Review of Lambda Interferons in Hepatitis B Virus Infection: Outcomes and Therapeutic Strategies

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Abstract: Hepatitis B virus (HBV) chronically infects over 250 million people worldwide and causes nearly 1 million deaths per year due to cirrhosis and liver cancer. Approved treatments for chronic infection include injectable type-I interferons and nucleos(t)ide reverse transcriptase inhibitors. A small minority of patients achieve seroclearance after treatment with type-I interferons, defined as sustained absence of detectable HBV DNA and surface antigen (HBsAg) antigenemia. However, type-I interferons cause significant side effects, are costly, must be administered for months, and most patients have viral rebound or non-response. Nucleos(t)ide reverse transcriptase inhibitors reduce HBV viral load and improve liver-related outcomes, but do not lower HBsAg levels or impart seroclearance. Thus, new therapeutics are urgently needed. Lambda interferons (IFNLs) have been tested as an alternative strategy to stimulate host antiviral pathways to treat HBV infection. IFNLs comprise an evolutionarily conserved innate immune pathway and have cell-type specific activity on hepatocytes, other epithelial cells found at mucosal surfaces, and some immune cells due to restricted cellular expression of the IFNL receptor. This article will review work that examined expression of IFNLs during acute and chronic HBV infection, the impact of IFNLs on HBV replication in vitro and in vivo, the association of polymorphisms in IFNL genes with clinical outcomes, and the therapeutic evaluation of IFNLs for the treatment of chronic HBV infection.

Keywords: hepatitis B virus; interferon lambda; innate immunity; seroclearance

1. Hepatitis B Virus

Hepatitis B virus (HBV) belongs to the Hepadnaviridae family, a group of enveloped, hepatotropic DNA viruses that infect mammals and birds with species-specific tropism [1]. After HBV establishes a chronic infection (as reviewed in [2]), the HBV covalently closed circular DNA genome (cccDNA) resides indefinitely as a mini-chromosome within the nuclei of infected hepatocytes and is a stable template for synthesis of HBV transcripts and nascent virion production [2–5]. During chronic infection, HBV replication within hepatocytes is largely unrestricted, in part as a consequence of the liver’s well-established pre-disposition to antigenic tolerance [6–8].

Chronic HBV infection causes significant morbidity and mortality worldwide by inducing cirrhosis and hepatocellular carcinoma that result in nearly 1 million deaths per year [9–11]. Currently, there are no approved therapies that reliably eliminate or silence cccDNA once chronic infection is established [12–14]. Although nucleos(t)ide reverse transcriptase inhibitors (NRTIs) reduce HBV DNA by inhibiting the HBV polymerase,
thereby lowering hepatic inflammation and the risk of progressive liver disease, pre-made cccDNA is largely unaffected by NRTI therapy [15]. As such, viral protein production persists during therapy with NRTIs, including production of the HBV surface antigen (HBsAg), a serologic marker of active HBV infection. In addition, long-term NRTI therapy can potentially engender HBV resistance and cause bone and renal side effects which are difficult to manage clinically, underscoring the need for new HBV therapies.

The fate of HBV after an initial infection is highly contingent upon the maturity of the host immune system. Most adults can clear acute HBV infection by cytopathic and/or non-cytopathic mechanisms. This leads to clearance of serum HBV DNA and HBsAg, appearance of antibodies specific for HBsAg, and cessation of de novo viral production. Patients with spontaneous HBV clearance do not have an increased longitudinal risk of the hepatic sequelae associated with chronic infection [6,9,16]. Although there is little direct evidence demonstrating hepatic cccDNA in patients who have spontaneously recovered, HBV can reactivate when immunosuppressive medications are given, providing indirect evidence that intrahepatic cccDNA can persist after spontaneous clearance [17–19]. In contrast, neonates or infants infected with HBV typically develop a chronic lifelong infection and are unable to clear cccDNA or virions [6,9]. Understanding the mechanisms by which host immunity influences variable HBV outcomes after infection will aid design of novel therapeutic approaches.

As the source of continual HBV production during chronic infection, cccDNA is one of the critical targets for therapeutic modulation [6,13,20]. The optimal treatment outcome is inducing a functional cure, which attempts to recapitulate the fate of HBV in most persons who are infected as adults but then resolve active infection; i.e., cccDNA may still persist in the liver but is silenced and there is seroclearance of serum HBV DNA and HBsAg [6,10,13,21]. As current therapies rarely impact cccDNA, achieving a functional cure will likely require novel immunomodulating therapies given alone or in combination with current antivirals.

2. Lambda Interferons

Interferons (IFNs) are a class of cytokines that play a key role in antiviral defense [22,23]. IFNs are amongst the first cytokines produced when host pattern recognition receptors sense pathogen-associated molecular patterns, and IFNs signal in both an autocrine and paracrine fashion [24]. Human IFNs are classified as type-I, type-II or type-III based on varied receptor binding and host cell receptor expression, as reviewed elsewhere [25,26]. Type-III or lambda IFNs (IFNLs) were first discovered in 2003 as a novel family of cytokines that induce a transcriptional program similar to type-I IFNs [23,27–29], but by signaling through a distinct receptor complex.

Type-I IFNs signal through a heterodimeric receptor composed of interferon receptor alpha-1 (IFNAR1) and IFNAR2, which are expressed on the surface of nearly all cells [23,30–32]. In contrast, IFNLs signal through a heterodimeric receptor composed of interferon lambda receptor-1 (IFNLR1) and interleukin-10 receptor subunit beta (IL10RB) [28,33–35]. IFNLR1 binds IFNLs with specificity and has restricted cellular expression, whereas IL10RB expression is more broadly distributed and also functions as part of the receptor for IL-10, IL-22 and IL-26 [23,33,36,37]. IFNLR1 is expressed primarily on epithelial cells, such as hepatocytes and those found at mucosal surfaces, and on select immune cells, including plasmacytoid dendritic cells and some B-lymphocytes [38–41]. There are 4 IFNLs (IFNL1, IFNL2, IFNL3, IFNL4) which all signal by binding IFNLR1 resulting in IL10RB recruitment and initiation of a JAK-STAT signaling cascade [25,26]. Signaling results in expression of hundreds of interferon stimulated genes (ISGs), and IFNL signaling has a slower onset and longer duration of action relative to type-I IFN signaling [42,43], in part due to reduced susceptibility of the IFNL signaling complex to negative regulation [43,44]. Notably, a dinucleotide polymorphism within an exon of IFNL4 imparts differential capacity to make IFNL4 protein, such that some individuals are
incapable of making functional IFNL4 [45], whereas all people can make IFNL1, IFNL2, and IFNL3.

3. Role of IFNL Polymorphisms in Hepatitis C Virus Outcomes

The importance of alterations in IFNL signaling were highlighted by clinical studies examining chronic hepatitis C virus (HCV) outcomes. These studies identified a strong association of IFNL polymorphisms with HCV clearance during the acute stage of infection and of achieving HCV cure with type-I IFN-based therapy of chronic infection [46–51]. Patients with the genetic capacity to make functional IFNL4 protein, imparted by variability in the rs368234815 dinucleotide nucleotide polymorphism [45], were less likely to clear acute infection and less likely to respond favorably to type-I IFN-based therapy, suggesting ability to make IFNL4 negatively influences HCV outcomes. An alternative explanation for the association of IFNL polymorphisms with HCV outcomes involves variable IFNL3 mRNA decay due to a functional single nucleotide polymorphism (SNP) (rs4803217) in the 3’ untranslated region of the IFNL3 transcript [52]. These data provide strong evidence that alterations in IFNL signaling can have functional consequences on outcomes after infection and that modulation of this innate immune pathway could have therapeutic potential for infectious diseases.

4. IFNL Polymorphisms and HBV Clinical Outcomes

A minority of chronic HBV patients treated with type-I IFNs and/or NRTIs achieve durable suppression of HBsAg production after treatment cessation, thereby achieving seroclearance [14,53,54]. Unfortunately, this favorable clinical outcome occurs infrequently and furthermore, IFN therapy is costly, can cause significant side effects, and must be given for months [14,54]. Understanding the genetic and mechanistic underpinnings of how and why some patients achieve seroclearance could facilitate differentially targeting or modulating IFN therapy to improve outcomes in more people. The strong association of IFNL polymorphisms with HCV outcomes prompted similar evaluations in HBV patient cohorts. Several studies in diverse ethnic and geographic cohorts comprised of healthy volunteers, patients who spontaneously cleared HBV infection, and patients who developed chronic HBV infection identified an association of IFNL polymorphisms with HBV infection outcomes [55–57]. However, multiple additional studies [58–61] and meta-analyses did not identify an association [62–66]. Most analyses examined SNPs within IFNL genes, but a case-control study in a Han Chinese cohort composed of 3128 patients (healthy controls, natural HBV clearance, or chronic HBV infection) found an association of IFNLR1 polymorphisms (rs7525481, rs4649203) with HBV susceptibility [60], which merits further evaluation in independent cohorts. Taken together, there is not a clear and reproducible association of IFNL polymorphisms with HBV infection outcomes, particularly relative to the strong association that was observed with HCV.

The association of IFNL polymorphisms with differential outcome after IFN-based therapy for chronic HBV infection has also been evaluated. Several studies identified a significant association of IFNL polymorphisms with either HBe antigen (HBeAg) or HBsAg clearance after receipt of IFN-based therapy [67–73], including several meta-analyses [74,75]. However, multiple additional studies did not identify a significant association [76–80], including several independently conducted meta-analyses (reviewed in [46], [81,82]). Varying genetic and ethnic backgrounds of the study populations, differences in HBV genotype, and sample size may have influenced these disparate results [70,82–84]. Taken together, although IFNL polymorphisms correlated with HBV outcomes after IFN-based therapy in some cohorts, this finding was not as robust or consistently observed across studies relative to HCV [46,84]. To date, a definitive genetic or immune mechanism to explain the variable response of HBV patients to type-I IFN treatment remains elusive [12,14], which hampers efforts to rationally design novel therapeutic approaches that are immunomodulatory.
5. IFNL Expression in Response to HBV Infection In Vitro and In Vivo

Hepatocytes express IFNLR1 and support IFNL signaling, prompting evaluation of IFNL expression during acute and chronic HBV infection. If HBV infection induces, inhibits, or is responsive to IFNLs, then modulation of IFNL expression endogenously or by exogenous administration could have therapeutic benefit. HBV reactivation during HCV treatment has been observed, likely due to a reduction in hepatic interferon signaling when HCV viral load declines due to antiviral treatment, implying endogenous interferons can suppress HBV infection [85]. The extent to which HBV is recognized within hepatocytes and either stimulates, suppresses, or avoids an innate immune response has differed across studies. These different findings may in part relate to differences in the systems used for evaluation (i.e. in vitro, in vivo, natural infection, or over-expression of viral proteins or virions) [6,86–88]. The following section and Figure 1 highlight key investigations providing support for alternative interpretations of how HBV and hepatocytes interact and the potential involvement of IFNLs.

Figure 1. Proposed models and selected mechanisms for HBV suppression or evasion of the host innate immune response in hepatocytes. (A) HBV is recognized by the host cell, an antiviral response is induced including expression of IFNLs, but this response is subsequently suppressed by viral elements. (B) HBV is not sensed by the host cell and IFNLs are not produced even though detection and signaling proteins are functional. Exposure of HBV-infected hepatocytes to endogenous IFNLs can overcome immune inactivity. Figure created with BioRender.com.

There are two possibilities for how HBV persists within an infected hepatocyte: (1) an antiviral response is induced, but subsequently suppressed, or (2) HBV is a stealth virus and therefore does not induce an IFN response. Viral infection typically is sensed by pathogen-recognition receptors (PRRs) that then induce immune activation. For example, the PRR MDA5 (or IFI18, interferon induced with helicase C domain 1) is shown to associate with HBV double stranded RNA (dsRNA) [89] and RIG-I (or DDX58, DexD/H-box helicase 58) is reported to recognize a specific region in HBV pre-genomic RNA [90,91]. Upon viral sensing it has been postulated that the resultant innate immune response is subsequently suppressed by HBV or viral components which leads to persistent infection. This result has
been shown in vitro in hepatocyte-derived cells lines, primary human hepatocytes, and in vivo in humanized models of HBV infection [90,92–95].

Studies with HepaRG cells and primary human hepatocytes also showed that HBV can inhibit host cell recognition of viral dsRNA, thus impeding immune signaling [96,97]. Additionally, expression of viral proteins, including the HBV e-antigen (HBeAg) can contribute to immune suppression. HBV infection of human hepatoma cells showed that HBeAg induces a member of the suppressor of cytokine signaling family, SOCS2, which impairs JAK-STAT signaling and leads to downregulation of type-I and IFNL receptors and thus inhibits ISG expression [98]. Moreover, the intracellular form of HBeAg, p22, interferes with IFN signaling in hepatoma cells by blocking nuclear translocation of STAT1 through interactions with the nuclear transport factor, karyopherin alpha1 [99]. These data and others suggest a mechanism by which HBeAg facilitates HBV replication and persistence [100].

The HBV protein x (HBx) has also been shown to interfere with multiple host cell functions. Independent studies show that HBx interacts with beta interferon promoter stimulator 1 (IPS-1) adaptor protein and thus interferes with the RIG-I pathway [101], as well as disrupts the assembly and promotes degradation of mitochondrial anti-viral signaling (MAVS) thereby inhibiting IRF3 (interferon regulatory factor 3) activation [102,103]. HBV polymerase has been demonstrated to inhibit the RIG-I pathway by disruption of DDX3 DEAD box RNA helicase [104] or blockade of IRF3 activation [105]. Studies in cell lines and mouse models suggest HBV represses expression and function of the cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS) DNA sensing pathway [106]. Use of a 3D microfluidic culture model designed to mimic the hepatic sinusoid structure and support long-term HBV infection in vitro showed that HBV suppresses type-I IFNs and IFNL expression in primary human hepatocytes, although the cells remained responsive to exogenous IFN treatment [86]. Collectively, these data imply that HBV is recognized within hepatocytes, an innate immune response is induced and includes expression of IFNLs, however there is subsequent suppression of IFN signaling by viral elements. These data also indicate that modulation of IFNL signaling can impact host cell detection of HBV and affect viral replication, and thus has therapeutic potential.

Conversely, other studies suggested HBV can act as a stealth virus which avoids IFNL induction during acute infection. In an analysis of peripheral blood from 21 patients with acute HBV infection, no soluble IFN-alpha or IFNL1 was detected during peak viremia, while expression of immunosuppressive IL-10 increased in parallel with an attenuated NK- and T-cell immune response [107]. This result was compatible with findings from a chimpanzee model of HBV infection where no ISG expression was observed in the liver during the early phases of infection, suggesting an IFN response was not triggered in hepatocytes with actively replicating HBV [16,108,109]. HBV may evade DNA sensing by the cGAS and STING (stimulator of interferon genes) pathway within hepatocytes in vivo [106,110]. Other in vitro and in vivo studies also suggest that HBV may not interfere with innate immunity in hepatocytes [85,111,112].

Co-infection studies with HCV or hepatitis D virus (HDV) provided added support that HBV is a stealth virus. HBV-infection of NTCP-expressing human hepatoma cells or primary human hepatocytes did not induce an inflammatory response; conversely mono-infection with HCV or HDV or co-infection with either virus plus HBV resulted in IFN-beta and IFNL expression and induction of ISGs [113,114]. Challenge of humanized mice with HBV and HDV resulted in ISG production and significant IFN-beta and IFNL expression, an outcome not detected in HBV-only infected animals [115]. These studies collectively showed that the target cells and murine models had the capacity to respond to viral challenge and that the lack of IFN induction by HBV was not due to blockade of intracellular pattern recognition receptors (RIG-I, MDA5 or TLR3) or from inhibition of JAK-STAT signaling, but rather was attributed to non-detection (i.e. stealth) based on retained susceptibility to exogenous IFN stimulation [112,113].
The immune response to HBV infection is not restricted solely to hepatocytes. As such, a study examined whether macrophages derived from the THP-1 cell line or human monocytes were as non-responsive as hepatocytes. HBV-exposed macrophages were found to be activated and secreted inflammatory cytokines shortly after challenge, although a high dose of virus ($10^2$ genomes/cell) was required to achieve a response [112]. Taken together, the extent to which HBV induces IFNL expression or modulates IFNL signaling may be highly contingent upon the cell type, assay system, and context in which the virus-host interaction is evaluated.

6. IFNL Expression during Chronic HBV Infection

Viral-host interactions may differ during acute and chronic HBV infection. Baseline differences in endogenous IFN expression associate with outcomes after type-I IFN treatment of chronic HCV infection, as patients with higher baseline hepatic ISG expression are less responsive to type-I IFN treatment [116]. As such, multiple studies evaluated whether IFNL expression is altered during chronic HBV infection. In clinical cohorts, IFNL levels were found to be elevated in serum or liver of chronic HBV patients in some [92,93,117], but not all studies [118,119]. During chronic HBV infection, BDCA3+ dendritic cells are enriched in the liver and produce high levels of IFNL upon exposure to synthetic RNA polyI:C, whereas peripheral BDCA3+ dendritic cells and plasmacytoid dendritic cells are impaired, potentially due to chronic exposure to HBsAg [120,121]. Examination of HBV-infected hepatocytes from liver biopsies of patients with chronic HBV infection showed no elevation of ISG or IFN expression as compared to neighboring non-infected hepatocytes or to hepatocytes collected from patients without HBV infection (most had fatty liver disease) [111]. However, IFN-treatment of HBV-infected cells showed retained capacity to induce an IFN-response in HBV-harboring hepatocytes, including expression of IFNLs in response to Sendai virus or poly I:C exposure [111]. Taken together, while modulation of IFNL expression may occur during chronic HBV infection, altered IFNL signaling does not appear to be a prominent feature within HBV-infected hepatocytes, but may occur in other uninfected liver-resident cells, such as dendritic cells or macrophages.

Currently approved NRTIs suppress HBV replication and improve hepatic inflammation, and several studies assessed whether they might also impact IFNL expression. Interestingly, HBV patients treated with nucleotide analogues (adefovir, tenofovir) had higher serum IFNL3 levels relative to patients treated with nucleoside analogues (entecavir and lamivudine) [122]. In vitro assays additionally showed a dose-dependent induction of IFNL3 by nucleotide-stimulated cells, induction of ISGs, and inhibition of HBsAg [122]. This suggests induction of IFNLs could contribute to the antiviral efficacy of HBV polymerase inhibition.

While HCV-infected hepatocytes exhibit a robust intracellular IFN response to infection, HBV-infected hepatocytes may not manifest a similar response in spite of high levels of HBV replication, as discussed above. HCV is a flavivirus that is readily detected by pattern recognition receptors and induces IFN production, but expresses viral proteins that actively interfere with the IFN signaling cascade (reviewed in [123]). In contrast, HBV is a hepadnavirus that appears to act more as a stealth virus that avoids detection by pattern recognition receptors and does not induce IFN production in infected hepatocytes, as discussed above. One theory for this lack of response is that hepatocytes intrinsically lack dsDNA sensing mechanisms, and thus HBV can replicate unchecked until surrounding immune cells, such as macrophages, detect high levels of circulating virions and stimulate an innate immune response [112,124]. Alternatively, because viral replication occurs intracellularly within nucleocapsid particles, HBV DNA may be hidden from pattern recognition receptors [3,16]. Differences in how the host detects and interacts with these distinct hepatotropic viruses likely helps explain the strong association of IFNL SNPs with HCV clearance during acute infection but the lack of strong association with HBV outcomes. Furthermore, it is likely that while IFNLs may not be actively or solely produced by hepatocytes during acute and chronic HBV infection, they may be produced
by immune or non-parenchymal liver-resident cells resident that influence host immune function and hepatic inflammation.

7. IFNL Impact on HBV Replication and cccDNA

Although IFNL polymorphisms do not strongly associate with HBV outcomes and although HBV does not clearly prompt IFNL production in hepatocytes, the ability to achieve seroclearance with type-I IFNs prompted interest in exploring the therapeutic potential of IFNLs for HBV. The receptivity of HBV-infected hepatocytes to IFN treatment, as outlined above, suggested IFNLs have the potential to impart a clinically significant antiviral effect. The restricted expression of IFNL1 raised the specter that IFNL therapy could impact cccDNA while causing less systemic side effects than exogenous type-I IFN therapy. This hypothesis was tested in in vitro and in vivo hepatocyte and HBV infection models in advance of clinical trial testing.

Type-I IFNs have been shown to lower HBV replication in vitro in cell lines and primary human hepatocytes and in vivo in humanized mouse models of infection. The mechanisms by which type-I IFNs impact cccDNA have been reviewed in detail elsewhere and include transcriptional repression of pregenomic and subgenomic RNA from cccDNA, cccDNA degradation (via APOBEC3A), RNA degradation, histone deacetylation, recruiting transcriptional repressors, lowering the binding of STAT1/2 to cccDNA, and inhibition of pregenomic RNA encapsidation [2,13,125–128].

Although the effect of IFNLs on cccDNA have been less well-characterized, overexpressing or inducing expression of IFNLs in hepatocyte cell lines and murine infection models results in ISG induction and inhibition of HBV replication [38,117,129–133]. IFNL3 treatment reduced HBV transcripts and intracellular DNA in HepG2 2.2.15 cells that have clonally integrated HBV, a phenotype linked to changes in the host transcriptome and proteome [132,134,135]. Exposure of primary human hepatocytes or HepaRG cells to type-I IFNs or IFNLs reduced open-circle and cccDNA by causing cccDNA deamination and degradation, a phenotype attributed to induction of APOBEC deaminases [136]. Activation of stellate cell lines through toll-like receptor 3 resulted in induction of type-I IFNs and IFNLs, which inhibited HBV replication in HepG2 cells transfected with an HBV plasmid [137]. Finally, administration of pegylated IFNL1 in a xenograft model mouse model of human hepatocellular carcinoma led to reduced HBsAg expression in vivo [130].

Taken together, the prevailing evidence indicates that IFNLs are capable of inducing an IFN-response in HBV-infected cells and can lower HBV viral load by reducing HBV transcripts and modulating cccDNA, thus inducing similar intracellular events to type-I IFNs. This suggests targeting cccDNA through modulation of IFNL signaling has the potential to contribute to achieving seroclearance.

8. IFNLs as HBV Therapeutics

Although type-I IFNs have the capacity to impact HBV replication in vitro by modulating cccDNA, as discussed above and as previously reviewed in detail [2,138], the majority of patients treated with type-I IFNs do not have durable HBV DNA and HBsAg seroclearance after treatment [13]. This prompted interest in using IFNLs to treat HBV infection. When pegylated IFNL1 was tested in clinical trials for chronic HCV infection, antiviral activity was demonstrated and treatment was generally well tolerated, although a minority of healthy volunteers and HCV subjects experienced hepatotoxicity, primarily at the greatest tested dose (7.5 µg/kg) [139,140]. Based on these results and the ability of IFNLs to suppress HBV replication in vitro and in animal models, IFNLs were tested in clinical trials of patients with chronic HBV infection.

In a phase 2 trial, pegylated IFNL1 treatment in HBeAg+ chronic HBV subjects led to greater on-treatment decline in HBsAg and HBV DNA relative to patients who received pegylated IFNα2 treatment and similar serologic/virologic responses at the end of treatment [141]. Pegylated IFNL1 treatment was generally well-tolerated, with the exception of a subset of patients who experienced alanine aminotransferase (ALT) flares either
during treatment or post-treatment in association with viral rebound [141]. Intriguingly, on-treatment HBV decline was observed in 12 of 13 patients who experienced early ALT flares, implying a mechanistic link between pegylated IFNL1-induced inflammation and antiviral efficacy [141]. Despite these on-treatment results, pegylated IFNL1 did not meet non-inferiority criteria as fewer subjects achieved HBsAg seroconversion relative to the pegylated IFNα2 group 24 weeks post-treatment [141]. In a separate arm of this trial, 13 subjects received twelve weeks of the NRTI entecavir prior to pegylated IFNL1 treatment. Interestingly, in a distinct subset of responders who exhibited HBV DNA and HBsAg decline, treatment with pegylated IFNL1 was found to increase NK-cell polyfunctionality and anti-HBV CD4+ and CD8+ T-cell function [142]. These data suggest differential host response to therapy could have a genetic or biologic basis [142], and that some patients may respond more favorably to IFNL therapy than others, much as has been observed for type-I IFN-based therapy for chronic HCV and HBV infection.

Although there are no current clinical trials evaluating IFNL therapy for HBV mono-infection, pegylated IFNL1 has been investigated for treatment of HDV in patients with HDV/HBV co-infection. Unlike HBV, HDV RNA is recognized by MDA5 in hepatocytes, and induces an innate immune response in cellular systems, which includes induction of type-I IFNs and IFNLs [114,143]. Pegylated IFNL1 was recently tested in combination with ritonavir and lonafarnib (which prevents prenylation of L-HDAg) (Clinical Trials.gov Identifier: NCT03600714) [143] based on studies demonstrating antiviral potential for HDV in murine models [144,145].

9. Conclusions and Future Directions

In conclusion, the association of IFNL polymorphisms with HBV infection outcomes and response to IFN-based treatment is either absent or weaker than the association observed with HCV. This difference may relate to the distinct ways each virus interfaces with host immunity. The predominance of evidence indicates that HCV stimulates and then interferes with antiviral mechanisms induced by IFNs, while HBV largely avoids stimulation of IFNs within hepatocytes in the first place. Despite reported antagonisms of IFN signaling by HBV, hepatocytes infected with HBV can induce a robust interferon response upon exposure to type-I IFNs and IFNLs, resulting in reduced HBV replication and suppression of cccDNA activity. Therapeutic use of IFNLs alone or in combination with entecavir led to on-treatment viral suppression in HBeAg+ HBV patients and augmented innate and adaptive immune function in a subset of participants, but clinical end points of seroclearance were not achieved, indicating IFNL therapy alone or in combination with entecavir was as-yet inadequate.

A number of observations suggest there is continued value in understanding the mechanisms and outcomes of IFNL signaling, particularly when considering their potential future use as combination therapy to achieve seroclearance for chronic HBV infection. The four IFNLs do not bind IFNLR1 with equivalent affinity [46,146,147], and some studies suggest IFNLR3 induces a more potent ISG transcriptional response relative to IFNL1 [42], the specific IFNL tested in clinical trials [141]. Whether use of a more potent IFNL ligand could result in improved outcomes merits further study, as has been suggested for type-I ligands [148,149]. Differential outcomes after HBV treatment using novel therapies should be evaluated for association with IFNL polymorphisms, given that some are immunostimulatory [20]. Of note, some immune cells express functional IFNLR1, whereas others express a soluble, truncated form of the receptor that does not support canonical signaling and may respond differently to stimulation [150–153]. Future studies should assess whether focused targeting of IFNL signaling by modulating IFNLs or IFNLR1 on innate and adaptive immune cells could promote antiviral activity against HBV, outside of their impact on hepatocytes harboring HBV. Finally, the use of IFNL mimetics, targeting IFNL activity specifically to the liver, and differential timing of NRTI combined with IFNL therapy merit further evaluation as potential therapeutic strategies.
In summary, IFNLs are a complex and highly regulated host innate immune defense system that can impact HBV replication and cccDNA. Additional studies are warranted to better understand how to harness the antiviral potential of IFNL signaling for therapeutic benefit in chronic HBV patients.

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