



Virus-driven dysregulation of the BCR pathway: a potential mechanism for the high prevalence of HIV related B-cell lymphoma

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Abstract

In people living with HIV (PLWH), the susceptibility to malignancies is notably augmented, with lymphoma emerging as a predominant malignancy. Even in the antiretroviral therapy (ART) era, aggressive B-cell lymphoma stands out as a paramount concern. Yet, the pathogenesis of HIV related lymphoma (HRL) largely remains an enigma. Recent insights underscore the pivotal role of the dysregulated B cell receptor (BCR) signaling cascade, evidencing its oncogenic potential across a spectrum of lymphomas. Intricate interplays between HIV and BCR structural-functional integrity have been identified in PLWH. In this review, we elucidated the mechanism by which the BCR signaling pathway is involved in HRL, mainly including the following aspects: HIV can reshape BCR structure by modulating of activation-induced cytidine deaminase (AID) and recombination-activating gene (RAG) dynamics; HIV can act as a chronic antigen to activate the BCR signaling pathway, such as upregulating PI3K and MAPK signaling pathway and reducing the expression of CD300a; HIV co-infection with other oncogenic viruses may also influence tumor formation mediated by the BCR signaling pathway. This review aims to elucidate the intricate regulation of the BCR signaling pathway by HIV in B cell lymphoma, providing a novel perspective on the pathogenesis of lymphoma in HIV-affected environments.

Keywords B-cell lymphoma · B cell receptor · Human immunodeficiency virus · HIV related lymphoma · Mechanism

Introduction

Human Immunodeficiency Virus (HIV) infection has emerged as a major challenge in the global healthcare sector due to its destructive impact on the immune system, leading to various complications, including lymphomas [1–3].

In the era of antiretroviral therapy (ART), the incidence of all AIDS-defining malignancies has significantly decreased. However, the risk for each subtype of AIDS-defining non-Hodgkin lymphoma (NHL) remains significantly higher than that of non-HIV-infected individuals, particularly with standardized incidence ratios (SIR) of 10 for diffuse large B-cell lymphoma (DLBCL) and 20 for Burkitt lymphoma (BL) [4, 5]. Notably, among patients using ART, the risk of Hodgkin lymphoma (HL) has become comparable to that of NHL (SIR 14) [6]. HIV instigates the onset of lymphomas, with underlying mechanisms spanning across chronic B-cell activation, inflammation and/or immune dysfunction, loss of control over oncogenic viruses, and reduced tumor immune surveillance [7–9]. Investigations into immunoglobulin genes and genetically engineered mouse models within the context of human lymphomas have provided compelling evidence supporting the pivotal role of B cell receptor (BCR) signaling in lymphomagenesis [10, 11]. Notably, within the context of HIV related lymphoma (HRL), an accentuated upregulation of the BCR signaling cascade is discernible, yet the intricacies of the underlying mechanisms warrant further elucidation.

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The BCR signaling cascade stands as an emblematic feature of B cells. Anomalies in its maturation or protracted stimulation can culminate in unchecked B cell proliferation and the bypassing of intrinsic apoptosis cues [12]. Significantly, the presence of antibodies specific to HIV proteins in PLWH implies a direct modulatory role of HIV on the BCR signaling continuum via the biological perturbations triggered by HIV proteins [13]. Currently, the main mechanisms by which HIV induces BCR signaling pathway activation encompass: (1) HIV-mediated alterations in BCR gene architecture and rearrangement, underscored by augmented activity of activation-induced cytidine deaminase (AID) and recombination-activating gene (RAG) [14]; (2) HIV upregulates the BCR signaling pathway, including an increase in the number and type of antigens, activate PI3K/ATK and RAS/MAPK signaling pathways [15]; (3) Against the backdrop of immune suppression instigated by HIV, concurrent infections with oncogenic viruses such as Epstein-Barr Virus (EBV), Kaposi's Sarcoma-Associated Herpesvirus (KSHV), and Hepatitis C Virus (HCV) further perturb the dynamics of BCR signaling pathways [1]. This review encapsulates prevailing evidence delineating the influence of HIV on BCR and sheds light on the nuanced expression and orchestration of BCR amidst HIV-propelled lymphoma progression.

HIV induces HRL by regulating the gene structure and rearrangement of BCR

B-cell development involves a meticulously regulated and intricate process marked by a multiple checkpoints [16]. A crucial initial checkpoint revolves around the selection of developing cells based on the assembly and specificity of the functional antigen receptor BCR genes. Within the confines of the bone marrow, the earliest progenitor B cells initiate rearrangements of the immunoglobulin locus, culminating in the creation of distinct antigen-binding BCRs comprising heavy and light peptide chains that encompass variable and constant regions, respectively. The variable regions within the heavy chain locus encompass variable (V), diversity (D), and joining (J) segments, while the variable regions within the light chain loci exclusively comprise V and J segments [17]. In order to enhance their antigen affinity, immature B cells migrate from the bone marrow to lymphoid tissues or organs, where they undergo a secondary diversification process of the BCR [18]. Within the germinal center (GC), BCR encoding genes accumulate mutations in their antigen-binding regions under the influence of AID [19]. This dynamic process leads to the emergence of multiple variants from the original germline BCR. Among these variants, B cells displaying the highest affinity for antigens prevail in the competitive selection within the GC reaction.

However, due to the extensive proliferation and concurrent exposure to mutagenic programs, GC B cells become more susceptible to carcinogenesis [20]. Somatic hypermutation (SHM) and class switch recombination (CSR) are indispensable physiological processes in the maturation of each BCR and represent key factors contributing to the origin of more than 90% of lymphomas arising from B lymphocytes [21]. RAG and AID are two pivotal enzymes governing this intricate process. Studies have revealed that in PLWH, HIV proteins can upregulate the expression of RAG and AID, particularly in the context of HRL [22, 23]. Therefore, the dysregulation of RAG and AID induced by HIV infection may be a potential pathogenic mechanism for HRL.

HIV remodels BCR gene structure by enhancing RAG expression

RAG is a protein required in the course of normal B lymphoid development, responsible for V, D and J recombination to yield μ Heavy chain, which associates with surrogate light chains, forming the pre-BCR [24]. The expression of RAG is meticulously controlled during the progression of lymphocyte development to avert genetic inaccuracies. Some studies suggest that RAG overexpressed, recombination errors (V, D and J) may not be adequately corrected in a timely manner, and lymphocytes are highly susceptible to signaling through the pre-BCR resulting in a proliferation burst [25]. Moreover, excessive RAG activity in mature B cells can lead to continuous V(D)J gene rearrangement, causing these B cells to continually produce new BCRs with abnormal antigen-binding properties, ultimately driving abnormal B cell proliferation and contributing to lymphomagenesis [26].

In the context of HIV infection, RAG was found to be enriched by gene expression microarray analysis in HIV-1 transgenic mice. Additionally, the HIV matrix protein p17 was detected in the bone marrow before the onset of symptoms [22]. Stimulation of human activated B cells with p17 protein was found to enhance RAG1 expression, suggesting that p17 protein might disrupt the stability of the BCR genome by regulating RAG1 [22]. Additionally, the expression of RAG genes is thought to be linked to the levels of HIV trans-activator of transcription (Tat) protein, which is a pivotal viral regulatory protein crucial for HIV-1 replication, the establishment of infection, and virus reactivation. Once Tat protein enters B cells, it can activate the transcription of the nuclease-encoding RAG gene and induce DNA damage. This damage is characterized by the relocation of the RAG-encoded gene from the MYC locus to the central region of the nucleus, where it consistently co-localizes with IGH at a tenfold higher frequency [27]. Therefore, the damage to the BCR gene mediated by RAG gene enrichment in PLWH

could potentially represent a mechanism of lymphoma susceptibility in this population. Moreover, a noteworthy finding emerges in the context of integrase inhibitors, a class of antiretroviral drugs employed in HIV/AIDS treatment, which exhibit structural and functional similarities to RAG1, potentially diminishing RAG expression and interfering with its oncogenic pathways, consequently mitigating the risk of HRL [28]. *Nilavar et al.* have shown that integrase inhibitors exhibit structural similarity with RAG1 and can interfere with the physiological processes of RAG, including binding, cleavage, and hairpin formation at the recombination signal sequence (RSS), thereby inhibiting the encoding of BCR in pro-B cells. Notably, the administration of integrase inhibitors led to a marked reduction in mature B lymphocytes in 70% of mice involved in the study [28, 29]. Therefore, in PLWH, viral products can escalate RAG expression or trigger abnormal RAG gene expression, leading to abnormal V(D)J gene rearrangement in B cells, ultimately contributing to the development of lymphoma (Fig. 1A).

HIV increase BCR affinity by promoting AID expression

AID is a critical enzyme responsible for immunoglobulin CSR, and the introduction of point mutations within V gene segment of immunoglobulin heavy chain genes that modulate the specificity and affinity of the BCR. However, beyond its physiological functions, overexpression of AID resulting in abnormal mutations and increased BCR affinity ultimately raises the risk of leukemia and lymphoma [30]. AID plays a pivotal role by introducing point mutations within the V gene segment of immunoglobulin heavy chain genes, which in turn alters the specificity and affinity of the BCR. Additionally, AID's activity is influenced by corresponding ligands, including CD40 ligand (CD40L), B-cell activating factor (BAFF), or Toll-like receptor ligand (TLR-L), which interact with CD40, BAFF-R, and TLR receptors on the cell surface and within the cell. AID is particularly active in the GC, and it's worth noting that most HRL, such as BL, DLBCL, and HL, originate from B cells within the GC.

Compared to HIV-negative individuals, HRL patients show significantly increased expression of AID in peripheral blood mononuclear cells and lymphoid tissues [23]. The upregulation of AID in HRL is impacted by several

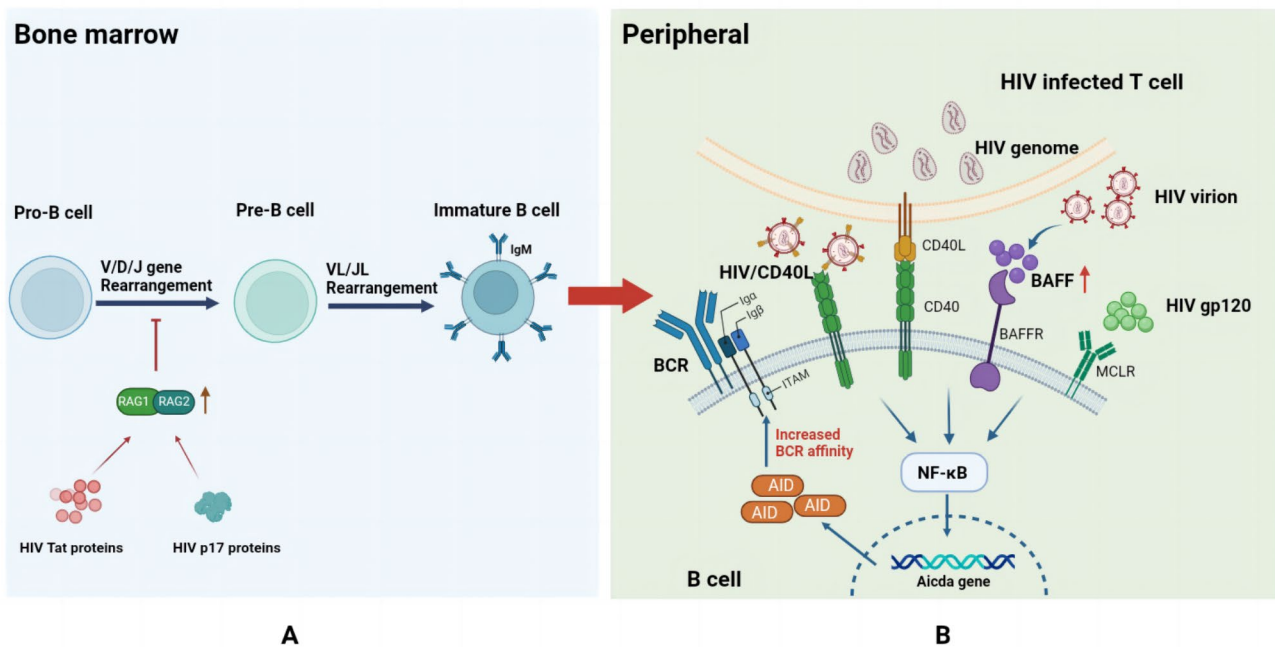


Fig. 1 HIV induces HRL by regulating the gene structure and rearrangement of BCR

HIV remodels BCR gene structure by enhancing RAG expression: In bone marrow, HIV Tat and p17 proteins can disrupt V/D/J gene rearrangement by enhancing the expression RAG1/2, which hampered the development of B cell (Fig.1 A). HIV increase BCR affinity by

promoting AID expression: HIV and HIV gp120 proteins can activate NF-κB through multiple pathways, ultimately leading to aberrant expression of AID, including CD40 ligand (CD40L), B-cell activating factor (BAFF), or Toll-like receptor ligand (TLR-L), which interact with CD40, BAFF-R, and TLR receptors on the cell surface and within the B cell (Fig.1 B).

factors, encompassing the co-stimulatory molecule CD40L, BAFF, and HIV viral particles. CD40L, expressed by activated T lymphocytes, can upregulate AID expression by binding to CD40 receptors on B cell surfaces. This interaction activates the NF- κ B transcription factor, resulting in increased AID expression [13]. Interestingly, recent investigations have revealed that following the release of HIV from infected cells, the immune-stimulatory CD40L expressed on activated T cells interacts with HIV viral particles, thereby triggering the activation of B cells through CD40 engagement. The binding of CD40L to HIV virions has been shown to elicit AID expression in B cells, and possesses the capacity to prompt IgH CSR and SHM, along with potential oncogenic alterations [31, 32]. Notably, it was found that only viruses expressing functional CD40L were capable of inducing AID expression; CD40L-negative HIV did not induce AID expression [33]. BAFF binds to BAFF-R on B cells, activating the NF- κ B pathway and subsequently upregulating AID expression. It's worth highlighting that even in the blood of PLWH who have successfully undergone ART, excessive levels of BAFF can still be observed [34]. HIV Tat protein can penetrate the cell membrane and enhance the SHM of the BCR V region mediated by AID by regulating the endogenous polymerase II (Pol II) transcription process [14]. Moreover, it can activate the Akt/mTORC1 pathway, leading to mTORC1-dependent inhibition of AID repressors c-Myb and E2F8, resulting in AID overexpression [35]. In addition, the binding of gp120, a protein on the viral envelope, to C-type lectins expressed on B cells has been demonstrated to induce immunoglobulin transformation, which is also mediated by AID [36]. Consequently, HIV may activate NF- κ B through multiple mechanisms, including the presence of CD40L in HIV viral particles, increased levels of BAFF, and direct binding of viral proteins to B cell membranes, ultimately leading to aberrant expression of AID, and contribute to the lymphomagenesis observed in HRL (Fig. 1B).

HIV regulates the BCR signaling pathway

The BCR signaling pathway serves as a vital conduit for transmitting signals within B cells, governing their growth, differentiation, and immune response [37]. When antigens bind to the BCR, downstream signaling pathways are activated, setting off a cascade of reactions. Ultimately, these pathways converge to activate transcription factors NF- κ B and nuclear factor of activated T cells, culminating in the initiation of gene expression. This gene expression process is pivotal for B cell activation, proliferation, and differentiation, highlighting the essential role of the BCR signaling pathway in normal B cell development and adaptive immunity [38]. Immunogenetic evidence indicate that in diseases

such as B cell leukemia and lymphoma, the BCR creates a conducive environment for the survival and expansion of malignant B cells [39].

In PLWH, HIV can exert a sustained and gradual influence on the microenvironment, activating the BCR signaling pathway. Subsequently, this activation drives aberrant B cell proliferation and contributes to lymphomagenesis. Research has revealed that PLWH experience an overactivation of the BCR signaling pathway through various mechanisms, including chronic antigen stimulation and activation of the PI3K and MAPK signaling pathways (Fig. 2). Consequently, the excessive activation of BCRs may be linked to the heightened risk of lymphoma in PLWH. The following section explores the complex mechanisms that lead to heightened activation of the BCR signaling pathway due to HIV infection.

Although the advent of rituximab has significantly improved the prognosis of lymphoma, its application and efficacy in HRL patients are limited due to the typically lower CD4⁺ T cell counts in these individuals [40]. Compared to HIV-negative patients, factors such as immunosuppression, drug interactions, co-infections, and immune reconstitution contribute to poorer prognosis in HRL patients [1, 41]. However, as our understanding of HRL pathogenesis deepens, it is evident that patients who do not respond to first- and second-line therapies require more personalized treatment strategies. Emerging evidence indicates that treatments based on BTK inhibitors—small molecule inhibitors that block the BCR signaling pathway—can achieve sustained remission in patients with HIV-related primary central nervous system lymphoma (PCNSL) and HIV-related BL [42, 43].

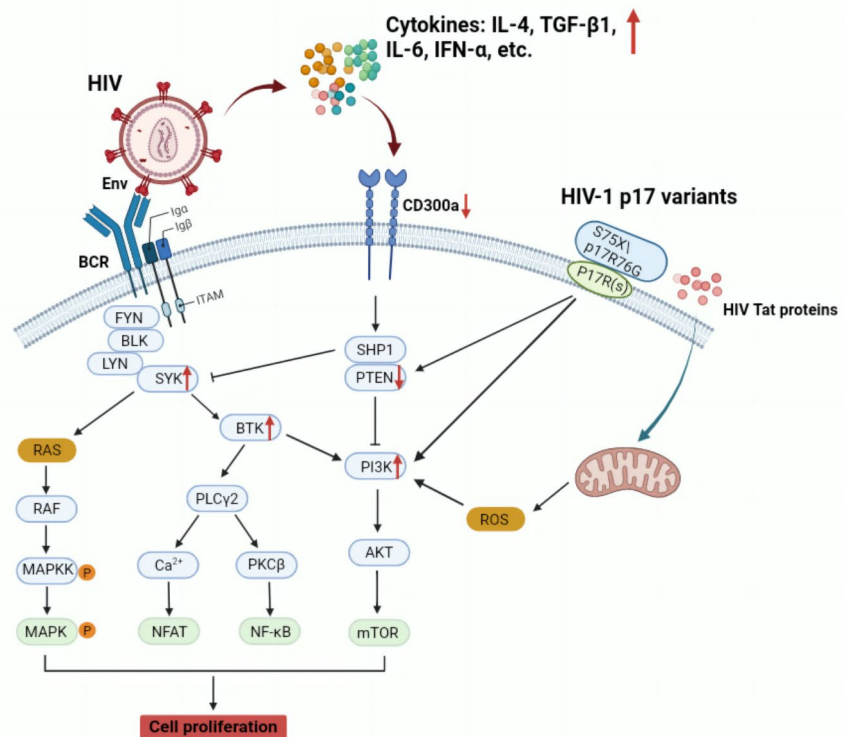
HIV acts as a chronic antigen to upregulate the BCR signaling pathway

The disruption of regular B cell responses to antigens, resulting in persistent BCR signaling, has spurred in-depth research into the role of antigens in lymphoma [44]. *Sutton et al.* underscored the immunogenetic data that unequivocally link antigens to lymphomagenesis, including skewed immunoglobulin gene usage, quasi-identical or “stereotyped” BCRs, and ongoing SHM [45]. Antigens that contribute to lymphoma formation through the activation of the BCR signaling pathway encompass microbial antigens persistently present in the tissue microenvironment or self-antigens.

Although HIV rarely directly targets B lymphocytes, research suggests that the virus can serve as an antigen to trigger and sustain specific abnormal activation of BCR [46]. It has been demonstrated that HIV can bind to B cells through the interaction between the viral envelope protein gp120 and the variable heavy chain 3 (VH3) of

Fig. 2 HIV regulates the BCR signaling pathway

HIV can regulate the BCR signaling pathway via various mechanisms: HIV acts as a chronic antigen to upregulate the BCR signaling pathway; HIV and HIV proteins can elevate levels of cytokines such as IL-4, IL-6, and IL-10, which contribute to the downregulation of CD300a; HIV increases the frequency of Ras mutations; the variant S75X of HIV p17, upon binding to the p17 receptor on B cells, can directly induce PI3K activation and reduce the activity of the PI3K inhibitor PTEN, further enhancing the PI3K signaling pathway; HIV Tat can directly penetrate B lymphocytes and induce mitochondrial ROS production. These processes ultimately activate NF- κ B, PI3K and MAPK signaling pathways, leading to excessive proliferation of B cells.



immunoglobulins, referred to as a superantigen interaction [47]. In PLWH, high frequencies of actively secreting anti-HIV antibodies by B cells have been noted in the peripheral blood, accompanied by increased levels of anti-HIV antibodies in the serum. As HIV viral load decreases with ART, the frequency of polyclonal B cell activation and high gamma globulin levels also decreased, along with the frequency of HIV-specific B cells and anti-HIV antibodies [48]. Interestingly, in PLWH with undetectable HIV-1 replication, these viral structural proteins and glycoproteins persist in lymph nodes (LNs), coexisting with specific anti-HIV-1 antibodies in the patient's serum [49]. Furthermore, the risk of lymphoma formation in transgenic (TG) mice expressing HIV genes is closely associated with elevated levels of HIV proteins (p17, gp120, and Nef) [50]. Hence, uncontrolled and prolonged stimulation of B cells by HIV proteins can result in the expansion of monoclonal B cells, heightening the risk of acquiring significant genetic alterations and ultimately playing a role in the development of lymphomas.

HIV activates PI3K signal pathway by interacting with BCR

Recently, the main effectors of activation of BCR signal pathway mediated by PI3K has received increasing attention

in the pathogenesis of lymphoma [51]. The downstream molecules of this pathway encompass various subtypes of the PI3K family, which can convert phosphatidylinositol on the cell membrane into phosphatidylinositol-3,4,5-trisphosphate (PIP3), thereby activating signaling molecules like Akt [52]. Phosphatase and tensin homolog (PTEN) serve as negative regulators of PI3K by inhibiting PI3K-dependent Akt activation through the dephosphorylation of PIP3 to PIP2 [53]. Interestingly, the presence of PI3K molecules alone is adequate to support the survival of mature B cells, even in the lack of BCR expression. This suggests that beyond the conventional mechanism of antigen-triggered PI3K pathway stimulation through BCR binding, numerous other factors, such as direct PI3K stimulation or PTEN inhibition, can potentiate this pathway.

Accumulating evidence highlights the role of HIV in the regulation of the BCR via the PI3K/Akt signaling pathway. Studies have demonstrated that the HIV p17 protein can downregulate pAkt levels by activating PTEN in human B cell line Raji cells that stably express p17 receptors on their surface [54, 55]. The activation of PTEN is triggered by the serin/threonine (Ser/Thr) kinase ROCK, which is a downstream effector of RhoA and is known to control PTEN activity [56]. These effects are mediated by the COOH-terminal region of p17 and involve cooperate with at least

two different functional epitopes on viral protein. Interestingly, among patients with HRL, a p17 variant exhibiting B-cell clonality has been identified. The prevalence of this p17 variant in lymphoma patients is notably greater than in PLWH without lymphoma, suggesting its potential involvement in lymphoma development [57]. In particular, *Cinzia et al.* found that p17 has different variants, among which a variant named S75X from the Uganda HIV-1 strain directly triggers the PI3K/Akt signaling pathway by binding to p17R on B cells, leading to increased B cell proliferation and malignant transformation [54, 58]. Subsequent studies in HIV-related DLBCL have shown that the p17 variant inhibits PTEN activity, indicating that it not only directly induces PI3K activation but also reduces the activity of PI3K inhibitors, thereby further enhancing the PI3K signaling pathway [59, 60]. The p17 variant with lymphoma-associated characteristics may be enriched in some PLWH who are potentially prone to lymphoma. Additionally, HIV Tat protein induces ROS production by activating NADPH and spermine oxidase in B cells [61], contributing to activate AKT/mTORC1 signaling pathway [35].

HIV activates MAPK signal pathway by interacting with BCR

The MAPK signaling pathway is one of the signal pathways activated after antigen binding to BCR, ultimately triggering the transcription of various anti-apoptotic genes. Adapter proteins from the growth factor receptor-bound protein 2 (Grb2) family have been identified as playing a vital role in lymphocytes. Grb2 and Grb2-related adaptor protein (GRAP) function to amplify signals through the immunoglobulin tail tyrosine (ITT) motifs present in BCRs containing mIgE. These proteins effectively transmit signals from ITAM to the Ras-controlled Erk MAP kinase pathway, culminating in activation within the MAPK signaling pathway [62]. In this process, BCR initiates the activation of the Ras protein, triggering a cascade reaction that stimulates the connecting enzymes MEK and ERK, ultimately leading to the transcription of various anti-apoptotic genes [63]. Therefore, the MAPK signaling pathway is intimately linked with the BCR and can regulate and influence BCR's ability to recognize foreign antigens and initiate an immune response. Abnormalities in the MAPK signaling pathway have been associated with the development of various diseases. RAS-MAPK mutations are often regarded as late-stage driver events in mature B-cell tumors. They are found in both clones and subclones and are frequently associated with disease progression and treatment resistance [64–66].

Research conducted by *Liu and colleagues* targeted resequencing in 110 cases of South African HIV-associated plasmablastic lymphoma (PBL) and found functional acquired mutations in 28% of cases in RAS family members. These

mutations included NRAS (14%), KRAS (9%), BRAF (5.5%), and MAP2K1 (3%) [67]. In the context of AIDS-related NHL, the genes of N-, H-, and K-Ras were assessed using PCR-direct sequencing. Characteristic mutations of Ras genes in AIDS-NHL primarily involved the N-Ras gene and the K-Ras gene [66]. Additionally, in mice with HRL, the expression of the K-RAS gene is increased, and this abnormal expression is typically associated with alterations in the T/B cell ratio [50]. Therefore, it is conjectured that HIV infection could potentially raise the frequency of RAS mutations, thus playing a role in the development of lymphomas.

HIV downregulates the negative regulator of BCR

B cells utilize a diverse array of surface receptors, such as Fc γ RIIB, CD22, CD72, paired Ig-like receptor (PIR)-B, Fc receptor-like (FCRL)4, and CD300a, to regulate BCR-induced signaling pathways effectively [68]. CD300a, characterized by its type I transmembrane structure, features extracellular domains similar to immunoglobulin variable (IGV) domains. Its cytoplasmic tail contains three canonical immunoreceptor tyrosine-based inhibition motif (ITIM) motifs, which significantly contribute to the regulatory process of BCR signaling. Studies involving the reduction of CD300a expression in primary B cells through small interfering RNA (siRNA) have demonstrated that diminished CD300a levels lead to enhanced BCR-mediated proliferation. This confirms the suppressive capacity of CD300a in modulating BCR signaling pathways [69].

Numerous studies have highlighted that HIV employs a strategy involving the upregulation of negative regulatory factors associated with the BCR to interfere with B-cell function and promote viral dissemination [70]. A notable decrease in CD300a expression has been observed in PLWH, and this reduction cannot be reversed through effective ART. The decline in CD300a expression is in contrast to the increased expression of various inhibitory receptors with the atypical (exhausted) memory B-cell subset, which is notably expanded in PLWH. In contrast, CD300a expression has decreased across all circulating mature B cell subpopulations, potentially contributing to the hyperactivation of B cells seen in PLWH [71]. However, the underlying mechanisms that to the expression of CD300a in B cells was downregulated by HIV remains unclear. Previous research has demonstrated that cytokines such as IL-4 and transforming growth factor (TGF) can downregulate CD300a expression [72]. Interestingly, elevated levels of cytokines such as IL-4, IL-6, and IL-10 have been reported during HIV infection [73]. It is plausible that the increased cytokine levels during HIV infection contribute to the downregulation of CD300a.

Other co-infected viruses over-activate BCR

HIV infection not only directly impact the BCR signaling pathway, potentially leading to cancer, but also create an immunological environment that allows other viruses to evade immune control and induce tumors [74, 75]. A spectrum of viruses, such as EBV, KSHV, HCV, and others are frequently associated with B lymphomas. Extensive research has revealed that these viruses possess specialized mechanisms for BCR activation, further contributing to B cell dysregulation and lymphoma development.

EBV

EBV, a B-lymphotropic human herpesvirus, is intricately linked to a spectrum of hematopoietic cancers, including endemic BL, HL, and lymphoproliferative disorders in immunocompromised individuals [76]. EBV preferentially infects B cells by binding to the CD21 receptor on the surface of B cells via the major viral envelope glycoprotein gp350 [77]. Upon successful B cell colonization by EBV, specific antigens, products of its genomic segments, manifest on the B cell membrane. This triggers a robust T cell-mediated immune onslaught, aiming to curb B cell infection. Consequently, PLWH exhibit a markedly elevated prevalence and incidence of EBV relative to their immunocompetent counterparts [78]. In PLWH, 100% of PCNSL, 30–90% of DLBCL depending on the subtype, 30–60% of BL, and 70–80% of PBL are associated with EBV [79].

Upon infecting naïve B cells, EBV orchestrates the expression of an ensemble of viral latent genes, encompassing six EBV nuclear antigens (EBNA1, 2, 3 A, 3B, 3 C, and -LP) and a trinity of latent membrane proteins (LMP1, 2 A, and 2B), which modulates the BCR signaling cascade in myriad ways, with LMP2A being the focal point of extensive research. Evidence underscores that LMP2A expression culminates in the persistent phosphorylation of ERK/MAPK and PI3K/Akt in nascent B cells, even in the absence of functional BCR, indicating that LMP2A provides pre-BCR-like signals to support B cell development [80, 81]. Yet, LMP2A isn't a mere simulacrum of BCR; it refashions intracellular directives in EBV-invaded BCR-affluent B cells, amplifying antigen's stimulatory cues on the BCR, sculpting an ambience conducive for cell survival, proliferation, and, eventually, oncogenic metamorphosis [82, 83]. Additionally, LMP-1, emulating an invigorated member of the tumor necrosis factor receptor (TNFR) superfamily, can tap into the MAP kinase cascade, invigorating ERK, JNK, and p38 [84]. Inhibiting ROS might have therapeutic benefits for treating EBV-induced tumors. Additionally, EBV transcriptional regulators, notably EBNA2, 3a, 3b, and 3 C, anchor themselves to genomic territories encircling an array

of BCR pathway genes, modulating their expression and thereby influencing the BCR signaling symphony [85].

KSHV

KSHV, also known as Human Herpesvirus 8, is intricately tethered to the genesis of primary effusion lymphoma (PEL), which emerges from B lymphocytes ensconced in the germinal center, and is also implicated in select instances of DLBCL [86]. While PEL is generally a low-incidence disease, its prevalence has significantly increased in regions with high HIV prevalence such as sub-Saharan Africa (SSA) [87, 88]. Current evidence supports that HIV-1, in addition to inducing immunosuppression, may also regulate the life cycle of KSHV through the secretion of regulatory proteins such as Tat, Vpr, and Nef [89].

KSHV intricately modulates the BCR signaling trajectory primarily through the orchestration of its encoded transmembrane proteins, K1 and K15 [90]. At the onset, KSHV's engagement with the BCR mirrors the antigenic incitement seen with other viral entities. However, a peculiar paradigm emerges when KSHV-infected B cells transform into PEL: the striking lack of BCR expression, a situation typically contradictory to cellular viability. Within this BCR-devoid PEL milieu, K1 and K15 jointly shoulder pivotal roles in cell survival, activation, and proliferation—drawing parallels with the *modus operandi* of EBV's LMP-2 A. K1 adeptly impersonates the BCR signaling cascade, augmenting the transcriptional activity of NFAT and NF- κ B. K1's NH2-terminal region forging specific liaisons with the μ chains of BCR complexes, thereby sequestering them within the endoplasmic reticulum and impeding their intracellular conveyance to the cellular facade. Such a mechanism potentially underpins the sustenance of KSHV latency or curtails apoptotic pathways [91]. Additionally, another protein of KSHV, viral FLICE-inhibitory protein (vFLIP), can bind to I κ B kinase γ (IKK γ), inducing the phosphorylation of IKK α/β , degradation of I κ B α , and cleavage of p100, thereby leading to the activation of NF- κ B pathways [92]. NF- κ B is a crucial component of the BCR downstream signaling pathway, exhibiting constitutive activity in PEL, and is essential for maintaining the tumor phenotype [93]. The purine scaffold HSP90 inhibitor BIIB021 can partially reduce the constitutive NF- κ B activity present in PEL cells by disrupting the interaction between vFLIP and IKK complex subunits, further confirming the importance of the BCR signaling pathway in KSHV-mediated survival of PEL cells [94].

HCV

Three evidence substantiate the connection between HCV and B-NHL: Firstly, compared to HCV-negative individuals, patients with non-HIV chronic active HCV infection have a 2–3 times higher risk of developing B-NHL [95]. Secondly, antiviral therapy leads to lymphoma remission in HCV-positive rather than HCV-negative NHL patients [96]. Lastly, transgenic mice with specific expression of the full-length HCV genome in B cells have a higher incidence of B-cell NHL, mainly DLBCL [97]. In the ART era, chronic HCV infection is associated with an increased risk of NHL in PLWH and tends to have an adverse effect on overall survival [98, 99].

HCV can activate the BCR signaling pathway through various mechanisms. Firstly, studies have shown that chronic antigen stimulation by HCV plays an important role in amplifying the BCR signaling pathway [100]. Secondly, the HCV envelope protein E2 can bind to CD81 expressed on B cells [101]. This receptor is upregulated during HCV infection and correlates positively with viral load [102]. CD81 forms a complex with CD19 and CD21 on human B cells, and the binding of the BCR to any component of this complex reduces the threshold required for BCR-mediated B cell proliferation [103, 104]. In addition, CARD11, integral for the activation of NF- κ B signaling and the sustenance of activated B-cell (ABC) DLBCL cells, appears to be upregulated amidst chronic HCV infection. This molecular augmentation is ascribed to the suppression of CHK2 activity by HCV's non-structural protein NS3/4A, known to restrain DNA damage repair. In HCV chronic infection, the interaction between HCV NS3/4A and CHK2 causes a reduction in CHK2 activity, leading to the posttranscriptional modulation of the target mRNA network linkage of the B-cell lymphoproliferative disorders by HuR. The increased association of the target transcripts with HuR in the BCR signaling framework amplifies the likelihood of B-cell lymphoma in HCV-infected subjects [105]. Another potential mechanism for BCR activation is the promotion of the BCR signaling pathway by HCV-induced EBV infection. BZLF1 mRNA, the molecule initiating EBV reactivation, has been detected in a significantly higher proportion in peripheral blood mononuclear cells of HCV-infected patients in contrast to their healthy counterparts. Furthermore, BZLF1 mRNA disappears after anti-HCV viral treatment [106, 107].

Conclusions

Extensive research has indicated that abnormalities in the structure and function of the BCR signaling pathway may instigate lymphomagenesis. Previous studies have primarily focused on BCR abnormalities in HIV-negative lymphoma patients, while the precise mechanisms of BCR abnormalities in HRL remain unclear. In this review, we focus on the impact of HIV and its products on the BCR signaling pathway, and explore how HIV and other oncogenic viruses may promote the progression and development of HRL by affecting the BCR signaling pathway, providing potential therapeutic approaches for HRL, including the use of BCR signaling pathway inhibitors such as Btk inhibitors, PI3K inhibitors, and Syk inhibitors. However, there exist several constraints in comprehending the intricate interplay between HIV and BCRs: firstly, the immune response to HIV infections encompasses a myriad of elements, encompassing BCRs, T cells, antibodies, cytokines, and other immune cells. Deciphering the precise contribution of BCRs within this intricate interplay presents a formidable challenge. Secondly, the progression of HIV infection is dynamic, and the understanding of the interaction between viruses and BCR may vary with different stages of infection. Furthermore, HIV infection provides a complex background for lymphoma tissue, often accompanied by co-infection with other oncogenic viruses, necessitating research into the effects of interactions between these viruses on BCR. Therefore, it is necessary to clarify the complex interactions and mechanisms between viruses and the BCR signaling pathway in the context of HIV infection, ultimately paving the way for novel therapeutic interventions to prevent or halt the progression of this malignancy.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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