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Review article

Contradictory Mechanisms of rheumatoid arthritis and hepatitis B virus infection activation

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ABSTRACT

Rheumatoid arthritis (RA) is associated with a high rate of hepatitis B virus (HBV) infection. A large proportion of HBV reactivation may occur in RA patients after immunosuppression treatment, while fulminant hepatitis may occur in severe cases. Immunosuppressants are fundamental medications for the treatment of RA but carry the risk of inducing HBV reactivation. This inherent contradiction poses challenges throughout the immunosuppressive treatment process in patients with RA. Recently, numerous studies have been conducted on the contradictory therapeutic mechanisms between RA treatment and HBV infection, including aspects of innate immunity, adaptive immunity, and related signalling pathways. In this article, we review the immunological mechanisms underlying the onset of RA and HBV infections, providing a reference for determining appropriate treatment plans to reduce therapeutic contradictions and thereby reduce the risk of HBV reactivation in patients with RA combined with HBV infection.

1. Introduction

The prevalence of rheumatoid arthritis (RA) worldwide is approximately 0.5–1.0 %. Hepatitis B virus (HBV) infection is prevalent worldwide, and the HBV infection rate considerably varies across geographical regions. In some Asian countries, the infection rate is higher than 8 % [1]. HBV infection is very common in patients with RA [2]. Research has shown that the proportion of chronic HBV infection in patients with RA is higher than that in the general population without RA [3]. Previous or current HBV infection is more common in patients with active RA than in those with inactive RA [4]. A meta-analysis revealed that the overall risk of hepatitis B virus

Abbreviations: rheumatoid arthritis, (RA); hepatitis B virus, (HBV); chronic hepatitis B virus, (CHB); hepatitis B virus core antibody, (HBcAb); hepatitis B virus surface antigen, (HBsAg); hepatitis B virus e antigen, (HBeAg); tumour necrosis factor alpha, (TNF-α); mucosal-associated invariant T cells, (MAIT cells); interleukin, (IL); nuclear factor kappa B, (NF-κB); Janus kinase, (JAK); signal transducer and activator of transcription, (STAT); Toll-like receptor, (TLR); B and T lymphocyte attenuator, (BTLA); Fas ligand, (FasL); inhibitor of κB, (IκB); inhibitor of κB kinase complex, (IKK); interferon, (IFN); receptor activator of NF-κB ligand, (RANKL); myeloid differentiation primary response gene, (MyD88); death domain, (DD).

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(HBV) reactivation in rheumatoid arthritis (RA) patients coexisting with chronic hepatitis B is 6.7 %. This risk increases to 37 % when only RA patients with chronic hepatitis B who are not receiving antiviral prophylaxis are included [5]. During a follow-up of 3459 person, 30 patients (24.4 %) experienced HBV reactivation (HBVr). Glucocorticoids significantly increased the risk of HBVr, with the highest risk occurring in patients on a combination of glucocorticoids, biological disease-modifying antirheumatic drugs, and synthetic disease-modifying antirheumatic drugs [6]. Treatment with the biological agent rituximab poses the highest potential risk of HBV reactivation [7]; HBV reactivation also occurs after anti-tumour necrosis factor alpha (TNF-α) treatment [8]. In order to inhibit the activity of autoreactive T cells, the main goal of immunotherapy for HBV infection is to activate T-cell responses, but the treatment goals for HBV and RA are opposite. After RA immunosuppression treatment, the risk of HBV reactivation increases, presenting a crucial dilemma. However, it is not clear whether this contradiction in treatment goals arises from fundamental differences in the underlying mechanisms of the diseases. This review discusses the contradiction of immune mechanisms in the pathogenesis of the two diseases, with the aim of elucidating a more appropriate treatment plan to reduce treatment contradictions and the risk of HBV reactivation (see Table 1).

2. Contradictory immunological mechanisms of RA and HBV infection

The immune system modulates a delicate balance. On the one hand, it protects the host from external pathogens such as HBV; on the other hand, it prevents "self" damage caused by excessive immune responses, as seen in RA. Imbalances in immunoregulatory mechanisms can lead to autoimmune diseases and chronic infections. HBV negatively modulates immune responses during chronic infection phases, rendering them ineffective in the context of autoimmunity [9], thus contributing to the development of autoimmune diseases. Immune tolerance mechanisms prevent autoimmune diseases by limiting overactive immunopathology through "protective" immune responses to non-self-antigens [10]. In RA, the imbalance of regulatory T cells (Tregs)/Th17 and Th1/Th2 cells disrupts immune tolerance, causing the occurrence and development of RA. In HBV, under the condition of chronic long-term antigen stimulation, immune cell dysfunction, T cell exhaustion, and an increase in inhibitory cells and cytokines result in the establishment of immune tolerance [11]. T cell immune tolerance plays a significant role in the pathogenesis of RA and HBV. In RA, pathogenesis arises from the breakdown of immune tolerance, where microorganisms, for example, may citrullinate host and bacterial polypeptides, disrupting immune tolerance and eventually inducing the formation of anti-cyclic citrullinated antibodies [12]. In contrast, HBV infection is characterised by the establishment of immune tolerance, with the immune system playing a core role in controlling HBV infection and promoting virus reactivation [13]. Dysfunction within the immune system, particularly the impaired host immune response against HBV-infected cells, is a key mechanism underlying HBV reactivation [14]. Chekol et al. emphasised that inflammatory reactions can lead to the production of immune regulatory substances, including Tregs and anti-inflammatory cytokines, which may hinder immune surveillance and promote immune tolerance [15]. This allows the modified hepatocytes to avoid immune detection and subsequent immune responses. The immunosuppressive cytokine IL-10, produced by dendritic cells, can inhibit immune activation, promote immune tolerance, and support viral persistence. It can also interact with other immune cells, affecting their activity and contributing to a delicate balance between immune control and tolerance [16]. HBV reactivation is more concerning in individuals receiving immunosuppressive therapy those in those with chronic inflammatory diseases or impaired immune systems [17,18]. The immune mechanisms of RA and HBV intersect, overlap, and interact, forming a complex immune network. An in-depth understanding of the immunological basis of HBV reactivation offers an opportunity to develop targeted personalised management strategies. Using this understanding, healthcare professionals can tailor treatment interventions to enhance immune responses and prevent reactivation in vulnerable groups [19].

2.1. Immune cells

2.1.1. Mucosal-associated invariant T cells (MAIT cells)

MAIT cells play a significant role in innate immunity in RA and HBV infections. MAIT cells can recognise the antigens presented by MHCI-related molecules and express homing receptors, such as CCR5, CCR6, and CCR9 [20].The proportion of MAIT cells in RA

Table 1
Immune cells and related molecular proteins.

Disease	RA		HBV infection	
	Expression	Effect	Expression	Effect
MAIT cells	Increase [20]	Pro-inflammatory [20]	Reduced [34]	Antiviral role [22,34]
GzmB	Increase [13]	Pro-inflammatory [13]	Reduced [22]	Antiviral role [22]
Perforin	Increase [13]	Pro-inflammatory, apoptosis [13]	Reduced [22]	Antiviral role [22]
CD4 T Cells	–	Pro-inflammatory [4]	–	Antiviral role [23]
CD8 T Cells	–	Protect or regulate RA [4]	Reduced [23]	HBV infection persistence [23]
TNF-α	Increased [4]	Pro-inflammatory [4]	Increased [25]	Antiviral role [25]
IL-6	Increased [4]	Pro-inflammatory [4]	Increased [25]	Antiviral role [25]
B Cells	Increased [21]	Pro-inflammatory [29]	Increased [35]	Antiviral role [35]
		Pro-inflammatory, aggravating RA [30]		

Note: RA: rheumatoid arthritis; HBV: hepatitis B virus; MAIT cells: mucosal-associated invariant T cells; GzmB: granzyme B; TNF-α: tumour necrosis factor-alpha; IL-6: interleukin-6.

synovial fluid is high, and the proinflammatory environment may actively regulate MAIT cells. Treatment of these cells with IL-1β leads to increased cell proliferation, while treatment with IL-23 produces IL-17, which indicates that MAIT cells play a direct role in the expansion and continuation of RA [20]. In RA, the proportion of MAIT cells in the synovial fluid is high, and these cells directly contribute to the amplification and persistence of inflammation. MAIT cells can be activated in a T-cell receptor-dependent manner as well as by inflammatory cytokines, such as interleukin (IL)-12, IL-18, and IL-7 [20]. Upon activation, they secrete Th1- and Th17-type cytokines and release granzyme B and perforin, mediating inflammation in RA and degradation of the extracellular matrix. Granzyme B, the strongest apoptotic member of the granzyme family, has the caspase-like ability to cleave substrates at aspartic acid residues, thereby directly activating precursor enzymes and cleaving caspase substrates to trigger apoptosis, which is an important mechanism in the pathogenesis of RA [21]. Activated MAIT cells in the liver can also inhibit HBV replication [22]. Liu et al. assessed MAIT cells in liver tissue and blood and found a reduction in MAIT cell numbers in both compartments, and these cells exhibited anti-HBV activity [22].

MAIT cells are increased in RA and play a pro-inflammatory role, whereas in HBV, their reduction leads to weakened anti-HBV effects. Granzyme B and perforin have a pathogenic role in RA and an antiviral role in HBV infection, demonstrating opposite effects in the pathogenesis of RA and HBV infections.

2.1.2. T cells

T cells play a role in RA and HBV infections. T cells primarily include CD4 T helper and CD8 cytotoxic T cells. CD4 Th1 cells that secrete TNF-α and IL-6 are key factors in promoting the inflammatory cascade reaction in the pathogenesis of RA, whereas $CD8^+$ T cells have a protective or regulatory role in the development of RA [4]. In HBV, $CD4^+$ and $CD8^+$ T cells produce robust responses to control

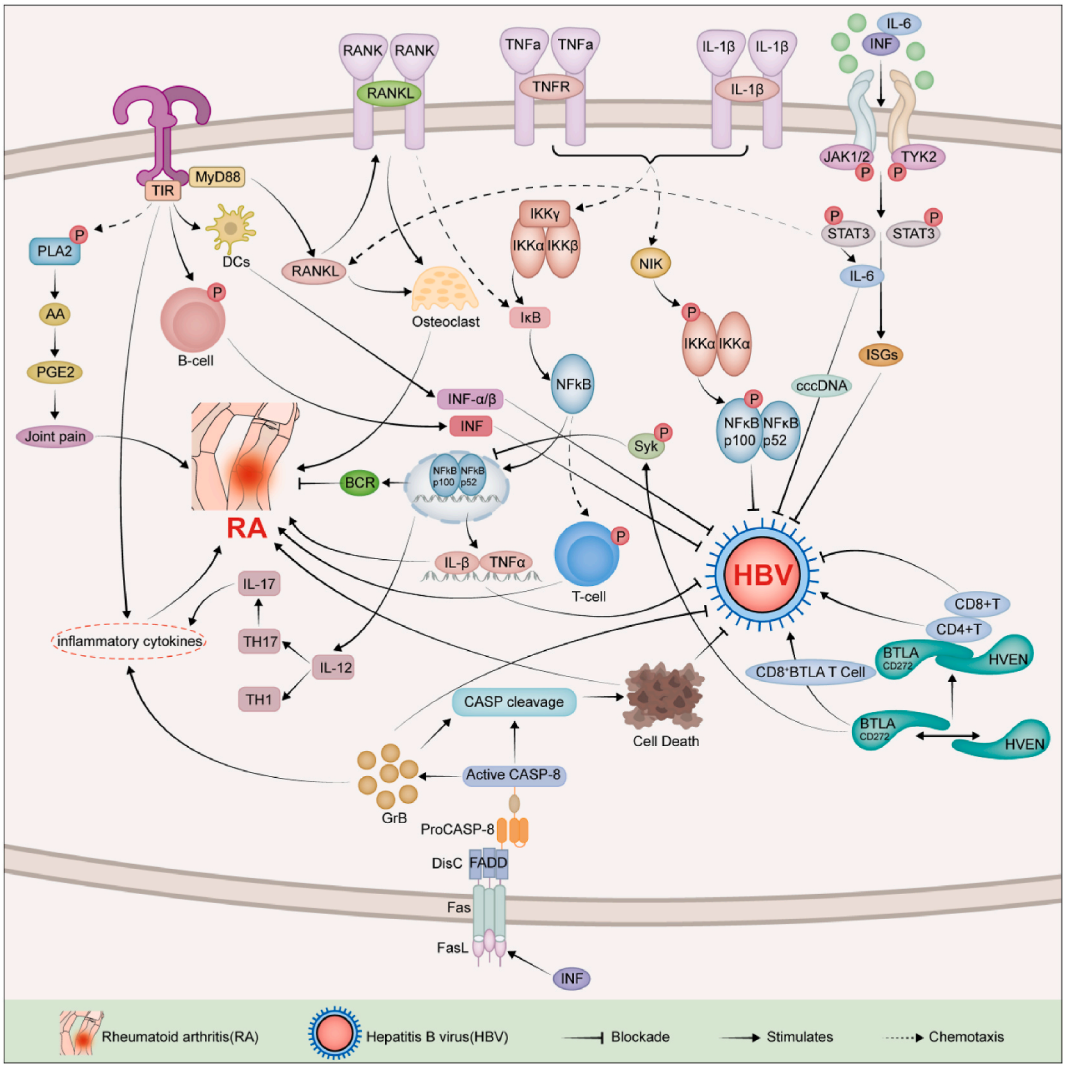

Fig. 1. Contradictory mechanisms in signalling pathways.

and clear the virus. In chronic HBV (CHB) infection, effector $CD8^+$ T cells exhibit a multi-level "exhaustion" phenotype [23]. The ratio of $CD4^+$ to $CD8^+$ T cells in patients with active RA was shown to be significantly higher than that in patients with stable RA and in healthy controls. Moreover, HBV DNA promoted the apoptosis of $CD8^{high}$ T cells in patients with RA, thus exacerbating the condition [24]. $CD4^+$ T cells promote inflammation by secreting TNF-α and IL-6 in RA, while they play an antiviral role in HBV [25]; for example, IL-6 can exert anti-HBV effects by inducing the decay of covalently closed circular DNA and reducing HBV transcription [26]. Elevated CD8 levels have a certain protective effect against RA and HBV infections. However, the differing roles of CD4 in RA and HBV infections may be contradictory, resulting in HBV activation during RA treatment. The pro-inflammatory factors TNF-α and IL-6 secreted by CD4 are the primary targets in RA treatment. However, in RA, there is a certain risk of HBV reactivation to some extent after treatment with TNF-α and IL-inhibitors, such as etanercept and tocilizumab, respectively [27,28]. Anti-IL-6 therapy carries a major risk of HBV in patients with RA combined with CHB, which is reduced when antiviral prophylaxis is used [18].

2.1.3. B cells

B cells play a role in RA and HBV infections by producing antibodies. In RA, B cells produce autoantibodies, such as anti-citrullinated protein antibodies, which form immune complexes with antigens or T cells that produce pro-inflammatory factors, leading to a cascade effect. This feedback loop stimulates monocytes/macrophages, amplifying the effects of pro-inflammatory factors and exacerbating RA [29]. An increase in age-associated B cells in the peripheral blood and synovial fluid of patients with RA may affect their ability to migrate to inflamed joints. The rise in age-associated B cells correlates with RA disease activity and has been shown to play a pathogenic role [30]. In HBV, B cells under the co-stimulation of T cells produce antibodies conjugated to HBsAg, which clear antigens and HBV from the circulation and prevent or limit HBV reinfection [31]. B cells efficiently produce high-affinity virus-specific antibodies to neutralise the virus [32], acting as negative regulators. Lam et al. reported that the memory B cells generated during acute HBV infection can provide a rapid and powerful antibody response when re-exposed to the virus, which is helpful for subsequent immune control. CHB infection can lead to B-cell dysfunction, antibody responses, and impaired immune tolerance [33]. B cell activation leads to the production of autoantibodies, such as rheumatoid factor and anti-citrullinated protein antibodies, which induce and maintain the onset of RA [4]. The suppression of B cells is the primary target of RA treatment. Patients with RA combined with HBV infection have the highest potential risk of HBV reactivation after treatment with the B cell inhibitor rituximab [7].

3. Contradictory Mechanisms in Signalling Pathways

The primary signalling pathways of RA and HBV infections activate and interact with each other, partially inhibiting one another, and together form a complex immune signal transduction network. We will discuss the contradictions within the major signalling pathways, including the nuclear factor kappa B (NF-κB), Janus kinase (JAK)/signal transducer and activator of transcription (STAT), Toll-like receptor (TLR), B and T lymphocyte attenuator (BTLA), and Fas/Fas ligand (FasL) signalling pathways in RA and HBV infections (Fig. 1).

3.1. NF-κB signalling pathway

The main components of the NF-κB signalling pathway are NF-κB, IκB, and IKK [35]. The pathway includes classical, non-classical, and other pathways. The classical NF-κB pathway is mediated by IKK, while the non-classical pathway is mediated by NF-κB-inducing kinase [36] (Fig. 1).

Activated NF-κB has been observed in T cells and antigen-presenting cells in both early- and late-stage RA synovial tissues, where it can trigger inflammation involved in RA and the initiation of inflammation [37]. In RA, dysregulated NF-κB signalling contributes to the pathogenic process by regulating the transcription of inflammatory mediators, such as IL-1β and TNF-α. These NF-κB-regulated inflammatory mediators play a crucial role in the pathogenesis of RA by activating immune and non-immune cells. TNF-α has been shown to reduce the number of T cells producing interferon (IFN)-γ, including Th1 and Th17 cells, and increase the production of IL-17, which indicates that TNF-α plays a role in maintaining the Th17 phenotype and promoting the persistence of Th17 cells [38]. Dysregulation of the NF-κB pathway leads to abnormal activation of T cells, with each member of the NF-κB family responsible for activating different types of T cells in RA [39]. NF-κB induces the differentiation of Th1 and Th17 cells by inducing the production of IL-12, which in turn promotes the synthesis of IL-17 in Th17 cells. IL-17 recruits neutrophils and monocytes to the site of inflammation, exacerbating arthritis [40].

Various viruses can modulate the activation of the non-classical NF-κB pathway through different adaptor proteins, thereby regulating antiviral immunity [41]. The non-classical NF-κB pathway also plays a role in the host response to HBV infection [42]. TNF-α disrupts capsid integrity via NF-κB signalling, thereby inhibiting HBV replication [43], while IL-1β is an important cytokine in NF-κB signalling that exerts anti-HBV effects by inhibiting HBV infection [44]. Kar et al. showed that exosomes from patients with CHB infection play a role in HBV nucleic acid transport to NK cells. This process inhibits NK-cell activity during HBV infection by inhibiting various signalling pathways such as the NF-κB pathway [45]. The researchers observed that HBsAg and HBeAg limit the cytotoxicity and cytokine production of NK cells, and this restriction occurs through interference with NF-κB activation [46].

It is evident that the important cytokines in the NF-κB signalling pathway, IL-1β and TNF-α, play opposite roles in the pathogenesis of RA and HBV, making it one of the signalling pathways where RA treatment can induce HBV activation. Currently, NF-κB inhibitors are still in the experimental stage, with no clinical reports on their use. However, inhibition of the expression of TNF-α, which is an important cytokine in cell-, complement-, and antibody-mediated immunity, can indirectly favour HBV DNA replication [2]. In a

review of patients receiving anti-TNF-α treatment for various diseases (including RA) [47], up to 39 % of chronic HBV carriers experienced reactivation without appropriate antiviral prophylaxis, particularly those treated with infliximab. Additionally, in 1–3% of occult carriers (with undetectable HBV but still infectious) experienced reactivation [47]. Furthermore, anti-HB-negative occult carriers and those receiving monoclonal antibodies, corticosteroids, or traditional DMARD therapy exhibited a significantly increased risk of reactivation [47].

3.2. JAK/STAT signalling pathway

The JAK/STAT signalling pathway is critical for the inflammatory process and forms a positive feedback loop after initiation. As inflammatory factors, cytokines/chemokines play a key role in signalling pathways by activating JAK and STAT signalling proteins and are also major drivers of autoimmune responses [48]; blocking this pathway can reduce the inflammatory cascade (Fig. 1).

Several cytokines activate JAK/STAT3 via IL-6 and influence osteoblast maturation and differentiation in RA. Following activation of the JAK/STAT pathway, receptor activator of NF-κB ligand (RANKL) is highly expressed, and osteoprotegerin expression is suppressed. When RANKL binds to RANK on the surface of osteoclast precursors, the NF-κB signalling pathway is activated, which promotes osteoclast differentiation and causes bone destruction in RA [49]. Most cytokines associated with RA pathogenesis and pain transmit signals either directly or indirectly via the JAK/STAT pathway [50,51]. Multiple cytokines are involved in pain signalling and are directly or indirectly regulated by the JAK/STAT pathway, thus playing important roles in mediating the multiple pain mechanisms of RA [52].

Various infections evade host antiviral defence mechanisms through proteins that suppress the inflammatory cascade, particularly the JAK/STAT pathway [48]. During HBV infection, the IFN-α/β receptor complex activates the JAK/STAT pathway and recruits and phosphorylates its components, ultimately leading to the nuclear translocation of various proteins to induce the expression of downstream genes. IFNs induce the expression of IFN-stimulated genes, which act as downstream effector molecules that control viral replication and regulate immunity. Pro-inflammatory cytokines, such as IL-6, IL-1β, IL-4, and TGF-β, induced by IFN have shown antiviral effects at different stages of HBV replication [25]. The antiviral effect of IL-6 on HBV replication is also associated with STAT3 binding to covalently closed circular DNA and IL-6 cellular target-mediated redistribution [51].

In the JAK/STAT pathway, IFN and IL-6 promote inflammation in RA and indicate antiviral replication in HBV infection, which is a positive feedback loop in RA and a negative feedback loop in HBV infection. In patients with RA treated with baricitinib, HBV reactivation may occur because of prior HBV exposure [53]. Additionally, decreased phosphorylation of STAT1 in the JAK-STAT signalling pathway may render them susceptible to HBV resistance to IFN [54].

3.3. TLR signalling pathway

Pathogen-associated molecular patterns activate TLRs (TLR1/2, TLR2/6, TLR4, and TLR5 on the cell membrane; TLR3, TLR7/8, and TLR9 in endosomes), leading to: 1. Conformational changes in the Toll/IL-1 receptor domain, which activate the myeloid differentiation primary response gene (MyD88)-dependent pathway (including TLR7/8 and TLR9). MyD88 activates IRAK4, which then phosphorylates and activates IRAK1 and TRAF6. This can further activate downstream IRF7, which enters the cell nucleus and activates the transcription of type I IFNs (IFN-α/β). Alternatively, it can activate downstream TAK1, TAB1, and TAB2, triggering the NF-κB pathway and resulting in the production of inflammatory cytokines (IL-6, IL-1β, and TNF-α) and activation of the P38 and JNK signalling pathways. 2. Activation of the MyD88-independent pathway involves TRIF, which activates TRAF3, leading to the activation of IRF3 and the transcriptional activation of IFN-α/β once within the nucleus (Fig. 1).

In RA synovial cells, the expression of TLR2, TLR3, TLR4, and TLR5 is increased, with TLR activation leading to exacerbated joint inflammation [55]. Increased expression of TLR1/2 and TLR2/6 promotes the release of arachidonic acid, production of prostaglandin E2, and expression of proinflammatory factors by upregulating the phosphorylation of Phospholipase A2 [56], causing joint pain in patients with RA. Moreover, the activation of TLR in synoviocytes induces the differentiation of monocytes into osteoclasts by promoting the production of RANKL [55], leading to joint bone destruction in patients with RA. The increase in TLR7 expression in circulating $CD8^+$ T cells in patients with RA has been shown to contribute to the continuation of the inflammatory process [57].

Hepatocytes express TLRs that, upon stimulation by their homologous ligands, activate downstream antiviral and inflammatory pathways [58]. TLR2 and TLR4 signalling leads to the activation of hepatocellular pathways and reduces HBV replication in a non-IFN-dependent manner [59], while TLR3, 7, and 9 play key roles in mediating the immune response against HBV infection in an IFN-dependent manner [60]. TLR2 significantly enhances the anti-HBV function of immune cells, with HBV particles activating B cells through the TLR2-MyD88 axis producing virus-specific antibodies for antiviral effects [61]. Beyond TLR2, the ligands of several TLRs can inhibit HBV infection [62]. The inverse relationship between the HBV DNA load and TLR7 expression observed in biopsy samples highlights the antiviral role of TLR7 against HBV infection [63]. Dendritic cells within the liver are likely partially or completely activated by TLR ligands, producing IFN-α/β, thereby suppressing HBV replication in hepatocytes *in vivo* [60].

In RA, TLR signalling pathways are activated, and downstream signalling activates NF-κB, resulting in the production of pro-inflammatory cytokines [25] and exacerbating RA joint inflammation, bone destruction, and pain. In HBV infection, the activation of TLR signalling pathways primarily serves an antiviral function, reducing HBV replication, with IFN-induced cytokines like IL-6 and IL-1β showing antiviral effects at different stages of HBV replication [25]. During HBV infection, the activation of the MyD88 axis in B cells leads to antibody production. These antibodies bind to HBV antigens and play an antiviral role [64]. In the case of RA, the activation of B cells leads to the production of rheumatoid factor and anti-citrullinated protein antibodies, among other autoantibodies, which induce and maintain RA onset [4]. The functions of TLRs in RA synovial and liver cells show intriguing tissue-specific

differences, which merit further research. Hence, it is one of the signalling pathways involved in HBV reactivation during RA treatment. There are currently no reports on the use of TLR agents. However, reactivation of HBV has been observed after the inhibition of important cytokines, such as IL-6, in this pathway. In clinical settings, HBV reactivation occurs after treatment with an IL-6 inhibitor such as tocilizumab [65].

3.4. BTLA signalling pathway

BTLA (CD272) suppresses T cell responses and cytokine production. It is highly expressed in virus-specific T-cells and strongly inhibits T-cell proliferation and cytokine secretion [66]. BTLA attenuates B cell receptor signal intensity by recruiting and phosphorylating the protein tyrosine kinase Syk, which results in the downregulation of B-cell connexin, phospholipase E2, and NF-κB [67] (Fig. 1).

Because BTLA expression is biased in Th1 cells, it may participate in controlling RA. Patients with RA usually have weakened BTLA expression, and disease activity is closely related to weakened BTLA expression. Improving joint symptoms in patients with RA after treatment can reduce immune inflammation and oxidative stress by increasing BTLA expression [68]. In HBV infection, Shen et al. found that $CD8^+$ $BTLA^+$ T cells isolated from CHB liver tissue contribute to HBV evasion from immune clearance [69]. In patients with CHB, BTLA of CD4 T and CD8 T cells was significantly upregulated and involved in CHB progression during T cell failure [70]. Liao et al. showed that the expression of BTLA is significantly upregulated during the progression of CHB from HBV to hepatocellular carcinoma, indicating that BTLA plays an important role in CHB progression [71].

The role of the BTLA pathway differs between RA and HBV infection, leading to opposing treatment approaches. BTLA downregulates B-cell junction proteins and NF-κB, attenuates B-cell receptor signal intensity, reduces inflammatory factors and antibody secretion, and diminishes RA disease activity. It also attenuated the anti-HBV effect and aggravated HBV infection. BTLA expression is reduced in RA and is inversely correlated with disease activity, and treatment consists of enhancing BTLA expression. Increased HBV expression positively correlates with disease progression, and treatment is directed towards decreasing BTLA expression. There are currently no reports on the use of BTLA agents.

3.5. Fas/FasL signalling pathway

In the extrinsic apoptotic signalling pathway, the apoptotic signal ligand FasL binds to the death receptor Fas, exposing its death domain (DD). The DD then binds to Fas-associated DD protein and procaspase-8, forming the DISC complex, which consists of FasL, Fas, DD, Fas-associated DD, and procaspase-8. The DISC complex converts procaspase-8 into active caspase-8, releasing granzyme B and cleaving caspase substrates to induce cell apoptosis [21], which is an important mechanism in the pathogenesis of RA. Caspase-8 releases granzyme B, which triggers apoptosis and plays a significant role in both RA and HBV infections. In the context of Th1 polarisation, Fas-mediated T cell apoptosis is dependent on IFN-γ [72] (Fig. 1).

In RA, IFN-γ produced by Th1 and Th1/Th17 cells is associated with increased Fas ligand (FasL) expression [73], making it a key factor in the development and maintenance of RA pathology [72]. Fas-mediated apoptosis contributes to RA development [74], with caspase-8 releasing granzyme B during apoptosis, which mediates inflammation in RA [13]. Fas is also abundantly distributed on the hepatocyte membrane, where the binding of FasL or agonistic anti-Fas antibodies can trigger apoptosis signalling. In HBV infection, Fas-mediated T cell apoptosis depends on IFN-γ, while IFN-α/β, -γ, and -λ can reduce HBV replication or promote adaptive immunity [75]. However, HBeAg (a marker of HBV infection) can protect hepatocytes from Fas/FasL-induced apoptosis, leading to the survival of infected hepatocytes and the chronic progression of HBV infection [76]. Furthermore, during apoptosis, the caspase-8-mediated release of granzyme B can inhibit HBV replication [22]. In summary, Fas/FasL signalling pathway-induced apoptosis promotes the development of RA.

In the context of HBV, Fas/FasL can induce hepatocyte apoptosis, while HBeAg can prevent this apoptosis, resulting in the chronic persistence of HBV infection. IFN-γ plays a crucial role in initiating the Fas/FasL signalling pathway. During apoptosis, caspase-8 releases granzyme B, which is important for both RA and HBV infection. Granzyme B and IFN-γ have contradictory effects: they promote RA development while also exerting antiviral effects against HBV. To date, no inhibitors of the Fas/FasL pathway have been reported.

Nuclear factor kappa B (NF-κB), Janus kinase (JAK)/signal transducer and activator of transcription (STAT), Toll-like receptor (TLR), B and T lymphocyte attenuator (BTLA), and Fas/Fas ligand (FasL) signalling pathways. Activation of NF-κB, JAK/STAT, TLR, and Fas/FasL signalling pathways promotes inflammation in RA, whereas in HBV infection, they primarily exert antiviral effects. In the BTLA signalling pathway, BTLA expression is reduced in RA, while in HBV infection, upregulated BTLA expression contributes to disease progression.

4. Summary

The infection rate of HBV is relatively high in RA, and treatment with biological agents and glucocorticoids for RA can lead to HBV reactivation. RA biological agent therapies and glucocorticoids mainly inhibit the secretion of TNF-α and IL-6 by Th cells, thereby reducing antiviral effects while exerting anti-inflammatory effects. In RA treatment, CD20 monoclonal antibody therapy primarily inhibits B cells, leading to a reduction in antibody production and antiviral capacity in B cells, which results in HBV reactivation. From an immunological perspective, the pathogenesis of RA is associated with the breakdown of immune tolerance, while HBV infection is related to the establishment of immune tolerance. In innate immunity, MAIT cells are increased in RA, playing a pro-inflammatory

role, but are reduced in HBV, leading to diminished antiviral effects.

In adaptive immunity, CD8 plays a protective role in RA, and CD8 exhaustion leads to persistent HBV infection. B cells produce antibodies that induce RA, whereas in HBV, virus-specific antibodies produced by B cells help alleviate HBV infection. The activation of the JAK/STAT and TLR signalling pathways in RA primarily promotes inflammation, while in HBV, their main function is antiviral. The NF-κB signalling pathway's key cytokines, IL-1β and TNF-α, are pro-inflammatory in RA but exhibit antiviral effects in HBV. IFN-γ plays an important role in the initiation of the Fas/FasL signalling pathway, and while it contributes to RA pathogenesis, it also has an anti-HBV effect. During apoptosis, granzyme B mediates RA inflammation but inhibits HBV replication. In the BTLA signalling pathway, the expression of BTLA is reduced in RA, while upregulated BTLA in HBV infection facilitates HBV immune escape and progression. It is evident that the opposing immune mechanisms of RA and HBV infection create challenges in developing effective treatment strategies.

5. Outlook

Based on clinical observations, immunosuppressive therapy in patients with RA combined with HBV infection may lead to HBV reactivation. This review explores how immunosuppressive therapy for these patients poses a risk of HBV activation, possibly due to the contradictory immunological mechanisms underlying the pathogenesis of both conditions. It is crucial to find ways to prevent HBV reactivation during the treatment of patients with RA combined with HBV infection. Numerous microRNAs are abnormally expressed in RA-derived cells and can regulate target genes and pathways, including the NF-κB, Fas-FasL, and JAK-STAT pathways [77]. Certain microRNAs in RA are defined as biomarkers of disease activity, potentially representing new therapeutic targets for further drug development [78]. Additionally, mesenchymal stem cells and gut microbiota therapies are novel immunotherapies, and non-pharmacologic treatment approaches are applicable to both RA and HBV infection. Dietary changes can directly benefit the function of the gut microbiota in patients with RA, thereby improving the gut barrier and alleviating systemic inflammatory conditions [79] and exhibiting therapeutic potential.

Rigorous screening and monitoring of HBV are required for the appropriate selection of treatment regimens for patients with RA combined with HBV infection. In clinical practice, major advances in the research of biomarkers for DMARD response underscore the importance of precision medicine in RA management. Accurate and timely information collection, along with effective disease monitoring, is crucial for the prevention and treatment of HBV infection in patients with RA. Currently, patient-reported electronic outcomes have emerged as a promising tool in RA management [80].

The information compiled in this review article serves as a valuable foundation for guiding clinical practice, enhancing our understanding of HBV reactivation dynamics, and fostering the development of more effective management strategies in an era marked by advancements in immunotherapy [14].

CRediT authorship contribution statement

Fenglin Zhu: Data curation, Conceptualization. **Miao Wang:** Formal analysis. **Guoqing Zhao:** Supervision. **Hongyan Gao:** Writing – original draft. **Lamei Zhou:** Writing – review & editing.

Ethical statement

Not applicable.

Data availability statement

Not applicable.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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