Cell. Mol. Biol. (ISSN: 1165-158X)

Journal Homepage: www.cellmolbiol.org

Cellular and Molecular Biology

Review

Toll-like receptor 3 in hepatitis B and C: a determinant of infection

Abdoul Karim Ouattara[1,2,3], Issoufou Tao[2,3,4], Julien Dembélé[5], Jacques Simpore[2,3]*

[1] Biological Sciences Department, Université Norbert Zongo/ Centre Universitaire de Manga, BP 376 Koudougou, Burkina Faso
[2] Biochemistry and Microbiology Departemnt, Laboratoire de Biologie Moléculaire et de Génétique (LABIOGENE) - Université Joseph KI-ZERBO, 03 BP 7021 Ouagadougou 03, Burkina Faso
[3] Molecular Biology Unit, Centre de Recherche Biomoléculaire Pietro Annigoni (CERBA), 01 BP 364 Ouagadougou 01, Burkina Faso
[4] Institute of Sciences and Technology, High Normal School, Ouagadougou, Burkina Faso
[5]Laboratory of Toxicology, Environment and Health, Doctoral School of Health Sciences, University Joseph Ki-Zerbo, 03 BP 7021 Ouagadougou 03, Burkina Faso

Article Info

Article history:

Received: September 19, 2025
Accepted: December 06, 2025
Published: December 31, 2025

Use your device to scan and read the article online

Abstract

Toll-like receptor 3 (TLR3) is a key component of the innate immune system that recognizes viral double-stranded RNA (dsRNA) as well as endogenous RNA released from necrotic cells. Unlike other TLRs, TLR3 signals exclusively through the TIR-domain-containing adaptor inducing interferon-β (TRIF). This activation triggers downstream cascades that culminate in the translocation of IRF3 and NF-κB, inducing type I and type III interferons (IFNs) alongside interferon-stimulated genes (ISGs) and pro-inflammatory cytokines. These responses are essential for shaping antiviral immunity in hepatitis virus infections. In hepatitis B virus (HBV) infection, exogenous stimulation of TLR3 using synthetic agonists such as polyriboinosinic: polyribocytidylic acid [poly(I:C)] suppresses viral replication in experimental models and promotes interferon-dependent viral clearance, underscoring its therapeutic potential. In hepatitis C virus (HCV) infection, TLR3-mediated antiviral defenses are directly antagonized, most notably through cleavage or downregulation of TRIF by viral proteins, thereby impairing IFN induction and facilitating viral persistence. Furthermore, human genetic studies reveal that TLR3 polymorphisms, such as the non-synonymous rs3775290 (1377 C > T), are associated with differential susceptibility, chronicity, and progression of HBV and HCV infections. Collectively, the evidence highlights TLR3 as a central determinant of host-virus interactions in hepatitis, influencing viral clearance, persistence, and clinical outcomes, and as a promising target for novel therapeutic strategies. This review provides an updated overview of TLR3 expression and genetic variants in relation to HBV and HCV infection outcomes.

Keywords: TLR3, polymorphisms, hepatitis B virus, hepatitis C virus, liver disease

1. Introduction

HBV is a small, enveloped, partially double-stranded deoxyribonucleic (DNA) virus of the *Hepadnaviridae* family that specifically infects hepatocytes [1]. Transmission occurs through exposure to infected blood or body fluids, including perinatal, sexual, and parenteral routes [2-4]. Globally, an estimated 254 million people were living with chronic HBV infection in 2022, with the highest prevalence in sub-Saharan Africa and the Western Pacific region [5, 6]. HBV pathogenesis is mainly immune-mediated. Virus-specific cytotoxic T cells target infected hepatocytes, leading to hepatocellular injury [7, 8]. Inadequate or dysregulated immune responses allow viral persistence and chronic infection, which may progress to fibrosis, cirrhosis, and hepatocellular carcinoma. Effective vaccines have substantially reduced HBV incidence in many regions, but curative therapies are still lacking; current treatments with nucleos(t)ide analogues or pegylated interferon suppress viral replication without fully eradicating the virus [7].

HCV is a positive-sense, single-stranded ribonucleic (RNA) virus of the *Flaviviridae* family, transmitted mainly through exposure to infected blood, injection drug use, and unsafe medical practices, with less efficient sexual and perinatal transmission [9, 10]. Approximately 58 million people are chronically infected worldwide, with 1.5 million new infections occurring annually [11]. Unlike HBV, no vaccine is available [12]. HCV pathogenesis is shaped by high genetic variability, which facilitates immune evasion and persistence [13, 14]. Chronic infection drives sustained hepatic inflammation, steatosis, and fibrogenesis, leading to cirrhosis and hepatocellular carcinoma in a significant fraction of patients [15]. The advent of direct-acting antivirals (DAAs) has revolutionized HCV therapy,

* Corresponding author.
E-mail address: abdoul-karim.ouattara@unz.bf (J. Simpore).
Doi: http://dx.doi.org/10.14715/cmb/2025.71.12.10

achieving cure rates exceeding 95%, though challenges remain in access, reinfection risk, and elimination of long-term liver disease burden [16].

The outcome of HBV and HCV infection depends largely on the balance between viral evasion strategies and host immune responses [17, 18]. While adaptive immunity is essential for long-term viral clearance, growing evidence highlights the critical contribution of innate immunity via Toll-like receptors in shaping disease outcomes [19, 20]. Toll-like receptors (TLRs) are a major family of pattern-recognition receptors (PRRs) in innate immunity, responsible for monitoring both the extracellular and intracellular environments to detect pathogen-associated molecular patterns (PAMPs) and mount an appropriate immune response [21]. TLRs were the first PRRs to be identified and remain the best characterized to date [21, 22]. In mammals, thirteen TLRs have been described including ten functional subtypes (TLR1–TLR10) in humans and twelve (TLR1–TLR9 and TLR11–TLR13) in mice. TLR1 to TLR9 are conserved in both species. However, murine TLR10 is non-functional due to the insertion of an endogenous retrovirus into its gene, whereas the genes encoding TLR11, TLR12, and TLR13 have been lost in the human genome during evolution [21]. Each TLR recognizes specific PAMPs and triggers distinct signaling cascades. For instance, cell-surface TLRs detect microbial components such as lipopolysaccharide (LPS), flagellin, or lipoteichoic acid, whereas intracellular TLRs sense nucleic acids [21]. TLR3 belongs to the group of intracellular TLRs that recognize dsRNA and its synthetic analogue poly(I:C) [23]. Increasing evidence also suggests that TLR3 can sense self-derived RNA and RNA molecules of various sizes, although the underlying mechanisms remain to be fully elucidated [24].

In both HBV and HCV infections, TLR3-mediated sensing has been implicated in the induction of type I and type III interferons, pro-inflammatory cytokines, and antiviral restriction factors, which together contribute to viral control and, in some cases, infection resolution [25]. Conversely, impaired or dysregulated TLR3 responses may facilitate viral persistence, chronic inflammation, and progression to liver disease [26, 27]. These observations underscore the importance of TLRs, particularly TLR3, the endosomal receptor for dsRNA, in the pathogenesis, clearance, and potential therapeutic targeting of hepatitis viruses. In this context, the present review highlights the importance of TLR3 in the clearance of HBV and HCV infections. Evidence from experimental models and clinical studies shows that TLR3 activation can promote antiviral defense and infection resolution, whereas viral interference with TLR3 signaling facilitates persistence and progression to chronic liver disease. Understanding the dual role of TLR3 in antiviral immunity and viral immune evasion is therefore critical, not only for elucidating the pathogenesis of HBV and HCV but also for identifying novel therapeutic targets and designing innovative strategies to enhance viral clearance and prevent disease progression.

2. Overview of TLR3

TLR3 is a key component of the innate immune system and plays a central role in antiviral defense by sensing dsRNA, a molecular pattern associated with many viral infections [24]. The following subsection synthesizes the genomic organization, signaling mechanisms, and hepatic expression of TLR3.

2.1. Gene and protein

The TLR3 gene is located on chromosome 4 (4q35.1) of the human genome and spans approximately 19,163 base pairs. Among its five exons, four (exons 2 - 5) are coding (Figure 1).

The TLR3 protein consists of 904 amino acids with a molecular mass of about 103,829 Daltons [28]. TLRs are type I integral membrane receptors characterized by common structural features (Figure 2), including an N-terminal leucine-rich repeat (LRR) domain, a single transmembrane (TM) domain, and a C-terminal Toll/interleukin-1 receptor (TIR) homology domain [29]. The extracellular domain of TLR3 contains 23 LRR motifs that assemble into a horseshoe-shaped, right-handed curved solenoid responsible for recognizing PAMPs, whereas the cytoplasmic TIR domain mediates adaptor recruitment and signal transduction [30].

2.2. Nucleic acid sensing

TLR3 is a sensor of virus-derived dsRNA and its synthetic analog, poly(I:C) [31]. In addition, TLR3 can recognize self-derived RNAs released during tissue damage, such as U1 RNA [32] and structured RNAs containing partial stem-loop secondary structures in single-stranded RNA [33]. The TLR3 ectodomain binds dsRNA efficiently only at acidic pH (≤ 6.5), consistent with its localization to endosomal compartments in most cell types [34]. The recognition of dsRNA by TLR3 occurs mainly within endosomes and requires TLR3 homodimerization for ligand binding [35], although it can also signal from the cell sur-

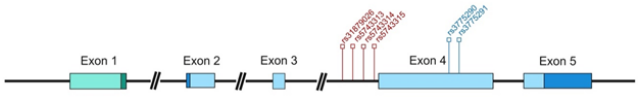

Fig. 1. Structure of the human TLR3 gene. A physical map of the human TLR3 gene. The proximal promoter region is shown in light green, and exons are represented as boxes (non-coding sequences in dark blue; coding sequences in light blue). A few SNPs reported in HBV and HCV association studies are represented. Intronic SNPs are shown in red, and exonic SNPs in blue (located in exon 4). The break symbol (//) indicates that the intron is long and has been shortened in this schematic for clarity.

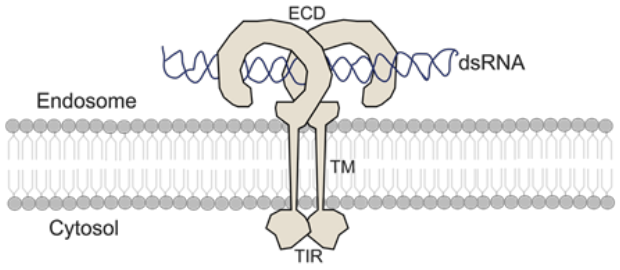

Fig. 2. Schematic representation of human TLR3-dsRNA complex. The TLR3 ectodomain (ECD) domain is a horseshoe-shaped solenoid in which LRR forms one turn of the solenoid. The LRRs are at the N-terminal and C-terminal regions, flanked by a cysteine-rich Cap domain. The transmembrane domain (TM) is made up of one single-helix. The cytoplasmic C-terminal Toll/interleukin-1 receptor (TIR) homology domain is responsible for downstream signaling cascade.

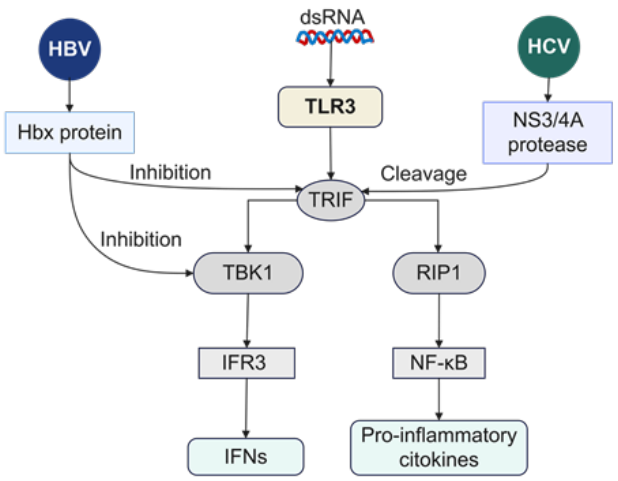

Fig. 3. TLR3 signaling and viral interference in hepatitis. TLR3, located on endosomal membranes, detects dsRNA and signals through the adaptor TRIF, activating two pathways: (1) TBK1/IKKε-mediated phosphorylation and nuclear translocation of IRF3, and (2) RIP1/TRAF6-dependent activation of NF-κB via the IKK complex. IRF3 and NF-κB enter the nucleus to induce type I interferons and pro-inflammatory cytokines. HCV NS3/4A cleaves TRIF, blocking IFN-β induction, while HBV HBx disrupts TBK1 and IRF3 activation, suppressing type I IFN production and promoting viral persistence.

face in certain cell types through unclear mechanisms [36, 37]. The ligand binding sites of TLR3 are separated by approximately 120 Å, equivalent to the ~46 bp minimal dsRNA length required for stable binding [34, 38]. Furthermore, a recent study revealed that these dimeric TLR3 units are clustered along the dsRNA helix in a highly organized and cooperative fashion with a uniform inter-dimer spacing of 103 Å [39]. Thus, the ability of longer dsRNAs to engage a greater number of TLR3 dimers directly explains why they induce stronger TLR3 responses [40].

2.3. Signaling pathways

Nucleic acid sensing by TLR3 is a key mediator of the type I interferon (IFN) response. Upon ligand binding, TLR3 dimers recruit the cytosolic adaptor protein TRIF (Toll-like receptor adaptor molecule 1, or TICAM-1) to initiate signaling [35]. The TLR3-TRIF pathway then activates two key transcription factors, which induce the phosphorylation and nuclear translocation of IRF3, leading to the production of IFN-β, and it activates NF-κB to drive the transcription of inflammatory cytokines [23]. This induction of type I IFN and inflammatory responses not only provides innate antiviral defense but also enhances adaptive immunity [23]. The importance of this pathway is highlighted by its targeting for immune evasion; both HBV and HCV can interfere with it to establish viral persistence (Figure 3).

2.4. Expression of TLR3 in the liver

TLR3 is broadly expressed across key hepatic cell populations, forming a key sentinel network for antiviral defense. Its presence in primary hepatocytes [41], Kupffer cells [41, 42], hepatic dendritic cells [43], liver sinusoidal endothelial cells [42] and hepatic stellate cells [42, 44] enables the liver to mount a robust and coordinated immune response. Located within endosomal compartments, TLR3 detects viral dsRNA, triggering the production of type I and type III IFNs that establish a cell-intrinsic antiviral state [37]. This multi-cellular IFN response is crucial; it not only directly inhibits viral replication but also orchestrates a broader adaptive immune response, thereby providing a critical layer of protection against hepatotropic viruses like HBV and HCV.

3. TLR3 in HBV infection

3.1. Viral clearance

TLR3 is broadly expressed by hepatocytes and is a key component of the liver early antiviral defense against HBV. *In vitro* and *in vivo* evidence consistently demonstrates that TLR3 activation triggers a potent antiviral state. In human hepatic stellate cells (LX-2), activation of TLR3 with poly(I:C) induces the secretion of soluble factors that significantly suppress HBV replication in HepG2 hepatoma cells [44]. This cell-intrinsic mechanism is corroborated *in vivo* in immunocompetent murine models. A single intravenous injection of poly(I:C) in HBV transgenic mice [45] or in a hydrodynamic injection (HDI) model [46] leads to a strong inhibition of HBV replication within the liver, primarily mediated by the induction of type I interferons (IFNs). However, the translatability of these findings is challenged by key physiological differences. While poly(I:C) delivered via HDI can achieve viral clearance in mice, this method is highly invasive and not clinically applicable [46].

Furthermore, standard murine models cannot fully recapitulate the complex immune tolerance mechanisms that characterize chronic HBV infection in humans [47]. To bridge this translational gap, next-generation approaches are focusing on targeted delivery systems. For instance, encapsulating poly(I:C) within calcium phosphate (CaP) nanoparticles coated with antibodies specific to liver cells (e.g., Kupffer cells and liver sinusoidal endothelial cells) is under investigation [46, 48]. This strategy aims to enhance liver-specific targeting while mitigating the systemic toxicity associated with naked poly(I:C), representing a critical step toward a viable therapeutic application.

3.2. Immune evasion and viral persistence

HBV actively suppresses TLR3 signaling to evade innate immunity and establish chronic infection, as evidenced by consistent findings from patient studies and animal models. Analyses of human liver specimens reveal a fundamental impairment, with no significant upregulation of IFNs or ISGs [47] and a pronounced repression of TLR3 that is influenced by HBeAg status [49, 50]. This suppression is systemic, as TLR3 and its key adaptor TRIF are consistently reduced in patient PBMCs [50, 51]. The functional consequence is a delayed and inadequate response, with abnormally slow TLR3 induction kinetics in chronically infected patients [52]. The pathological significance of this suppression is confirmed by the Tupaia model, where absent TLR3 induction and suppressed IFN-β expression correlate with viral persistence [53]. Furthermore, the pathway importance for viral control is highlighted by the more evident restoration of TLR3 in patients who achieve a sustained virological response with interferon-based therapy compared to nucleos(t)ide analog treatment [50]. In summary, HBV orchestrates a multi-faceted dampening of the TLR3 pathway, from receptor expression to adaptor signaling, which is a major contributor to viral chronicity.

3.3. Animal models and human translation

The role of TLR3 signaling in inhibiting viral replication and promoting clearance has been elucidated using a range of experimental models, each with distinct advantages and limitations for translating findings to human disease [54]. A significant challenge in HBV research is the virus high species specificity, infecting only humans and higher primates. This has necessitated the development of diverse animal models, each offering unique insights but also possessing considerable limitations for studying the complex interplay between HBV, the host immune system, and TLR3-mediated antiviral responses.

Critically, standard murine models cannot fully recapitulate the complex immune tolerance mechanisms that characterize chronic HBV infection in humans [54], making the choice of model a paramount consideration. While chimpanzees represent the gold standard due to their susceptible immune system and ability to mimic human acute infection and immune responses, their use is now severely restricted [54]. Alternative models like the Tupaia (tree shrew) are infectable and phylogenetically closer to primates, but their transient infection limits studies on chronic TLR3 dysfunction. The woodchuck model, infected with woodchuck hepatitis virus (WHV), is highly valuable as it naturally progresses to chronicity and hepatocellular carcinoma, and its observed blunted intrahepatic interferon response mirrors that of human CHB, providing a strong rationale for TLR3 agonist therapy [55, 56]. However, its poorly characterized immune system hinders detailed mechanistic studies. Commonly used mouse models, including transgenics [45] or those subjected to hydrodynamic injection [46], are accessible and genetically tractable but are fundamentally flawed for immunology studies as they lack natural infection and cccDNA formation, and their artificially induced tolerance does not mimic human chronicity [54]. Even humanized liver mice, which support genuine HBV infection in human hepatocytes, are limited by their dysfunctional human immune system. Consequently, while these models are useful for initial virological screening, the profound gap in modeling human immune tolerance means that preclinical data on TLR3-driven immune restoration must be interpreted with extreme caution, representing a major translational hurdle for this therapeutic approach.

3.4. TLR3 polymorphisms

The association between TLR3 polymorphisms and HBV outcomes demonstrates significant heterogeneity, largely driven by disparities in study design, statistical power, and population-specific genetic background (Table 1). The most robust findings originate from studies with large, well-defined cohorts. The investigation by Chen et *al*.[57] in China (n = 1,374) provides high-confidence evidence due to its substantial sample size and clear stratification of clinical outcomes (natural clearance, chronic carriers, HCC). Similarly, Al-Qahtani et *al*.[58], and Fischer et *al*.[59], each with over 1,000 participants, offers reliable insights into the protective role of specific alleles and haplotypes. Conversely, several studies are critically limited by small sample sizes, rendering their findings exploratory. The reports by Awadelkarim et *al*.[60], Elyass et *al*.[61], and EzzEl-Din et *al*.[62] all have fewer than 150 cases. While they report significant associations, these results are highly susceptible to type I error (false positives) and overestimation of effect sizes. Their primary value is in generating hypotheses for validation in larger cohorts.

The role of the rs3775290 (1377 C>T) polymorphism exemplifies how genetic associations can produce seemingly contradictory results across different cohorts. For instance, while the T allele has been identified as a risk factor for chronic HBV infection [63, 64], the TT genotype has also been linked to protection against chronic hepatitis and cirrhosis [64]. Other studies report genotype-specific links to viral load (TT) and active (CC) or symptomatic (CC) disease [60, 65]. Rather than being mutually exclusive, these findings highlight the polymorphism complex and context-dependent role, where its effect may differ for initial infection susceptibility, subsequent disease activity, and long-term progression to cirrhosis or HCC.

A key factor in reconciling these outcomes is the definition of the control group. Studies using stringently defined healthy controls [58, 61] minimize misclassification bias. In contrast, the "natural immunity" group in Tuncel et *al*.[66], individuals who cleared the virus represent a distinct immune outcome compared to unexposed controls, potentially explaining their negative finding for rs5743313 (C>T). Furthermore, studies focusing on specific transmission routes, such as the mother-to-child cohort by Gao et *al*.[67], investigate a unique phenotypic niche that is not directly comparable to studies of adult horizontal transmission.

Ethnic background is also a major confounder. The studies span Saudi [58, 60], Sudanese [61], Mauritanian [63], Turkish [65], Tunisian [68], Egypt [62], German [59], Chinese [57, 64, 67, 69-71], and Brazilian [72] populations, each with distinct genetic backgrounds and TLR3 haplotype structures. An allele tagged as a risk factor in one population may be in linkage disequilibrium with a different causal variant in another, or its effect may be modified by the overall genetic background. This underscores the necessity of replicating findings across diverse ethnicities rather than direct comparison.

The collective evidence firmly implicates TLR3 as a genetic modulator of the host response to HBV. However, the effect is not monolithic; it is profoundly influenced by the clinical context of the infection (e.g., susceptibility, clearance, disease activity, progression) and the population-specific genetic landscape. Future research should prioritize large, multi-ethnic genome-wide association studies (GWAS) with standardized, precise phenotypic definitions to disentangle these complex genotype-phenotype relationships and identify core causal variants.

3.5. Insights from African cohorts

Data on TLR3 polymorphisms in viral hepatitis from African populations remain notably scarce, creating a critical gap in the global literature. Recent studies from Mauritania [63], Sudan [61], and North Africa [62, 68] provide a preliminary yet invaluable perspective, highlighting both unique associations and the profound influence of genetic diversity on disease outcomes.

Findings from these cohorts underscore that allele frequencies and associated disease risks are not uniform across populations. For instance, the rs3775290 (1377 C>T) T allele, identified as a risk factor for chronic HBV infection in Mauritanian and Tunisian populations [63, 68], has been associated with both risk and protection in Asian cohorts. This apparent contradiction can be explai-

Table 1. Studies on TLR3 polymorphisms and HBV infection.

Author	Year	Country	Study Design	Sample Size	Polymorphism(s)	Key Finding	Population
Awadelkarim et al.	2025	Saudi Arabia	Case-Control	66/70	rs3775290 (c.1377C>T)	CC genotype associated with symptomatic disease.	Symptomatic vs. Asymptomatic HBV
Elyass et al.	2025	Sudan	Case-Control	66/70	rs3775290, rs3775291 (c.1234 C>T)	rs3775290-CT increased risk; CC protective. No association for rs3775291.	Chronic HBV vs. Healthy controls
Soumbara et al.	2024	Mauritania	Case-Control	102/86	rs3775290	TT-genotype had increased frequency in chronic patients; a risk factor.	Chronic HBV vs. Spontaneously cleared
Tuncel et al.	2023	Turkey	Case-Control	100/100	rs5743313 (c.2593C>T)	No association with susceptibility.	Naturally immune vs. Chronic HBV
Sghaier et al.	2019	Tunisia	Case-Control	100/360	rs3775290	T allele increased risk of chronic HBV; CC/CT protective against HCC.	Chronic HBV vs. Healthy controls
Fischer et al.	2018	Germany	Retrospective	860/254	rs3775291, rs5743305 (-1077 T>A)	rs3775291-A allele linked to increased chronicity and reduced viral clearance. Haplotype rs3775291A/rs5743305A had the lowest likelihood of HBsAg SC.	HBV infected vs. Healthy controls
Qiu et al.	2018	China	Case-Control	135/140	rs1879026 (G>T)	T allele protective against neonatal severe hepatitis.	Neonates with severe hepatitis
Chen et al.	2017	China	Case-Control	686/688	rs3775291	Protective against HBV-related hepatocellular carcinoma (HCC).	Natural clearance vs. Chronic vs. HCC
EzzEl-Din et al.	2017	Egypt	Case-Control	41/13	Haplotype	Specific haplotypes associated with immunization.	Chronic vs. Spontaneously cleared HBV
Goktas et al.	2016	Turkey	Case-Control	93/43	rs3775290	TT genotype linked to higher viral load; CC to active CHB.	Chronic HBV vs. Healthy controls
Sá et al.	2015	Brazil	Case-Control	35/299	rs5743305, rs3775291	No association with susceptibility.	Chronic HBV vs. Healthy controls
Gao et al.	2015	China	Cohort	399	rs3775290	T allele increased risk of mother-to-child transmission.	Neonates born to HBsAg+ mothers
Huang et al.	2015	China	Case-Control	437/186	rs3775290, rs1879026	rs3775290-TT genotype decreased risk of chronic hepatitis B (CHB) and liver cirrhosis (LC).	HBV liver disease vs. Healthy controls
Li et al.	2013	China	Case-Control	466/482	rs3775291	T allele increased risk of chronic HBV infection.	Chronic HBV vs. Healthy controls
Rong et al.	2013	China	Case-Control	452/462	rs3775291	T allele increased risk of chronic infection.	Chronic HBV vs. Healthy controls
Al-Qahtani et al.	2012	Saudi Arabia	Case-Control	707/600	rs1879026	T allele protective; specific haplotype increased susceptibility.	Chronic HBV vs. Healthy controls

ned by several factors inherent to the genetic landscape of sub-Saharan Africa, which harbors the greatest human genetic diversity globally [73]. Consequently, a single nucleotide polymorphism (SNP) like rs3775290 (1377 C>T) may be in linkage disequilibrium with different causal variants in African versus non-African populations. Thus, a tag SNP predictive in one population may not be informative in another, leading to divergent association signals. Furthermore, the haplotype structure of the TLR3 locus and the effect of genetic modifiers likely differ significantly in African genomes, potentially altering the functional outcome of the same polymorphism.

The limited sample sizes of existing African studies (e.g., n = 188 in Soumbara et *al*.[63]; n = 136 in Elyass et *al*.[61]) remain a major constraint, increasing their susceptibility to type I error and effect size overestimation. However, their value lies in highlighting these population-specific signals. The Sudanese study [61] adds a layer of complexity by identifying the heterozygous CT genotype of rs3775290 (1377 C>T) as a risk factor, a finding less commonly reported elsewhere, which may indicate a unique mode of inheritance or interaction in this population.

The emerging data from Africa do not simply fill a quota for geographic representation; they challenge the universality of genetic associations established in other populations and emphasize the necessity of conducting large-scale, well-powered genetic studies within the continent. Future research must prioritize African cohorts not only to validate existing associations but, more importantly, to identify the true causal variants and haplotypes relevant to these populations. This is critical for developing a truly global understanding of host genetics in hepatitis and for ensuring that future personalized medicine approaches are equitable and effective across all ethnicities.

4. TLR3 and HCV infection

4.1. Viral clearance

The activation of TLR3 by dsRNA generated during HCV replication is a critical frontline defense for initiating viral clearance. This process occurs through coordinated actions in different liver cell types. In hepatocytes, intrinsic TLR3 signaling directly induces the production of type I and type III IFNs and ISGs, creating a cell-autonomous antiviral state that potently restricts viral replication [74, 75]. The efficiency of this response depends on the co-factor glucose-regulated protein 78 kDa (GRP78), as its depletion impairs TLR3-dependent signaling by reducing IRF3 phosphorylation [76-78]. Simultaneously, immune cells like macrophages amplify the antiviral response. Upon TLR3 activation, macrophages release exosomes enriched with anti-viral miRNAs, such as those from the miRNA-29 family. These exosomes can be taken up by neighboring hepatocytes, where they mediate a potent inhibition of HCV replication, demonstrating a crucial paracrine mechanism for containing the infection [79].

4.2. Immune evasion and viral persistence

Despite robust host defense mechanisms, HCV has evolved multiple, sophisticated strategies to evade TLR3-mediated immunity and establish persistent infection. A primary viral tactic is the active disruption of the TLR3 signaling pathway. The HCV NS4B protein directly downregulates the levels of the essential TLR3 adaptor protein TRIF, effectively blunting the downstream interferon response [47]. Clinically, this sabotage is reflected in the significant downregulation of both TLR3 and TRIF observed in patients with chronic hepatitis C, with lower expression levels correlating with higher viral loads, increased disease severity, and adverse clinical outcomes [26]. Furthermore, HCV employs stealth strategies to avoid detection. The virus packages its positive- and negative-strand RNA genomes into extracellular vesicles (EVs) for secretion. This export of viral RNA intermediates serves to reduce the intracellular concentration of dsRNA, the very ligand for TLR3, thereby limiting receptor activation. When this EV release is inhibited, the accumulated intracellular dsRNA leads to stronger TLR3 activation and subsequently reduced viral replication [80]. HCV replication itself also directly impairs poly(I:C)-induced innate immune responses in hepatocytes, providing another layer of interference to ensure its persistence [81].

4.3. TLR3 polymorphisms

The relationship between TLR3 polymorphisms and HCV infection is also characterized by significant heterogeneity, largely attributable to methodological variations in statistical power, clinical endpoint definitions [82, 83], and population genetics (Table 2). Robust evidence originates from large-scale, well-powered studies. The investigation by El-Bendary et *al*.[84] (n = 3,368), which stratified participants into chronic HCV, spontaneous clearance, and healthy control groups, consistently identified the C allele of rs3775290 (1377 C>T), rs3775291 (1234 C>T), and rs5743312 (C>T,G) as protective against chronic infection. Similarly, the large cohort study by Al-Anazi et *al*.[85] (n=1,162) provides strong evidence for the role of specific polymorphisms in susceptibility and cirrhosis risk. In contrast, studies with limited sample sizes yield findings that are primarily exploratory [86, 87]. For instance, the reported association between the rs3775291 (1234 C>T) TT genotype and HCC by El-Sharawy et *al*.[88] is based on a small cohort (n = 70), increasing its susceptibility to type I error and limiting generalizability. The finding of a risk-associated heterozygous CT genotype (rs3775290, 1377 C>T) by Mosaad et *al*.[89] is also intriguing but stems from a modest sample (n = 225) and requires validation. Similarly, findings from Nurlanova et *al*.[90] on rs1879026 (C>A) and Medhi et *al*.[91] on the -705A/G promoter polymorphism is compelling but necessitates confirmation in larger cohorts.

An example of apparent contradiction involves the rs3775290 (1377 C>T) polymorphism, which has been linked to both risk and protective outcomes. For instance, Hamdy et *al*.[92] and Sghaier et *al*. [93] associated the CC genotype and T allele, respectively, with increased risk of chronic HCV, while Abdelwahab et *al*.[94] and Sghaier et *al*.[93] linked the CC genotype to viral clearance and treatment response. These discrepancies reflect the polymorphism context-dependent role, as the studies measured different clinical endpoints, from initial susceptibility and chronicity to treatment response and progression to cirrhosis. Finally, ethnic background constitutes a major source of heterogeneity, and the choice of control group is a critical confounding factor. The study by Barkhash et *al*.[95], which found no association, used a control group with unknown HCV status, a significant limitation, as misclassifying infected individuals as controls can obscure a

Table 2. Studies on TLR3 polymorphisms and HCV infection.

Author	Year	Country	Study Design	Sample Size	Polymorphism(s)	Key Finding	Population
Nurlanova et al.	2023	Kazakhstan	Case-Control	102/127	rs5743312 (C>T), rs5743305 (A>T), rs3775291, rs5743311 (C>T), rs1879026 (C>A),	rs1879026 CC genotype increased risk of chronic HCV.	Chronic HCV vs. Healthy controls
Talaat et al.	2022	Egypt	Cohort	139	rs3775290, rs3775291	No association with liver cirrhosis.	HCV patients: Cirrhotic vs. Non-cirrhotic
Abdelwahab et al.	2021	Egypt	Cohort	265	rs3775290	CC genotype associated with viral clearance.	Healthcare workers: Spontaneously cleared vs. Chronic HCV
El-Sharawy et al.	2020	Egypt	Case-Control	50/20	rs3775291	TT genotype associated with increased severity and HCC.	HCV cirrhotic patients with vs. without HCC
Mosaad et al.	2019	Egypt	Case-Control	125/100	rs3775290	CT genotype increased risk of chronic HCV.	Chronic HCV vs. Healthy controls
Sghaier et al.	2019	Tunisia	Case-Control	174/360	rs3775290	T allele increased risk of chronic infection and severe disease.	Chronic HCV vs. Healthy controls
El-Bendary et al.	2018	Egypt	Case-Control	3368	rs3775290, rs3775291, rs5743312	C allele of the three SNPs protective against HCV infection.	Spontaneously cleared vs. Chronic HCV vs. Healthy controls
Hamdy et al.	2018	Egypt	Case-Control	409/137	rs3775290	CC genotype increased risk of chronic HCV.	Chronic HCV vs. Spontaneously cleared
Zayed et al.	2017	Egypt	Case-Control	100/100	rs3775290, rs3775296 (_7 C>A)	No association with susceptibility; T allele linked to advanced fibrosis.	Chronic HCV vs. Healthy controls
Al-Anazi et al.	2017	Saudi Arabia	Case-Control	563/599	rs78726532 (A>G), rs5743314 (G>C)	rs78726532-GG increased HCV risk; rs5743314-GC increased cirrhosis risk.	Chronic HCV vs. Healthy controls
Sghaier et al.	2017	Tunisia	Cohort	120	rs3775290	CC genotype associated with sustained virologic response (SVR).	HCV patients: Treatment Responders vs. Non-responders
Citores et al.	2016	Germany	Cohort	176	rs3775291	CC genotype linked to severe HCV recurrence post-transplant.	Liver transplant recipients
Sá et al.	2015	Brazil	Case-Control	74/299	rs5743305, rs3775291	No association with susceptibility.	Chronic HCV vs. Healthy controls
Jiménez-Sousa et al.	2015	Spain	Retrospective	321	rs3775291	A allele reduced likelihood of treatment response.	HCV patients on PegIFN/RBV therapy
Barkhash et al.	2014	Russia	Case-Control	75/269	rs3775291	No association with HCV.	Chronic HCV vs. Population controls (HCV status unknown)
Lee et al.	2013	USA	Nested Case-Control	153/458	rs3775291	Associated with progression to chronic hepatitis C.	Liver recipients: HCV-infected vs. Uninfected
Citores et al.	2011	Germany	Cohort	100	rs3775291	TT genotype reduced rejection post-liver transplant.	Liver transplant recipients for HCV
Medhi et al.	2011	India	Case-Control	180/180	-705A/G	-705G allele increased susceptibility to HCV.	Chronic HCV vs. Healthy blood donors

true genetic association.

4.4. Insights from African cohorts

The evidence from African cohorts, predominantly from North Africa, reveals distinct patterns and underscores the critical influence of regional genetics on TLR3-associated HCV outcomes. Egyptian studies, representing the largest body of evidence from Africa (Table II), highlight the complex role of the rs3775290 (1377 C>T) polymorphism. The same CC genotype has been associated with contradictory outcomes. Hamdy et *al*.[92] identified it as a risk factor for chronic infection, while Abdelwahab et *al*.[94] found it associated with spontaneous viral clearance in healthcare workers. This suggests the effect of this genotype is highly sensitive to other factors, such as the route and level of viral exposure. Furthermore, Zayed et *al*.[96] found no association with susceptibility but linked the T allele to advanced fibrosis, indicating a role in disease progression rather than initial infection. Other notable risk associations from Egypt include the rs3775291 (1234 C>T) TT genotype with HCC severity [88] and the CT genotype of rs3775290 (1377 C>T) with chronic infection. In contrast to the mixed signals from Egypt, Tunisian studies report a more consistent risk association for the rs3775290 (1377 C>T) T allele. Sghaier et *al*.[68] found it increased the risk of chronic infection and severe disease. Interestingly, the same team [93] also associated the CC genotype with a positive outcome, Sustained Virologic Response (SVR) to interferon-based therapy. This reinforces the context-dependent model, where a genotype can be detrimental for spontaneous clearance but beneficial in a treatment context.

When compared to studies from Europe, Brazil, and the USA, the African data often show divergent association signals. For instance, the strong risk effect of the T allele seen in Tunisia is not consistently replicated elsewhere. This divergence can be attributed to the unique genetic architecture of African populations.

The collective evidence from African cohorts firmly establishes that the genetic architecture of the TLR3 pathway is not uniform. The associations discovered in these populations are crucial for understanding the global genetic epidemiology of HCV and underscore the necessity of including diverse African cohorts in future research to identify population-specific causal variants and the equity of personalized medicine approaches.

5. TLR3 and hepatitis antiviral therapy

5.1. HBV therapy

TLR3 agonists have shown promising antiviral activity against HBV in preclinical settings. It is expressed in both primary human hepatocyte and HepaRG cells, and its activation induces high levels of IL-6, IP-10 secretion, and type I interferons [25]. Specific TLR3 agonists, such as poly(I:C)-HWM and Riboxxol, have shown potent antiviral effects in HBV-infected primary human hepatocytes and differentiated HepaRG cells, reducing all measured HBV parameters [97]. Notably, in contrast to the viral rebound typically seen after stopping nucleos(t)ide analogue therapy, little to no rebound was observed following the cessation of TLR3 agonist treatment. This suggests a long-lasting effect on cccDNA and further supports the therapeutic potential of TLR3 activation [97].

Beyond their direct antiviral effects, TLR3 ligands have also been investigated as vaccine adjuvants. For instance, when used as an adjuvant in an HBV therapeutic vaccine, Poly(I:C) was shown to efficiently and safely decrease HBsAg and HBV DNA in HBV-carrier mice. This vaccine boosted HBV-specific T cell responses, which play a crucial role in protecting against HBV reinfection, and reduced viral load [98]. Furthermore, targeted delivery of poly(I:C) to the liver enhanced viral clearance in mice, underscoring the importance of optimized delivery systems [48]. Collectively, these findings indicate that TLR3 agonists like poly(I:C) hold significant potential as vaccine adjuvants to enhance immune responses against HBV.

Combination strategies are another area of interest, where TLR3 agonists paired with other TLR ligands or conventional antivirals may amplify immune responses and improve viral control [97]. Recent reviews emphasize that TLR3, together with TLR7 and TLR8 agonists, represents a promising class of immunomodulators for chronic HBV therapy, although most evidence remains limited to *in vitro* studies and animal models [48, 99].

Several challenges and considerations remain for advancing TLR3-based therapies against HBV. Safety is a major concern, since TLR3 agonists induce strong interferon and inflammatory responses that, if not properly controlled, may cause toxicity [100]. Careful optimization of route, dose, and cell-specific targeting is therefore critical, with nanoparticle-based delivery systems offering promise for restricting activation to hepatocytes and minimizing off-target effects. Another unresolved issue is the impact on covalently closed circular DNA (cccDNA), the key barrier to HBV cure [97, 100]. While some TLR3 ligands have been shown to reduce cccDNA transcriptional activity, robust evidence for direct elimination is still lacking. For a functional cure, TLR3 agonists may need to be combined with other immune modulators, such as checkpoint inhibitors, therapeutic vaccines, or existing antivirals, to simultaneously suppress replication and enhance adaptive immunity [100]. The current body of evidence for TLR3-based therapies is predominantly derived from preclinical models, and clinical data from human trials remain scarce. For the successful translation of these promising approaches, several key challenges must be addressed. These include the development of safe and effective drug formulations, a deeper understanding of the potential bias in TLR3 signaling responses, and the stratification of patient populations to identify those who would derive the greatest therapeutic benefit [99].

Finally, human genetic variation in TLR3 may affect therapeutic efficacy [101], suggesting that host genotyping could help stratify patients and guide personalized treatment approaches. However, it is crucial to emphasize that the current evidence is largely preclinical and associative; routine TLR3 genotyping is not yet justified in clinical practice for HBV management. Before translation can occur, specific research gaps must be addressed, including the validation of polymorphisms in large, diverse cohorts, the mechanistic elucidation of their functional impact, and studies on their interaction with TLR3 agonist therapies. In the short term, the utility of TLR3 genetics remains confined to research, where it can help identify patient subgroups for clinical trials. In the long term, if these gaps are filled, it holds the potential to become a biomarker for personalizing immunotherapeutic strategies. Collectively, addressing these factors defines the necessary path forward

for developing TLR3 agonists into clinically viable and precisely targeted HBV therapies.

5.2. HCV therapy

Evidence suggests that stimulating TLR3 can suppress HCV replication by enhancing interferon signaling and ISG induction. In hepatocyte models, poly(I:C) treatment reduces HCV RNA and protein levels, and epigallocatechin-3-gallate (EGCG) further augments poly(I:C)-induced TLR3 expression and antiviral activity [81]. Nanoparticle-based delivery systems, such as calcium phosphate nanoparticles loaded with poly(I:C), have been proposed to achieve selective activation of TLR3 with reduced systemic toxicity [102]. In addition, TLR3-activated macrophages release exosomes enriched in antiviral miR-29 family members, which efficiently inhibit HCV replication in hepatocytes, pointing toward the development of exosome-based delivery strategies [79].

Despite these advances, several challenges remain. HCV has evolved mechanisms to antagonize TLR3, notably through cleavage or downregulation of TRIF by viral proteins, which diminishes interferon induction and contributes to chronicity. Given the success of DAAs in curing HCV, TLR3 agonists are more likely to find utility as **adjunct immunotherapies** for example, to enhance host immunity, reduce reinfection risk, or target residual viral reservoirs. As with HBV, host genetic variation in TLR3 may influence treatment response, making patient stratification an important consideration for future development.

6. Conclusion

TLR3 plays a pivotal role in the host innate immune response against hepatitis viruses by sensing viral dsRNA and triggering TRIF-dependent signaling that drives interferon and ISG induction. In HBV infection, exogenous stimulation of TLR3 with synthetic ligands such as poly(I:C) or more selective analogs like Riboxxol has been shown to suppress replication and, in experimental models, promote viral clearance. In HCV, TLR3 activation restricts viral replication, though the virus has evolved strategies such as TRIF cleavage and extracellular vesicle release to evade detection, thereby contributing to chronicity. Human genetic studies further underscore the importance of TLR3, with specific polymorphisms linked to susceptibility, disease progression, or viral persistence in both HBV and HCV. While these findings highlight TLR3 as an attractive antiviral target, challenges remain regarding safety, delivery, and consistent effects on cccDNA in HBV or viral reservoirs in HCV. Most evidence is still preclinical, and clinical translation requires careful consideration of host genetic variability, biomarkers of response, and rational combination with other antivirals or immunomodulators. Nevertheless, leveraging TLR3 agonists, nanoparticle delivery systems, and exosome-based strategies holds promise for next-generation immunotherapies aimed at enhancing viral clearance, preventing chronic liver disease, and advancing toward a functional cure for HBV and HCV.

Conflict of Interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

No human or animals were used in the present research.

Informed Consent

The authors declare that no patients were used in this study.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

Abdoul Karim Ouattara: Study conception, literature search, manuscript drafting, and critical revision. **Issoufou Tao**: Literature search and critical revision. **Julien Dembele**: Literature search and critical revision. **Jacques Simpore**: Study design, critical revision, and supervision.

Funding

None.

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