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Immune Activation: Contribution to AIDS-Associated Non-Hodgkin Lymphoma

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Abstract

HIV infection is associated with a greatly elevated risk for the development of non-Hodgkin lymphoma (NHL), which while diminished, remains elevated in the highly active antiretroviral therapy (HAART) era. Chronic B cell activation, driven by contact with HIV virions, B cell-stimulatory cytokines, viruses (EBV, HPV, HCV), and by high levels of antigenic stimulation occurs in HIV infected persons, and it is seen at even higher levels in those who go on to develop AIDS-NHL. Evidence from multiple studies indicates that elevated serum levels of several B cell-stimulatory cytokines and biomarkers are seen preceding AIDS-NHL, as well as in immunocompetent persons that develop NHL. Phenotypic changes in circulating B cells also are seen preceding AIDS-NHL, including the expression of AICDA, and of cell-surface molecules and miRNA that are associated with activated B cells. HAART only partially normalizes the immune system of treated HIV^+ persons as they still show clear evidence for ongoing inflammation and immune activation in, even those who show complete suppression of HIV viremia. Together, this provides ample evidence to support the notion that chronic activation of B cells contributes to the genesis of B cell lymphomas.

Keywords

AIDS; HIV; immune activation; lymphoma; NHL

I. INTRODUCTION

The development of cancer is often associated with infection with oncogenic viruses, immunodeficiency, or with immune dysfunction characterized by the chronic activation of some components of the immune system. In infection with the human immunodeficiency virus (HIV) and the acquired immunodeficiency syndrome (AIDS), where all three of these factors are present, one of the most common cancers that develops is non-Hodgkin B cell lymphoma (NHL).

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NHL has long been recognized as an AIDS-associated cancer, with initial reports of NHL in persons with AIDS published in 1984.[1,2] Before the availability of highly active antiretroviral therapy (HAART), NHL was the second most common cancer seen in AIDS patients, following Kaposi's sarcoma (KS) in incidence.[3] The risk of developing lymphoma was 60 times greater in HIV-positive persons than in the general population.[4–6] Unlike KS, which was most frequent among homosexual men, NHL was widely distributed among AIDS patients,[7] suggesting that environmental factors were not as important in this malignancy.[3,8] Since the introduction of HAART, the incidence of AIDS-associated KS (AIDS-KS) has decreased markedly but the impact of HAART on AIDS-associated NHL (AIDS-NHL) has not been as great. AIDS-NHL is now the most common cancer in AIDS patients in the United States and other countries in which HIV-positive persons have access to HAART.[9–12] While the incidence of AIDS, and AIDS-NHL, has decreased with HAART, AIDS-NHL is still a significant clinical problem, accounting for 23–30% of AIDS-related deaths in developed countries.[13–16] The availability of HAART appears to have had differential effects on the incidence of the different AIDS-NHL subtypes; on one hand, the incidence of primary central nervous system lymphoma (PCNSL) has decreased significantly, while the incidence of other AIDS-NHL subtypes, such as Burkitt's lymphoma (BL) or diffuse large B cell lymphoma (DLBCL), has either decreased modestly or remained unchanged.[17] This probably reflects the etiology of these cancers. PCNSL are believed to develop due to the loss of immune control of Epstein-Barr virus (EBV) infected cells, while the development of BL and DLBCL is more likely due to HIV infection-associated chronic B cell activation.[18–21]

John Fahey's research group at UCLA in the 1980s was not only one of the first to identify and characterize AIDS, the first reported cases of which were seen at UCLA in the early 1980s,[22,23] but also, early on, recognized that chronic immune activation and inflammation was a hallmark of HIV infection and AIDS. This included work that documented B cell activation,[24–26] and T cell activation, in HIV/AIDS, as well as the overproduction of inflammation-associated cytokines, including interleukin (IL)-6, tumor necrosis factor alpha (TNFa), and interferon-gamma (IFNg),[24,25,27–29] and biomarkers of inflammation, such as neopterin,[30,31] One of us (O.M.M.) was focusing on the study of B cell activation and the production of B cell-stimulatory factors in HIV/AIDS in the mid-1980s; discussions with John Fahey at that time led us to explore the role of B cell dysfunction in the pathogenesis of AIDS-NHL. These initial discussions with John led to much of our work over the subsequent 25 years, including the work that is covered in this review. His seminal role HIV/AIDS research, as well as his ongoing mentorship, encouragement, and friendship, are greatly appreciated.

II. INFECTION WITH EPSTEIN-BARR VIRUS (EBV), B CELL ACTIVATION, AND LYMPHOMAGENESIS

There are two major mechanisms that are thought to lead to the development of lymphoma in HIV infected individuals: (i) loss of immunoregulatory control of EBV infected B cells[32–34] and (ii) chronic B cell activation.[16,19,35] EBV has both B cell-stimulatory effects as well as direct oncogenic potential.

The mechanism by which NHL develops may be related to lymphoma subtype since PCNSL are all EBV^+ and typically occur in persons who have very low numbers of circulating CD4 T cells and are severely immunodeficient.[32] Therefore, these cancers are thought to arise due to the loss of immunoregulatory control of EBV-infected B cells, which allows the uncontrolled growth of EBV-infected B cells, allowing the accumulation of genetic lesions that result in NHL. Interestingly, infection of B cells with EBV leads to the ongoing expression of activation-induced cytidine deaminase (AICDA),[36,37] a DNA-mutating enzyme that mediates normal DNA-modifying events in activated B cells, immunoglobulin gene (Ig) somatic hypermutation (SHM), and class switch recombination (CSR),[38,39] but which is also centrally involved in lymphomagenesis.[40–44] As might be expected, after the introduction of HAART, which restores T cell immunity, the incidence of EBV^+ NHL (mainly PCNSL) has decreased markedly.[45]

Chronic B cell activation not driven by EBV infection can also result in errors in SHM and CSR, leading to oncogenic lesions, such as *Ig*:*c-MYC* chromosomal translocations and/or mutations in proto-oncogenes.[46] Many BL and DLBCL are not infected with EBV, and these cancers often arise in persons who have relatively high levels of CD4 T cells, and are presumably not profoundly immune deficient.[21] In addition to the loss of $CD4^+$ T cells, HIV infection is also characterized by chronic immune activation. More concretely, there is a marked increase in B cell activation in HIV infection,[47] especially in those individuals who go on to develop NHL,[31,48,49] which may be driven by multiple factors, including the overproduction of B cell-stimulatory cytokines, such as IL-6 and IL-10,[31,48] as well as by the direct stimulation of B cells by HIV, and the antigenic and polyclonal activation of B cells by other microbial agents.[50–52] Interestingly, recent studies indicate that while HAART can restore functional T cell immunity, HAART does not lead to the normalization of the chronic immune activation and inflammation that is seen in HIV infection, with elevated levels of cytokines and biomarkers of inflammation and immune activation seen to persist in those receiving HAART, even those who have optimal control of HIV infection.[53,54] This ongoing B cell activation is believed to lead to lymphomagenesis by driving the chronic AICDA expression and activity.[55]

It is important to note that the presence of B cell activation leading to NHL development is not exclusive to those persons who have HIV infection, as also it has been observed that B cell activation associated with autoimmunity,[56] or chronic infections other than HIV (e.g., hepatitis C, *H. pylori*),[57,58] increases the risk for the development of NHL. Hence, it seems that chronic B cell activation can lead to lymphomagenesis, not only in HIV infection, but in other settings as well.

III. ROLE OF IMMUNE ACTIVATION IN AIDS-NHL: EPIDEMIOLOGICAL EVIDENCE

Various factors associated with B cell activation, including B cell-stimulatory cytokines (IL-6, IL-10, TNFa, CXCL13, IP10/CXCL10), as well as soluble receptors [soluble (s) CD23, sCD27, sCD30, sCD44], and Ig free-light chains (FLC) and inflammation (neopterin) have been seen to be associated with risk for AIDS-NHL, in nested case:control studies done

in the Multicenter AIDS Cohort Study (MACS) and the Women's Interagency HIV Study (WIHS).[31,49,59] Other researchers have also reported increased cytokines[60,61] or B cell activation markers (FLC)[62] pre-AIDS-NHL diagnosis. Most recently, Vendrame et al. looked at TH1, TH2, and TH17/T follicular helper cells (TFH) cytokines, using multiplexed (Luminex platform) assays, during the one to five years preceding AIDS-NHL diagnosis in 180 AIDS-NHL cases in the MACS.[31] In these studies, elevated serum levels of TH17/TFH cytokines (IL-6, TNFa, CXCL13, IP10) were seen preceding AIDS-NHL, along with unchanged or decreased levels of TH1 (IL-12) and TH2 (IL-4) cytokines. TFH cells are B cell-interacting helper cells that are found in germinal centers, and are characterized by the production of CXCL13 and other B cell-stimulatory cytokines, and by the expression of CXCR5, the receptor for CXCL13.[63–65] The notion that TH17/TFH cytokines are elevated prior to NHL diagnosis is intriguing, as these cytokines, in addition to supporting B cell activation, also would be expected to shape the phenotype of $CD4^+$ T cells, as some of these (IL6) have the capability to induce a TFH phenotype in $CD4^+$ T cells. This is even more relevant, since TFH have been recently described in different reports as one of the major cell reservoirs of HIV.[66,67] Hence, the notion that TFH are present at higher numbers in chronically infected individuals raises the possibility that chronic B cell activation may be contributing to the survival of this specific $CD4^+$ T cell subset, which is a major HIV reservoir, as most other types of $CD4^+$ T cells die on infection with HIV.

Additionally, we observed that elevated serum levels of Ig free light chains (FLC), a marker for B cell activation, are associated with risk for AIDS-NHL, confirming prior work by Landgren et al.[62] FLC are also elevated in autoimmune diseases, such as rheumatoid arthritis and Sjögren's syndrome, and correlate with other B cell activating factors.[68] Interestingly, the risk for developing NHL is greatly elevated in people with Sjögren's syndrome,[69] as well as in those who have other forms of autoimmunity that involve chronic B cell activation,[56] providing additional evidence that chronic B cell activation may contribute to the genesis of lymphoma.

Risk for NHL in HIV-uninfected persons also has been seen to be associated with elevated pre-diagnosis levels of B cell stimulatory cytokines (e.g., CXCL13, IL-10, TNFa, IL-2) and immune activation biomarkers (sCD23, sCD27, sCD30, sCD44, sTNFR1, sTNFR2, sVEGF2, ICAM, sIL-2R) in several cohort-based studies,[70–80] suggesting that the immune system changes that precede the appearance of B cell NHL in presumably immunocompetent persons echo those seen preceding the diagnosis of AIDS-NHL.

Genetic polymorphisms in genes encoding B cell-stimulatory molecules, or their receptors, have also been seen to be associated with risk for AIDS-NHL. In prior work, an *IL-10* polymorphism associated with elevated cytokine production was seen to be associated with AIDS-NHL.[81] More recently, Hussain et al.[59,82] showed that genetic variation in *CXCL13* and its receptor, *CXCR5*, was associated with risk for AIDS-NHL.[49] Interestingly, a recently published International Lymphoma Epidemiology Consortium (InterLymph) pooled analysis of genome-wide association studies showed that a single-nucleotide polymorphism near *CXCR5*, rs4938573, was highly associated with risk for follicular lymphoma, a form of B cell NHL.[83] Together with multiple independent cohort studies that have identified serum

levels of CXCL13 as a risk factor for NHL, this provides additional support for a role for this B cell-stimulatory chemokine in the genesis of B cell NHL.

It is interesting to note, in this context, that inhibition of CXCL13:CXCR5 binding prevents the growth of an AIDS-associated BL cell line (2F7) in immune deficient mice implanted with these tumors, which also show greatly elevated levels of murine, but not human, CXCL13 in their circulation.[84] Additionally, high plasma levels of CXCL13 were seen to be associated with a poorer clinical outcome in an AIDS Malignancies Consortium trial of AIDS-NHL with chemotherapy plus rituximab.[85] Therefore, the CXCL13:CXCR5 axis may be playing a role in supporting the growth of established NHL cells, as well as in driving B cell activation leading to lymphomagenesis.

In addition to soluble factors in serum/plasma, we have observed in a small study done in the MACS that *AICDA* expression is present more commonly in those individuals who go on to develop AIDS-NHL.[55] Interestingly, detectable *AICDA* expression was observed to be elevated in PBMCs of AIDS-NHL individuals of non-CNS origin, but not in those who developed PCNSL (EBV-positive).[86] More recently, this has been confirmed and extended by assessing pre-AIDS-NHL *AICDA* expression in B cells isolated from all MACS AIDS-NHL cases (unpublished results). AICDA is a DNA-mutating enzyme that is normally expressed in germinal center (GC) B cells and is essential for CSR and SHM.[38,39] As mentioned above, errors in *Ig* CSR and SHM may lead to lymphomagenesis.[43,46,87,88] Therefore, aberrant expression of *AICDA* would be expected to increase risk for the development of B cell lymphomas.

Phenotypic changes, other than elevated AICDA expression, have been observed on circulating B cells preceding AIDS-NHL diagnosis. In a recent study in the MACS,[51] Guo and coworkers noted an elevated fraction of B cells expressing CD10, CD71, and CD86 in those who went on to develop AIDS-NHL. *AICDA* expression was detected in some who developed AIDS-NHL, but not in HIV^+ or HIV-negative controls. Other recent studies assessed micro-RNA (miRNA) expression in circulating B cells preceding AIDS-NHL diagnosis, finding that miR-21 was significantly elevated in peripheral B cells of HIV-infected individuals who went on to develop AIDS-NHL.[89] Moreover, miR-21 was found to be overexpressed in activated B cells, including GC-like and memory B cells, as well as B cells activated by CD40 or immunoglobulin M co-stimulation, and lipopolysaccharides, suggesting that miR-21 may help maintain B cell hyperactivation, thereby contributing to lymphomagenesis.[89] Together, these studies indicate that an activated, GC B cell-like phenotype is present in a subset of circulating B cells preceding AIDS-NHL diagnosis. The role of these phenotypically aberrant B cells in lymphomagenesis remains to be elucidated.

Overall, there is ample support for the notion that B cell hyperactivation is associated with HIV infection, and particularly that elevated levels of B cell stimulatory factors precede the appearance of AIDS-NHL, especially those subtypes that are not associated with EBV infection.

IV. FACTORS THAT DRIVE B CELL ACTIVATION IN HIV INFECTION

As mentioned earlier, chronic B cell activation associated with HIV infection appears to contribute to the development of lymphoma. At first glance, one might conclude that HIV virions themselves induce B cell activation, since it has been found that other viruses, such as EBV,[90–93] human papillomavirus (HPV),[94] and HCV,[95] can directly activate B cells. Additionally, it has been shown that the cumulative duration of HIV viremia is predictive of AIDS-NHL development,[86] underscoring the potential relevance of the ongoing presence of HIV virions in B cell activation leading to the development of AIDS-NHL. In fact, there is growing evidence that HIV virions can contribute to B cell activation via direct interactions with B cells. Early observations that HIV virions could lead to B cell activation were reported by Schnittman et al.,[96] but it was unclear how HIV was mediating this activation. Recent reports have shown that HIV gp120 has the capability to induce B cell activation: CSR, interleukin secretion, and *AICDA* expression were seen to be induced by exposure to gp120, which interacted with DC-SIGN on B cells.[97] In a similar manner, HIV tat seems to be involved in lymphomagenesis in mice: tat expression in lymphoid tissue of transgenic mice promoted the development of B cell lymphoma, as well as the production of B cell-stimulatory, lymphoma-associated cytokines, such as IL-6 and IL-10.[98] Additionally, it was recently shown that the expression of the pNL4-3 HIV-1 provirus lacking parts of *gag-pol* in a HIV transgenic mice leads to B cell activation and expression of B cell stimulatory cytokines, and ultimately to lymphoma development.[99]

Martin et al. showed that CD40 ligand (CD40L/CD154), which is normally expressed on the surface of activated T cells, was incorporated into HIV virions, and could stimulate B cells via its interactions with CD40, leading to interleukin secretion.[100] In agreement with this, we and others have shown that CD40L incorporated into HIV virions could induce B cell activation, including the expression of AICDA in B cells,[50,52] with the potential to induce *IgH* CSR and SHM, as well as other oncogenic changes. More specifically, HIV virions engineered to express CD40L, but not CD40L-negative virions, induced *AICDA* expression at the mRNA and protein level. These AICDA-positive cells also displayed B cell surface activation markers, such as CD71 and CD10.[50] This is of great importance, since AICDA is expressed in activated GC B cells, where CSR and SHM occur, and it has been seen that GC cells that express AICDA also express cell surface CD71.[101] Additionally, $CD40L^+$ virions also induced the expression of ICAM-1 and CD80, a co-stimulatory molecule for T cells.[102] Hence, CD40L incorporated into HIV virions can directly activate B cells through CD40, inducing AICDA and CD71 expression, rendering them phenotypically similar to GC B cells, and presumably placing these cells at greater risk for acquiring lymphomagenic molecular changes. We and others also observed that these B cells, in addition to having an activated phenotype, also secrete B cell-activating cytokines, including IL-6, IL-8, IL-10, CCL17, CCL22, CCL17, and GM-CSF.[50,52] Therefore, simulation of B cells with $CD40L^+$ virions has the potential to lead to activation of T cells via these cytokines and chemokines, as well as via direct B:T cell interactions, maybe even leading to a TFH phenotype, as suggested earlier.

It is also important to note that $CD40L^+$ virions are inducing IL-10 expression by B cells. IL-10 expression is characteristic of a specific population of B cells with regulatory

function, which have been termed “regulatory B cells” (Bregs), a B cell subset that has been recently recognized. Bregs are analogous to regulatory T cells (Tregs), which are T cells that can dampen adaptive immune responses via the secretion of inhibitory cytokines, such as IL-10 and TGFb. Bregs require the interaction of CD40L and CD40, expressed on T and B cells, respectively, to function. Recently it was shown that HIV^+ persons, even those who are on HAART, display high levels of IL-10 expressing B cells and that Bregs from HIV^+ individuals can suppress CD8 function in an IL-10 dependent manner.[103] Therefore, it is interesting to consider that $CD40L^+$ HIV virions may, in addition to stimulating B cells toward a GC-like phneotype, also induce Bregs expressing IL-10, which may modulate other immune cell subsets, including T cells.

The HIV envelope membrane contains various types of proteins with diverse functions including adhesion molecules, MHC molecules, B cell markers, T cell markers, and macrophage surface proteins.[104] Among this varied spectrum of HIV membrane-incorporated molecules, it is important to identify other proteins that activate B cells, and thereby potentially contribute to lymphomagenesis. Interesting candidates include CD4, as it has been shown to be present on HIV envelope,[105,106] and CD4-positive virions could potentially bind MHC class II molecules, whose signaling can activate B cells,[106,107] as well as molecules in the TNF super-family other than CD40L, or other transmembrane proteins with stimulatory potential, such as CD80 and CD86.[108] Both CD80 and CD86 interact with CD28, a potent lymphocyte stimulator, normally present on T cells, but also expressed by EBV-positive B cell lines,[109] representing a potential additional pathogenetic mechanism in EBV-induced lymphomagenesis. Clearly, it is of great interest to identify which other proteins may be incorporated in HIV virions, as any B cell-stimulating and/or immunomodulating transmembrane proteins expressed by HIV-infected cells could be incorporated into the HIV envelope and contribute to B cell activation and to lymphomagenesis.

Another potential source of chronic B cell activation in the setting of HIV infection is microbial translocation, the translocation of microbial products from the gut lumen into the circulation, a process that is central to the immunopathogenesis of HIV/AIDS.[110,111] There is ample evidence from multiple cohort-based studies that elevated levels of inflammatory, B cell-stimulatory cytokines, such as IL-6, IL-10, TNFa, IP10, and CXCL13, are seen for several years preceding AIDS-NHL diagnosis.[31,48] The factors that drive the production of these inflammatory cytokines are not completely understood. However, it is probable that microbial translocation contributes to this ongoing cytokine overproduction, as microbial molecules, including lipopolysaccharide and other toll-like receptor (TLR) ligands are known to potently stimulate cytokine production by macrophages and other immune system, and nonimmune system, cells.[51,112,113] Additionally, we have seen that exposure of human B cells to TLR ligands (TLR2 ligand) led to the development of a GC-like B cell phenotype, similar to that seen preceding the development of AIDS-NHL.[51,113]

Therefore, HIV infection-associated microbial translocation, driving the production of these B cell-stimulatory cytokines, may be contributing to the risk for the development of AIDS-NHL. In fact, one epidemiological study has provided some support for this notion, showing that markers of microbial translocation were associated an increased risk for AIDS-NHL.[114]

We are currently examining this issue in a larger study based in the MACS, where we will quantify several markers for microbial translocation, inflammation and immune activation markers, and risk for developing AIDS-NHL.

V. CONCLUSIONS

HIV infection is associated with a greatly elevated risk for the development of NHL, which is only partially decreased by HAART. Chronic B cell activation, driven by contact with HIV virions, B cell-stimulatory cytokines, exposure to viruses (EBV, HPV, HCV), and by high levels of antigenic stimulation, occurs in HIV-infected persons, and is seen at elevated levels preceding the development of AIDS-NHL. Evidence from multiple cohort studies indicates that elevated serum levels of several B cell-stimulatory cytokines and biomarkers are seen preceding AIDS-NHL, as well as NHL that occur in presumably immunocompetent persons. Phenotypic changes in circulating B cells also are seen pre-AIDS-NHL, including the expression of cell-surface molecules and miRNA that are associated with GC B cells or activated B cells. HAART only partially normalizes the immune system of treated HIV^+ persons, with clear evidence for ongoing inflammation and immune activation in HAART recipients, even those who show complete suppression of HIV viremia. Together, this suggests that therapeutic strategies that dampen this ongoing, post-HAART immune activation, such as the use of anti-inflammatory drugs (i.e., statins, aspirin, non-steroidal anti-inflammatory drugs), or even neutraceuticals that inhibit inflammation (e.g., curcumin, green tea extract), in addition to HAART, may reduce risk for the development of AIDS-NHL. Additionally, different HAART regimens may have differential effects on post-HAART inflammation, as might the earlier initiation of HAART. Further research on this topic is needed to determine if residual post-HAART inflammation can be dampened, and if this leads to a decrease in the incidence of AIDS-NHL and other cancers.

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(NIH), Johns Hopkins ICTR, or NCATS. The MACS website is located at http://www.statepi.jhsph.edu/macs/macs.html.

ABBREVIATIONS

AICDA	Activation induced cytidine deaminase
AIDS	acquired immune deficiency syndrome
BL	Burkitt's lymphoma
Breg	B regulatory
CD	cluster of differentiation
CSR	class switch recombination
DLBCL	diffuse large B cell lymphoma
EBV	Epstein-Barr Virus
FLC	free light chain
GC	germinal center
HAART	highly active antiretroviral therapy
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPV	human papilloma virus
IFNg	interferon gamma
Ig	immunoglobulin
IL	interleukin
KS	Kaposi's sarcoma
MACS	Multicenter AIDS Cohort Study
miR	micro-RNA
NHL	non-Hodgkin lymphoma
PCNSL	primary central nervous system lymphoma
SHM	somatic hypermutation
TFH	T follicular helper
TNFa	tumor necrosis alpha
Treg	T regulatory

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