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Authors

Epeldegui, Marta

Hussain, Shehnaz K

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The Role of Microbial Translocation and Immune Activation in AIDS-Associated Non-Hodgkin Lymphoma Pathogenesis: What Have We Learned?

Marta Epeldegui[1], **Shehnaz K. Hussain**[2]

[1]Department of Obstetrics and Gynecology, UCLA AIDS Institute, David Geffen School of Medicine, University of California, Los Angeles;

[2]Cedars-Sinai Cancer and Department of Medicine, Cedars-Sinai Medical Center, Los Angeles

Abstract

HIV infection is associated with a greatly increased risk for the development of non-Hodgkin lymphoma (NHL). Nearly all AIDS-associated non-Hodgkin lymphomas (AIDS-NHL) are of B cell origin. Two major mechanisms are believed to contribute to the genesis of AIDS-NHL: 1) loss of immunoregulation of EBV+ B cells resulting from impaired T cell function late in the course of HIV disease, and 2) chronic B cell activation leading to DNA-modifying events that contribute to oncogene mutations/translocations. HIV infection has long been known to be associated with chronic inflammation, polyclonal B cell activation, and more recently, has been associated with microbial translocation. Microbial translocation is the leakage of bacterial products from the gut lumen into the peripheral circulation, resulting in high levels of LPS in the peripheral circulation leading to chronic immune activation and inflammation. This review aims to review recent literature linking microbial translocation to lymphomagenesis. This includes epidemiological studies of biomarkers of microbial translocation with risk of AIDS-NHL, as well as emerging data on the mechanisms by which microbial translocation may lead to AIDS-NHL development.

Keywords

Microbial Translocation; Non-Hodgkin Lymphoma; HIV

Introduction

Profound immune dysregulation, as observed in the setting of HIV infection, is a major risk factor for non-Hodgkin lymphoma (NHL). B cell lymphoma, specifically, is markedly increased among HIV infected individuals, which remains true in the current combination antiretroviral therapy (cART) era [(1)]. While AIDS-associated NHL (AIDS-NHL) remains a burdensome cancer, its etiology is not very well understood. Chronic immune activation and inflammation are hallmarks of progressive HIV infection, and are linked to several chief causes of morbidity and mortality in HIV. There is substantial evidence from prospective

Correspondence: Marta Epeldegui, University of California Los Angeles, 615 Charles Young Dr. S., BSRB 173, Los Angeles, CA, 90095-1740, mepeldegui@mednet.ucla.edu.

epidemiological studies that serologic measurements of immune markers, such as cytokines, chemokines, and soluble receptors, are altered several years prior to AIDS-NHL diagnosis, suggesting that chronic immune activation is key to lymphomagenesis (2, Hussain, 2013 #1719, 3, 4). Importantly, systemic immune activation and inflammation are dampened, but not resolved, with cART (5, 6). Several factors may be contributing to chronic immune activation in the setting of HIV infection. In recent years, it has become apparent that the gut is centrally involved in HIV infection and pathogenesis, and may be at the root of the systemic immune activation and inflammation seen in HIV, predisposing to AIDS-NHL. Not only is the gut the largest reservoir for $CD4^+$ T cells in the body (7, 8), gut dysbiosis and permeability are also increased in HIV-infected persons (9, 10). HIV infection is known to damage the gut soon after primary infection leading to reduced barrier function and leakage of bacterial products into the circulation. This microbial translocation may be an important driver of chronic immune activation. There is a growing literature reporting on the pathogenic role of microbial translocation in the setting of HIV (9, 11). Identification of pathways and biomarkers contributing to AIDS-NHL risk could help lead to strategies for prevention, early detection, or therapeutic intervention. The objective of this review is to summarize the available literature on associations between biomarkers related to microbial translocation in people with HIV, with and without NHL, and to summarize what is known regarding the mechanisms whereby microbial translocation may be contributing to lymphomagenesis.

1. Global burden of AIDS-NHL

NHL comprises several histologically heterogeneous subtypes of malignant neoplasms of lymphocyte cells. AIDS-NHL are almost always of B-cell origin, and include diffuse large B cell lymphoma (DLBCL), primary central nervous system lymphoma (PCNSL), Burkitt's lymphoma (BL), and primary effusion lymphoma. Compared to NHL in the general population, AIDS-NHL often present at a more advanced disease stage with extranodal involvement (12). AIDS-NHL continues to be the most frequently diagnosed HIV-related malignancy in the U.S. and other developed countries, even in the era of multi-agent highly active anti-retroviral therapy (HAART) (13, 14). A wide range of increased risks for lymphoma has been reported in population-based studies, depending on the population and calendar years studied (12). In the early years of the HIV epidemic, the risk of AIDS-NHL in the U.S. was >100-fold higher than the general population (15). More recent studies conducted in the U.S. and Switzerland reported elevated risks of AIDS-NHL between 10–20 fold higher than in the general population (13, 16). In the cART era, the incidence of AIDS-NHL has substantially decreased, yet remains elevated compared to the general population (1). In Italy, 500 fold higher risk to develop NHL than in the general population was reported in persons with AIDS between 1986–1996 and 90 fold higher between 1997–2004 (17).

2. AIDS-NHL pathogenesis

There are two primary putative pathogenic mechanisms responsible for AIDS-NHL (18, 19). The first involves the dysregulated proliferation of Epstein-Barr virus (EBV)-transformed B-cells where T-cell mediated regulation of B-cell growth has been impaired resulting in the development of EBV-positive AIDS-NHL subtypes. The other mechanism involves chronic B-cell activation and resultant processes that promote oncogenic mutations and

translocations. There are several B-cell activation related mechanisms. First, chronic antigenic stimulation of B-cells by HIV infection itself may promote B-cell hyperactivation and transformation leading to AIDS-NHL. B-cell genetic mutations due to chronic stimulation during other viral infections (including EBV, HPV and HCV), chromosomal rearrangements (BCL-6 and c-MYC) and deletions (6q), as well as mutations in RAS and p53 genes have been shown to be associated with chronic B-cell hyperactivation [20, 21]. Another proposed mechanism involves HIV-infected macrophages contributing B-cell stimulatory signals that result in a B-cell activation and malignant B-cell growth [22]. Lastly, the leakage of bacterial components and products from intestinal walls into the bloodstream (microbial translocation) is considered a potential cause of chronic immune activation predisposing to AIDS-NHL.

3. Microbial Translocation

Only a single layer of enterocytes forms the physical barrier separating the sterile host from the microbial biomass of gut. Tight junctions maintain a permeability seal; however, HIV-induced intestinal barrier dysfunction permits the translocation of microbial components, such as lipopolysaccharide (LPS, a potent immunogenic component of the bacterial cell membrane), into circulation [23]. The specific mechanisms that are directly responsible for intestinal permeability and microbial translocation during chronic HIV infection are unclear [24]. CD4+ T cells are depleted in the gut within the first few weeks of infection with HIV, which is accompanied by defective mucosal immunity and a proinflammatory cytokine milieu that causes enterocyte apoptosis and disrupts junctions [24–26]. Therefore, one may speculate that residual viral replication in the gut mucosa leads to defective intestinal barrier function during chronic infection.

Prior studies have identified systemic biomarkers of microbial translocation, many of which are altered in HIV infection, [27] and include: elevated levels of LPS, highly immunogenic bacterial membrane component [23], elevated sCD14, soluble form of the LPS co-receptor for TLR4 activation [28], elevated LBP, LPS binding protein which promotes binding of LPS to CD14/TLR4 [28], depleted EndoCAb, neutralizing antibodies against LPS core antigen [29], elevated FABP2, lipid transport protein and marker of enterocyte damage; [30–35] and elevated zonulin, a physiological modulator of intracellular tight junctions [36, Fasano, 2012 #1748, 37, 38]. Other serological markers may also be indicative of microbial translocation, although they are not as well-described. For example, LPS can stimulate expression of several cytokines *in vitro*, and therfore serum levels may be elevated in response to LPS translocation [39]. Also, CXCL13 is expressed by Paneth cells (key mediators of microbiome-host homeostasis) in intestinal crypts [40], and LPS can induce T follicular helper cell expression of CXCR5, the sole receptor for CXCL13. Thus, elevated CXCL13 in the serum may be an indicator of LPS exposure.

4. Molecular Epidemiology: Biomarkers of Microbial Translocation and AIDS-NHL

A few key epidemiological studies have provided the basis for our understanding of the role of microbial translocation in AIDS-NHL development. These are prospective cohort studies with pre-AIDS-NHL diagnostic specimens.

In one study, a nested case–control was conducted within four cohorts of HIV-infected individuals [41], including the District of Columbia/New York gay men's cohort (DCG) [42], the Multicenter Hemophilia Cohort Studies I and II (MHCS I and MHCS II) [43, 44], and the AIDS Cancer Cohort Study (ACC) [45]. The study included 56 incident AIDS-NHL cases ascertained through active follow-up and pathologic confirmation, which were matched to 190 HIV-infected controls on age, sex, race, CD4, parent cohort, and specimen type (plasma vs serum).

In another study, a nested case-control study was conducted within the Multicenter AIDS Cohort (MACS), a prospective cohort study of the natural and treated history of HIV/AIDS in men who report sex with men [46–48]. Pre-diagnostic serum specimens were analyzed in 200 HIV-infected men who developed pathologically confirmed AIDS-NHL diagnosis (average of 4 years prior to diagnosis), and 200 HIV-infected controls matched on CD4+ T cell count, prior antiretroviral drug use, and recruitment year into the cohort.

LPS: In the four cohorts study, the *Limulus* amoebocyte lysate assay was used to measure LPS. In order to address the technical challenges posed by substances inherent to archival serum and plasma that interfere with the assay, the percentage recovery of LPS from each sample after spiking it with LPS was measured and samples were only included if recovery was at the recommended 50–200% of the spiked LPS. In a subgroup analysis, the authors reported that elevated LPS levels were significantly associated with a three-fold increased risk of AIDS-NHL [41].

sCD14, the soluble form of the LPS co-receptor CD14, is produced by macrophages after exposure to LPS and other inflammatory activators [49, 50]. In the four cohorts study, levels of sCD14 greater than or equal to 1.76 ×106 pg/ml (median value in controls) were associated with a 2.7-fold increased risk of AIDS-NHL [41]. In the MACS study, which had more cases/controls and a longer lag time from specimen collection to AIDS-NHL diagnosis, sCD14 was also strongly associated with AIDS-NHL (3.71-fold increased risk for each unit increase on the natural log scale) [48]. In the MACS, sCD14 was more strongly associated with primary central nervous system lymphoma (PCNSL) than systemic lymphoma. PCNSL is an aggressive presentation of AIDS-NHL believed to arise primarily due to the oncogenic properties of uncontrolled EBV reactivation in severely immunocompromised individuals. Furthermore, sCD14 was more strongly associated with AIDS-NHL when measured close to the diagnosis date (< 4 years). This observation is consistent with the hypothesis that microbial translocation is a consequence of compromised gut immunity (lower CD4+ T cell count), which occurs close to the time of AIDS-NHL diagnosis [51].

LBP is an LPS binding protein which promotes binding of LPS to its receptor. In the four cohorts study, LBP was not found to be significantly associated with AIDS-NHL [41]. In the MACS, LBP was strongly associated with subsequent AIDS-NHL diagnosis, with a 2.97-fold increased risk for each unit increase on the natural log scale [48]. As was seen with sCD14, LBP was more strongly associated with AIDS-NHL when measured close to AIDS-NHL diagnosis date.

EndoCAb: Prior research suggests that HIV-infection impairs EndoCAb response, a neutralizing antibody against LPS [52]. As one would expect, EndoCAb levels are inversely associated with LPS levels [23]. In the four cohorts study, EndoCAb was not associated with AIDS-NHL [41]. In the MACS study, participants with the highest versus lowest quartile of EndoCAb levels were at a 2-fold reduced risk of AIDS-NHL, with consistent associations across lag times from blood collection to AIDS-NHL diagnosis, and between systemic lymphoma and PCNSL [48]. The observed inverse association between EndoCAb levels and AIDS-NHL risk is consistent with the notion that LPS in circulation among HIV-infected persons at risk for AIDS-NHL depletes circulating EndoCAb, further supporting the hypothesized role of microbial translocation in ARL.

FABP2 and Haptoglobulin.—FABP2 (a lipid transport protein and marker of enterocyte damage) and haptoglobin (a physiological modulator of intercellular tight junctions) are markers of loss of integrity and structural damage to the gastrointestinal barrier. In the MACS study, a significantly increased risk for AIDS-NHL risk was observed only among participants with the highest levels (4th quartile), for both of these markers [48].

5. Mechanisms relating microbial translocation, B cell activation, and ARL

HIV infection has long been known to be associated with chronic, polyclonal B cell activation [5, 19, 53–61]. This is of great pathogenetic importance, as this chronic B cell activation contributes both to the genesis of AIDS-NHL [18, 19, 62], as well as to B cell dysfunction that impairs the generation of *de novo* antibody responses [61, 63–65], and potentially, to the ongoing growth of AIDS-NHL tumors [66]. Several features of HIV infection may contribute to this chronic B cell activation, including ongoing antigenic stimulation by HIV and other pathogens [56], dysregulated cytokine production [58, 59, 67, 68], and direct polyclonal (non-antigenic) stimulation of B cells by HIV [19, 54, 60, 69–72] and microbial translocation [48].

The development of BL and DLBCL is believed to occur due to B cell activation since the molecular lesions seen in BL and DLBCL result from errors that occur in activated B cells. Of particular importance are the DNA-modifying events that contribute to oncogene mutations and translocations, such as errors in immunoglobulin heavy chain gene (*IGH*) Class Switch Recombination (CSR) and Somatic Hypermutation (SHM) [18, 19, 73]. The association of chronic B cell activation and B cell NHL is not restricted to HIV+ persons, as autoimmunity that is associated with chronic B cell activation [74], as well as B cell activation driven by chronic infection (*Helicobacter pylori*, hepatitis C virus) [75, 76], are associated with a marked increase in risk for B cell lymphoma. Therefore, the molecular events that occur normally following activation of B cells place these cells at risk for molecular mistakes that can lead to NHL. In essence, more B cell activation = higher risk for NHL.

The hallmark of BL is the *MYC:IgH* translocation which results from an error in *IgH* CSR, a somatic DNA recombination event that occurs normally in germinal center (GC) B cells and requires double-strand DNA breaks, which shift the variable region from μ to another Ig heavy chain gene (γ, α, ε). Similarly, the mutation and/or translocation of *BCL6* that is seen

in DLBCL occurs during the process of Ig SHM [77–79], another GC B cell DNA-modifying process which normally results in the generation of antibodies with enhanced binding affinity for antigen.

Both *IGH* CSR and SHM are mediated by activation-induced cytidine deaminase (AICDA) [80–83], a DNA-mutating enzyme [84] which is induced in B cells by immune stimulatory molecules. AICDA expression is driven by exposure of B cells to cytokines and/or immune stimulatory molecules on helper T cells. In fact, AICDA activity is required for myc:IgH translocations [85] and the genesis of NHL [86]. In a molecular epidemiological study, AICDA expression in B cells was observed over a period of several years preceding the development of AIDS-NHL of the BL/DLBCL subtypes, confirming the important role of AICDA in AIDS-NHL development [87].

While the important role of AICDA in AIDS-NHL has been demonstrated, it is less clear how AICDA expression is induced. Several studies have reported that *in vitro* EBV infection results in AICDA expression and in the accrual of oncogene mutations [88, 89]. Moreover, HIV virions can directly interact with B cells leading to markers of B cell activation such as CD10 and AICDA expression [71, 90]. Therefore, both EBV and HIV can directly induce AICDA. AICDA expression induced by EBV infection is mediated by the expression of LMP1, an EBV-encoded ortholog of human CD40, which is expressed by EBV-infected B cells [88]. On the other hand, AICDA expression by B cells driven by HIV is due, in part, to the interaction of CD40L on virions with CD40 on B cells [71, 90]. CD40L is incorporated in the envelope membrane of HIV virions, since HIV virions acquire T cell surface membrane molecules when they bud out of infected cells [91]. Therefore, HIV virions expressing CD40L can activate B cells through CD40L:CD40 interactions, leading to AICDA expression [71, 90]. Additionally, B cells activated by CD40L virions also secrete cytokines, such as IL-10, which may promote B cell activation and lymphomagenesis [71]. HIV gp120 may also induce AICDA expression, by itself or in combination with other cytokines, such as IL-10 and IL4, both of which are known to be elevated prior to AIDS-NHL [92].

Another possibility is that AICDA is induced by the inflammatory response to microbial translocation, which includes CpG, IL-10 and other inflammatory cytokines. In mouse models, LPS has been shown to induce AICDA expression by B cells, which may also be the case in humans [93]. Therefore, microbial translocation has the potential to induce AICDA expression by B cells, which leads to *IgH:MYC* translocation and *BCL-6* rearrangements, leading to AIDS-NHL development.

6. Mechanisms relating microbial translocation, B regulatory cells and ARL.

B regulatory cells (Bregs) are a subpopulation of B cells that have regulatory functions contributing to tolerance and modulating inflammatory responses and T cell function [94, 95]. Bregs are analogous to T regulatory cells and characteristically secrete IL10 and are $CD24^{++}$ $CD38^{++}$ [94, 95]. Bregs can also exert regulatory function, express the program cell death-1 ligand (PDL1) and can regulate T cells through IL-10 expression and also through PD1:PDL1 interactions [95]. B regulatory cells (Bregs) are elevated prior to AIDS-NHL [96, 97]. Therefore, Bregs that express PDL1 have the potential to contribute to lymphomagenesis in multiple ways, by: 1) enhancing B cell activation through IL-10, a B

cell stimulatory cytokine, 2) enhancing B cell viability, via PDL1 signaling, and 3) inhibiting T cell function, including that of cytotoxic T cells (CTL), through the effects of IL-10 and PD1:PDL1 interactions [98]. CTL are involved in the immunoregulation of EBV infected B cells as well as HIV-infected cells, including CD4 T cells.

$PDL1^+$ B cells ($CD19^+PDL1^+$) are elevated prior to AIDS-NHL diagnosis [96]. Bregs can express PDL1 and $CD19^+PDL1^+$ B cells appear to be a subpopulation of Bregs [96]. Additionally, exposure to HIV virions expressing CD40L can modestly induce the expression of PD-L1 on B cells, as well as IL-10 secretion, suggesting a mechanism for how $PDL1^+$ B cells may arise. Recent studies have shown that HIV can directly induce a Breg-like immunosuppressive phenotype ($CD19^+CD24^{++}CD38^{++}$). Additionally, LPS can enhance the induction of Bregs in combination with HIV and CD40L: Lopez-Abente and co-workers showed that LPS ,in combination with HIV, not only induced a Breg phenotype but also induced PDL1 expression on B cells [99]. Together, this suggests that microbial translocation, in the context of HIV infection, may be inducing B cells to express PDL1, a population that is elevated prior to AIDS-NHL diagnosis. It is important to note that AIDS-NHL tumor cells express PD-L1 and that the expression of PD-L1 on tumor cells can allow such cells to evade immune surveillance. Together, these findings lead us to speculate that the induction of PD-L1 on B cells, driven by microbial translocation in HIV infection, may be an early event driving lymphomagenesis.

Future perspectives

There is a growing body of literature on microbial translocation biomarkers and mechanisms of pathogenesis as they relate to NHL development in the setting of HIV. However, several outstanding questions remain. Prior studies have demonstrated that serum levels of several immune markers, including markers that would be expected to be elevated in response to LPS, not are normalized in HIV-infected participants following cART therapy [100]. It is possible that HIV suppression dampens microbial translocation and subsequent immune activation, yet this has not been studied directly in relation to AIDS-NHL risk. Furthermore, microbiome changes are known to occur in the relation to HIV infection status, HAART exposure, and viral suppression; as a common theme, there is a decrease in diversity and abundance of commensal ‘anti-inflammatory’ taxa in HIV-infected, HAART-naïve, and viremic persons [10, 101–105]. Dysbiosis exacerbates microbial translocation [106, 107]; however, microbiome composition or diversity has not been previously studied in relation to microbial translocation and AIDS-NHL development. Additionally, certain bacterial metabolites are linked to intestinal permeability and systemic inflammation by LPS, yet the association between metabolites and AIDS-NHL has not been previously reported. Moreover, biomarkers of microbial translocation may not only be markers of AIDS-NHL risk, but they may also have prognostic value. Further study of the prognostic value of biomarkers of microbial translocation may provide insights relevant to choosing optimal treatment strategies for AIDS-NHL.

There is a growing body of evidence showing that microbial translocation is associated with lymphomagenesis; however, the mechanism/s by which microbial translocation contributes to lymphomagenesis are still unclear. It has been shown that LPS can induce, in combination

with other factors, B cells activation [71, 92, 99]. However, it has not been demonstrated whether it also induces *AICDA* expression, and subsequently, SHM and CSR events that will ultimately lead to the molecular lesions characteristic of AIDS-NHL (*IgH:MYC* translocations and *BCL6* rearrangements).

Moreover, it has been demonstrated that PDL1 expression is elevated in B cells prior to AIDS-NHL diagnosis and that this expression may be induced by both microbial translation and HIV virions [96, 99]. However, the role of these $PDL1^+$ B cells in AIDS-NHL development is unclear. One possibility is that $PDL1^+$ B cells present in circulation prior to AIDS-NHL diagnosis are pre-tumor cells, since AIDS-NHL tumors express PDL1[108]. Expression of PDL1 would confer on these cells the ability to inhibit T cell function, which will give them a growth advantage by allowing them to evade immune responses. Moreover, PDL1 expression may be conferring to these cells unknown properties that need to be defined. For example, it will be important to determine whether $PDL1^+$ B cells express AICDA. Addressing these questions will be of great relevance, as this will provide new insights on the pathogenesis of AIDS-NHL, as well as for new therapeutic and diagnostic strategies.

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Abbreviations:

NHL	non-Hodgkin lymphoma
AIDS-NHL	AIDS-associated Non-Hodgkin Lymphoma
cART	combination antiretroviral therapy
DLBCL	diffuse large B cell lymphoma
PCNSL	primary central nervous system lymphoma
BL	Burkitt’s lymphoma
IGH	immunoglobulin heavy chain gene
CSR	Class Switch Recombination
SHM	Somatic Hypermutation
AICDA	activation-induced cytidine deaminase
GC	germinal center

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