Microbial translocation and AIDS-associated lymphomas: crux of the problem

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In this issue of *AIDS*, Marks *et al.* [1] have reported significant associations between markers of microbial translocation and increased risk for non-Hodgkin's lymphoma (NHL) in HIV-infected individuals. The authors examined prediagnostic blood samples from NHL and non-NHL HIV-infected individuals for different markers of microbial translocation. The results show that elevated plasma levels of sCD14 associated independently with 2.5-fold increased risk for NHL. The authors used Limulus Amebocyte Lysate Assay for measuring lipopolysaccharide (LPS). As plasma/serum contains substances that interfere with the assay, the authors measured percentage recovery of LPS from each sample after spiking it with LPS. Considering the samples from which they recovered the recommended (50–200) percentage of the spiked LPS, they found significant associations of the above-median values with increased (3.0-fold) risk for NHL. These results suggest, for the first time, an etiologic role of microbial translocation across gut mucosa in lymphomagenesis in HIV-infected individuals.

Increased plasma LPS concentrations occurring in chronic HIV infection, described first in 2006 [2], result from defective intestinal barrier in the virus-infected individuals. Many factors are likely to contribute towards this defect: direct effect of HIV-1, gp-120, defective mucosal immune function due to depletion of gut-homing $\alpha4\beta7^+$ $CD4^+$ T cells in the gut mucosa, and so on [3,4]. The virus is known to replicate massively and cause depletion of $CD4^+$ T cells in the gut within the first few weeks of the infection. The virus and its products induce this defect at least in part through induction of proinflammatory mediators, for example, TNF-α, IFN-γ, IL-6, and the like. These mediators destabilize perijunctional actomyosin cytoskeleton associated with tight junctions and subjacent adherens junctions (collectively known as apical junctional complex; APC) via activating nonmuscle-myosin light chain kinase and/or rho-like kinases. The kinases disturb normal homeostatic polymerization and depolymerization (treadmilling) of F-actin. The defective junctions are accompanied by changes in the expression and spatial distribution of various junction proteins (ZO-1, claudins, occludin, E-cadheins, etc). APC defines cell polarity and controls diffusion of molecules through interepithelial (paracellular) spaces [5]. The defective APC and consequently increased paracellular permeability results in translocation of bacterial products (LPS, flagellin, DNA, etc) into body tissues and circulation. Barring some in-vitro studies, little is known about the exact defects occurring *in vivo* in APC in the intestines of HIV-infected persons. In addition to increased paracellular intestinal permeability, certain proinflammatory mediators (e.g. TNF-α) and viral proteins (e.g. Tat) cause death of intestinal epithelial cells and may result in localized denuded mucosal surfaces [6]. Bacterial products can easily diffuse through such surfaces [5]. Bacteria can also attach to the denuded surfaces and enter into body tissues. Moreover, depletion of $CD4^+$ T cells in the gut mucosa also results in defective mucosal immunity. This may lead to changes in the composition of gut flora resulting in their dysbiosis with the host, stimulating local inflammation and further

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aggravating microbial translocation. Translocated microbial products induce immune activation and systemic inflammation by activating a variety of pattern recognition receptors (e.g. toll-like receptors, retinoic acid-induced gene-like helicases, inflammasomes, etc.) expressed by different body cells. Chronic inflammation is increasingly being realized as a promoter of malignancy. It promotes tumorigenesis by inducing DNA-damaging oxidative and nitrative stress and suppressing DNA repair [7]. The main mediators of inflammation, cytokines and chemokines, play a dual role in this process. Although they suppress tumors by enhancing immune responses, they also promote them by inducing cell proliferation, angiogenesis, metastasis and genomic instability. In this context, the association between markers of microbial translocation and risk for NHL in HIV-infected individuals, demonstrated by Marks *et al.* [1], is a welcome news, and highlights the role of chronic inflammation in the cause of lymphomagenesis. Increased microbial translocation has been observed in hematological malignancies; however, it was thought to result mainly from chemotherapy [8].

HIV-induced AIDS is accompanied by increased incidence of different types of cancers including NHL, Kaposi sarcoma, invasive cervical cancer, and primary central nervous system lymphoma. Their occurrence is considered as an AIDS-defining condition. Tumor-promoting opportunistic infections like HHV-8 and Epstein–Barr virus play a role in the development of these AIDS-defining cancers. Since the advent of combination antiretroviral therapy (cART) in mid-1990s, the incidence of opportunistic infections has decreased considerably, and so has the incidence of these so-called 'AIDS-defining' cancers. However, the incidence of NHL still remains two-fold to three-fold higher in HIV-infected individuals undergoing cART [9]. Ironically, the incidence of so-called non-AIDS-defining cancers like Hodgkin's lymphoma, cancer of lung, liver, kidney, anus, skin, head and neck has, compared with the general population, increased in the cART-treated patients. The potential causes include coinfection with oncogenic viruses, tobacco and alcohol consumption, psychological stress, cART, and HIV itself [9]. In this regard, the Marks *et al.* [1] study highlights the role of defective intestinal barrier function, microbial translocation and consequently low-grade chronic inflammation in the increased incidence of these cancers. It is tempting to speculate that undetectable residual viral replication occurring in the gut mucosa is the cause of this defective intestinal barrier function. Gut mucosa is the site wherein the viral reservoir establishes itself early in the course of the infection before initiation of the therapy [10]. It would be interesting to investigate intestinal barrier function in cART-treated, HIV-infected individuals, and examine the potential role of cART as a contributing factor toward increased intestinal permeability.

In the final analysis, low-grade chronic inflammation induced by microbial translocation is the crux of the problem in increased incidence of NHL and possibly other non-AIDS-defining cancers in cART-treated HIV-infected individuals. It may also be an underlying cause in other non-AIDS ailments like frailty, premature aging, and atherosclerosis in these patients. An immediate solution to the problem lies in resorting to anti-inflammatory and intestinal permeability-enhancing measures. A longer term solution, albeit a difficult one, remains finding means of depleting residual viral reservoirs, especially from the gut mucosa.

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Conflicts of interest

The authors declare no conflict of interest

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