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Review Article

Hepatitis Virus-associated Non-hodgkin Lymphoma: Pathogenesis and Treatment Strategies

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Abstract

Over the last decade, epidemiological studies have discovered a link between hepatitis C virus (HCV) and hepatitis B virus (HBV) infection and non-Hodgkin lymphoma (NHL). The regression of HCV-associated NHL after HCV eradication is the most compelling proof supporting HCV infection's role in lymphoproliferative diseases. HBV infection was found to significantly enhance the incidence of NHL, according to the epidemiological data. The exact mechanism of HCV leading to NHL has not been fully clarified, and there are mainly the following possible mechanisms: (1) Indirect mechanisms: stimulation of B lymphocytes by extracellular HCV and cytokines; (2) Direct mechanisms: oncogenic effects mediated by intracellular HCV proteins; (3) hit-and-run mechanism: permanent genetic B lymphocytes damage by the transitional entry of HCV. The specific role of HBV in the occurrence of NHL is still unclear, and the research on its mechanism is less extensively explored than HCV, and there are mainly the following possible mechanisms: (1) Indirect mechanisms: stimulation of B lymphocytes by extracellular HBV; (2) Direct mechanisms: oncogenic effects mediated by intracellular HBV DNA. In fact, it is reasonable to consider direct-acting antivirals (DAAs) as first-line therapy for indolent HCV-associated B-NHL patients who do not require immediate chemotherapy. Chemotherapy for NHL is affected by HBV infection and replication. At the same time, chemotherapy can also activate HBV replication. Following recent guidelines, all patients with HBsAg positive/HBV DNA≥2,000 IU/mL should be treated for HBV. The data on epidemiology, interventional studies, and molecular mechanisms of HCV and HBV-associated B-NHL are systematically summarized in this review.

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Introduction

Currently, hepatitis B virus (HBV) and hepatitis C virus (HCV) infection affects hundreds of millions of individuals worldwide, which can result in hepatic complications such as liver cirrhosis and hepatocellular carcinoma (HCC) as well as extrahepatic complications including B-cell lymphatic neoplasms. Therefore, this issue may bring a significant burden to the health system and is of clinical relevance, especially in countries with high HBV and HCV prevalence. This review presents an overview of epidemiology, possible mechanisms of pathogenesis, and treatment options.

Non-hodgkin lymphoma (NHL), HBV and HCV: an overview

NHL is one of the most common hematologic malignancies in humans. In the USA, about 81,560 people are diagnosed with NHL, and 20,720 die of the disease, accounting for 4.3% of malignant tumors and 3.3% of cancer mortality in 2021. The etiology of NHL is still largely unknown, and 15–20% of NHL relate to a particular virus infection, including HIV, Epstein-Barr virus (EBV), HPV8, human T lymphocyte virus type I (HTLV-I), HCV, or HBV.[1]

HCV belongs to genus *Hepacivirus* of *Flaviviridae*, is a single-stranded positive RNA virus with no reverse transcriptional activity. It has a diameter of 30–60 nm and consists of about 9.6×10^3 nucleotides. It is hepatotropic and lymphotropic and can infect peripheral blood mononuclear cells (PBMCs) and replicate in them. The length of the HCV genome is 9.5 KB, which is composed of highly conserved 5′-terminal,

Keywords: Hepatitis C virus; Hepatitis B virus; Non-hodgkin lymphoma; B cell.
Abbreviations: AID, activity-induced cytosine deaminase; BAFF, B-cell activating factor; BCR, B-cell receptor; cccDNA, closed circular DNA; CLL, chronic lymphocytic leukemia; CR, complete response; DAAs, direct antiviral agents; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIVID, high-throughput virus integration assay; HTLV-I, human T lymphocyte virus type I; I-CT, immunochemotherapy; IFN, interferon; IgH, immunoglobulin heavy -chain gene; IL, interleukin; LDR, lymphoproliferative disease response; LPD, lymphoproliferative disease; MC, mixed cryoglobulinemia; miRNAs, microRNAs; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; NOS, nitric oxide synthase; OS, overall survival; PBMCs, peripheral blood mononuclear cells; PD, progressive disease; PFS, progression-free survival; ROS, reactive oxygen species; SCID, severe combined immune deficiency; SVR, sustained virological response; TNF, tumor necrosis factor; TNF-α, tumor necrosis factor α.

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3′- terminal, and a single open reading frame between the two ends.[2] The open coding region can encode a polyprotein precursor, spliced into three structural proteins (core protein, E1, E2) and seven nonstructural proteins (NS1, NS2, NS3, NS4A, NS4B, NS5A, NS5B) by host and virus signaling enzymes. The HCV gene is easy to mutate and can be divided into at least six genotypes and multiple subtypes.[3] In 2019, the World Health Organization reported that 58 million individuals worldwide suffered from hepatitis C infection, with 290,000 people dying from the disease.

HBV is a hepatotropic DNA virus of family *Viroviridae* consisting of incomplete circular double-stranded DNA. The negative strand contains about 3,200 base pairs, and the length of the positive strand is variable, equivalent to 50–80% of the negative strand. The four open reading frames in the HBV genome, i.e., S, C, P, and X regions, are all located in the negative strand. S region mainly encodes HBsAg, the C region mainly encodes HBeAg and HBcAg, the P region encodes a macromolecule alkaline polyskin that participates in HBV replication, and the X region encodes X protein that has a transactivation effect and activates various regulatory genes of HBV itself.[4] Currently, Hepatitis B is a serious public health problem. According to the World Health Organization, around 296 million individuals worldwide have chronic HBV infection and approximately 820,000 people died from HBV-related liver illnesses in 2019.

Association between HCV and NHL: epidemiological data

An extensive investigation of this correlation between the hepatitis C virus and NHL initially found that patients with mixed cryoglobulinemia (MC) had a high HCV seroprevalence of nearly 100%.[5,6] MC is a chronic lymphoproliferative disease, usually presented as small vessel vasculitis due to immune complex accumulation in the vascular wall and complement activation. The clinical manifestations include weakness, Raynaud's phenomenon, rash, membranous proliferative glomerulonephritis, etc. The prominent feature is the presence of cryoglobulins, a kind of globulin that precipitate at temperatures below 37°C. Cryoglobulins are usually categorized into three types by their structure. Type I is made up of a single monoclonal immunoglobulin, whereas types II and III are mixed cryoglobulins.[6] According to epidemiological research, 8–10% of MC patients are vulnerable to NHL, with a 35-fold increased risk of HCV-associated NHL than the general population.[7]

Clinical practice proves the causal connection between HCV and B-NHL. HCV infection was found in 53 (2.9%) of lymphoma patients and 41 (2.3%) healthy controls in a large, multicenter, case-control study involving five European countries [OR 1.42; (95% CI: 0.93–2.15)].[8] The link between HCV and B-NHL has been verified in large-scale epidemiological investigations. Gisbert *et al*.[9] published a systematic review of 48 studies (5,542 patients) with a mean HCV infection rate of 13%. HCV prevalence was much higher in B-NHL patients than in healthy controls (17% vs. 1.5%) in 10 studies. In subtype-specific studies, HCV was mainly linked to lymphoplasmacytic lymphoma (Morbus Waldenström), diffuse large B-cell lymphoma (DLBCL), and marginal zone lymphoma (MZL). Notably, the risk estimations for follicular lymphoma were not increased.[10] A large prospective French ANRS-Lympho-C study reported similar results in that MZL (39%) and DLBCL (39%) were the most prevalent NHL subtypes linked to HCV infection.[11] HCV infection was shown to lead to inferior survival of patients with DLBCL.[12] Successful anti-HCV therapy greatly reduces the risk of NHL among HCV patients, but only noted in patients <65 years of age but not those >65 years of age, suggesting HCV patients should be treated with antivirals as early as possible.[13]

Several investigations have shown that HCV has an etiological role in lymphoma development. Similar to the degradation of gastric mucosa-related lymphoid tissue lymphoma after *Helicobacter pylori* extinction,[14] many studies have demonstrated that patients suffering from HCV-associated lymphoma can obtain remission of lymphoma after antiviral therapy. This was first found in nine individuals with splenic lymphoma treated with interferon and Ribavirin as first-line therapy.[15] All individuals who achieved HCV clearance (undetectable HCV RNA) acquired a lymphoma response. None of the six other patients in the study who did not have HCV infection and received antiviral medication experienced lymphoma regression. In HCV-infected patients, immunoglobulin heavy chain gene (IgH) rearrangement and t (14;18) translocation in PBMCs disappeared after antiviral treatment.[16] In t (14;18) translocation, BCL-2 is translocated from its normal site 18q21 to co-located with the IgH seat at 14q32, which results in the initiation of transcription of the gene in lymphoma cells, resulting in overexpression of the BCL-2 protein or activation by the NF-κB anti-apoptotic pathway. The BCL-2 gene is considered closely related to the genesis and development of DLBCL.

For NHL patients with HCV infection, the antiviral regimen based on an interferon and Ribavirin combination can completely or partially relieve some indolent lymphoma.[15,17] And recurrence of the virus after the initial virological response leads to lymphoma progression.[18] Antiviral therapy reduces extrahepatic manifestations (e.g., cryoglobulinemia vasculitis, malignant B-cell lymphoproliferative diseases) related to HCV when a sustained virological response (SVR) is achieved. In patients with cryoglobulinemia vasculitis, SVR was associated with higher complete response (CR) [OR 20.76, (95% CI: 6.73–64.05)], while in patients with malignant B-cell lymphoproliferative disease, SVR was related to higher objective response [OR 6.49, (95% CI: 2.02–20.85)]. According to the results of four HCV study populations including over 7,000 patients, SVR reduced extrahepatic mortality [OR 2.29, (95% CI: 1.49–3.52); $p<0.001$].[19]

Association between HBV and NHL: epidemiological data

Studies in China, South Korea, Japan, and other HBV-endemic areas have shown that the HBV infection rate in NHL is much higher than in the general population.[20–23] In a prospective cohort study of 603,585 enrolled Korean population, Engels *et al*.[24] found 53,045 HBsAg positive (8.8%), suggesting that South Korea is a high epidemic area of HBV. After over 10 years of follow-up, the risk of NHL in the HBsAg positive group was considerably higher than in the negative group [OR 1.74, (95% CI: 1.45–2.09)]. In NHL subtypes, positive HBsAg was linked to a higher risk of DLBCL (OR 2.01, 95% CI: 1.48–2.75) than negative HBsAg. Li *et al*.[25] analyzed a large-scale retrospective cohort study of Chinese patients. They found that the risk of B-cell NHL, multiple myeloma, and acute lymphoblastic leukemia in the HBV infection group was more significant than in the non-HBV infection group. The HBV infection rate was higher, especially in aggressive B-NHL (including DLBCL, MCL, primary mediastinal large B-cell lymphoma, and Burkitt lymphoma). The aggressive B-NHL group had a considerably higher HBsAg-positive rate than the indolent B-NHL group. Meanwhile, the prevalence of positive HBeAg status, positive anti-HBe status, and antiHBc status in the aggressive B-NHL group was significantly higher

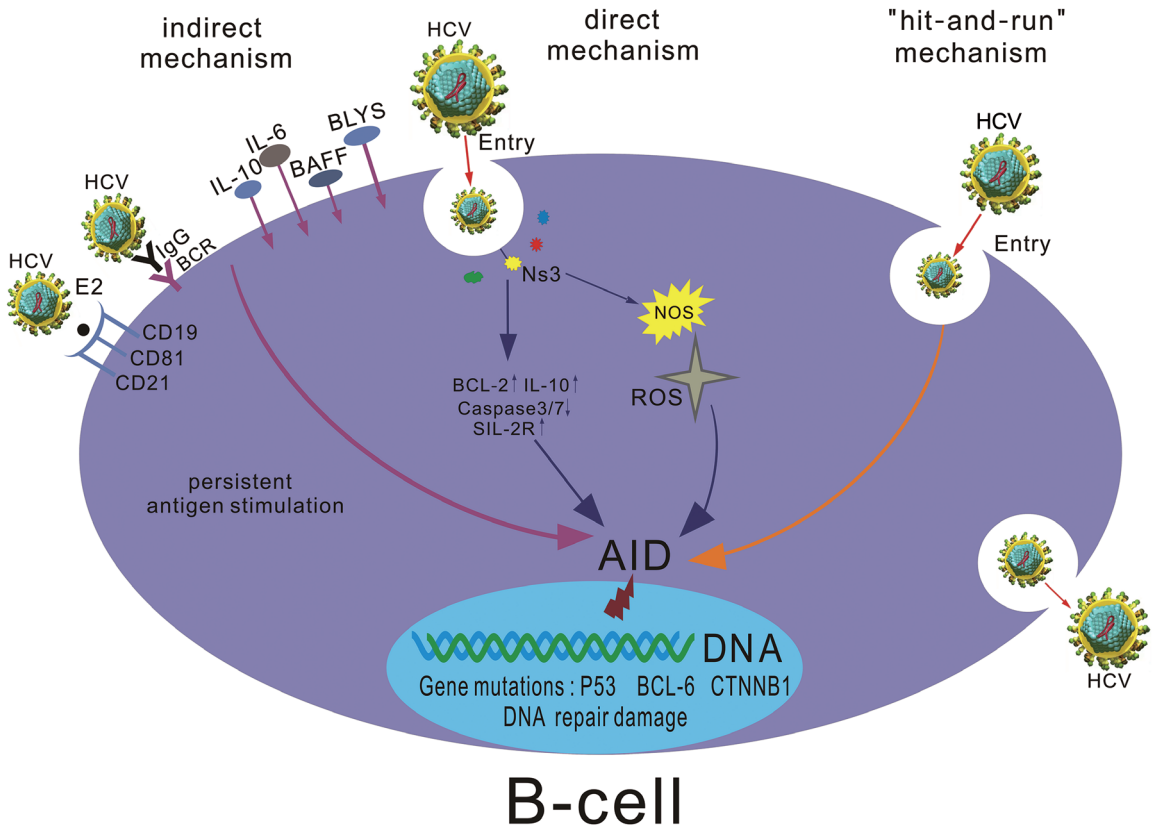

Fig. 1. Pathogenesis of HCV-associated NHL. (1) Indirect mechanisms: Stimulation of B lymphocytes by extracellular HCV and cytokines; Chronic antigenic stimulation of a B cell that interacts with the cognate HCV antigen via its surface Igs; HCV-E2 protein binds to the high-affinity receptor CD81 on B cells; Viral antigens stimulate lymphocyte receptors on a continuous basis, resulting in proliferation; Evidence of oncogenic signal upregulation (IL10, IL6, BAFF, BLyS). (2) Direct mechanisms: Oncogenic effects mediated by intracellular HCV proteins; Oncogenic effects of HCV replication in B cells mediated by intracellular viral proteins; Induction of oncogenic signals (BCL2, IL10, sIL2R) and reduced sensitivity to Fas-induced apoptosis (decreased levels of caspases 3/7); *In vitro* expression of HCV core protein and NS3 proteins induce NOS and ROS generation; These cause DNA repair damage and mitochondrial injury that may precede cellular transformation. (3) Hit-and-run mechanism: Permanent genetic B lymphocytes damage by the transitional entry of HCV; The hit-and-run theory proposes that a transiently intracellular virus causes permanent genetic B-cell damage. HCV, hepatitis C virus; NHL, non-Hodgkin lymphoma; IL, interleukin; BAFF, B-cell activating factor; BLyS, B lymphocyte stimulator; BCR, B-cell receptor; NOS, nitric oxide synthase; ROS, reactive oxygen species; AID, activity-induced cytosine deaminase.

than in the indolent B-NHL group, respectively.[26] In addition, three meta-analyses showed that the risk of NHL in HBV-positive individuals was 2–3 times greater than in the general population.[27–29] According to a study using the Taiwan health insurance research database from 1997 to 2013, hepatitis B vaccination, being the most effective method of preventing hepatitis B infection, can significantly reduce the prevalence of HBV-associated NHL in adolescents and young adults <20 years of age.[30] HBV infection was found to significantly enhance the incidence of NHL, particularly B-NHL, in all of the studies mentioned above.

In addition, populations in HBV-endemic areas have high rates of occult HBV infection.[23,31] Occult HBV infection is defined as HBV DNA being continuously expressed in serum or tissues or both, but HBsAg is negative in patients.[32] In contrast with normal subjects and other patients with non-liver solid tumors, NHL patients are more likely to have an occult HBV infection. This may indicate a link between occult HBV infection and the occurrence and progression of NHL.[23,33] The stable existence of HBV covalently closed circular DNA (cccDNA) in cells, which may be employed as a template for gene transcription, causes occult infection. Extrasomal HBV cccDNA exists in staining virus microchromosomes, which are very stable and persistent. Additionally, HBV infection can persist for life once initiated, even after successful immune control, due to the long half-life of hepatocytes.[34] It means that HBV can reactivate even after the infection has been resolved.[35]

Pathogenesis of HCV-associated NHL

The exact mechanism of HCV leading to NHL has not been fully clarified, and there are mainly the following possible mechanisms. (1) Indirect mechanisms: stimulation of B lymphocytes by extracellular HCV and cytokines; (2) Direct mechanisms: oncogenic effects mediated by intracellular HCV proteins; (3) hit-and-run mechanism: permanent genetic B lymphocyte damage by the transitional entry of HCV (Fig. 1).

Indirect mechanisms: stimulation of B lymphocytes by extracellular HCV and cytokines

Increasing evidence shows that HCV-associated antigens can induce nonmalignant clonal expansion of B cells by chronic stimulation of B cells, leading to malignant lymphoproliferative diseases by a gene mutation. Antibody responses against HCV are mainly directed toward the HCV-E2 protein. Quinn *et al*.[36] found that HCV-E2 protein can activate B lymphocytes in patients with HCV-associated lymphoma, which confirmed

that HCV as a chronic antigen could stimulate B-cell proliferation. It was shown that in most patients with HCV-associated lymphoma, the monoclonal IgM was encoded by a limited set of variable (V) region genes, notably the germline genes VH1-69 (also named 51p1) and VkA27 (also named kv325). Interestingly, MC patients expressed the same set of genes (VH1-69 and VkA27).[37] Chan *et al*.[38] explored 10 human B-cell hybridomas from the peripheral blood B cells from a patient with an asymptomatic HCV infection. They demonstrated that the VH1-69 gene found in HCV-related lymphoma and MC is involved in the anti-E2 immune response. These outcomes link the HCV-associated lymphoproliferative diseases with the immune response to HCV antigens.

Marasca *et al*.[39] studied five HCV-positive nodal marginal zone B-cell lymphoma cases and found that the VH1-69 gene was used expressed in three cases, and the CDR 3s of the three cases were highly similar. This suggests that the selection of B cells involves a common antigen, which may be HCV antigen epitope. This indicates that B-cell selection involves a common antigen, possibly an HCV epitope. Correspondingly, MC (especially MC II) can transform into malignant lymphocytic diseases, and about 8–10% of MC II patients can transform into B-NHL.[7] In a case series,[40] 20 of 231 MC patients developed B-NHL within a median time of 8.8 years. Sequential variable-diversity-joining pattern exploration in one patient during both MC and B-cell small lymphocytic lymphoma revealed that the lymphoma was caused by a clone of overstimulation during MC,[41] confirming the effect of chronic antigenic stimulation on the growth of HCV-related lymphoma.

CD81 is a cell surface adhesion molecule expressed in various tissue cells, including B, T, and natural killer cells. The role of CD81 on B cells is to form activated co-receptors with CD19, CD21, and Leul 3 and cooperate with B-cell receptor (BCR) to transmit antigen and complement recognition signals to B cells to reduce the activation threshold of B cells.[37,42] CD81 is thought to be an HCV-E2 protein receptor, and the interactions between CD81 and HCV-E2 protein can cause genomic instability in the host. Purified E2 protein binding to B cells can lead to a double-strand DNA break in the variable region of the IGVH gene resulting in hypermutation.[38,43] Somatic cells need to activate the activity-induced cytosine deaminase (AID) during hypermutation, and CD81/E2 can increase AID expression. Overexpression of AID can lead to DNA base mismatch and mutation of Ig and non-Ig genes. AID activation by HCV has been correlated with the induction of mutations in the beta-catenin, BCL6, and p53 genes in B cells.[44] HCV in conjunction with CD81 and BCR may cause gene mutation, such as high expression of Bcl-2, the double-strand break of DNA, and eventually lead to malignant clonal proliferation of cells.[39,40,45,46] HCV has been shown to protect human B cells against Fas-mediated apoptosis even in the absence of viral entrance into the human B-cell through E2-CD81 interaction.[47]

Cytokines are also involved in the progression of HCV-associated lymphoma. B-cell activating factor (BAFF), a member of the tumor necrosis factor (TNF) family, is involved in B-cell proliferation.[48] In chronic HCV infection, upregulation of BAFF has been observed.[49] HCV patients without MC have lower BAFF levels, while those with cryoglobulinemia have intermediate levels and those with NHL have higher levels.[50] BAFF expression was upregulated by HCV-induced GU-enriched miRNAs via exosome transmission and TLR7 activation. The mechanisms of miRNA action are important in the development of extrahepatic manifestations in HCV-infected hepatocyte-immune system communication.[51] In addition, dysregulated microRNAs (miRNAs), particularly miR-26b downregulation, may contribute to the deterioration of tumor suppression.[52] Cytokines including interleukin (IL)-6 and IL-10 have also been linked to the proliferation of hepatitis C virus-infected B cells.[53,54]

Direct mechanisms: oncogenic effects mediated by intracellular HCV proteins

Virological lymphotropic has been assumed to play a critical role in the pathogenesis of HCV-related lymphoproliferative disease (LPD) since the first evidence of HCV potential to infect peripheral mononuclear cells.[55] It has been demonstrated that HCV causes lymphotropic infection.[56–58] Studies have shown that HCV replicates in B cells, T cells, macrophages, monocytes, Kupffer cells, and dendrocytes.[57,59] HCV RNA-negative strands (i.e., the viral replicative intermediates) were found in neutrophils,[60] peripheral mononuclear cells,[61] and $CD34^+$ stem cells[62] by some investigators. A negative-strand strand of HCV RNA cannot be attributed solely to passive absorption by HCV circulation in peripheral blood, as evidenced by the expression of HCV-encoding proteins NS3 and NS5 in PBMCs,[63–65] suggesting that HCV replicates and generates HCV proteins.

Other studies have shown that HCV persists in PBMCs from immune-deficient mice with severe combined immunodeficiency. They injected intraperitoneally PBMCs taken from HCV patients suffering from LPDs into severe combined immune deficiency (SCID) mice and discovered viral RNA (such as negative-strand HCV RNA) at various times following the injection.[66] It was found that, based on results from injecting lymphoid cells from HCV-positive patients in SCID mice, the samples derived from HCV patients with malignant LPD had a high number of HCV replicative intermediates, more significant signals when DNA sequences of the viral genome were analyzed. Serial passage of these infected cells took place successfully in various mice. Transgenic mice with malignant lymphoma expressed HCV core mRNA in enlarged lymph nodes. According to these results, HCV core proteins may significantly affect the growth of malignant lymphomas.[67]

In addition, Sung *et al*.[68] established B-cell lines that consistently produced infectious viruses from an HCV-positive lymphoma. By detecting both HCV negative-strand RNA by reverse transcription-polymerase chain reaction, as well as the NS5A protein, Nakai discovered that the recombinant strain of HCV J6JFH1 was capable of infecting human B cells separated from human peripheral blood. Despite HCV replication being less efficient in B lymphocytes than in hepatocyte line (Huh7) cells, their outcomes show that human B lymphocytes without other non-B cells can be infected with HCV.[69]

Intracellular viral proteins have been demonstrated to potentially contribute to direct oncogenic transformation in several mouse models. For instance, following a latency period of between 180 and 600 days, mice with the combination of interferon regulatory factor-1 inactivation and persistent expression of HCV structural proteins, such as CN2, develop lymphoproliferative diseases.[70] The main events that were discovered to cause lymphoproliferation in this model included increased levels of IL2, IL10, and Bcl-2 as well as increased Bcl-2 expression.

It has been demonstrated that the HCV core protein and NS3 proteins increase the production of nitric oxide synthase (NOS) and reactive oxygen species (ROS), which lead to DNA repair damage and mitochondrial injury and may precede cellular transformation,[71] which might be one of the factors causing DNA mutations and double-strand breaks. Overall, the decreased ability of HCV-infected cells to effectively repair DNA damage combined with HCV's capacity to cause DNA damage would cause random rearrangements to occur in the genome, increasing the risk of developing cancer.

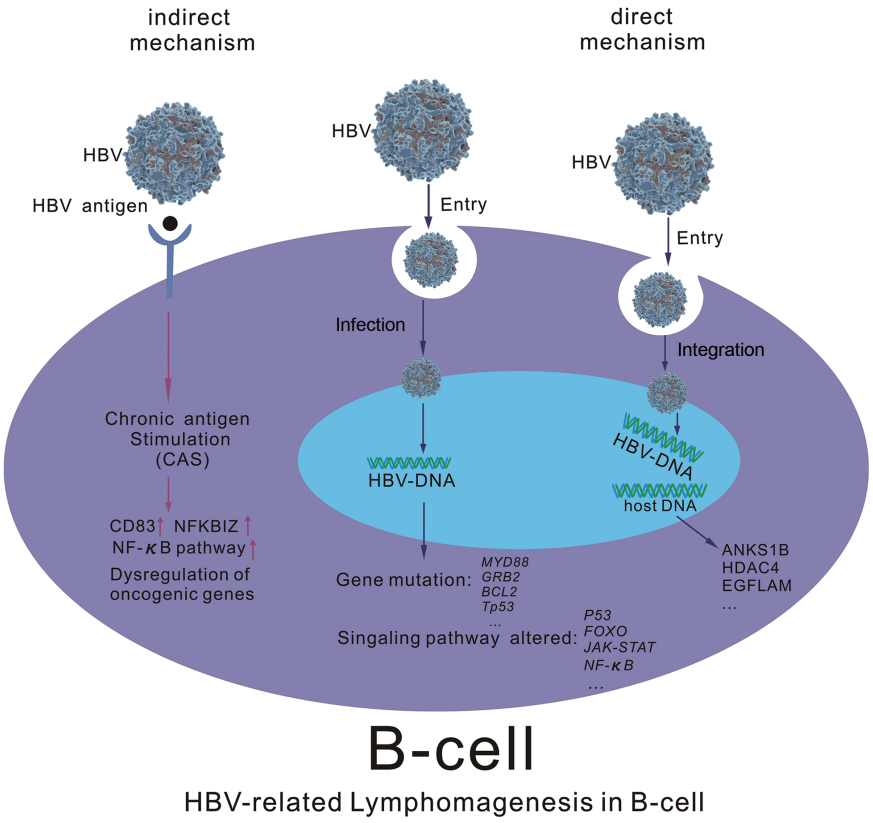

Fig. 2. Pathogenesis of HBV-associated NHL. (1) Indirect mechanisms: Stimulation of B lymphocytes by extracellular HBV; Antigens of HBV can also trigger chronic antigenic stimulation that causes immune response, genetic damage, and lymphocyte proliferation. B-cell antigen stimulation-related genes (e.g., CD83, NFKBIZ, etc.) were upregulated. Among them, mutations in NFKBIZ gene were associated with abnormal NF-κB pathway and dysregulation of pro-oncogenes, which could lead to the development of ABC subtype DLBCL. (2) Direct mechanisms: Oncogenic effects mediated by intracellular HBV DNA; HBV infects B cells directly, causing genetic mutations (MYD88, GRB2, BCL2, TP53, NFKBIA, FAS, MYC, STAT3, PRKCB) and signaling pathway altered (p53, FOXO, BCR, JAK-STAT, NF-κB) that lead to the development of cancerous tumors; HBV DNA can repeatedly target and integrate protein-coding genes (ANKS1B, CAPZB, CTNNA3, EGFLAM, FHOD3, HDAC4, OPCML), which have significantly altered expression levels in NHL and may be potential candidate oncogenes for DLBCL. HBV, hepatitis C virus; NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma.

Permanent B-cell damage, the hit-and-run theory

The basic idea in hit-and-run mechanisms is that they lead to permanent genetic mutations even after viral clearance due to transient intracellular reproduction and proliferation of viral proteins. In B-cell lines and PBMCs *in vitro*, HCV has been discovered to produce a high mutation frequency of cellular genes (p53, Bcl-6, immunoglobulin heavy chain, and beta-catenin genes) by causing double-strand breaks and motivating AID and error-prone polymerases, stimulating tumor necrosis factor α (TNF-α) generation. The amplification of HCV-induced mutations in tumor suppressor genes and protooncogenes is realized in HCV-related B-NHL in vivo, indicating that they may transform the B cells into oncogenes. It may be regarded as a hit-and-run mode of cell change to induce the mutator phenotype in B cells by HCV infection, neither acute nor chronic.[44,45] Green *et al*.[72] proposed that in human ABC-like DLBCL, genetic changes of BCL6 may work in a hit-and-run fashion in early precursors. At the same time, dependence on alternative oncogenic mechanisms, including nuclear-factor kB and BCR signaling pathways, are developed by evolved tumor cells. The overexpression of AID in B cells of HCV-infected individuals may exert a critical effect on lymphomagenesis. As a result, the CD19+ cell subset of B cells from PBMCs overexpress many lymphomagenesis genes, including AID.[73] However, similar results have not been repeated in vivo,[74] and more research shall confirm these findings.

Pathogenesis of HBV-associated NHL

The presence of HBV DNA in B cells, plasma, and tumor tissues of DLBCL patients has recently been discovered using next-generation sequencing, confirming HBV's lymphoid and carcinogenic potential.[75] The specific role of HBV in the occurrence of NHL is still unclear, and the research on its mechanism is less extensively explored than HCV,[76] and there are mainly the following possible mechanisms.1) Indirect mechanisms: stimulation of B lymphocytes by extracellular HBV; 2) Direct mechanisms: oncogenic effects mediated by intracellular HBV DNA (Fig. 2).

Indirect mechanisms: stimulation of B lymphocytes by extracellular HBV

One mechanism may be the long-term stimulation of HBV antigen in patients with hepatitis B, which induces an immune response and promotes abnormal proliferation of lymphocytes. Gene expression analysis revealed that B-cell antigen stimulation-related genes (e.g., CD83, NFKBIZ, etc.) were upregulated. Among them, mutations in the NFKBIZ gene were associated with abnormal NF-κB pathway and

dysregulation of pro-oncogenes, which could lead to the development of ABC subtype DLBCL.[77] By studying HBV immunoglobulin variable region gene fragments in the DLBCL tissues of patients with positive HBsAg, Deng *et al*.[78] found that HBsAg-positive DLBCL patients tended to use the heavy chain gene IGHV4-34 (42.1%) and light chain gene IgKV4-1 (65.5%), which were higher than normal peripheral blood B cells. IGHV4-34 gene fragment mainly encodes antibodies to recognize viral antigens and autoantigens. Therefore, it is suggested that specific antigens are involved in the pathogenesis of DLBCL. It was also found that almost all HCDR3, KCDR3, and LCDR3 showed high homology with specific antibody sequences of HBV-associated antigens (mainly HBsAg), confirming that HBV antigenic stimulation is one of the pathogenetic mechanisms. However, Ren *et al*.[79] found by gene sequencing comparison that there was no biased usage of the IGVH gene in HBsAg-positive DLBCL patients, and that the CDR3 region in HBsAg-positive DLBCL patients did not have a fixed type, nor was there any sequence identity with hepatitis B virus surface antibody (anti-HBs). They propose that HBV infection of B cells may lead to an overactive state, resulting in enhanced mutations mediated in part by APOBEC and AID. Finally, it increases the overall mutation burden in HBsAg-positive DLBCLs.

In conclusion, the evidence and literature related to the chronic antigen stimulation theory are still scarce and the findings are not yet uniform, so further studies are still needed to validate it. However, in general, more findings support the idea that HBV infection of lymphocytes leads to DLBCL.

Direct mechanisms: oncogenic effects mediated by intracellular HBV DNA

Another possible mechanism is that, similar to EBV-driven lymphoma, HBV infects B cells directly, causing genetic alterations in the formation of malignant tumors.[80] HBV has the characteristics of the hepatotropic virus, which can cause chronic hepatitis and may lead to HCC; simultaneously, it can survive in extrahepatic sites such as lymph nodes, lymphoblastoid cells, vascular elements, and bile ducts in the liver.[81] The main area of HBV replication is in the liver, but the lymphatic system is a virtual repository for the virus. Some studies have isolated HBV DNA from PBMCs.[82–84] *In vitro*, HBV can infect B lymphocytes directly, and HBV nucleic acid and antigen have been found in the lymphoma tissues of HBV-positive patients. In tissues from DLBCL patients who were serum HBsAg positive, HBx protein, a transcription factor that plays an important role in tumorigenesis, was highly expressed.[85] Analysis by whole genome sequencing/whole exome sequencing , transcriptome sequencing, and targeted sequencing techniques revealed significantly enhanced gene mutations with unique mutation features in HBsAg-positive DLBCL patients.[79] Mutation tag analysis identified tags associated with APOBEC, suggesting that the frequency of gene mutations is increased in patients with HBV-positive DLBCL and is partially due to APOBEC/AID. The most critical mutational pathways in patients with HBV-positive DLBCL are consistent with those involved in HBV-associated pathways, and these genes include MYD88, GRB2, BCL2, TP53, NFKBIA, FAS, MYC, STAT3, and PRKCB. In addition, high-frequency mutations identified in patients with HBV-positive DLBCL involve other important signaling pathways, including p53, FOXO, BCR, JAK-STAT, NF-κB, and related signaling pathways such as epigenetic modifications, immune escape, and cell migration.

HBV DNA may integrate into the B-cell genome and directly destroy tumor suppressors or activate tumor genes, as in HBV-induced HCC.[86] It has been shown that HBV DNA can be integrated into PBMCs.[82] Using a high-throughput virus integration assay (HIVID), HBV DNA was also discovered to be integrated into the NHL cell genome.[87] Combining HIVID and immunohistochemical analysis, HBV DNA was found to repeatedly target and integrate seven protein-coding genes, namely ANKS1B, CAPZB, CTNNA3, EGFLAM, FHOD3, HDAC4, and OPCML, in lymphoma tissues, which have significantly altered expression levels in NHL and may be potential candidate oncogenes for DLBCL. Thus, it provides strong evidence for the connection between NHL and HBV infection.

According to Zhou *et al*.,[76] serum HBV activity may not significantly impact the pathogenesis of aggressive B-NHL. Like HCV-associated B-NHL, transient intracellular virus-induced permanent genetic cell damage may be more related to the pathogenesis of invasive B-NHL than to viral activity in the serum. They discovered that patients with indolent B-NHL and HBV infection had higher HBV DNA levels when they were first diagnosed with B-NHL than those with aggressive B-NHL. Patients with both indolent B-NHL and HBV infection showed considerably higher serological HBV activity than those with aggressive B-NHL.

Treatment for HCV-associated NHL

Because of its antiviral and immunostimulatory properties, interferon (IFN) has been used to treat chronic HCV for more than 20 years.[88] Its pegylation (PEG-IFN) made it possible to administer subcutaneous injections weekly rather than at least triweekly, and the combination with Ribavirin significantly increased the effectiveness of the treatment.[89,90] Clinical tolerability (flu-like syndrome, acute dysimmunological pathologies, neurocognitive disorders) and biological toxicity (neutropenia and thrombocytopenia for IFN, hemolytic anemia for Ribavirin) were the main limitations of this combination. Hematological toxicity is the main obstacle to concurrent chemotherapy and antiviral therapy. In recent years, IFN-free direct antiviral agents (DAAs) have been introduced to treat HCV infection, and these drugs demonstrated high efficacy in promoting (SVR), ranging from 90–100%.[91,92]

The regression of HCV-associated NHLs after HCV eradication is the most compelling proof supporting HCV infection's role in LPDs. As an additional benefit, eradicating HCV after cytotoxic chemotherapy may prevent HCV exacerbations. The treatment of HCV-associated B-NHL still needs to be optimized. There are three different approaches to timing HCV treatment: first-line (DAAs) for hematological conditions, second-line DAAs after chemotherapy, and DAAs concurrently with chemotherapy. Table 1 shows the main studies of DAAs conducted in HCV patients with associated NHL.[93–98]

It is reasonable to consider DAAs administration as first-line therapy for indolent lymphoma patients who would not need instant chemotherapy. As found with (IFN), the HCV-associated lymphoma might be regressed after HCV eradication.[99] There are few case reports of DAAs all-oral treatment of the hematological disease being completely response. Arcaini *et al*.[94] explored the virological and lymphoproliferative disease response (LDR) of 46 patients who had chronic HCV infection and indolent B-cell NHLs, or chronic lymphocytic leukemia (CLL) treated with DAAs. The DAAs therapy lasted 12 weeks on average (6–24 weeks). At week 12 after completing DAAs, 45 patients (98%) had an SVR; the total LDR rate was 67%. The 1-year progression-free and total survival rates were 75% and 98%, respectively, following a median follow-up of 8 months. A recent prospective study treated patients with HCV-associated indolent lymphomas with genotype-appropriate DAAs. 100% of patients experienced a persistent virologic response. The overall response rate for

Table 1. Current evidence from DAA-based antiviral therapy for the treatment of HCV-positive NHLs

Reference	Study design	Patients, *n*	Lymphoma subtype, *n* (%)	HCV RNA (genotype), *n* (%)	Cirrhosis, *n* (%)	MC, *n* (%)	DAAs therapy, *n* (%)	Chemotherapy, *n* (%)	Sustained virologic response, *n* (%)	MC response, *n* (%)	NHL response, *n* (%)	Follow-up, m
Alric *et al*., 2016[93]	Prospective cohort	10	MZL: 6 (60); DLBCL: 3 (30); Other: 1 (10)	Genotype 1: 6 (60); Genotype 2: 1 (10); Genotype 3: 1 (10); Genotype 5: 1 (10); Genotype 6: 1 (10)	1 (10)	7 (70)	SOF-based regimen	Concomitant: 9 (90)	9 (90)	–	CR: 9 (90); PR: 1 (10)	12
Arcaini *et al*., 2016[94]	Retrospective cohort	46	MZL: 37 (80); LPL: 2 (4); FL: 2 (4); CLL/SLL: 4 (9); NHL NOS: 1 (2)	Genotype 1: 29 (63); Genotype 2: 12 (26); Genotype 3: 3 (7); Genotype 4: 2 (4)	7 (15)	15 (33)	SOF-based regimen: 39 (85); Other regimen: 7 (11)	No.	45 (98)	CR: 7 (15)	CR: 12 (26); PR: 19 (41); SD: 11 (24); PD or NR: 4 (9)	8
Persico *et al*., 2018[95]	Prospective cohort	20	DLBCL	Genotype 1b: 20 (100)	4 (20)	–	SOF-based regimen: 20 (100)	Concomitant: 20 (100)	20 (100)	–	CR: 19 (95); PD: 1 (5)	12
Merli *et al*., 2019[96]	Retrospective cohort	47	DLBCL: 45 (96); FL: 2 (4)	Genotype 1: 26 (56); Genotype 2: 16 (34); Other 3: 5 (10)	12 (25)	5 (11)	SOF-based regimen: 47 (100)	Before DAA: 38 (81); Concomitant: 9 (19)	45 (96)	–	CR: 46 (98); PD: 1 (2)	33.6
Frigeni *et al*., 2020[97]	Retrospective cohort	66	MZL: 53 (80); Non-MZL: 13 (20)	Genotype 1: 38 (59); Genotype 2: 19 (29); Other 3: 8 (12)	7 (11)	27 (41)	SOF-based regimen: 66 (100)	No.	65 (98)		CR: 14 (21); PR: 31 (47); SD: 15 (23); PD: 5 (8)	17
Merli *et al*., 2022[98]	Prospective cohort	40	MZL: 27; Non-MZL: 13	1: 16 (40); 2: 21 (53); 3: 2 (5); 4: 1 (2)	0	14 (35)	SOF-based regimen: 40 (100)	No.	40 (100)	CR:8 (57); PR: 1 (7)	CR: 8 (20); PR: 10 (25); SD: 16 (40); PD: 6 (15)	37

CLL, chronic lymphocytic leukemia; DAA, direct antiviral agent; DLBCL, diffuse large B-cell lymphoma; HCV, hepatitis C virus; LPD, lymphoproliferative disease; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma.

lymphoma was 45%, with eight patients (20%) obtaining a CR and 10 patients (25%) having a partial response. Six patients advanced and 16 had stable disease.[98] These results suggest that DAAs based antiviral therapy is beneficial for patients with indolent B-NHL, particularly those with marginal zone type, and reveal the etiological role of HCV in B-NHL.

Conversely, antiviral therapy alone is unlikely to be sufficient in treating aggressive NHL, and therefore immediate chemotherapy is necessary. This is often in conjunction with the CD20 antibody rituximab (chemo-immunotherapy, as CIT, is known). Despite limited data,[100] revised international hematology (National Comprehensive Cancer Network) and hepatology (European Association for the Study of the Liver) guidelines recommend patients with HCV-related DLBCL achieve a CR after first-line immunochemotherapy (I-CT) before undergoing HCV eradication with DAAs.[101–102] Moreover, recent studies have shown that concurrent DAAs and R-CHOP management for the prevention of hepatic toxicity could be feasible, efficient, and ideally preferable to deferred management of DAAs.[95,96] An international retrospective analysis[96] of 47 HCV-related DLBCL patients treated concurrently (coincident cohort: *n*=9) or sequentially (sequential cohort: *n*=38) in 23 Italian and French centers examined the hematological and virological outcomes and survival. This cohort of HCV-related DLBCL patients had an excellent outcome, with a high SVR rate, well tolerance, and high progression-free survival, indicating that DAAs are beneficial to eradicating HCV both after and during I-CT. This group of HCV-positive DLBCL patients had an excellent result, with a high SVR rate, well tolerance, and prolonged progression-free survival, indicating that DAAs are beneficial to eradicating HCV both after and during I-CT. Future research should evaluate the ideal time for HCV treatment with DAAs in patients with aggressive lymphomas. As a result, HCV testing at the time of NHL diagnosis and HCV load detection along the course of the disease are required.[103,104] A retrospective study showed that the cumulative incidence rate of lymphoma in HCV-infected patients after antiviral therapy was lower than that in untreated HCV-infected patients, indicating the preventive effect of antiviral treatment on B-NHL,[105,106] and early initiation of antiviral treatment is recommended.

Treatment of HBV-associated NHL

HBV increases the risk of NHL and further affects the chemotherapy effect and prognosis of NHL patients.[107,108] According to a meta-analysis,[108] DLBCL patients with chronic HBV infection had significantly poorer progression-free survival (PFS) at 2- and 5-years and overall survival (OS). Patients who were seronegative for HBsAg had a lower CR rate, higher progressive disease (PD) rate, and more advanced clinical features.[109] Chemotherapy for NHL is affected by HBV infection and replication. At the same time, chemotherapy can also activate HBV replication.[110] According to studies, HBV reactivation is a risk for HBsAg-positive NHL patients who receive rituximab-containing immunochemotherapy R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) and the rate of HBV reactivation can be as high as 70%. Compared to the CHOP group, abnormal liver function is significantly higher, and fulminant hepatitis can occur in severe cases in the R-CHOP group.[111,112] Wei *et al*.[113] conducted a multicenter large-sample data analysis that showed HBV infection status had no significant effect on prognosis in patients with DLBCL receiving CHOP chemotherapy. Compared to HBsAg-negative patients, OS in R-CHOP chemotherapy was worse in HBsAg-positive patients, and prognostic factor analysis revealed that HBsAg constituted an independent negative prognostic factor.

Following recent guidelines, all patients with HBsAg positive/HBV DNA≥2,000 IU/mL should be treated for HBV. In most patients, anti-HBV treatment should be continued indefinitely.[112] Although immunocompetent patients with HBsAg positive/HBV DNA<2,000 IU/mL do not need HBV treatment, those undergoing immune-inhibitive therapy are at a high risk of progressing to the immune-reactive stage and should begin antiviral therapy as soon as possible before starting chemotherapy.[114–116] In patients with a hematological disease in remission, ECIL recommendations indicate 12-month continuing prophylaxis after stopping immunosuppressive treatment,[115] whereas other authors advocate continuing for 12–24 months after stopping Chemotherapy.[116]

Using cohort studies on B-cell lymphomas and concomitant HBV infection, Wang *et al*.[117] found CAR-T-cell therapy to be safe and efficient for patients with advanced B-cell malignancies and chronic or resolved HBV infection. Antiviral treatment with tenofovir disoproxil, entecavir, or lamivudine was sustained with a good compliance rate in patients with chronic HBV infection. Patients with resolved HBV infection were supervised for HBsAg, ALT, and HBV DNA and given antiviral drugs if HBV reactivation was examined. In two patients with chronic HBV infection and one with resolved HBV infection, HBV was reactivated. No HBV-associated hepatitis flare occurred. The three cohorts' responses to CAR-T cell treatment were not significantly different. No great diversity was found between the cohorts in neurologic toxicity and cytokine release syndrome. The cohorts were similar in PFS and OS (HBV-Chronic, HBV Resolved, and No HBV infection).

Hepatitis B vaccines have been found to reduce the incidence of NHL. For example, Huang and colleagues[30] found that anti-HBV treatment significantly reduced the risk of HBV-associated NHL in a cohort study with 16 years of follow-up. Hepatitis B vaccination, being the most effective method of preventing hepatitis B infection, can significantly reduce the prevalence of HBV-associated NHL in adolescents. It was also reported that some HBsAg-positive B-NHL patients achieved CR of lymphoma for many years after anti-HBV therapy.[118,119] These results suggest that HBV is related to B-NHL, and antiviral therapy can reduce the activation of chemotherapy-related hepatitis B and have a therapeutic effect on some types of NHL. The above evidence from case reports or small studies, which need further investigation in the future.

Conclusions and further considerations

Current evidence on the link between HCV or HBV and NHL has been summarized in this review. The mechanism of hepatitis virus-related lymphoma is not fully understood and needs further research. The results of antiviral therapy in HCV-associated indolent NHL are encouraging. DAAs are recommended for their high SVR rate, short-term treatment and are generally well tolerated; this will further improve the remission rate of HCV-NHL. In addition, some studies have demonstrated that early anti-HCV treatment has a preventive effect on B-NHL, which has to be verified in further large-scale prospective epidemiological studies. Hepatitis B vaccines have been found to reduce the incidence of NHL. Investigations have demonstrated poor overall treatment outcomes and prognosis in HBV-NHL, and current studies have confirmed that CAR-T-cell therapy is safe and effective in HBV-NHL.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

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