Cytokine 124 (2019) 154518

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Interferon signaling during Hepatitis B Virus (HBV) infection and HBV-associated hepatocellular carcinoma

Saravana Kumar Kailasam Mani, Ourania Andrisani*

Department of Basic Medical Sciences and Purdue Center for Cancer Research, Purdue University, West Lafayette, IN 47907, USA

ARTICLE INFO

Keywords:
Hepatitis B Virus (HBV)
Innate immunity
Interferon (IFN) signaling
Hepatocellular carcinoma
Cancer stem cells

ABSTRACT

Chronic Hepatitis B Virus (HBV) infection is linked to hepatocellular carcinoma (HCC) pathogenesis. The World Health Organization estimates that globally 257 million people are chronic HBV carriers at risk of developing liver cancer. Current therapies for prevention and treatment of HCC are inadequate. Although interferon-based treatment strategies hold great promise for combating chronic infection and HCC, many patients do not respond to the IFN-based drugs for reasons not completely understood. Interferon signaling plays key roles in activation of innate and adaptive immunity. However, HBV has evolved various mechanisms to suppress IFN signaling. In this review, we present the basics about HBV infection and interferon signaling. Next, we discuss mechanisms through which HBV downregulates the function -activity and transcription- of the transcription factor STAT1 during acute and chronic infection. STAT1 is activated in response to all types (I/II/III) of interferon signaling and is essential in mediating all types (I/II/III) of interferon responses. Lastly, we discuss emerging evidence from different human cancers linking loss of interferon signaling to aggressive cancer and cancer stem cells. Whether the same occurs during HBV-associated hepatocarcinogenesis is discussed and currently under investigation.

1. Hepatitis B Virus

Hepatitis B Virus is a non-cytopathic, hepatotropic virus that belongs to the hepadnaviral family. Following acute infection of the liver, 90–95% of the patients clear the infection and fully recover. The remaining 5–10% of the patients develop chronic HBV infection, and are at greater risk of developing hepatocellular carcinoma (HCC) [1], which is usually fatal. The World Health Organization (WHO) estimates that 257 million people worldwide are chronically infected with HBV, with approximately 887,000 deaths every year due to HBV/HCC complications [2].

HBV is a partially double-stranded DNA virus that infects hepatocytes. It has a compact genome of 3.2 kb encoding four proteins: the Core antigen (HBc), the DNA Polymerase (P), Surface (S) and X (HBx) proteins [3]. The HBV receptor is the Sodium Taurocholate Co-transporting Polypeptide (NTCP) protein, a hepatocyte transmembrane protein. HBV binds the NTCP receptor and becomes internalized [4]. The viral capsid is then transported to the nucleus where the partially double-stranded DNA is repaired to form the covalently closed circular (ccc) DNA [5–7]. In HBV-associated liver tumors the viral DNA is integrated into the host genome following DNA repair. cccDNA assumes a minichromosome-like structure, serving as the template for viral transcription. The mRNA transcripts are exported to the cytoplasm and used for translation of the HBV proteins. The longest transcript, the pregenomic RNA (pgRNA), also functions as the template for viral replication, which occurs within nucleocapsids in the cytoplasm [3]. Nucleocapsids are enveloped during their passage through the endoplasmic reticulum (ER) and/or Golgi complex and secreted from the cell (Fig. 1).

2. Prevalence, transmission, risks and prevention

According to the WHO [2], HBV has highest prevalence in Western Pacific and African regions, followed by the Eastern Mediterranean, the South-East Asia and the European Regions (Fig. 2). HBV is a blood-borne pathogen, transmitted by blood and other bodily fluids. In highly

Abbreviations: HBV, Hepatitis B Virus; NTCP, Sodium Taurocholate Co-transporting Polypeptide; cccDNA, covalently closed circular DNA; pgRNA, pregenomic RNA; IFN, Interferon; ISGs, Interferon Stimulated Genes; STAT, Signal Transducer and Activator of Transcription; BER, base excision repair; PRC2, Polycomb Repressive Complex 2; RNA Seq, RNA sequencing; HCC, hepatocellular carcinoma; hCSC, hepatic cancer stem cell; GBM, glioblastoma; DLBCL, diffuse large B cell lymphoma

* Corresponding author.
E-mail addresses: skailasa@purdue.edu (S.K.K. Mani), andrisao@purdue.edu (O. Andrisani).

https://doi.org/10.1016/j.cyto.2018.08.012
Received 18 June 2018; Received in revised form 9 August 2018; Accepted 11 August 2018
Available online 17 August 2018

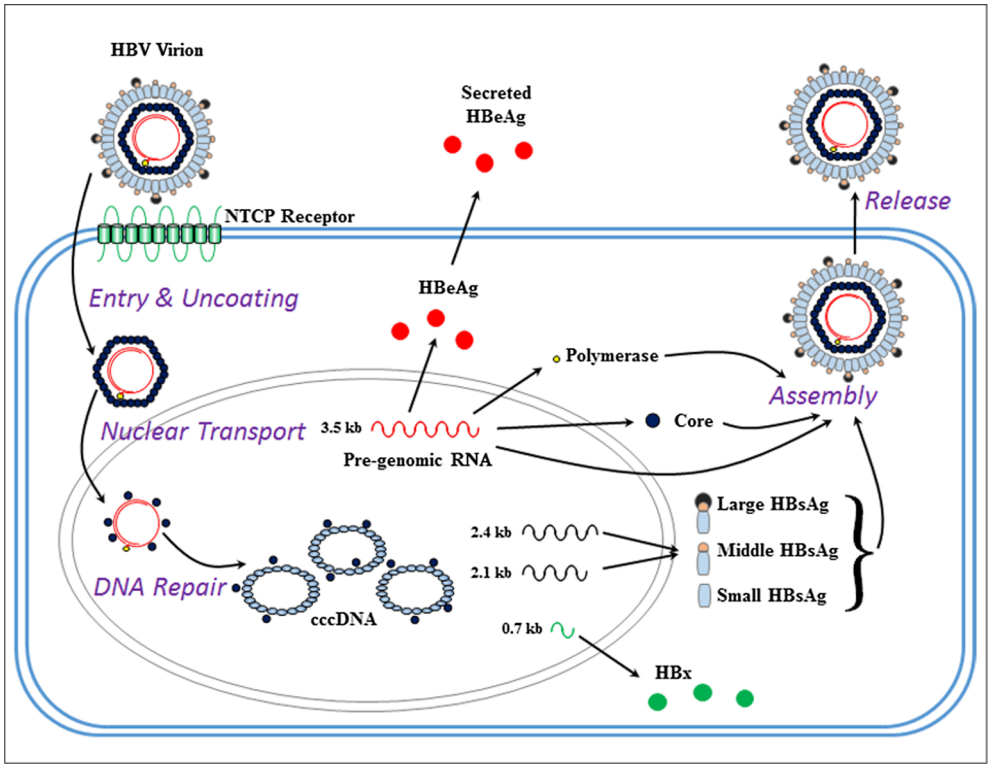

Fig. 1. Diagram highlights key steps of the HBV life cycle: viral entry and uncoating, nuclear transport of the viral genome, formation of cccDNA, viral transcription and replication, viral assembly and release.

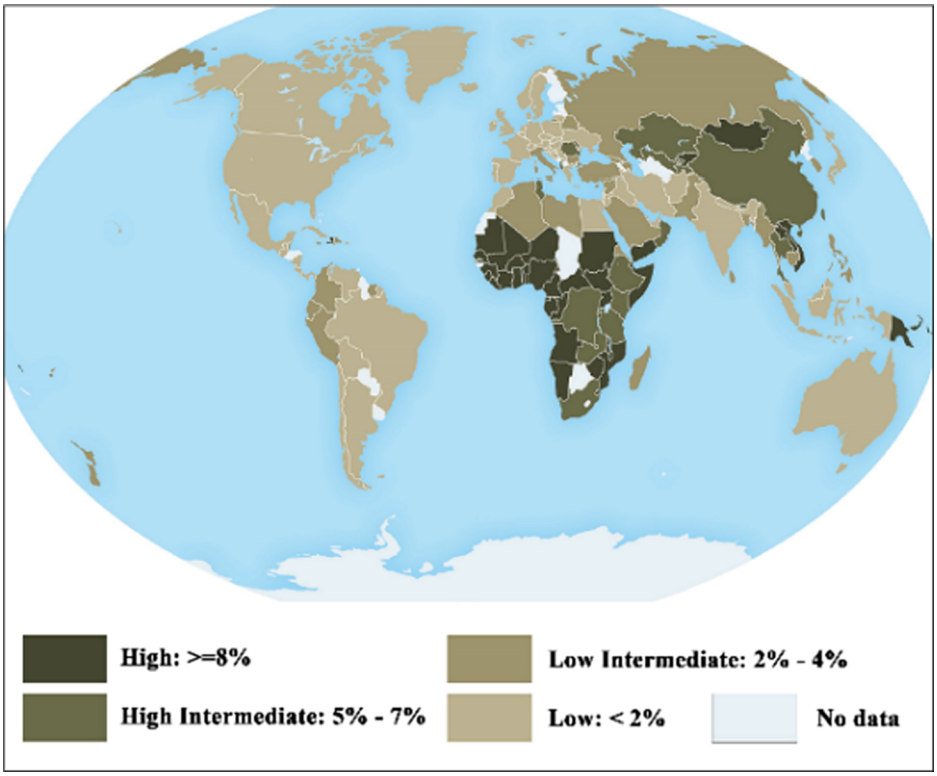

Fig. 2. Global HBV infection patterns according to the WHO [2].

endemic regions, perinatal transmission (spread from mother to child at birth) is the major route of transmission. Since HBV is capable of surviving and causing infection for at least 7 days outside the human body, transmission may also occur via percutaneous or mucosal exposure to infected blood and various bodily fluids [8–10]. The risk of developing chronic HBV infection after acute exposure ranges from 80 to 90% in newborns of HBeAg-positive mothers; 30–50% in children (under six years age) and less than 5% in adults [11–15]. In general,

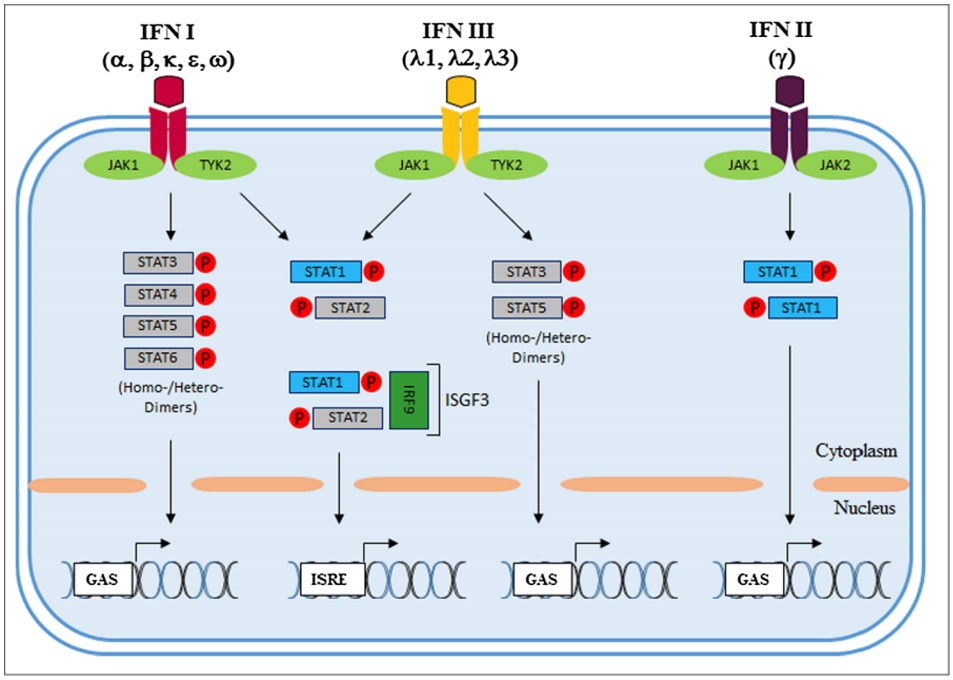

Fig. 3. Diagram outlines the key features of type I/II/III IFN signaling pathways. The blue boxes indicate STAT1, while the red circles indicate the activating phosphorylation of all STATs. STAT1 can be activated by all types of IFN signaling, and is essential for all types of IFN responses.

immunosuppressed persons have higher chance of developing chronic HBV infection [16]. The HBV vaccine, available since 1982, can prevent chronic infection in 95% of recipients and should be administered within 24 hrs of birth [17].

3. Treatment

Current treatment options for chronic HBV infection [18–20] are (i) immune modulator drugs, (ii) antiviral drugs, and (iii) liver transplantation. Immune modulator drugs are interferon (IFN)-type drugs that boost the immune system, while antiviral drugs include nucleoside analogs that halt HBV replication by inhibiting the viral polymerase. Currently [20], there are eight approved drugs for hepatitis B in the United States - two types of injectable interferons (PEGylated-IFN-α and IFN-α), and six oral antivirals (Tenofovir dipovoxil fumarate, Tenofovir alafenamide, Entecavir, Telbivudine, Adefovir and Lamivudine). Studies have found that IFN-α treatment reduced the incidence of cirrhosis, and liver-related deaths [21]. Unfortunately, a large percentage of chronic HBV patients do not respond to IFN treatment for reasons that remain to be understood [18]. Regarding the effect of nucleoside analogs, viral resistance limits their long term success [22–24]. Furthermore, persistence of cccDNA is mainly responsible for recurrence of HBV in patients, even years after anti-viral therapy [25]. Liver transplantation can overcome the pitfalls of immune modulator drugs and antiviral drugs, however, the procedure carries significant risks. Moreover, it is not an option for everyone, and there are millions of people chronically infected by HBV. Hence, we need to identify new strategies to effectively treat chronic HBV patients.

4. HBV infection and activation of the innate immune response

HBV persistence or viral clearance is dependent on the host immune response. Immediately after infection by most viruses the innate immune response becomes activated by IFNs, as an early defense mechanism to inhibit viral replication thus limiting the spread of the infection. Regarding HBV infection and activation of the innate immune response, studies in experimentally infected chimpanzees, also a natural HBV host, demonstrated absence of activation of the innate immune response, namely, IFN production and induction of Interferon Stimulated Genes (ISGs) [26]. Similar studies in humans are not available, because HBV infection is usually detected 10–12 weeks after the patient becomes infected. The results derived from the experimental infection of chimpanzees were interpreted to mean that HBV is a stealth virus [26,27]. Based on the lifecycle of HBV and because viral replication occurs within the nucleocapsid, it was proposed that the virus has evolved mechanisms to hide recognition of viral nucleic acids by the cellular innate response sensors [27]. However, one must also consider that viral proteins are in the cytoplasm of infected cells. Interestingly, *in vitro* studies employing non-transformed/non-neoplastic human HepaRG cells, transduced with baculovirus carrying the full length HBV genome, demonstrated that a strong HBV replication does/can induce a robust and HBV-specific innate immune response [28]. These results challenge the idea that HBV is a stealth virus [29]. In addition, many studies have identified mechanisms by which viral proteins counteract the innate immune response, reviewed in [29], and also discussed herein, partially explaining the “stealthy” nature of HBV [30].

Various HBV infection cellular and animal models have been established which have allowed a more in depth understanding of the mechanisms of these virus/host interactions. An in depth description of these HBV infection models can be found in the recent and comprehensive review by Allweiss and Dandri [31]. Some of these *in vitro* and *in vivo* animal models have been used to investigate how HBV bypasses cellular antiviral mechanisms, with focus on IFN signaling, as will be discussed herein.

5. The IFN signaling pathways

In response to viral infection, the host cell releases cytokines called “Interferons”. All classes of interferons (IFNs I, II and III) signal through the JAK/STAT pathway which results in transcriptional activation of Interferon Stimulated Genes (ISGs) [32]. IFN receptors usually exist as heterodimers. The cytoplasmic domain of all IFN receptors is bound by inactive Janus kinases (JAKs). Following IFN binding, the IFN receptors undergo conformational change bringing the inactive JAKs in close proximity. This results in auto-phosphorylation and activation of JAKs.

Activated JAKs phosphorylate specific tyrosine residues in specific STATs (STAT1-5) leading to their activation (Fig. 3). Activated STATs undergo homo/hetero-dimerization and translocate to the nucleus via the Importin-RanGDP complex [33,34]. STATs activate transcription of ISGs by binding to consensus DNA motifs in the promoter region of ISGs. Nuclear phosphatases (SHP-2, TC45) dephosphorylate STATs leading to STAT inactivation, and subsequent transport out of the nucleus by the exportin-RanGTP complex [35,36].

STAT1 is the only member of the STAT family of transcription factors that can be activated by all types of IFNs (I/II/III), and significantly, STAT1 is a required component in the signal transduction mechanism of all IFN (I/II/III) types (Fig. 3). Specifically, IFN-II binding to its receptor promotes homodimerization of phosphorylated STAT1 which translocates to the nucleus and binds to Gamma-IFN–activated sequence (GAS) sequence upstream of ISGs [37]. IFN types I and III signal via heterodimers of phosphorylated STAT1 and STAT2 in association with IRF9 (Fig. 3). These heterodimers translocate to nucleus and bind to IFN-stimulated response elements (ISRE) in the promoters of ISGs [38].

6. HBV infection and IFN signaling

Initially, *in vitro* cell culture studies identified various mechanisms by which HBV could interfere with IFN signaling. For instance, the HBV core protein (HBc) inhibits transcription of *Ifnβ* [39,40] and MxA upon IFN-α stimulation [41]; the C-terminal domain of the viral polymerase inhibits expression of MyD88 [42], and the HBV X and S proteins block nuclear import of phosphorylated STAT1 via upregulation of protein phosphatase 2A (PP2A) [43].

Employing animal models of HBV infection, various studies have examined HBV effects on IFN-signaling. HBV infected and uninfected human liver chimeric mice (uPA/SCID) were treated with human IFN-α [44]. Changes in viral DNA and expression of human ISGs were measured by RT-PCR, and immunohistochemistry. Although IFN-α activated expression of human ISGs in hepatocytes that repopulated the livers of uninfected mice, it failed to increase expression of ISGs in HBV-infected mice, and did not induce nuclear translocation of phospho-STAT1 in HBV-infected human hepatocytes. Thus, HBV prevents induction of IFN-α signaling genes by inhibiting nuclear import of activated STAT1, although in this study the level of total, non-activated/unphosphorylated STAT1 was not assessed. On the other hand, it was shown, using both HBV replicating HepG2 cells and human liver chimeric mice (uPA/SCID) infected with HBV, that IFN-α inhibits HBV replication by decreasing viral transcription from the cccDNA minichromosome. Administration of IFN-α resulted in hypoacetylation of histones bound to cccDNA, and recruitment of transcriptional corepressors HDAC1, SIRT1, EZH2, and YY1 to the cccDNA. IFN-α treatment reduced binding of STAT1 and STAT2 to cccDNA. Furthermore, an HBV mutant lacking the STAT1/STAT2 DNA binding could not be repressed by IFN-α. These results demonstrate how IFN-α antagonizes viral biosynthesis by epigenetically repressing STAT1/2-mediated transcription from the cccDNA [45].

7. STAT1 regulation and HBV infection

Since STAT1 is required for all types (I/II/III) of interferon signaling pathways (Fig. 3), the inhibition of STAT1 activation by HBV [43–45], identifies STAT1 as a critical cellular inhibition target by HBV infection. However, the mechanism (s) and cellular contexts by which HBV interferes with STAT1 activity are not fully understood. It was shown that arginine methylation of STAT1 by arginine methyltransferase 1 (PRMT1) modulates transcription of ISGs [46], and that protein phosphatase 2A (PP2A) inhibits PRMT1 [47]. In turn, hypomethylated STAT1 is less active because it is bound by its inhibitor PIAS1 [48,49]. Interestingly, the levels of PP2A were found elevated in biopsy tissue of chronic HBV patients [50], suggesting that PP2A induction has a primary role in HBV-mediated inhibition of IFN signaling. More recent studies have identified via an RNAi screen, the methyltransferase SETD2 as the enzyme that also methylates STAT1 on lysine-525 [51]. It was shown that this is a critical modification in promoting the IFN-activated STAT1 phosphorylation, and the antiviral IFN response. Conditional knockout mice with hepatocyte-specific deletion of *Setd2* exhibited enhanced HBV infection. In addition, chromatin immunoprecipitation assays demonstrated that SETD2 mediates the trimethylation of H3K36 bound to ISG promoters, including ISG15. This study identified SETD2 as an essential player in the IFN antiviral response. However, how HBV infection inactivates and counteracts SETD2 to allow virus biosynthesis is currently unknown.

Another mechanism that regulates STAT1 function involves the nuclear E3 ligase RNF2 as an inhibitor of IFN function by promoting STAT1 dissociation from DNA [52]. Specifically, it was shown that RNF2 directly bound to STAT1 after IFN stimulation and increased K33-linked polyubiquitination of the DNA-binding domain of STAT1 at position K379. This post-translational modification of STAT1 promoted dissociation of STAT1/STAT2 from DNA, and suppressed transcription of ISGs [52]. Whether this mechanism of regulation is operational during HBV infection is unknown.

Other molecules involved in the antiviral/innate immune response include viral nucleic acid sensors such as RIG-I [53]. RIG-I can detect viral RNAs in the cytoplasm during infection with a variety of viruses, including HBV [54]. Studies by Sato et al [55] demonstrated that RIG-I senses the stem-loop secondary structure of 5′-ε region of the HBV pgRNA, and interferes with its interaction with the viral polymerase, thereby suppressing viral replication. Overexpression of RNA containing the 5′-ε region in the liver of chimeric mice with humanized liver inhibited HBV replication by binding to the viral polymerase and competing/blocking polymerase binding to pgRNA. Thus, these studies showed that RIG-I functions not only as an RNA sensor but also as a host antiviral factor for HBV infection. Interestingly, RIG-I, which is an ISG, is the most significantly downregulated ISG in HCC, including poor prognosis HBV-related HCC [56]. It was shown [56] that RIG-I facilitated the nuclear translocation of activated STAT1, by reducing the association of STAT1 with its negative regulator SHP-1 [56]. The significance of reducing nuclear STAT1 in hepatocarcinogenesis is not understood. Moreover, whether this mechanism exerts any effect on STAT1 nuclear translocation during HBV infection is unknown.

8. Chronic HBV infection and the innate immune response

Chronic HBV infection is linked to liver pathology, including fibrosis, cirrhosis and hepatocellular carcinoma. Although the mechanism responsible for establishment of chronic infection is not well understood, a likely cause is suppression of host immune responses. The examples discussed earlier demonstrate how HBV inhibits the innate response in the context of experimental HBV infection, modeling acute infection in patients. In this section studies will be presented on the effect of HBV infection on interferon signaling in chronically infected patients.

The Zoulim group [50] analyzed a large number of chronic HBV patients for intrahepatic expression of 67 genes that belong to multiple pathways of the innate immune response. The expression data of these ISGs were correlated to markers of viral infection in the serum and in liver biopsy tissue, including quantification of the S antigen (HBs), total HBV DNA, pgRNA, and cccDNA. The results demonstrate that chronic HBV infection suppresses immune responses of type I/II/III IFN signaling, including transcription of STAT1 in some patients [50]. Significantly, the suppression is more pronounced with higher levels of viral HBs antigen, which can be transcribed either from cccDNA or the integrated HBV DNA that occurs during hepatocellular carcinoma. In addition, several genes were found to be upregulated, including the PP2A phosphatase that was shown earlier to inhibit STAT1 signaling [43], the DNA methyltransferase DNMT3A that can silence viral and

host genes including tumor suppressor genes and immunoregulatory genes [57], and STAT2, which was shown to suppress ISGs in hepatocytes after IFN stimulation [58]. Thus, these studies highlight the significance of chronic HBV infection in suppressing innate immunity, which influences both viral clearance and also pathways associated with anti-tumor immunity and apoptosis [59].

In terms of viral clearance, a major issue is the persistence of the HBV cccDNA in infected hepatocytes. Lucifora et al. [60] presented studies of how IFN-α treatment of HBV infected primary hepatocytes induces specific degradation of cccDNA without hepatotoxicity, by upregulating the cytidine deaminases APOBEC3A and APOBEC3B. Cytidine deamination of cccDNA and formation of apurinic sites results in cccDNA degradation and clearance of HBV reactivation, without cytolysis. Repair of apurinic DNA involves the base excision repair (BER) mechanism which removes DNA lesions and maintains genomic integrity [61]. Interestingly, chronic HBV infected patients that respond to IFN treatment in comparison to non-responders, exhibit downregulated expression of the BER gene NEIL3; conversely, the APOBEC3A expression level was significantly increased [62]. This inverse correlation between APOBEC3A and NEIL3 expression during IFN treatment suggests that absence of cccDNA repair by the BER mechanism is important in cccDNA degradation. How IFN-α suppresses NEIL3 expression is unknown. Thus, this study supports that the IFN signaling pathway in conjunction with the BER pathway have an important role in viral clearance and persistence. Importantly, less than 30% of chronically HBV infected patients respond to IFN-α treatment [18], raising the question whether IFN non-responders have “defects” in the IFN signaling pathway.

In addition to the hepatocyte-specific effects of IFN signaling, HBV-specific T cells secrete IFN-γ and TNF-α [63]. Increased serum levels of IFN-γ and TNF-α were quantified during acute HBV infection vs. chronic infection. These results indicate that HBV-specific T cells, via cytokine secretion, can reduce the levels of cccDNA in infected hepatocytes via APOBEC-mediated deamination and subsequent cccDNA decay [63]. APOBEC3 can be induced by IFN-α, IFN-γ, TNF-α and lymphotoxin β-receptor activation [60,64]. Indeed, recent studies have demonstrated direct antiviral properties of Toll-Like-Receptor (TLR) agonists in suppressing HBV replication in hepatocytes [65].

9. HBV-associated HCC and IFN signaling

IFNs can mediate both antiviral and anti-proliferative effects [66]. ISGs expressed in response to IFN-α therapy mediate diverse biological functions including anti-tumor activity [67]. Thus, adjuvant IFN-α therapy is used for the treatment of various types of cancers [68–70] including hepatocellular carcinoma [71]. Unfortunately, many HCC patients do not respond to treatment with IFN-α [18]. The study by Yang et al [72] compared ISG expression between the IFN-α responsive vs. non-responsive patients with HCC and HBV-related HCC, and identified the differential expression of the ISG IFIT3 between the two groups. The higher expression of IFIT3, in comparison to the other IFIT genes (IFIT1, IFIT2 or IFIT5), predicted better response to IFN-α therapy. Accordingly, it was proposed that IFIT3 could serve as a biomarker for predicting IFN-α responsiveness of HCC patients [72]. IFIT3, also known as RIG-G, is a direct transcription target of STAT1 [73]. Since expression of IFIT3 as well as of the other IFTs, is significantly reduced in liver tumors from IFN-α non-responders, one would predict defects in the mechanism(s) activating STAT1. For example, as described earlier, RIG-I promotes the nuclear translocation of activated STAT1 by disrupting STAT1 interaction with its negative regulator SHP-1 [56]. Importantly, RIG-I is severely downregulated in HCC, including poor prognosis HBV-related HCC [56]. Whether RIG-1 expression is also reduced in the IFN-α non-responders has not been investigated. Certainly, deregulation of various mechanisms that are functional in the context of HBV infection [43,51] could mediate loss of STAT1 activation (Fig. 4).

Another possibility is that poor prognosis HCCs from IFN-α non-responders [72] lack transcription of STAT1. Interestingly, our studies (Andrisani et al unpublished data), presented at the 2nd International Conference on Cytokine Signaling in Cancer, reported that reduced transcription of STAT1 maybe a feature of hepatic cancer stem cells (hCSCs).

We have identified a cellular mechanism hijacked by HBV and linked to poor prognosis HBV-associated HCC [74–76]. This novel mechanism involves the chromatin modifying PRC2 complex, RNA helicase DDX5, and lncRNA HOTAIR. PRC2 [77] mediates repressive histone modifications (H3K27me3), while the RNA helicase DDX5 stabilizes/activates the HOTAIR/PRC2 complex and inhibits expression of pluripotency genes. HBV infection downregulates DDX5 [74–76]. Moreover, HBV-related HCCs associated with poor prognosis exhibit reduced expression of DDX5, supporting the clinical relevance of this mechanism [75]. We have also demonstrated [78] that loss of PRC2 function in a subpopulation of HBV replicating cells is associated with enhanced expression of pluripotency genes and hCSC genes. Interestingly, this subpopulation of HBV replicating cells also exhibits Wnt activation and resistance to chemotherapeutic agents, suggesting that these cells have CSC properties [78]. Employing RNA Seq analyses we mapped the transcriptome of these HBV replicating cells with hCSCs properties and Wnt activation. To our surprise, we observed reduced expression of interferon signaling genes, including STAT1, only in HBV replicating cells with hCSC properties and Wnt activation (Andrisani et al, Unpublished data). It is well established that in the context of oncogenesis, STAT1 can be either pro-apoptotic and anti-immunity, or pro-oncogenic [79]. However, what determines these opposing functions of STAT1 is not yet understood [79]. We propose that cell intrinsic changes, for example the cellular status of epigenetic chromatin modifiers, e.g., the DDX5/HOTAIR/PRC2 complex, influenced by HBV infection [75], could influence the function of STAT1 as oncogenic vs. pro-apoptotic.

10. Loss of IFN signaling in aggressive tumors and cancer stem cells (CSCs)

Accumulating evidence from the study of other cancer types supports the hypothesis that loss of IFN signaling is linked to aggressive/metastatic cancer and CSCs, as discussed below.

In a subset of metastatic prostate tumors both the *IFNGR1* gene and its downstream genes were found to be downregulated [80]. Interestingly, this subset of metastatic tumors exhibited enhanced expression of c-MYC and of the essential PRC2 subunit EZH2. It was shown that in MYC-driven prostate cancer the *IFNGR1* promoter is the direct target of EZH2. Importantly, EZH2 knockdown restores *IFNGR1* expression and sensitizes cells to IFN-γ treatment [80]. In another study of metastatic melanoma, loss of IFN-γ pathway genes was identified as a mechanism of resistance in anti-CTLA-4 (Ipilimumab) therapy [81]. They observed that cell lines generated from patient-derived primary tumors that were Ipilimumab-resistant melanomas contained genomic mutations in IFN-γ pathway genes [81]. Also, recent studies with glioblastoma multiforme (GBM), the most lethal/malignant brain tumor, demonstrated loss of function/inhibition of the IFN regulatory factor 3 (IRF3). GBM tumors are characterized by remarkable proliferation, chemo-resistance, and invasion capacity. Significantly, the observed loss of function of IRF3 was linked to the invasion potential of GMB, through its surrounding neural tissue. IRF3 represses transcription of pro-invasive extracellular matrix (ECM) proteins [82]. It is unknown whether GBMs express reduced levels of IRF3, or whether inactivating mutations are associated with loss of IRF3 function. Another study from Yibin Kang’s laboratory recently demonstrated that CSCs exhibit the same properties as normal stem cells in evading IFN responses and cellular differentiation [83]. Specifically, they demonstrated that increased expression of the microRNA miR-199a both in normal mammary stem cells and breast CSCs targets the downregulation of the nuclear corepressor LCOR which

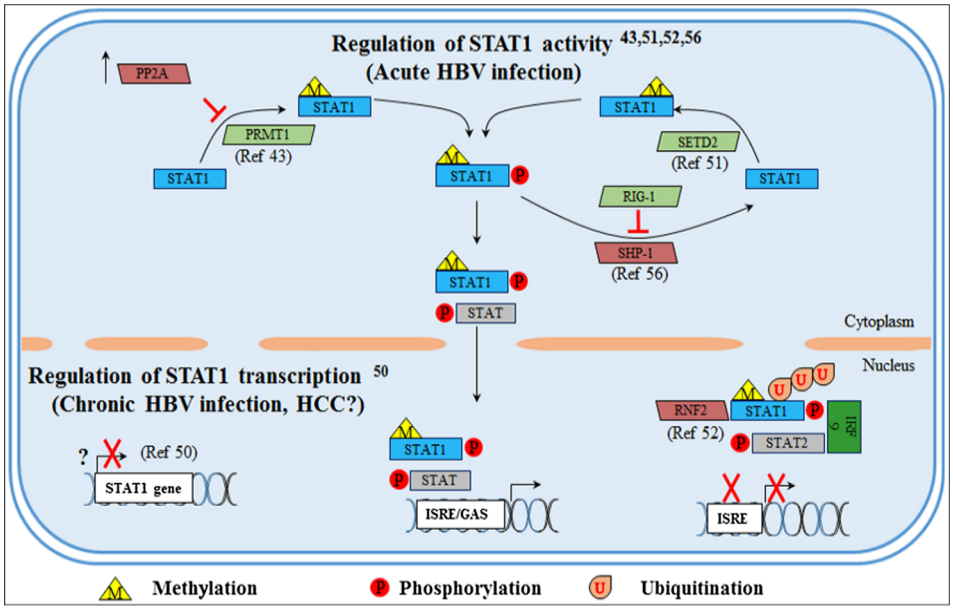

Fig. 4. Mechanisms that regulate STAT1 function in HBV infected cells. Molecules (PRMT1, SETD2, RIG-I) depicted by green boxes facilitate STAT1 activation, whereas those in red boxes (PP2A, SHP-1, RNF2) are negative regulators of STAT1 activity.

sensitizes cells to IFN-induced differentiation and senescence. More recent studies in diffuse large B cell lymphoma (DLBCL) identified the targets of the constitutively activated STAT3, employing whole transcriptome analysis [84]. Interestingly, they found that STAT3 not only activates multiple oncogenic pathways, but STAT3 negatively regulates the IFN signaling pathway by suppressing transcription of STAT1, STAT2, IRF7 and IRF9 [84].

In terms of HCC and HBV-associated HCC the significance of downregulation of IFN signaling and STAT1, remains to be understood. IFNs act directly to inhibit tumor cell growth, and indirectly to activate anti-tumor immunity. Interestingly, Her2/neu transgenic mice carrying a nonfunctional mutation of INFAR1, exhibited earlier onset and increased tumor formation [85]. Significantly, these tumors displayed enhanced expression of the breast cancer stem cell marker ALDH1A1. These studies demonstrate that disruption of IFN signaling promotes Her2/neu tumor progression and formation of CSCs [85]. Whether, the transcriptional downregulation of STAT1 that we observed in the subset of HBV replicating cells with Wnt activation, is indicative of the hCSC phenotype is currently under investigation (Andrisani et al unpublished results). Interestingly, recent studies from C. Rice's laboratory demonstrated that normal stem cells are resistant to viral infection due to intrinsic expression of a subset of ISGs that confers protection from viral infection, and that only upon differentiation the cells assume inducible IFN expression of ISGs [86]. Whether the undifferentiated cells exhibit changes in STAT1 transcription or activity was not examined [86]. Thus, the reduced expression of STAT1 that we have observed in the subset of Wnt-positive HBV replicating cells (Andrisani et al unpublished data), may be linked to a hCSC phenotype.

11. Concluding remarks

HBV has evolved mechanisms to inhibit IFN signaling during the phases of acute and chronic infection, and during the process of hepatocyte transformation. These mechanisms, described herein, focus on the essential IFN signaling transcription factor STAT1 (Figs. 3 and 4). While during acute infection, HBV inhibits the activity and nuclear translocation of phospho-STAT1 [15,16,22,27], intrinsic changes, such as cellular reprogramming of the HBV transformed hepatocyte associated with a hCSC phenotype, may also alter the transcription/expression level of STAT1. Ongoing studies address this hypothesis.

Acknowledgments

Supported by NIH grant DK044533-20 to OA, NIH grant P30CA023168 to Purdue Center for Cancer Research, and a Resource Program grant to OA from the Purdue Center for Cancer Research.

Conflict of interest

The authors declare no conflict of interest.

References

[1] R.P. Beasley, L.Y. Hwang, C.C. Lin, C.S. Chien, Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22,707 men in Taiwan, Lancet 2 (8256) (1981) 1129–1133.
[2] A. Schweitzer, J. Horn, R.T. Mikolajczyk, G. Krause, J.J. Ott, Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013, Lancet 386 (10003) (2015) 1546–1555.
[3] C. Seeger, W.S. Mason, Molecular biology of hepatitis B virus infection, Virology 479–480C (2015) 672–686.
[4] Y. Ni, F.A. Lempp, S. Mehrle, S. Nkongolo, C. Kaufman, M. Falth, J. Stindt, C. Koniger, M. Nassal, R. Kubitz, H. Sultmann, S. Urban, Hepatitis B and D viruses exploit sodium taurocholate co-transporting polypeptide for species-specific entry into hepatocytes, Gastroenterology 146 (4) (2014) 1070–1083.
[5] A. Diab, A. Foca, F. Zoulim, D. Durantel, O. Andrisani, The diverse functions of the hepatitis B core/capsid protein (HBc) in the viral life cycle: implications for the development of HBc-targeting antivirals, Antiviral Res. 149 (2018) 211–220.
[6] C. Koniger, I. Wingert, M. Marsmann, C. Rosler, J. Beck, M. Nassal, Involvement of the host DNA-repair enzyme TDP2 in formation of the covalently closed circular DNA persistence reservoir of hepatitis B viruses, Proc. Natl. Acad. Sci. U S A 111 (40) (2014) E4244–E4253.
[7] S. Schreiner, M. Nassal, A role for the host DNA damage response in hepatitis B virus cccDNA formation-and beyond? Viruses 9 (5) (2017).
[8] W.W. Bond, M.S. Favero, N.J. Petersen, C.R. Gravelle, J.W. Ebert, J.E. Maynard, Survival of hepatitis B virus after drying and storage for one week, Lancet 1 (8219) (1981) 550–551.
[9] E.E. Mast, H.S. Margolis, A.E. Fiore, E.W. Brink, S.T. Goldstein, S.A. Wang, L.A. Moyer, B.P. Bell, M.J. Alter, P. Advisory Committee on Immunization, A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents, MMWR Recomm. Rep. 54 (RR-16) (2005) 1–31.
[10] N.J. Petersen, D.H. Barrett, W.W. Bond, K.R. Berquist, M.S. Favero, T.R. Bender, J.E. Maynard, Hepatitis B surface antigen in saliva, impetiginous lesions, and the environment in two remote Alaskan villages, Appl. Environ. Microbiol. 32 (4) (1976) 572–574.
[11] R.P. Beasley, L.Y. Hwang, Postnatal infectivity of hepatitis B surface antigen-carrier mothers, J. Infect. Dis. 147 (2) (1983) 185–190.
[12] R.P. Beasley, L.Y. Hwang, C.C. Lin, M.L. Leu, C.E. Stevens, W. Szmuness, K.P. Chen,

Incidence of hepatitis B virus infections in preschool children in Taiwan, J. Infect. Dis. 146 (2) (1982) 198–204.
[13] N.C. Tassopoulos, G.J. Papaevangelou, A. Roumeliotou-Karayannis, J.R. Ticehurst, S.M. Feinstone, R.H. Purcell, Detection of hepatitis B virus DNA in asymptomatic hepatitis B surface antigen carriers: relation to sexual transmission, Am. J. Epidemiol. 126 (4) (1987) 587–591.
[14] B.J. McMahon, W.L. Alward, D.B. Hall, W.L. Heyward, T.R. Bender, D.P. Francis, J.E. Maynard, Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state, J. Infect. Dis. 151 (4) (1985) 599–603.
[15] P. Coursaget, B. Yvonnet, J. Chotard, P. Vincelot, M. Sarr, C. Diouf, J.P. Chiron, I. Diop-Mar, Age- and sex-related study of hepatitis B virus chronic carrier state in infants from an endemic area (Senegal), J. Med. Virol. 22 (1) (1987) 1–5.
[16] N.J. Bodsworth, D.A. Cooper, B. Donovan, The influence of human immunodeficiency virus type 1 infection on the development of the hepatitis B virus carrier state, J. Infect. Dis. 163 (5) (1991) 1138–1140.
[17] C.E. Stevens, P.T. Toy, M.J. Tong, P.E. Taylor, G.N. Vyas, P.V. Nair, M. Gudavalli, S. Krugman, Perinatal hepatitis B virus transmission in the United States. Prevention by passive-active immunization, Jama 253 (12) (1985) 1740–1745.
[18] H. Kwon, A.S. Lok, Hepatitis B therapy, Nat. Rev. Gastroenterol. Hepatol. 8 (2011) 275.
[19] M. Levrero, M. Subic, F. Villeret, F. Zoulim, Perspectives and limitations for nucleo (t)side analogs in future HBV therapies, Curr. Opin. Virol. 30 (2018) 80–89.
[20] M.G. Ghany, Current treatment guidelines of chronic hepatitis B: the role of nucleos (t)ide analogues and peginterferon, Best Pract. Res. Clin. Gastroenterol. 31 (3) (2017) 299–309.
[21] S.M. Lin, M.L. Yu, C.M. Lee, R.N. Chien, I.S. Sheen, C.M. Chu, Y.F. Liaw, Interferon therapy in HBeAg positive chronic hepatitis reduces progression to cirrhosis and hepatocellular carcinoma, J. Hepatol. 46 (1) (2007) 45–52.
[22] C.L. Lai, E. Gane, Y.F. Liaw, C.W. Hsu, S. Thongsawat, Y. Wang, Y. Chen, E.J. Heathcote, J. Rasenack, N. Bzowej, N.V. Naoumov, A.M. Di Bisceglie, S. Zeuzem, Y.M. Moon, Z. Goodman, G. Chao, B.F. Constance, N.A. Brown, G. Globe Study, Telbivudine versus lamivudine in patients with chronic hepatitis B, N. Engl. J. Med. 357 (25) (2007) 2576–2588.
[23] P. Marcellin, E.J. Heathcote, M. Buti, E. Gane, R.A. de Man, Z. Krastev, G. Germanidis, S.S. Lee, R. Flisiak, K. Kaita, M. Manns, I. Kotzev, K. Tchernev, P. Buggisch, F. Weilert, O.O. Kurdas, M.L. Shiffman, H. Trinh, M.K. Washington, J. Sorbel, J. Anderson, A. Snow-Lampart, E. Mondou, J. Quinn, F. Rousseau, Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B, N. Engl. J. Med. 359 (23) (2008) 2442–2455.
[24] N.A. Terrault, N.H. Bzowej, K.M. Chang, J.P. Hwang, M.M. Jonas, M.H. Murad, D. American, Association for the study of liver, AASLD guidelines for treatment of chronic hepatitis B, Hepatology 63 (1) (2016) 261–283.
[25] H.C. Yang, J.H. Kao, Persistence of hepatitis B virus covalently closed circular DNA in hepatocytes: molecular mechanisms and clinical significance, Emerg. Microbes Infect. 3 (9) (2014) e64.
[26] S. Wieland, R. Thimme, R.H. Purcell, F.V. Chisari, Genomic analysis of the host response to hepatitis B virus infection, Proc. Natl. Acad. Sci. U S A 101 (17) (2004) 6669–6674.
[27] S.F. Wieland, F.V. Chisari, Stealth and cunning: hepatitis B and hepatitis C viruses, J. Virol. 79 (15) (2005) 9369–9380.
[28] J. Lucifora, D. Durantel, B. Testoni, O. Hantz, M. Levrero, F. Zoulim, Control of hepatitis B virus replication by innate response of HepaRG cells, Hepatology 51 (1) (2010) 63–72.
[29] M. Ait-Goughoulte, J. Lucifora, F. Zoulim, D. Durantel, Innate antiviral immune responses to hepatitis B virus, Viruses 2 (7) (2010) 1394–1410.
[30] S. Luangsay, M. Gruffaz, N. Isorce, B. Testoni, M. Michelet, S. Faure-Dupuy, S. Maadadi, M. Ait-Goughoulte, R. Parent, M. Rivoire, H. Javanbakht, J. Lucifora, D. Durantel, F. Zoulim, Early inhibition of hepatocyte innate responses by hepatitis B virus, J. Hepatol. 63 (6) (2015) 1314–1322.
[31] L. Allweiss, M. Dandri, Experimental in vitro and in vivo models for the study of human hepatitis B virus infection, J. Hepatol. 64 (1 Suppl) (2016) S17–S31.
[32] W.M. Schneider, M.D. Chevillotte, C.M. Rice, Interferon-stimulated genes: a complex web of host defenses, Annu. Rev. Immunol. 32 (2014) 513–545.
[33] N.C. Reich, STAT dynamics, Cytokine Growth Factor Rev. 18 (5–6) (2007) 511–518.
[34] I. Najjar, R. Fagard, STAT1 and pathogens, not a friendly relationship, Biochimie 92 (5) (2010) 425–444.
[35] T.R. Wu, Y.K. Hong, X.D. Wang, M.Y. Ling, A.M. Dragoi, A.S. Chung, A.G. Campbell, Z.Y. Han, G.S. Feng, Y.E. Chin, SHP-2 is a dual-specificity phosphatase involved in Stat1 dephosphorylation at both tyrosine and serine residues in nuclei, J. Biol. Chem. 277 (49) (2002) 47572–47580.
[36] J. ten Hoeve, M. de Jesus Ibarra-Sanchez, Y. Fu, W. Zhu, M. Tremblay, M. David, K. Shuai, Identification of a nuclear Stat1 protein tyrosine phosphatase, Mol. Cell. Biol. 22 (16) (2002) 5662–5668.
[37] T.C. Dale, A.M. Imam, I.M. Kerr, G.R. Stark, Rapid activation by interferon alpha of a latent DNA-binding protein present in the cytoplasm of untreated cells, Proc. Natl. Acad. Sci. U S A 86 (4) (1989) 1203–1207.
[38] J. Vogel, M. Kress, G. Khoury, G. Jay, A transcriptional enhancer and an interferon-responsive sequence in major histocompatibility complex class I genes, Mol. Cell. Biol. 6 (10) (1986) 3550–3554.
[39] J.S. Twu, C.H. Lee, P.M. Lin, R.H. Schloemer, Hepatitis B virus suppresses expression of human beta-interferon, Proc. Natl. Acad. Sci. U S A 85 (1) (1988) 252–256.
[40] T.M. Whitten, A.T. Quets, R.H. Schloemer, Identification of the hepatitis B virus factor that inhibits expression of the beta interferon gene, J. Virol. 65 (9) (1991) 4699–4704.
[41] M. Fernandez, J.A. Quiroga, V. Carreno, Hepatitis B virus downregulates the human interferon-inducible MxA promoter through direct interaction of precore/core proteins, J. Gen. Virol. 84 (Pt 8) (2003) 2073–2082.
[42] M. Wu, Y. Xu, S. Lin, X. Zhang, L. Xiang, Z. Yuan, Hepatitis B virus polymerase inhibits the interferon-inducible MyD88 promoter by blocking nuclear translocation of Stat1, J. Gen. Virol. 88 (Pt 12) (2007) 3260–3269.
[43] V. Christen, F. Duong, C. Bernsmeier, D. Sun, M. Nassal, M.H. Heim, Inhibition of alpha interferon signaling by hepatitis B virus, J. Virol. 81 (1) (2007) 159–165.
[44] M. Lutgehetmann, T. Bornscheuer, T. Volz, L. Allweiss, J.H. Bockmann, J.M. Pollok, A.W. Lohse, J. Petersen, M. Dandri, Hepatitis B virus limits response of human hepatocytes to interferon-alpha in chimeric mice, Gastroenterology 140 (7) (2011) 2074-83, 2083 e1-2.
[45] L. Belloni, L. Allweiss, F. Guerrieri, N. Pediconi, T. Volz, T. Pollicino, J. Petersen, G. Raimondo, M. Dandri, M. Levrero, IFN-alpha inhibits HBV transcription and replication in cell culture and in humanized mice by targeting the epigenetic regulation of the nuclear cccDNA minichromosome, J. Clin. Investig. 122 (2) (2012) 529–537.
[46] K.A. Mowen, J. Tang, W. Zhu, B.T. Schurter, K. Shuai, H.R. Herschman, M. David, Arginine methylation of STAT1 modulates IFNalpha/beta-induced transcription, Cell 104 (5) (2001) 731–741.
[47] F.H. Duong, V. Christen, J.M. Berke, S.H. Penna, D. Moradpour, M.H. Heim, Upregulation of protein phosphatase 2Ac by hepatitis C virus modulates NS3 helicase activity through inhibition of protein arginine methyltransferase 1, J. Virol. 79 (24) (2005) 15342–15350.
[48] F.H. Duong, M. Filipowicz, M. Tripodi, N. La Monica, M.H. Heim, Hepatitis C virus inhibits interferon signaling through up-regulation of protein phosphatase 2A, Gastroenterology 126 (1) (2004) 263–277.
[49] J. Li, F. Chen, M. Zheng, H. Zhu, D. Zhao, W. Liu, W. Liu, Z. Chen, Inhibition of STAT1 methylation is involved in the resistance of hepatitis B virus to Interferon alpha, Antiviral Res. 85 (3) (2010) 463–469.
[50] F. Lebosse, B. Testoni, J. Fresquet, F. Facchetti, E. Galmozzi, M. Fournier, V. Hervieu, P. Berthillon, F. Berby, I. Bordes, D. Durantel, M. Levrero, P. Lampertico, F. Zoulim, Intrahepatic innate immune response pathways are downregulated in untreated chronic hepatitis B, J. Hepatol. 66 (5) (2017) 897–909.
[51] K. Chen, J. Liu, S. Liu, M. Xia, X. Zhang, D. Han, Y. Jiang, C. Wang, X. Cao, Methyltransferase SETD2-mediated methylation of STAT1 Is critical for interferon antiviral activity, Cell 170 (3) (2017) pp. 492–506 e14.
[52] S. Liu, M. Jiang, W. Wang, W. Liu, X. Song, Z. Ma, S. Zhang, L. Liu, Y. Liu, X. Cao, Nuclear RNF2 inhibits interferon function by promoting K33-linked STAT1 disassociation from DNA, Nat. Immunol. 19 (1) (2018) 41–52.
[53] M. Yoneyama, M. Kikuchi, T. Natsukawa, N. Shinobu, T. Imaizumi, M. Miyagishi, K. Taira, S. Akira, T. Fujita, The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses, Nat. Immunol. 5 (7) (2004) 730–737.
[54] S. Yu, J. Chen, M. Wu, H. Chen, N. Kato, Z. Yuan, Hepatitis B virus polymerase inhibits RIG-I- and Toll-like receptor 3-mediated beta interferon induction in human hepatocytes through interference with interferon regulatory factor 3 activation and dampening of the interaction between TBK1/IKKepsilon and DDX3, J. Gen. Virol. 91 (Pt 8) (2010) 2080–2090.
[55] S. Sato, K. Li, T. Kameyama, T. Hayashi, Y. Ishida, S. Murakami, T. Watanabe, S. Iijima, Y. Sakurai, K. Watashi, S. Tsutsumi, Y. Sato, H. Akita, T. Wakita, C.M. Rice, H. Harashima, M. Kohara, Y. Tanaka, A. Takaoka, The RNA sensor RIG-I dually functions as an innate sensor and direct antiviral factor for hepatitis B virus, Immunity 42 (1) (2015) 123–132.
[56] J. Hou, Y. Zhou, Y. Zheng, J. Fan, W. Zhou, I.O. Ng, H. Sun, L. Qin, S. Qiu, J.M. Lee, C.M. Lo, K. Man, Y. Yang, Y. Yang, Y. Yang, Q. Zhang, X. Zhu, N. Li, Z. Wang, G. Ding, S.M. Zhuang, L. Zheng, X. Luo, Y. Xie, A. Liang, Z. Wang, M. Zhang, Q. Xia, T. Liang, Y. Yu, X. Cao, Hepatic RIG-I predicts survival and interferon-alpha therapeutic response in hepatocellular carcinoma, Cancer Cell 25 (1) (2014) 49–63.
[57] P. Vivekanandan, H.D. Daniel, R. Kannangai, F. Martinez-Murillo, M. Torbenson, Hepatitis B virus replication induces methylation of both host and viral DNA, J. Virol. 84 (9) (2010) 4321–4329.
[58] B. Testoni, C. Vollenkle, F. Guerrieri, S. Gerbal-Chaloin, G. Blandino, M. Levrero, Chromatin dynamics of gene activation and repression in response to interferon alpha (IFN(alpha)) reveal new roles for phosphorylated and unphosphorylated forms of the transcription factor STAT2, J. Biol. Chem. 286 (23) (2011) 20217–20227.
[59] H. Yu, D. Pardoll, R. Jove, STATs in cancer inflammation and immunity: a leading role for STAT3, Nat. Rev. Cancer 9 (11) (2009) 798–809.
[60] J. Lucifora, Y. Xia, F. Reisinger, K. Zhang, D. Stadler, X. Cheng, M.F. Sprinzl, H. Koppensteiner, Z. Makowska, T. Volz, C. Remouchamps, W.M. Chou, W.E. Thasler, N. Huser, D. Durantel, T.J. Liang, C. Munk, M.H. Heim, J.L. Browning, E. Dejardin, M. Dandri, M. Schindler, M. Heikenwalder, U. Protzer, Specific and nonhepatotoxic degradation of nuclear hepatitis B virus cccDNA, Science 343 (6176) (2014) 1221–1228.
[61] S.S. Wallace, Base excision repair: a critical player in many games, DNA Repair (Amst.) 19 (2014) 14–26.
[62] Y. Li, Y. Xia, M. Han, G. Chen, D. Zhang, W.E. Thasler, U. Protzer, Q. Ning, IFN-alpha-mediated base excision repair pathway correlates with antiviral response against Hepatitis B virus infection, Sci. Rep. 7 (1) (2017) 12715.
[63] Y. Xia, D. Stadler, J. Lucifora, F. Reisinger, D. Webb, M. Hosel, T. Michler, K. Wisskirchen, X. Cheng, K. Zhang, W.M. Chou, J.M. Wettengel, A. Malo, F. Bohne, D. Hoffmann, F. Eyer, R. Thimme, C.S. Falk, W.E. Thasler, M. Heikenwalder, U. Protzer, Interferon-gamma and tumor necrosis factor-alpha produced by T cells reduce the HBV persistence form, cccDNA, without cytolysis, Gastroenterology 150 (1) (2016) 194–205.
[64] M. Bonvin, F. Achermann, I. Greeve, D. Stroka, A. Keogh, D. Inderbitzin,

D. Candinas, P. Sommer, S. Wain-Hobson, J.P. Vartanian, J. Greeve, Interferon-inducible expression of APOBEC3 editing enzymes in human hepatocytes and inhibition of hepatitis B virus replication, Hepatology 43 (6) (2006) 1364–1374.
[65] J. Lucifora, M. Bonnin, L. Aillot, F. Fusil, S. Maadadi, L. Dimier, M. Michelet, O. Floriot, A. Ollivier, M. Rivoire, M. Ait-Goughoulte, S. Daffis, S.P. Fletcher, A. Salvetti, F.L. Cosset, F. Zoulim, D. Durantel, Direct antiviral properties of TLR ligands against HBV replication in immune-competent hepatocytes, Sci. Rep. 8 (1) (2018) 5390.
[66] T. Taniguchi, A. Takaoka, A weak signal for strong responses: interferon-alpha/beta revisited, Nat. Rev. Mol. Cell Biol. 2 (5) (2001) 378–386.
[67] L.C. Platanias, Mechanisms of type-I- and type-II-interferon-mediated signalling, Nat. Rev.Immunol 5 (5) (2005) 375–386.
[68] S. Suciu, A.M.M. Eggermont, P. Lorigan, J.M. Kirkwood, S.N. Markovic, C. Garbe, D. Cameron, S. Kotapati, T.T. Chen, K. Wheatley, N. Ives, G. de Schaetzen, A. Efendi, M. Buyse, Relapse-free survival as a surrogate for overall survival in the evaluation of stage II-III melanoma adjuvant therapy, J. Natl. Cancer Inst. 110 (1) (2018).
[69] K.A. Ohman, J. Liu, D.C. Linehan, M.C. Tan, B.R. Tan, R.C. Fields, S.M. Strasberg, W.G. Hawkins, Interferon-based chemoradiation followed by gemcitabine for resected pancreatic adenocarcinoma: long-term follow-up, HPB (Oxford) 19 (5) (2017) 449–457.
[70] I.M. Montagner, A. Merlo, D. Carpanese, A. Dalla Pieta, A. Mero, A. Grigoletto, A. Loregian, D. Renier, M. Campisi, P. Zanovello, G. Pasut, A. Rosato, A site-selective hyaluronan-interferonalpha2a conjugate for the treatment of ovarian cancer, J. Controll. Release: Off. J. Controll. Release Soc. 236 (2016) 79–89.
[71] T. Kamiyama, T. Kakisaka, T. Orimo, K. Wakayama, Hepatectomy for hepatocellular carcinoma with portal vein tumor thrombus, World J Hepatol. 9 (36) (2017) 1296–1304.
[72] Y. Yang, Y. Zhou, J. Hou, C. Bai, Z. Li, J. Fan, I.O.L. Ng, W. Zhou, H. Sun, Q. Dong, J.M.F. Lee, C.M. Lo, K. Man, Y. Yang, N. Li, G. Ding, Y. Yu, X. Cao, Hepatic IFIT3 predicts interferon-alpha therapeutic response in patients of hepatocellular carcinoma, Hepatology 66 (1) (2017) 152–166.
[73] S. Xiao, D. Li, H.Q. Zhu, M.G. Song, X.R. Pan, P.M. Jia, L.L. Peng, A.X. Dou, G.Q. Chen, S.J. Chen, Z. Chen, J.H. Tong, RIG-G as a key mediator of the antiproliferative activity of interferon-related pathways through enhancing p21 and p27 proteins, Proc. Natl. Acad. Sci. U S A 103 (44) (2006) 16448–16453.
[74] H. Zhang, A. Diab, H. Fan, S.K. Mani, R. Hullinger, P. Merle, O. Andrisani, PLK1 and HOTAIR accelerate proteasomal degradation of SUZ12 and ZNF198 during hepatitis B virus-induced liver carcinogenesis, Cancer Res. 75 (11) (2015) 2363–2374.
[75] H. Zhang, Z. Xing, S.K. Mani, B. Bancel, D. Durantel, F. Zoulim, E.J. Tran, P. Merle, O. Andrisani, RNA helicase DEAD box protein 5 regulates Polycomb repressive complex 2/Hox transcript antisense intergenic RNA function in hepatitis B virus infection and hepatocarcinogenesis, Hepatology 64 (4) (2016) 1033–1048.
[76] S.K.K. Mani, O. Andrisani, Hepatitis B virus-associated hepatocellular carcinoma and hepatic cancer stem cells, Genes (Basel) 9 (3) (2018).
[77] R. Margueron, D. Reinberg, The Polycomb complex PRC2 and its mark in life, Nature 469 (7330) (2011) 343–349.
[78] S.K. Mani, H. Zhang, A. Diab, P.E. Pascuzzi, L. Lefrancois, N. Fares, B. Bancel, P. Merle, O. Andrisani, EpCAM-regulated intramembrane proteolysis induces a cancer stem cell-like gene signature in hepatitis B virus-infected hepatocytes, J. Hepatol. 65 (5) (2016) 888–898.
[79] H. Yu, R. Jove, The STATs of cancer–new molecular targets come of age, Nat. Rev. Cancer 4 (2) (2004) 97–105.
[80] Z.N. Wee, Z. Li, P.L. Lee, S.T. Lee, Y.P. Lim, Q. Yu, EZH2-mediated inactivation of IFN-gamma-JAK-STAT1 signaling is an effective therapeutic target in MYC-driven prostate cancer, Cell Rep. 8 (1) (2014) 204–216.
[81] J. Gao, L.Z. Shi, H. Zhao, J. Chen, L. Xiong, Q. He, T. Chen, J. Roszik, C. Bernatchez, S.E. Woodman, P.L. Chen, P. Hwu, J.P. Allison, A. Futreal, J.A. Wargo, P. Sharma, Loss of IFN-gamma pathway genes in tumor cells as a mechanism of resistance to anti-CTLA-4 therapy, Cell 167 (2) (2016) pp. 397–404 e9.
[82] N. Pencheva, M.C. de Gooijer, D.J. Vis, L.F.A. Wessels, T. Wurdinger, O. van Tellingen, R. Bernards, Identification of a druggable pathway controlling glioblastoma invasiveness, Cell Rep. 20 (1) (2017) 48–60.
[83] T. Celia-Terrassa, D.D. Liu, A. Choudhury, X. Hang, Y. Wei, J. Zamalloa, R. Alfaro-Aco, R. Chakrabarti, Y.Z. Jiang, B.I. Koh, H.A. Smith, C. DeCoste, J.J. Li, Z.M. Shao, Y. Kang, Normal and cancerous mammary stem cells evade interferon-induced constraint through the miR-199a-LCOR axis, Nat. Cell Biol. 19 (6) (2017) 711–723.
[84] L. Lu, F. Zhu, M. Zhang, Y. Li, A.C. Drennan, S. Kimpara, I. Rumball, C. Selzer, H. Cameron, A. Kellicut, A. Kelm, F. Wang, T.A. Waldmann, L. Rui, Gene regulation and suppression of type I interferon signaling by STAT3 in diffuse large B cell lymphoma, Proc. Natl. Acad. Sci. U S A 115 (3) (2018) E498–E505.
[85] L. Castiello, P. Sestili, G. Schiavoni, R. Dattilo, D.M. Monque, F. Ciaffoni, M. Iezzi, A. Lamolinara, A. Sistigu, F. Moschella, A.M. Pacca, D. Macchia, M. Ferrantini, A. Zeuner, M. Biffoni, E. Proietti, F. Belardelli, E. Arico, Disruption of IFN-I signaling promotes HER2/Neu tumor progression and breast cancer stem cells, Cancer Immunol. Res. (2018).
[86] X. Wu, V.L. Dao Thi, Y. Huang, E. Billerbeck, D. Saha, H.H. Hoffmann, Y. Wang, L.A.V. Silva, S. Sarbanes, T. Sun, L. Andrus, Y. Yu, C. Quirk, M. Li, M.R. MacDonald, W.M. Schneider, X. An, B.R. Rosenberg, C.M. Rice, Intrinsic immunity shapes viral resistance of stem cells, Cell 172 (3) (2018) pp. 423–438 e25.