpathogenic SIV infection of natural hosts such as sooty mangabeys and African green monkeys [6]. Moreno [4] reported the results from 18 elite controllers patients showing that there was a good correlation in the quantification of LPS, sCD14, and LBP levels, but not with bacterial 16S rDNA, and did not exists any significant association between these markers of microbial translocation and immune activation [49]. These findings imply that we should study microbial translocation through treatment naive HIV elite controllers in the future.

SIV infected natural hosts did not progress to AIDS despite high levels of virus replication, and did not have evidence of microbial translocation [3,50]. This may explain the lack of immune activation and disease progression in chronically SIV-infected natural hosts [11,51]. Furthermore, experimental administration of bacterial products in natural hosts induced immune activation [7]. These data supported a role of microbial translocation in immune activation and disease progression during progressive HIV/SIV infection [3]. Microbial translocation can induce immune activation in the absence of HIV or SIV infections. For example, in pigtail macaques, which have increased levels of damage to their gut intestinal tract even in the absence of SIV infection, microbial translocation into the lamina propria of the gut intestinal tract correlates with immune activation, both locally in mucosal tissues and systemically [52].

In nowadays, there are some contrary results in microbial translocation and immune active. So, we should do some research on the relationship between microbial translocation and immune active in HIV infected patients. At the meantime, studying the mechanism of microbial translocation with HIV also has importance.

Microbial translocation and ART

Although successful treatment with ART increased GALT CD4⁺ T cells, the numbers of these cells did not return to prior levels, even when viremia was completely suppressed [11,53]. In fact, advances in the administration of antiretroviral cocktails have dramatically increased the life expectancy of HIV infected patients in the past years [54]. However, reconstruction of GALT structure and function was markedly delayed [50,55]. Moreover, initiation of ART early in infection did not appear to promote significant maintenance of CD4⁺T cells in GALT [44,56]. Available data indicated that restoration of the intestinal mucosal barrier function was possible in patients on suppressive antiretroviral therapy despite persistence of structural and functional abnormalities of the mucosal immune system [57].

The role of microbial translocation in predicting disease progression in the absence of ART as well as the effects of ART have recently been investigated in several studies. For a cohort of HIV infected individuals from Rakai, Redd et al. failed to find significant associations between levels of sCD14, LPS, and endotoxin antibody and HIV disease progression [58]. A nested-control study from the strategies for management of anti-retroviral therapy (SMART) trial by Sandler et al. reported that plasma levels of sCD14 were independent predictors of overall mortality in HIV disease [2]. Gene expression studies showed that multiple biomarkers of mucosal growth remain repressed in GALT during chronic HIV infection despite suppressive therapy [59,60]. More recent evidence suggested that this residual immune dysregulation is most prevalent when ART fails to increase circulating CD4⁺T cells to normal levels [44,61]. Taken together, these data strongly suggest a negative effect of mucosal immune dysfunction and microbial translocation on HIV disease progression under ART.

Persistent immune activation has long been implicated as a factor impairing the immunological response to ART, the question as to whether microbial translocation might affect immune recovery after ART has been investigated by different study groups. Brenchley et al. observed an inverse correlation between CD4⁺T cell reconstitution and microbial translocation [11]. Marchetti revealed that increased plasma levels of LPS in immunological nonresponder (INR) ART-treated HIV-infected individuals compared to levels in subjects with full immunological recovery after ART [48]. Jiang et al. showed that higher levels of bacterial 16S rRNA genes were associated with greater T-cell activation and impaired CD4⁺T cell restoration after ART [12]. In one new study [47], HIV-infected patients with negative HIV viral load (<20 copies/ml) present less frequently microbial translocation and have lower levels of inflammation markers (tumor necrosis factor α and interleukin 6) than patients with low-level HIV viremias (20-200 copies/ml). Inflammation seems to be induced by microbial translocation and not by HIV viremia itself [47]. Toossi et al. supposed that circulating LPS levels in HIV/tuberculosis patients with CD4⁺T cell count $\geq 350/\mu\text{l}$ were unaffected by treatment of tuberculosis with or without ART and changes in circulating sCD14 and LPS are dependent on CD4⁺T cell count [62]. Likewise, successful ART has been associated with decreased levels of microbial products in the plasma, but again, there was failure to normalize to levels seen in HIV-seronegative persons [2,12]. Some studies reported decreased sCD14 levels while others demonstrated lower LPS levels among patients on ART; however, outcomes were not comparable to HIV uninfected individuals [6,63,64]. The possible mechanism by which ART decreased the translocation of microbes could be by partial restoration of Th17 cells and improved clearance of LPS [6,64,65]. ART has also helped in improving number of Kupffer cells, which has been shown to

contribute to intestinal healing [65,66]. Lozupone et al. [67] has shown that the microbiome of HIV infected patients with gastrointestinal inflammation presents a bacterial species profile that is distinct from that of other intestinal inflammatory diseases during ART. A recent study [68] of bacterial communities in the rectal mucosa of untreated and treated HIV-1 infected individuals revealed that dysbiosis was associated with elevated levels of tryptophan catabolism and increases in multiple biomarkers of inflammation and disease progression [44].

In this part, we will do further study on the changes microbial translocation in HIV-1 infected patients. And we would like to discuss the relationship between microbial translocation changes and with or without ART.

Conclusions

In conclusion, HIV infections characteristically cause damage to the gut mucosa, injury the epithelial barrier, compromising gut immunity, and exposing its host to a broad range of microbial bio products that have been implicated in the progression of HIV. Similarly, the gut micro biota is severely impacted and the altered bacterial communities play vital roles, directly or indirectly in HIV progression. ART alone does not may effectively control microbial translocation through the gastrointestinal tract. The contribution of gut microbes in HIV disease progression has been explored but conclusive knowledge is lacking. Therefore, an increased understanding of correlations between the proinflammatory bacteria composition and structure in the human gut and HIV infection status can contribute to an improved and holistic management of HIV progression.

Further investigation is needed to firmly establish microbial translocation as a cause of HIV progression. May be we can control the progression of HIV by monitor markers of microbial translocation. It will therefore be of interest to investigate any direct or indirect links of gut microbes and microbial products in other non-AIDS related disorders such as liver, cardiovascular, central nervous system, and cancer diseases among others.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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