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Review

Intrinsic Immune Response of HBV/HDV-Infected Cells and Corresponding Innate (Like) Immune Cell Activation

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Abstract: Infection of hepatitis B (HBV) patients with hepatitis D (HDV) can cause the most severe form of viral hepatitis, leading to liver fibrosis, liver failure, and hepatocellular carcinoma. HDV relies on simultaneous infection with HBV for the generation of infectious viral particles. The innate immune response, which is weakly induced in HBV infection, becomes strongly activated upon HDV co-infection. In HBV/HDV co-infection, the immune system comprises a cell-intrinsic strong IFN response, which leads to the induction of interferon-stimulated genes (ISGs), the local activation of liver-resident innate immune cells, and additional immune cell recruitment from the blood. Efficient innate immune responses are indispensable for successful viral control and spontaneous viral clearance. Despite this fact, innate immune cell activation can also contribute to adaptive immune cell inhibition and accelerate liver damage in HBV/HDV infection. While the intrinsic IFN response in HDV-infected cells is well characterized, far less is known about the cellular innate immune cell compartment. In this review, we summarize HBV/HDV replication characteristics and decipher the role of innate immune cell subsets in the anti-viral response in HBV/HDV infections. We further review the impact of epigenetic and metabolic changes in infected heptatocytes on the innate anti-viral response. Moreover, we discuss the potential of exploiting the innate immune response for improving vaccination strategies and treatment options, which is also discussed in this review.

Keywords: hepatitis virus; HBV; HDV; innate immunity; NK cells; γδ T cells; NKT cells; MAIT cells

Citation: Groth, C.; Wupper, S.; Gnouamozi, G.E.; Böttcher, K.; Cerwenka, A. Intrinsic Immune Response of HBV/HDV-Infected Cells and Corresponding Innate (Like) Immune Cell Activation. *Livers* **2024**, *4*, 562–593. https://doi.org/10.3390/livers4040040

Academic Editor: Yankai Wen

Received: 13 August 2024
Revised: 23 October 2024
Accepted: 25 October 2024
Published: 4 November 2024

1. Introduction

HBV infection represents a global health problem, with 250–300 million chronically infected patients worldwide [1]. In over 90% of cases, the patients' immune system is able to clear the infection spontaneously [2]. However, chronic HBV infection is established if the immune system is not able to limit HBV replication. This can ultimately lead to liver cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC). Worldwide HBV infection rates and HBV-associated mortality are steadily declining and were determined to be 4.1% and 7.2 per 100,000 individuals in 2019 [3]. HBV serves as a helper virus for the hepatitis D virus. Infection of HBV patients with HDV drastically accelerates liver damage and significantly contributes to HCC development [4]. Infection of cirrhotic HBV patients with HDV leads to a threefold increase in the development of HCC and doubling of hepatitis-associated mortality. In HBV infection, only a weak immune response is detectable, whereas upon HDV co-infection, a strong IFN response and subsequent innate immune cell activation is induced. This not only contributes to the elimination of infected

cells but also drives the development of liver fibrosis. In the following sections, we provide an overview on HBV and HDV replication, the hepatocyte intrinsic anti-viral IFN innate immune response, its impact on the function of respective innate immune cells during infection, and the occurrence of these cells in the liver, and discuss how they contribute to viral clearance and/or liver pathogenesis.

2. Molecular Mechanisms of HDV Viral Infections

HDV is considered to be the smallest pathogen that is infectious for humans. It is a single-stranded, blood-borne, negative-sensed RNA virus that can infect and replicate inside hepatocytes. The HDV genome of ~1.7 kb encodes for a small antigen (S-HDAg) and a large antigen (L-HDAg), which display differential expression and function during the viral life cycle [5,6]. HDV is capable of intracellular replication in hepatocytes, but the HDV genome does not provide genetic information for the expression of envelope proteins, which are needed for the secretion of HDV virions to promote intrahepatic spread (Figure 1).

Therefore, HDV as a satellite virus depends on simultaneous infection with HBV. Several studies suggested that concurrent infection with other viruses besides HBV may provide envelope glycoproteins for HDV ribonucleoprotein (RNP) packaging. Envelope proteins of vesiculovirus, flavivirus, and hepacivirus were shown to be able to package HDV-RNPs in vitro [7]. Experiments with humanized mice demonstrated that hepatitis C can promote the secretion of HDV virions for up to several months (3). However, anti-HDAg antibodies were only detectable in the blood of two out of 160 HCV patients [8]. These findings implicate that, although suggested by in vitro studies, HBV is likely to be the only physiological relevant helper virus for HDV. HBV has several features distinguishing it from other DNA viruses. HBV has a ~3.2 kb large genome and is considered to be the smallest DNA virus capable of infecting humans [9,10]. The partially double-stranded circular genome encodes for four genes (S (surface), C (core), P (polymerase), X (X protein)), which, due to overlapping open reading frames (ORFs), can be transcribed and translated into seven different proteins [10,11]. The S-gene together with its preceding preS1 and preS2 genes encode for the small (S) protein, middle (M, pre-S2 + S region) protein, and large (L, pre-S1 + pre-S2 + S region) protein form of the hepatitis B surface antigen (HBsAg), which are essential for the packaging of successfully replicated HDV genomes [12,13]. All three proteins contain the same C-terminus but differ in their N-terminal additions and glycosylation status [14]. HBV entry is dependent on the expression of heparan sulfate proteoglycans (HSPGs) and sodium taurocholate co-transporting polypeptide (NTCP) receptors on the target cell membrane. NTCP as a sodium-dependent transporter for the uptake of bile acids from the sinusoids is solely expressed on hepatocytes, which explains HBV and HDV hepatropism [15]. The identification of NTCP as a functional receptor for both HBV and HDV in 2012 allowed for the development of entry inhibitors for the treatment of HBV/HDV patients (bulevirtide) [16]. In addition, once identified, overexpression of the NTCP receptor in hepatoma cell lines made the development of in vitro models to study viral replication and the consequent immune responses possible [17,18]. Importantly, NTCP overexpression in in vitro models is superior to infection models employing primary hepatocytes, which rapidly lose NTCP expression in vitro, limiting infection efficacy [16].

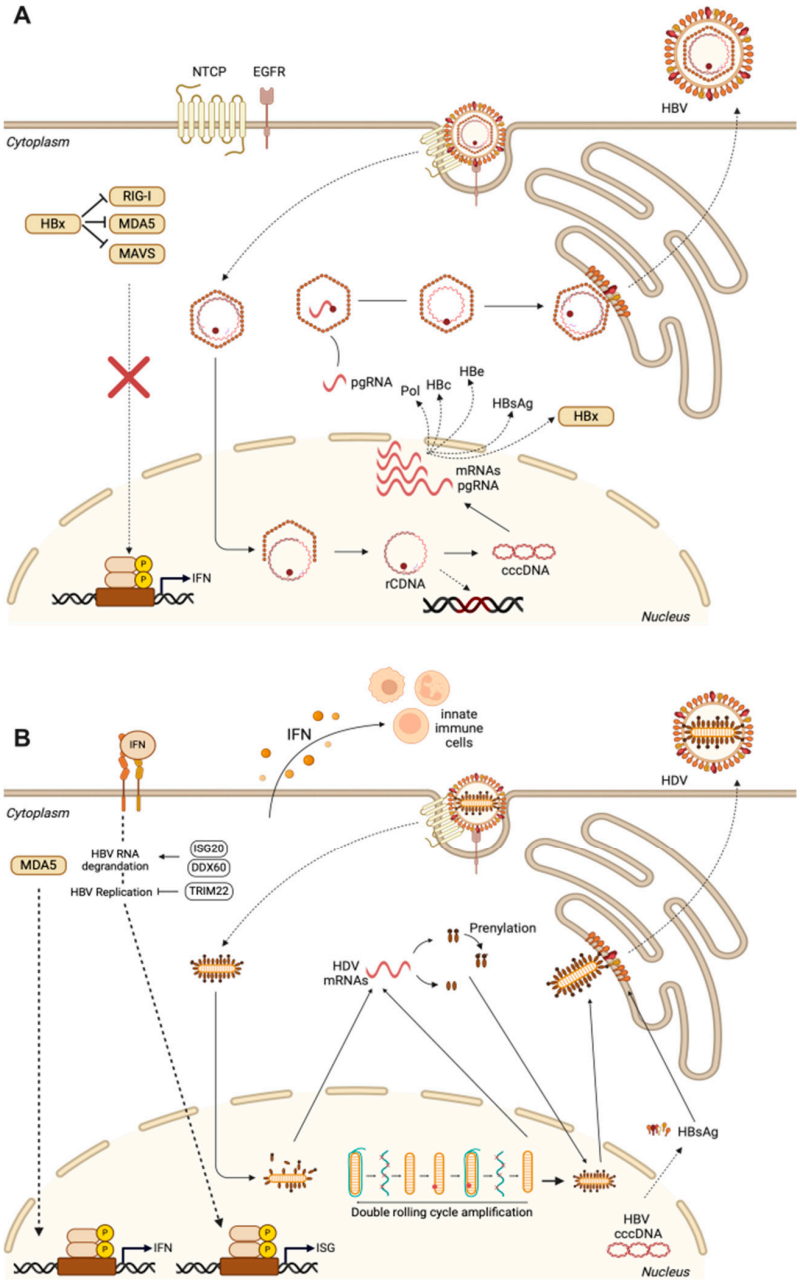

Figure 1. Schematic overview of HBV mono-infection and HBV/HDV co-infection replication cycles and initiated interferon response. (**A**) HBV attaches to the host cell surface through binding to factors, including heparan sulfate proteoglycans (HSPGs), and then interacts with its entry receptor, sodium taurocholate co-transporting peptide (NTCP). Virus–receptor interactions are believed to trigger virus internalization into cells in an endocytosis-dependent manner. Epidermal growth factor receptor (EGFR) triggers the internalization of HBV/HDV through its direct interaction with NTCP. The incoming nucleocapsid in the cytoplasm is directed to the nucleus along with the microtubules and is imported into the nucleus. The relaxed circular DNA (rcDNA) is converted, inside the host cell nucleus, into a plasmid-like covalently closed circular DNA (cccDNA) from which several genomic and subgenomic RNAs are transcribed by cellular RNA polymerase II, from which functional viral proteins are produced. The pregenomic RNA (pgRNA) is selectively packaged into progeny capsids and is reverse transcribed by the co-packaged P protein into rcDNA. HBV is regarded as a stealth virus not inducing an innate immune response. Hepatitis B virus X protein (HBx) has a critical role in suppressing the host innate immune response. To facilitate HBV replication, HBx can suppress retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated gene 5 (MDA5), and mitochondrial anti-viral signaling (MAVS),

thus inhibiting retinoic acid-inducible gene I-like receptors and the subsequent interferon (IFN) response. (**B**) HDV virions bind to HSPGs followed by binding to the viral receptor NTCP. Membrane fusion occurs and the ribonucleoprotein (RNP) is released into the cytoplasm. Next, the RNP is transported into the nucleus via the nuclear pore complex, where RNA replication occurs. The incoming genome is the template for the first rolling circle amplification. The resulting antigenome multimers are cleaved in cis by the intrinsic ribozyme and ligated into circular antigenome monomers. The HDV antigenome is edited by cellular adenosine deaminases acting on RNA 1 (ADAR1), producing an extended HDAg ORF. The antigenome serves as a template for a second rolling cycle. HDV genome multimers are synthesized and self-cleaved to produce circular HDV genome monomers. mRNAs encoding S-HDAg and L-HDAg are exported from the nucleus, followed by their translation. A portion of L-HDAg is prenylated. S-HDAg and L-HDAg are transported back into the nucleus to regulate replication or bind to the genome, resulting in the formation of the RNP, which is exported to the cytoplasm. The RNP acquires the HBV-derived envelop through budding into an ER-derived lipid bilayer carrying the three HBV envelope proteins encoded by either covalently closed circular DNA (cccDNA) or integrated HBV DNA. The HDV genome is sensed by MDA5, resulting in a subsequent IFN response. IFNs mediate the synthesis of interferon-stimulated genes (ISGs), including ISG20, DDX60, and TRIM22, which impede HBV replication. On the other hand, secreted IFNs activate innate immune cells. The figure was created using biorender.com.

Since HDV and HBV share envelope proteins, a similar pathway of target cell infection by both viruses is assumed. Initial attachment of HBV and HDV to hepatocytes is mediated by low-affinity reversible electrostatic interactions. These occur between HSPGs, which consist of a core protein linked to one or more linear heparan sulfate (HS) chains, and R122 and K141 residues in the antigenic loop of the HBV envelope S protein [19,20]. Upon loose binding of the virus to the cell membrane, mediated by HSPG interaction, the myristoylated 75aa N-terminus of the preS1 region (myr-preS1 2–48) of the LHBs antigen interacts with NTCP, which initiates endocytosis of the virus [21,22]. Recent structural analyses of NTCP suggest a mechanism whereby the preS1 protein competes with bile acids for the extracellular opening of NTCP [23]. For successful virion uptake, interaction of preS1-bound NTCP with epidermal growth factor receptor (EGFR) is required. This in turn triggers NTCP oligomerization and allows for HDV internalization in a clathrin-mediated manner [24,25]. Due to the high clinical efficacy of the conditionally approved entry inhibitor bulevirtide [26], several compounds are currently tested to target different stages of the internalization process to optimize HBV/HDV patients' treatment [27].

Upon endocytosis, the HDV RNP is transported to the nucleus via the nuclear pore complex [28,29]. This transport is presumably mediated by its interaction with karyopherin 2a [28,29]. In the nucleus, HDV genomic RNA (gRNA) is directly transcribed into S-HDAg mRNA and, in parallel, transported into the nucleolus. Once in the nucleolus, gRNA is assumed to be amplified in a rolling-circle mechanism, leading to the production of the antigenomic RNA (agRNA) replication intermediate [30,31]. HDV replication involves the autocleavage activity of ribozymes encoded in both the genomic and the antigenomic strands, which is crucial for the processing and maturation of the viral RNA. These ribozymes ensure proper RNA cleavage, facilitating the replication and circularization necessary for HDV's rolling-circle replication mechanism. agRNA is then transported into the nucleus, where it serves as a template for gRNA synthesis or is modified by adenosine deaminase acting on RNA (ADAR1) to produce the template for the L-HDAg mRNA. Synthesized S-HDAg and L-HDAg mRNAs are afterwards exported through the transcription export complex into the cytosol, where translation mediated by RNA polymerase II provided by the host cell is carried out [32]. Importantly, different host-derived factors, including eukaryotic translation elongation factor 1 alpha 1 (eEF1A1), are likely to be involved in viral replication [33]. S-HDAg is essential for HDV genome replication, whereas farnesylated L-HDAg that is generated by farnesyltransferase suppresses viral replication. Moreover, farnesylated L-HDAg is essential for HDV RNP interaction with

the HBV-derived envelope and thereby for the assembly of HDV virions [34–38]. Thus, treatment with the farnesylation inhibitor lonafarnib resulted in increased intracellular accumulation of HDV RNA [39]. In addition to the suppression of HDV RNA replication by farnesylated L-HDAg, suppression of viral RNA replication can be mediated by acetylation or methylation of the S-HDAg by histone acetyltransferase (HAT) or protein arginine methyltransferase 1 (PRMT1), respectively [40,41].

3. HBV/HDV Interplay

HDV infection can occur as a co-infection with HBV in susceptible individuals, which causes acute liver inflammation resembling acute HBV mono-infection [42]. In addition, HDV infection can occur as a subsequent superinfection in patients with chronic HBV infection. Notably, after an acute phase, HDV superinfection can lead to chronic HDV infection in 75% of cases [43]. In HDV superinfection, HDV encounters a pool of already HBV-infected cells, which allow for rapid HDV spread and replication. Therefore, the innate immune response is assumed to be more prominent compared to HBV/HDV co-infection [44]. As discussed above, HDV requires HBV envelope proteins for successful production of new virions to promote intrahepatic spread. In contrast, HDV replication is independent of HBV co-infection and relies on host RNA polymerases and additional factors [45]. Recently, cell division-mediated spread of HDV-mono-infected cells was demonstrated in vitro, supporting the hypothesis that HDV-mono-infected cells might occur in HBV/HDV patients [46]. Based on histological analysis, the frequency of $HDAg^+$ hepatocytes was determined to be around 15% in patients with chronic HDV infection [47]. Of note, similar infection rates can be achieved in HDV infection of hepatoma cells overexpressing the NCTP receptor, highlighting the importance of such in vitro models to study HDV infection and immune responses in co-culture models [39]. Liver transplantation is the ultima ratio for treatment of patients with hepatitis virus-induced liver failure. It has been shown that HDV can successfully replicate in patients with liver transplants for up to 18 months without HBV being detectable [48]. However, it is important to note that these patients received strong immunosuppressants, which may impact the anti-viral immune response as well as viral replication [48]. In addition, in HBV/HDV co-infection, appropriate detection of antigens for both viruses in hepatocytes or serum may not be possible due to suppressive effects of HDV on HBsAg expression [49]. Infection studies with chimpanzee hepatocytes demonstrated that hepatocytes can support the entire HDV replication cycle without HBV infection being present [50]. Together, these findings suggest that both HBV/HDV co-infected and HBV or HDV mono-infected cells might be present in HBV/HDV co-infected patients. HDV replication has been described to dominate over HBV infection in about 75% of co-infected individuals [51]. Since suppression of HBV replication by HDV is observed in isolated hepatocytes in vitro, this effect appears to be independent of the immune response [52,53]. In mouse models and in vitro cell culture, HDV co-infection impaired the synthesis of HBV RNA and promoted its decay [54]. Recent data demonstrated that HBV replication is suppressed by HDV through both interferon (IFN)-dependent and IFN-independent mechanisms [54]. In contrast to HBV, HDV is detected by host PRR MDA5, resulting in an IFN response and subsequent ISG induction [55,56]. The induction of ISGs in HDV-infected cells was linked to decreased HBV replication and HBsAg expression in vitro and in vivo [52,54].

HBV replication is controlled by four promoter regions and two enhancer (Enh) elements [55]. Initially, it was suggested that HDV impairs HBV replication by suppression of HBV Enh–1/2 function, while more recent studies identified an effect of HDV on HBV RNA transcription or stability as the primary cause [52,55]. In addition to the suppressive effect of HDV-induced ISGs such as TRIM22 on HBV RNA synthesis [57], the ISGs DDX60, a cytoplasmatic helicase, and the exo-ribonuclease ISG20 were able to promote HBV RNA degradation [58,59]. Of note, the HDV-induced IFN response did not limit HDV replication itself [54]. Besides ISG-mediated effects, L-HDAg and S-HDAg have been demonstrated to

directly bind to HBV RNAs in primary human hepatocytes in vitro and in liver chimeric humanized (HuHep) mice, thereby promoting their degradation [54].

Recently, a novel cell line (HepG2BD) that allows for long-term HBV and HDV replication has been published, which potentially allows for studying HBV/HDV interactions and immune responses against co-infection in vitro [60]. In this cell line, a 2kb HDV cDNA sequence was inserted into the adeno-associated virus safe harbor integration site 1 (AAVS1) of HBV-transfected HepG2 cells (HepG2.2.15) using a plasmid-based CRISPR-Cas9 approach [60]. Therefore, HDV RNA synthesis and virion production can be induced by doxycycline treatment, allowing for the analysis of different time points during HBV/HDV co-infection.

It is still an open question whether in HBV/HDV-infected patients HDV mono-infected cells are present and at which frequencies HDV or HBV mono-infected or co-infected cells occur. This issue is of high relevance, since the in vitro immune response to HBV and HDV mono-infected cells differs significantly, which is likely to be reflected in vivo in hepatitis virus-infected patients. In addition, secretion of cytokines and chemokines differs based on the infection status of the cells, which potentially impacts the liver microenvironment and immune cell reactivity. Thus, a histological assessment of viral Ags in livers of HBV/HDV-infected patients and the local microenvironment and immune response will lead to a better understanding of the complex interplay of HBV/ HDV infection and the immune system in the liver.

4. Cell Intrinsic Innate IFN Response

Recognition of viral replication intermediates is mediated by specialized intracellular pattern recognition receptors. In case of RNA viruses, RIG-I-like receptors (RLRs), which comprise retinoic acid-inducible gene I (RIG-I), melanoma differentiation antigen 5 (MDA5), and laboratory of physiology and genetics 2 (LGP2), play an essential role in viral RNA recognition and the subsequent immune response. Several studies with KO mice confirmed the importance of these receptors for a successful type I IFN response [61]. These receptors recognize sense, double-stranded foreign RNA and consist of a helicase, a carboxy-terminal domain (CTD), and a caspase activation and recruitment domain (CARD) [62]. The helicase domain is responsible for target RNA binding and enwraps the RNA in a C-clamp-like mode in cooperation with the CTD, which specifically binds to the 5′ end of the RNA [63]. Binding of double-stranded RNA leads to oligomerization of MDA5 and RIG-I in filament-like structures, which allows for dissociation of the CARD domain [64]. The released CARD domain of RIG-I and MDA5 then interacts with the CARD domain of mitochondrial anti-viral-signaling protein (MAVS). Subsequently, activated MAVS mediates activation of the transcription factor NF-κB as well as IFN regulatory factors 3 and 7, which ultimately leads to the expression of proinflammatory cytokines [65]. The RLR LGP2 is lacking a card domain and is therefore unable to mount an immune response by itself [66,67]. Nevertheless, LGP2 has been shown to be essential for the MDA5-mediated IFN response, although the exact mechanism is yet to be identified.

Importantly, in vitro studies with primary human hepatocytes, HepaRG and HepG2 cells showed that, in contrast to MDA5 knock-down, knock-down of RIG-I or other pattern recognition receptors such as TLR3 did not abrogate the HDV-induced IFN response. Moreover, recent work highlighted the important contribution of LGP2 as a cofactor for an efficient sensing of HDV replication [68]. These findings indicate the importance of MDA5 for immune cell activation in HDV infections. MDA5 RNA expression triggered by HDV infection in hepatoma cell lines in vitro strongly correlates with the downstream production of IFNs and ISG expression 7 days post infection [69]. This finding shows the importance of considering the kinetics of IFN induction for the study of innate immune cell activation in HDV infection in vitro. In the same study, pre-treatment of hepatoma cells with poly I:C to induce an IFN response did not affect infection efficacy or HDV replication [69]. Importantly, although the HDV-mediated IFN response and ISG induction was insufficient to control viral replication, it was able to boost the adaptive immune response. Thus, HBsAg-specific chimeric antigen receptor (S-CAR) T cells that recognize HBsAg on the

surface of HBV-infected cells independent of antigen presentation by HLA demonstrated a stronger cytototoxicty when HBV-infected target cells were co-infected with HDV [69,70]. The induction of an HLA-independent immune response by T cells upon HDV infection also suggests an induction of the HLA-independent innate immune response mediated by NK cells or γδ T cells, although this was not analyzed in this study. In another study, ISG induction through IFNa2b treatment in HDV-infected human pluripotent stem cell (hPSC)-derived hepatocyte-like cells (HLCs) reduced HDV infection efficacy [71]. Considering different results in the studies mentioned above, it is important to keep in mind that the IFN response and therefore the innate immune response differs based on the in vitro model used. Current data indicate hPSC-derived hepatocyte-like cells as a useful tool to study HBV/HDV infection in vitro. Additional in vitro models are based on the infection of primary human hepatocytes (PHHs), whose culture remains a challenge, or NCTP overexpressing hepatoma cells lines Huh-7, HepG2, or Hepa-RG cells that show bystander effects due to their cancerous background.

Since IFN production is a major driver of the innate immune response, HDV evolved different strategies to minimize its detection by the host cell. The most important one is minimized sensing by MDA5. This is achieved through different mechanisms. Thus, HDV replication takes place in the nucleus, while MDA5 is located in the cytoplasm. In the cytoplasm, HDV RNA can associate with HDAg to form RNPs, which are then further packed in HBV envelope proteins for virion secretion. In RNPs, HDV RNA is densely organized, which may hamper the recognition by PRRs [72]. In addition, HDV RNA formation as RNPs has been suggested to prevent its degradation by host-derived nucleases, which supports the concept that its association with HDAg prevents HDV RNA recognition by host-derived factors [73]. The production of IFNs by HDV-infected cells upon successful viral recognition can limit viral spreading through two main mechanisms. First, innate immune responses to HDV infection lead to the production and upregulation of IFNs and ISGs, which can limit viral replication, as reviewed above. Despite this, IFN stimulation has only a limited effect on HDV replication in non-dividing cells [46]. HDV-induced IFN responses and exogenous IFN treatments specifically target the spread of HDV through cell division. The specific mechanisms by which IFN targets cell division-mediated spread remain unclear. During mitosis, the disruption of the nuclear membrane could potentially expose HDV replication intermediates, making the viral RNA susceptible to PRR detection and subsequent degradation [74]. Additional research is required to fully understand and confirm the precise mechanism of IFN action on HDV persistence. Second, secretion of IFNs or soluble ISGs by infected cells can recruit and activate HBV/HDV-reactive innate immune cells to the liver. The following sections will discuss the phenotypes and functions of these innate immune cells and dissect the differences in innate immune cell responses between HBV and HDV/HBV infection.

5. The Innate Immune Cell Response in HBV/HDV Infection

The liver not only contains a high amount of innate immune cells but also constantly filters blood from the portal vein and is supplied with oxygenated blood through the hepatic artery, which leads to a high flow-through of foreign antigens, rendering the liver an important immunological organ [75,76]. Thus, liver-associated immune cells are constantly shaped by the liver microenvironment. The liver consists of parenchymal hepatocytes that exert detoxification and metabolic functions and account for approximately 65% of all liver cells [77]. Liver sinusoidal endothelial cells (LSECs) account for half of the non-parenchymal cell compartment [78,79]. These cells are characterized by a special morphological feature, so-called fenestrae, that allow macromolecules and innate immune cells from the blood stream to enter the sinusoidal space (space of Disse) and the parenchymal tissue [80,81]. The sinusoidal space comprises hepatic stellate cells (HSCs), which represent 5% of all non-parenchymal cells [78,79]. Under physiological conditions, HSCs are involved in vitamin A storage and metabolism. Upon HBV and/or HDV infection, HSCs become activated and promote liver fibrosis and cirrhosis, which can lead to HCC development [82]. The

remaining fraction of non-parenchymal liver cells is made up of biliary cells (5%), liver resident macrophages (Kupffer cells) (20%), and additional innate immune cell populations (25%) [78,79]. These immune cells are not equally distributed throughout the parenchyme but rather are located at strategic positions to maximize immune responses. In addition, upon inflammatory stimuli as present in viral infections, additional immune cells can extravasate from the hepatic sinusoids into the space of Disse and from there into the liver parenchyma, where they exert anti-viral effector functions, as previously summarized elsewhere [83]. The liver-associated innate immune cell compartment consists of innate lymphoid cells (ILCs) comprising NK cells and other subsets of ILCs (~10%); innate-like immune cells, such as invariant natural killer T (iNKT) cells, non-iNKT cells, γδ T cells, and mucosal-associated invariant T (MAIT) cells (~25%); as well as the myeloid cell compartment (65%) [84] (Figure 2).

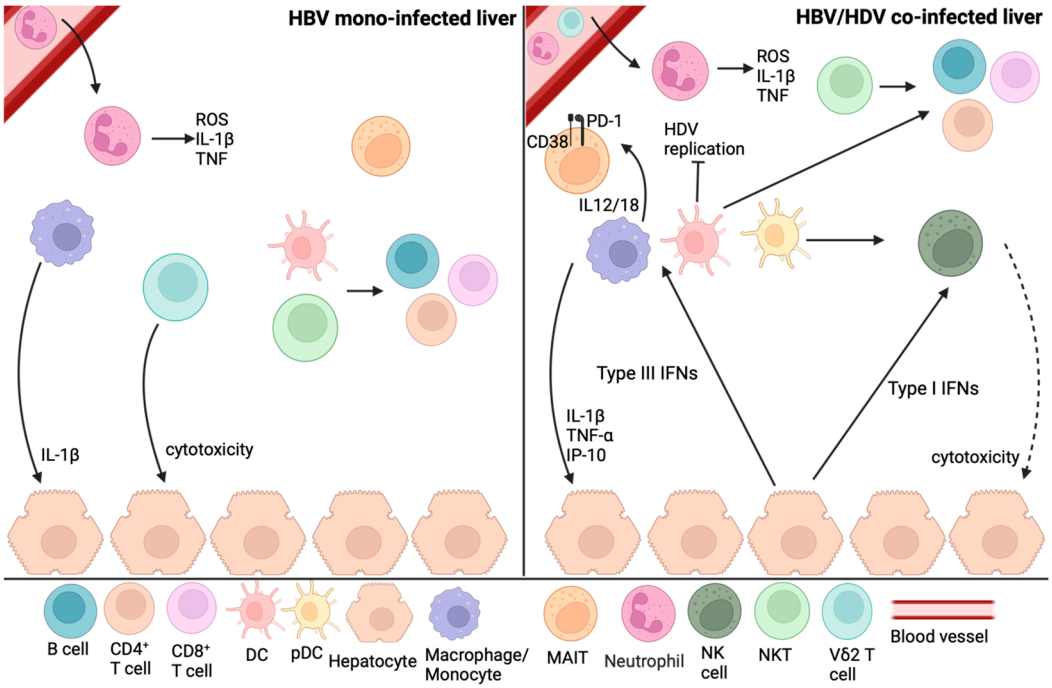

Figure 2. Cellular innate immunity in HBV mono- versus HBV/HDV co-infection. Different innate immune cell populations have been described to play crucial roles in the elimination of HBV/HDV virus-infected cells and the limitation of viral spread. In contrast to HBV infection, HDV induces the secretion of type I interferons (IFNs) and of type III IFNs by infected hepatocytes. Natural killer (NK) cells react to type I IFNs, which can result in NK cell-mediated cytotoxicity towards infected cells. Type III IFNs induce the activation of macrophages/monocytes and plasmacytoid dendritic cells (pDCs), which indirectly modulate NK cell activities. M1 macrophages demonstrated a suppressive effect on HBV replication through their secretion of IL-1β. In HBV/HDV co-infection, macrophages/monocytes further secreted TNF-α and IP-10. Dendritic cells (DCs) induced lymphocyte infiltration, possibly mediated by secretion of different cytokines in the liver. In HBV/HDV infection, MAIT cells demonstrated a high expression of CD38 and PD-1, indicative of their activation and subsequent exhaustion, which was linked to IL-12/18 production by monocytes. In acute HBV infections, Vδ2 T cells show a reduced frequency in the blood, likely due to their recruitment to the liver, where they exert strong cytotoxicity. NKT cells can be activated by small HbsAg, causing HBV antigen-specific B- and T-cell responses. Liver fibrosis was linked to granulocyte infiltration, accelerating liver damage primarily through their secretion of ROS, IL1-β, and TNF.

5.1. ILCs

Innate lymphoid cells (ILCs) can be broadly stratified into three groups: ILC1 (which includes conventional NK cells (cNK)), ILC2, and ILC3 [85]. ILC1 cells are characterized by

their production of IFN-γ and expression of the T-box transcription factor (T-bet) [86,87]. In contrast to other ILC1 cells, cNK cells express the transcription factor Eomes and the integrin alpha 2 (CD49b), and are generally considered to exert a stronger cytotoxicity due to their strong expression of granzyme B, perforin, and IFN-γ production in response to IL-12 stimulation [88,89]. Therefore, they are also referred to as cytotoxic ILCs. Although CD56 is considered a classical marker for NK cells, it is also expressed by non-cNK, ILC1, and ILC3, but not by ILC2 [90,91]. Moreover, since CD56 is expressed by some T cells, CD3 negativity is used for their exclusion. Most studies on human ILCs in HBV/HDV infections use CD3 negativity and CD56 positivity as markers to identify ILCs and do not focus on specific ILC subset functions. Thus, because cNK cells represent the majority of ILCs in liver tissue, we focus specifically on this subset in the context of HBV/HDV infection. Although ILC2 and ILC3 only account for ~5% of the liver ILC compartment, they recently attracted attention in the context of liver damage and fibrosis, which we discuss below [92,93]. In blood of chronic hepatitis B patients, factors important for ILC1 differentiation, including IFN-γ, T-bet, and IL-12, were elevated and strongly correlated with the degree of liver damage [94].

5.2. NK Cells

Conventional NK cells (cNKs) represent the largest group of liver-resident ILCs, which can exert direct anti-viral activity and play a key role in the body's anti-viral response [84]. Human NK cells as members of the innate lymphoid cells are classically described as $CD45^+$ $CD56^+CD3^-$ cells. Human NK cells can be further differentiated based on the relative expression of the adhesion molecule CD56 and the activating Fc receptor CD16 (FcγRIIIa) into $CD56^{dim}CD16^+$ NK cells, which represent 90% of circulating NK cells, and $CD56^{bright}CD16^{dim/-}$ cells [95]. CD16 on primary NK cells was shown to be shed by disintegrin and metalloprotease 17 (ADAM17) upon activation of these cells with IL-2 or IL-15 [96]. This finding is of great importance since IL-2 and IL-15 are present in patients with chronic inflammatory diseases such as chronic hepatitis, where the innate immune system fails to clear the acute infection [97]. Because NK cell-mediated antibody-dependent cellular cytotoxicity (ADCC) has been shown to be important for early HbsAg clearance, reduced CD16 expression by NK cells might contribute to HBV/HDV chronification and disease progression [98]. Peripheral $CD56^{dim}$ NK cells express lower levels of inhibitory receptors, including NKG2A, inhibitory killer cell immunoglobulin-like receptors (iKIRs), and immunoglobulin-like transcript 2 (ILT2), and are assumed to be terminally differentiated cells that arise from $CD56^{bright}$ precursor NK cells [99,100]. Due to their high expression of CD16 and subsequent high capability to mediate ADCC together with their strong IFN-γ production in response to IL-2/15, $CD56^{dim}$ NK cells have a high potential to fulfill cytotoxic effector functions [101,102]. The $CD56^{bright}$ compartment is characterized by high expression of the Il-2 high-affinity receptor and the stem cell marker c-kit (CD117) and is assumed to primarily exert immune modulation due to the high secretion of cytokines, including IFN-γ, TNF-α, GM-CSF, IL-10, and IL-13 [103–105]. Although resting $CD56^{bright}$ NK cells demonstrate a lower cytotoxicity compared to their $CD56^{dim}$ counterpart, their cytotoxic capacity can be strongly induced by IL-2 or IL-12 [106]. While $CD56^{bright}$ NK cells account for approximately 10% of circulating NK cells, they represent the majority of NK cells in secondary lymphoid tissue, approximately half of the NK cell compartment in the liver, and are assumed to outnumber $CD56^{dim}$ NK cells in total [107–109]. Accumulating evidence implicates a predominant role of $CD56^{bright}$ NK cells in viral infections [110]. $CD56^{bright}$ NK cells are expanded in chronic HBV/HDV patients and, in contrast to their $CD56^{dim}$ counterpart, express higher levels of the death receptor ligand TRAIL in patients with cHBV-related liver fibrosis [18,111]. Together with the high frequency of $CD56^{bright}$ NK cells in the liver, these findings highlight the importance of analyzing differential CD56 expression on NK cells and its functional consequences in further studies on hepatitis and other chronic inflammatory conditions.

Although the adhesion molecule CD56 is the archetypal marker for NK cells, it can also be expressed by αβ or γδ T cells, monocytes, or dendritic cells [112]. Therefore, other markers, such as the activating receptor NKp46 (natural cytotoxicity-triggering receptor 1), is useful for the identification of these cells. This marker has been shown to be expressed ubiquitously on both $CD56^{dim}CD16^{+}$ and $CD56^{bright}CD16^{-}$ NK cells regardless of their activation status [113]. In addition, NKp46 has been shown to be expressed only on ILC1, ILC3, γδ T cells, and some subsets of intraepithelial cytotoxic T lymphocytes [114–118].

Upon encounter of virus-infected cells, different modes of NK cell activation can take place. These include the activation of NK cells by soluble factors such as interleukins and IFNs secreted by innate immune cells or infected cells, reduced expression of MHC-I on virus infected cells, impairing iKIR engagement on NK cells, and increased expression of ligands for activating NK cell receptors such as natural killer group 2 member D (NKG2D) [119]. NK cell activation is strongly induced by type I IFNs, secreted by virus-infected cells and plasmacytoid dendritic cells (pDCs), and IL-2/12/18/27, which are secreted by T cells and antigen-presenting cells (APC) [120,121]. While studies on mouse cytomegalovirus (MCMV) infection suggest that type I IFNs are dispensable for NK cell proliferation in viral infections, they have been shown to increase IFN-γ and TNF-α secretion as well as tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) expression and degranulation by NK cells [122,123]. Although not necessary for NK cell proliferation, type I IFNs have been shown to protect NK cells from perforin and NKG2D-dependent fratricide in murine cytomegalovirus (MCMV) infections, demonstrating a type I IFN-dependent way how NK cells can evade cell death in viral infections [123]. It is important to mention that type I IFN signaling may also suppress NK cell function. Upon IFN type I stimulation in herpes simplex virus (HSV) type 2 infection, NK cells upregulated the TAM (Tyro3, Axl, and Mer) receptor Axl, which induced the expression of suppressor of cytokine signaling (SOCS) proteins, leading to reduced IFN-γ production [124]. In contrast to HBV, HDV induces the secretion of type I IFNs IFN-α and IFN-β and of type III IFNs IFN-λ1 (IL-29), -λ2 (IL-28A), and -λ3 (IL-28B) by infected hepatocytes [125]. A study by Dring and colleagues using peripheral blood mononuclear cells (PBMCs) from hepatitis C patients suggested a link between IFN-λ2 and reduced IFN-γ production by NK cells [126]. But follow-up studies using isolated NK cells did not observe an effect of IFN-λ stimulation of NK cells in vitro [127]. This is in line with findings that NK cells can react strongly to type I IFNs but do not express IFN-λ receptors [128]. Moreover, mouse studies demonstrated a dysfunction of NK cells upon IL28R KO in vivo [129]. This implicates indirect NK cell modulation by IFN-λ activated by IFN-λ receptor-positive cells such as monocytes/macrophages [130] or pDCs [131]. The absence of a type I IFN response in the liver by HBV might contribute to the low immunogenicity of HBV, thereby preventing an adequate immune response, which contributes to the chronification of acute HBV infection observed in 10% of patients [132–134]. Although innate immunity is not activated in HBV-infected chimpanzees or patients [135,136], it is not defective per se since production of IFNs and expression of ISG15 were induced in HBV patient samples ex vivo through stimulation of toll-like receptor (TLR)-3 or sendai virus infection [137]. One important factor mediating the suppression of the innate immune response in HBV infection is the Hbx protein, which has been shown to reduce the expression of MAVS, which leads to decreased IFN-β production [138–140]. Studies of PBMCs from untreated hepatitis patients revealed an increase in the frequency of both $CD56^{bright}$- and $CD56^{dim}$-circulating NK cells in chronic HBV/HDV but not in chronic HBV patient samples [141] compared to healthy donors (HDs). In addition, the frequency of peripheral NK cells in HBV/HDV patients was comparable to that of HDs upon successful therapy and clearance of the virus [18]. Of note, a comparison between peripheral and intrahepatic NK cells in HDs and HBV/HDV-infected patients showed a significant reduction in the latter upon HDV infection [142]. These findings indicate that differential frequencies of peripheral NK cells in HBV and HBV/HDV patients are likely a result of increased apoptosis or diminished NK cell proliferation in the bone marrow rather than increased sequestration of NK cells in

the liver. Liver-resident NK cells are characterized by their expression of the transcription factors Eomes and Hobit rather than T-bet, high expression of CD56, and expression of the chemokine receptors CXCR6, CCR5, and CXCR3 [143–145].

Since liver-resident NK cells represent a large proportion of intra-hepatic immune cells that can directly control viral spread and differ significantly from peripheral NK cells, analysis of NK cells in liver biopsies of HBV/HDV patients is of utmost relevance to further decipher the role of NK cells in HBV/HDV patients. However, the acquisition of appropriate patient samples remains a major challenge. Most liver biopsies suitable for the study of HBV/HDV infections are acquired for diagnostic purposes from patients with HCC caused by chronic HBV/HDV infection. Therefore, the impact of the tumor microenvironment on the surrounding non-malignant tissue has to be considered when analyzing these tissues. Since most of the obtained tissue from fine needle aspirations or core needle biopsies are used for diagnostic purposes, the amount of material available for research purposes is limited [146]. In addition, most tissue samples are fixed in paraffin for storage purposes and subsequent microscopic analysis, which prevents immune cell isolation from these samples for functional analysis. Larger amounts of patient material can be obtained from patients undergoing liver transplantation, performed as an ultima ratio for patients suffering from HBV/HDV-mediated liver cirrhosis and failure. Treatment options of HBV/HDV patients improved in recent years, leading to better patient outcomes. This progress provided significant benefits for patients, but due to the declining numbers of liver transplantations as treatment for HBV/HDV-infected patients, access to liver tissue from these patients for research purposes also became limited [147].

5.3. MAIT Cells

MAIT cells are unconventional T cells characterized by a semi-invariant T-cell receptor (TCR) consisting of an invariant α-chain (Vα7.2) combined with a limited number of β chains [148,149]. Their TCR allows MAIT cells to recognize bacteria-derived riboflavin metabolites as antigens that are presented by non-polymorphic MHC-related protein-1 (MR1) molecules [150]. Besides activation via TCR signaling, MAIT cells can be activated by cytokines such as IL-12 and IL-18 [151] as well as type I IFNs [152]. Under physiological conditions, MAIT cells account for up to 30% of all intrahepatic lymphocytes in humans [84,153], therefore representing the largest population of unconventional T cells in the human liver. Although MAIT cells cannot recognize viral antigens, they are thought to contribute to anti-viral immune responses [152,154]. Thus, MAIT cells engineered with a TCR reactive to the HBsAg (HBVs183-191) exert cytotoxic capacity against HBV antigen-presenting hepatoma cells and migrate towards HepG2 cells expressing PreS1 in vitro in 3D microdevices [155]. Similarly, activated MAIT cells kill HBV-expressing hepatoma cells such as HepG2.2.15 and L02 cells transfected with HBV in an in vitro model, suggesting a direct antiviral potential of MAIT cells against hepatitis viruses [156]. Of note, engineered HBV TCR-MAIT cells express IL-17A upon antigen recognition, which has been shown to induce an activated, pro-fibrogenic phenotype of HSCs, indicating that MAIT cells may also contribute to chronic liver damage in HBV and/or HDV infection [157]. In patients with HBV mono- and HBV/HDV co-infection, MAIT cells are highly activated [158]. Importantly, in contrast to patients with HBV mono-infection, MAIT cells show a dysfunctional phenotype and are decreased in frequency in peripheral blood of patients with HBV/HDV co-infection. Such MAIT cell dysfunction is linked to IL-12/18 expressed by activated monocytes, supporting the notion that HDV induces a stronger innate immune response than HBV [158]. Nevertheless, further research is needed to clarify the exact role of MAIT cells for antiviral immune responses and liver damage in HBV/HDV infection.

5.4. Monocytes/Macrophages

Under inflammatory conditions, such as in viral infections, circulating monocytes can migrate into inflamed tissues to differentiate either into antigen-presenting DCs or into phagocytotic macrophages (Kupffer cells) [159]. Besides their digestion of infected cells,

macrophages can suppress viral infections by the secretion of various cytokines. As myeloid cells, macrophages can heavily be shaped by their microenvironment and can be classified into different states. For simplification, previous studies differentiated macrophages into M1 pro-inflammatory or M2 immunosuppressive cells [160]. M1 macrophages with a high oxidative phosphorylation (OXPHOS) activity demonstrated a strong suppressive effect on HBV replication through their secretion of IL-1β [159,161]. A similar effect of macrophage-secreted IL-1β on HDV replication was demonstrated for infected HepaRG cells in vitro [162]. In addition to IL-1β, circulating monocytes from HBV/HDV-co-infected patients have been shown to secrete high levels of TNF-α in response to LPS ex vivo [163]. Upon stimulation with HDAg, $CD14^+$ monocytes released IP-10 (CXCL10), a chemokine that can be directly anti-angiogenic and, in addition, can mediate the recruitment of $CXCR3^+$ CD4 Th1 and $CD8^+$ T cells [164]. Moreover, IL-1β has been described as a marker of liver injury and inflammation in different liver pathologies, including viral hepatitis. Histological analysis of HBV and HBV/HDV patient liver biopsies revealed a strong correlation between $CD206^+$ macrophage infiltration and inflammation, characterized by high levels of TNF-α, IL-6, and IL-1β [165]. Macrophages as professional phagocytotic cells are able to present antigens via their MHC-II receptor. Although uptake and subsequent presentation of HBsAg by human macrophages in patients or ex vivo has not been described up to now, studies with THP-1 monocytes demonstrated the activation and secretion of IL-6, IL-12p40, and TNF-α upon the binding of HBsAg [166]. Secretion of IL-6 has mainly been associated with decreased function and cytotoxicity of NK cells, but whether this mechanism plays a role in HBV or HDV infections has not been studied yet [167]. Besides its modulating effect on immune cells, secretion of IL-6 has been described to repress HBV replication and NTCP expression in HepaRG cells and PHH in vitro, thereby limiting infection efficacy [168,169]. IL-12p40 as a monomer or homodimer can suppress the activity of IL-12p70 (IL-12), a heterodimer of IL-12p40 and IL-12p35, through competition for the IL-12 receptor [170]. IL-12 is a potent activator of NK cell function and induces IFN-γ production in these cells via activation of the STAT4 and T-bet [171]. Therefore, one could assume an inhibitory effect of macrophage activation on NK cells. In contrast, macrophage-derived TNF-α has been shown to promote NK cell function and proliferation through the induction of aerobic glycolysis [172]. Furthermore, macrophages, similar to DCs, can be a source of type I IFNs, which on the one hand directly suppress HBV and HDV replication and on the other hand activate other innate immune cells [173]. In addition, macrophages express IFN-λ receptors and can react to these cytokines, which are secreted by hepatocytes in HBV and HBV/HDV infections and could therefore potentially activate cytotoxic innate immune cells [174]. The balance between their direct anti-viral function and their immunoenhancing or immunosuppressive role is likely dependent on the duration, type, and level of receptors triggered. Because of their complexity and multifunctional role in hepatitis, liver-resident KCs and infiltrating monocytes/macrophages display a promising but challenging therapeutic target.

5.5. γδ T Cells

γδ T cells represent the second largest cell population of innate-like immune cells in the liver, where they account for up to 15% of lymphocytes [84]. In contrast to conventional αβ T cells, the TCR of γδ T cells consists of a gamma and a delta chain, which enables these cells to recognize a wide array of both endogenous and exogenous antigens in an MHC-independent fashion [175,176]. Based on the expression of different δ chains, γδ T cells can be classified as Vδ1/2/3/4/5 cells, which differ in their tissue localization, antigen recognition, and function [177,178]. Among these cells, Vδ1 and Vδ2 T cells account for 90% of the total γδ T-cell population. Vδ1 T cells are primarily found in epithelial barriers, but the ligands of the Vδ1 TCR receptor are poorly characterized [179].

Vδ2 T cells represent the majority of circulating γδ T cells, and their TCR is responding to pyrophosphate antigens (pAg) with a low molecular weight. These antigens can accumulate in cells due to alterations in the mevalonate pathway (isopentenyl pyrophosphate

(IPP)) due to malignant transformation. Additionally, the pAg (*E*)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMBPP) as a high-affinity ligand for the Vδ2 TCR can accumulate during the non-mevalonate pathway in protozoa and bacterial infections [180,181]. Although viral infections have not been described to lead to an accumulation of pAgs in vitro or in vivo, Vδ2 T cells have been shown to react rapidly to viral infections and demonstrate cytotoxicity against different viruses, including hepatotropic viruses such as HBV and HCV [182]. Although Vδ1 T cells are expected to be the primary tissue-resident γδ T cell population, Vδ2 T cells account for approximately half of liver-resident γδ T cells [183]. In addition, these cells have been described to consist of different subpopulations, of which $V\gamma9^{-}V\delta2^{+}$ liver-resident T cells can undergo clonal expansion and acquire an $CD27^{low}CD45RA^{+}CX3CR1^{+}$granzymeA/$B^{+}$ cytotoxic effector phenotype upon viral infection [184]. In acute HBV infections, these cells show a reduced frequency in the blood likely due to their recruitment to the liver via IP-10 (CXCL10) and CCR5 signaling, where they exert strong cytotoxicity [185]. Although highly active in acute HBV infections, circulating Vδ2 T cells displayed reduced production of IFN-γ and TNF-α in chronic HBV patients compared to HDs. Of note, lower levels of circulating γδ T cells were associated with a higher degree of liver damage, leading to higher levels of aminotransferases and bilirubin [186]. Besides TCR recognition, γδ T cells together with NK cells express a variety of both inhibiting and activating receptors [187,188]. MICA/B and ULBP proteins that serve as ligands for the activating receptor NKG2D or other NK cell/γδ T cell receptor ligands were not altered or were only moderately altered in HDV-infected Huh7 or HepG2 hepatoma cells in vitro upon HDV infection [18,142].

Similar to HDV infection, NKG2D ligand expression is not enhanced in HBV infection. In HBV infection, a decreased expression of MICA/B was observed [189]. In HBV infection, the Hbx protein has been shown to form complexes with the transcription factors GATA2–3, which inhibits MICA/B expression [189]. In addition, the HBc antigen was found to bind to CpG islands in the MICA/B promoter sequence, thereby reducing transcription [189]. The resulting reduced expression of NKG2D ligands is likely to contribute to the absence of a strong NK cell response in HBV patients. It is still an open question how Vδ1 or Vδ2 cells respond to HDV infection. Although protocols are available to expand these cells from PBMCs in vitro, their role in HBV/HDV infection remains under studied [190]. Moreover, immunohistochemistry analysis of liver biopsies from HBV/HDV patients will reveal their localization and functions in the liver tissue.

5.6. Natural Killer T (NKT) Cells

NKT cells can be divided into type I iNKT cells and type II (non-iNKT) cells. iNKT cells represent a set of specialized T cells that express a Vα24-Jα18/Vβ11 TCR α chain that is able to recognize lipid antigens presented by the cell-surface molecule CD1d, a non-polymorphic MHC class I-like molecule, and account for ~1% of liver-resident lymphocytes [84,191]. Type II NKT cells on the other hand can express a diverse range of TCRs that primarily react to phospholipids and sulfatides and represent a significantly larger number of innate-like lymphocytes in the liver. In contrast to iNKT cells, type II NKT cells are generally considered to exert anti-inflammatory functions [192,193]. NKT cells are of particular interest in liver disease since the liver displays the highest NKT/conventional T cell ratio in the human body [194]. So far, most data on NKT in hepatitis have been generated in mouse studies, where type I NKT cells represent up to 30% of liver-resident T cells, outnumbering the type II sub-population [195]. Studies in mouse models and with human hepatocytes, transduced with HBV-expressing adenoviral particles, demonstrated that activation of NKT cells precedes HBV antigen-specific B and T cell responses and are crucial for subsequent viral control [196,197]. Induction of NKT activity was correlated with expression of the small HbsAg. Since HbsAg is rapidly expressed in the early stages of HBV infection, this finding corroborates the view that NKT cells are important for the initiation of an efficient adaptive anti-HBV responses [196]. In addition, this finding indicates a pivotal role of HbsAg in the induction of innate immune responses and implies

that hepatoma cells overexpressing this antigen (HepNB2.7) are useful in this regard [39]. Lysophosphatidylethanolamine (LPE), a membrane lipid that accumulates in HBV-infected cells, has been shown to activate non-iNKT cells [198]. Furthermore, activation of iNKT cells in HBV-infected mice contributed to proliferation and activation of HBV-specific cytotoxic T cells, which led to faster viral clearance [199]. Direct application of these findings to the human situation is also difficult due to the differing frequencies of liver-resident type I and II NKT cells in humans and mice. In addition, functional differences between human and murine NKT cells have been described. While activation of NKT cells through injection with glycolipid α-galactosylceramide led to anti-tumor response in mice and treatment-associated liver toxicity, no such effects were detectable in tumor patients [200]. Therefore, additional data on human NKT cells are needed to further define their role in HBV/HDV pathogenesis.

5.7. DCs

DCs are professional antigen-expressing cells that are able to load antigen-derived peptides on MHC class I and II molecules to stimulate $CD8^+$ T cells or $CD4^+$ T cells, respectively [201]. Therefore, they show a wide distribution in different tissues to maximize antigen encounters to mediate subsequent immune cell activation. Dendritic cells can be divided into myeloid dendritic cells (human leukocyte antigen (HLA)-DR^+Lin-$1^-CD123^-CD11c^+$ cells) and pDCs ((HLA)-DR^+Lin-$1^-CD123^+CD11c^-$) in blood, which together account for 0.5% of PBMCs. In healthy liver tissue, myeloid and pDCs account for ~20% and 50% of Lin^-HLA-DR^+ cells, respectively, which is a slightly lower frequency compared to their circulating counterpart [202]. Despite their low frequency, studies demonstrated impaired function of circulating DCs, which related to decreased HBV-specific T-cell responses in chronic HBV patients [203]. Nevertheless, other studies showed that DCs from chronic HBV patients demonstrated a much stronger immune response after in vitro stimulation with HBV antigens, which was proposed to be caused by increased autophagy of these cells [204]. Dendritic cells have been shown to secrete exosomes loaded with MHC molecules and viral antigens. In a therapeutic setting, DC-derived exosomes loaded with ubiquitinated HDAg were able to mediate a JAK/STAT-dependent lymphocyte infiltration and reduction in HDV replication in livers of HDV-infected mice, suggesting DCs as a potential target for anti-viral immunotherapy [205]. In liver tissue, two populations of DCs can be found. Conventional dendritic cells (cDCs) are primarily found in the periportal and pericentral area, while pDCs are located in liver tissue [201]. Although liver-resident pDCs are only sparsely distributed and account for about 1% of non-parenchymal cells, they are of high importance for the anti-viral immune response since they are a major source of type I IFNs [201,206]. As a major source of type I IFNs, DCs represent an important bridge between the innate and adaptive immunity [173]. Since they lack NTCP expression, they are not infected by HBV/HDV but can take up viral antigens and RNA through endocytosis of extracellular vesicles, as published for HDV infection [74]. Internalization of HBsAg by DCs led to reduced TLR9-mediated recognition of HBV viral DNA, thereby impairing IFN-α secretion [207]. This represents another mechanism of HBV immune evasion contributing to chronification of this disease.

5.8. Granulocytes

Granulocytes consist of neutrophils, eosinophils, and basophils, which account for approximately 60%, 4%, and >1% of all circulating leukocytes, respectively [208]. The classical functions of neutrophils include direct cytotoxic effects against infected cells or pathogens or their entrapment by the formation of neutrophil extracellular traps (NETs) as well as the opsonization of pathogens [209]. Eosinophils have initially been described to combat parasites but have also been shown to be active in bacterial and viral infections [210]. Basophils are primarily involved in the modulation of regulating T helper 2 (Th2)-cell responses, chronic allergic reactions, and the formation of immunological memory [211]. To our knowledge, only neutrophils as the most frequent population of granulocytes have been studied

in the context of viral hepatitis. Compared to healthy controls, circulating neutrophils from chronic HBV patients displayed decreased capability to exert NET formation or to produce cytotoxic reactive oxygen species (ROS). This effect could be attributed in vitro to HBV C protein and HBV E protein [212]. Despite their reactivity towards hepatitis-infected cells, neutrophils are a prominent driver of viral hepatitis-associated liver damage, which we discuss in detail below. Neutrophils are the first line of defense against pathogens. Since the function of these cells is impaired in chronic HBV patients, these patients are prone to bacterial infections [213]. This issue is of further importance since, due to innate immune cell dysfunction, bacterial infections of patients with HBV-related liver failure significantly impair overall survival [214,215].

6. Innate Immune Cell-Mediated Liver Damage and Immunosuppression in HBV/HDV Infection

Innate immune cells represent a crucial part of the anti-viral immune response based on their fast activation by pathogen-associated molecular pattern molecules (PAMPs) or damage-associated molecular pattern molecules (DAMPs). Innate (-like) immune cells lack specific activation through antigen presentation by MHC molecules. Therefore, they exert a significantly broader anti-viral response upon activation, which can also cause damage to non-infected bystander cells. In addition, activated innate immune cells may also impair the adaptive immune response [216]. Activation of innate immune cells has been demonstrated to be a precursor of liver damage in HBV patients. This effect was primarily mediated by IFN secretion and subsequent activation of liver-associated immune cells. Innate immune cell-mediated tissue damage and IFN/ISG signatures were restricted to the liver and absent in circulating innate immune cells [216]. Since IFNs mediate paracrine and autocrine signaling within the liver tissue, these cytokines have no or only a minor effect on the circulating innate immune cell populations [18,122]. NK cells have been shown to respond to type I IFN stimulation through the upregulation of TRAIL. In this context, TRAIL not only contributes to the eradication of virus infected cells but can also mediate the death of non-infected hepatocytes [217]. Moreover, HBV-specific $CD8^+$ T cells have been shown to upregulate TRAIL-R2, rendering them especially susceptible to NK cell-mediated killing [218]. In addition, NK cells can interact with HBVAg-treated monocytes, secrete IL-10, and express PD-L1, thereby inhibiting the function of autologous T cells [219]. Although described in HBV infection, suppression of autologous T cell function by HDV-shaped NK cells could not be determined [18]. In addition, TRAIL expression by $CD56^{bright}$ NK cells has also been shown to positively correlate with liver fibrosis and negatively with liver function [111]. Up to now, the majority of direct ILC-mediated damage in viral hepatitis has been attributed to the TRAIL/TRAILR pathway. Most studies on HBV/HDV infection do not differentiate between cNK cells and other ILC1, but the stronger TRAIL expression on ILC1 suggests this subset to function as a potent driver of liver inflammation and fibrosis [89]. This assumption is supported by studies that demonstrated a correlation between ILC1 frequencies and liver damage in cHBV patients [94]. Similar studies showed comparable correlations between liver damage and ILC3 ($Lin^-CD127^+CD117^+CD294^-$ lymphocytes) frequencies in HBV patients [220].

MAIT cells have been shown to mediate liver fibrosis in mouse models [221], and pharmacological inhibition of MAIT cells through MR1 inhibitory ligands resulted in decreased liver fibrosis in mouse models [222]. Similarly, human MAIT cells mediate HSC activation, a process central for liver fibrosis development, in an IL-17A-dependent manner, suggesting a role for MAIT cells in HBV/HDV-mediated liver [157]. As highly reactive immune cells, neutrophils play a pivotal role in the course of liver fibrosis. HBV patients demonstrated an increased amount of intrahepatic T-cell-derived CXCL8, a strong chemoattractant for neutrophils [223]. Of note, CXCL8 production by HBV-specific T cells was dependent on IL-7 and IL-15 production. IL-17 has been shown to originate from liver resident Vδ2 or Th17 cells. Upon entry in the liver, granulocytes accelerate liver damage primarily through their secretion of ROS, IL1-β, and TNF [224].

7. Innate Immunity in HBV Treatment

Since recent pre-clinical research highlighted the importance of the IFN response in HBV/HDV infections, several clinical studies evaluated potential benefits of IFN administration. HDV-infected cells have been shown to secrete large amounts of IFN-ß and IFN-λ, which are known to activate innate immune cells, including macrophages and pDCs [18,131]. Upon activation, macrophages can directly impair HBV replication by secreting IL-1ß, while pDCs are a major source of IFN-α [161,225]. IFN-α not only activates NK cells but also induces $CD8^+$ T cells' clonal expansion, memory formation, and cytolytic function in viral infections [123,226]. In addition to the activation of the innate immune response, induction of the IFN response has been shown to limit intracellular viral replication and to improve therapy response [125], which is in line with IFN-α/pegylated(PEG)-IFN-α being the backbone of HBV/HDV treatment since the 1990s [227]. To further harness the IFN response in patients' treatment, the effectiveness of PEG-IFN-λ for the treatment of HBV/HDV was studied in a phase two clinical trial (NCT02765802) that enrolled 33 patients. In this study, PEG-IFN-λ treatment resulted in a comparable decline in HDV RNA in patients' serum compared to PEG-IFN-α. Of these 33 patients, 36% demonstrated a durable virological response 6 months after the start of the study [228]. In addition, analysis of liver biopsies of two patients showed a reduction in liver fibrosis 18 months post-IFN-λ treatment [229]. While type I IFN receptors are almost ubiquitously expressed in the human body, expression of type III receptors, including IFN-λ receptors, is primarily restricted to epithelial tissue and to immune cells [230]. This contributes to better tolerability and fewer adverse side effects of PEG-IFN-λ treatment compared to standard PEG-IFN-α treatment in HBV patients [231]. Together, these findings indicate the superiority of type III over type I IFN treatment of HBV/HDV patients. The prenylation inhibitor lonafarnib, which impairs farnesylation of the L-HDAg and subsequent release of infectious particles, is a promising additional option for the treatment of HBV/HDV [232]. A clinical phase three study investigating the efficacy and safety of combinational therapy of lonafarnib, the protease inhibitor ritonavir, and PEG-INF-α in chronic HDV patients receiving anti-HBV nucleos(t)ide therapy (D-LIVR) is currently ongoing (NCT03719313). Other approaches focus on nucleic acid polymers (NAPs), which have been described to limit HBV entry [233]. Investigation of the NAP REP2139 in combination with PEG-IFN-α in the REP 301-LTF study (NCT02876419) demonstrated a prolonged HBsAg seroconversion and functional HDV control [234]. Current research and treatment options are looking into different targets of HBV/HDV entry and their life cycle and their combinations. A phase 2a clinical trial combining lonafarnib, ritonavir, and PEG-IFN-λ yielded a significant reduction in HDV RNA serum levels in over 70% of HBV/HDV patients after 6 months of treatment (NCT03600714) [235]. Currently, the primary readout for clinical studies on HBV/HDV patients consists of parameters of liver function, HBV/HDV RNA serum levels, and patient outcomes. As we highlighted, the cellular innate immune cell response represents an important factor in combating HBV/HDV infections. In order to utilize this knowledge for therapeutic purposes, future clinical studies should include a comprehensive monitoring and functional evaluation of different immune cell populations.

8. HBV Vaccination and the Innate Immune Response

Vaccination approaches and novel HBV/HDV entry inhibitors are major components in combating HBV/HDV infections and have significantly improved patient care. Currently, the most frequently used HBV vaccine, which also effectively represses HDV replication, a second-generation vaccine, was generated by transfecting yeast cells with recombinant plasmids encoding for the small HBV surface antigen and was approved in 1986 [236]. Vaccination using this vaccine results in >90% immunity of vaccinated individuals. Although highly effective in most individuals, up to 10% of individuals are unable to mount an effective immune response due to their age (>40 years), impaired immune system function (HIV infection or cancerous diseases), or lifestyle (smoking, obesity body mass index >5 kg/m^2) [237]. This led to the development of third-generation vaccines that contain

pre-S1 and pre-S2 antigens and led to significantly higher response rates in individuals >45 years [238]. Obesity and smoking are known to impair HBV vaccination efficacy, which is assumed to be caused by a sustained inflammatory response, mainly mediated by innate immune cells [239]. Nevertheless, studies on the effect of vaccination against HBV on the innate immune response are rare. NK cells from vaccinated individuals demonstrated a stronger cytotoxic response and proliferation when encountering HBsAg-pulsed monocyte-derived dendritic cells [240]. The NK cells demonstrated a memory-like phenotype and were characterized as $CD56^{dim}CD57^{+}CD69^{+}KLRG1^{+}$ cells. Most importantly, activity of these cells was associated with lower serum levels of HBV DNA. To promote the response rates to HBV vaccination, activation of the innate immune system has been tested as an adjuvant for HBV vaccination. A meta-analysis of 13 studies including 734 individuals confirmed the benefit of GM-CSF administration on HBV vaccine-induced immune response and subsequent immunity [241]. Due to GM-CSF's pleiotropic role, several factors are considered to mediate the benefit of innate immune system activation. These include an increase in MHC class II-mediated antigen presentation, macrophage activation, B- and T-cell proliferation, and pro-inflammatory functions of this cytokine [242]. Taken together, the innate immune response does play an important supportive role in establishing long-lasting efficient immunity against HBV and HDV infection, and future vaccination approaches should consider this to further maximize its efficacy.

9. Role of Epigenetic Modulation and Host Cell Metabolism on the Innate Immune Response in HBV/HDV Infection

To evade and counter the sophisticated anti-viral immune response, HBV and HDV have developed multiple strategies. Both viruses are able exploit the host's epigenetic machinery to downregulate critical immune pathways. Epigenetic alterations are caused by enzymes adding covalent modifications to histones or DNA directly (DNA methyltransferases (DNMTs), histone acetyl-transferases (HATs), and histone methyltransferases (HMTs), their erasing counterpart (histone demethylases (HDMs) or deacetylases (HDACs), or bromodomain (BRD)-containing proteins that recruit additional factors in gene transcription [243]. Acetylation of histones occurs at lysine residues and generally leads to enhanced gene expression, while methylation, most commonly found on lysine but also on arginine residues, leads to gene silencing [244]. DNA methylation, miRNA expression, histone acetylation, and post-translational N6-methyladenosine (m^6A) modification of RNA in the coding region of HBx are epigenetic mechanisms that promote HBV replication and HBsAg protein levels [245,246]. One important factor, how HBV alters the epigenetic landscape to its advantage, is the HBV core protein (HBc). HBc, a component of the HBV minichromosome (a structural organization of the cccDNA), was reported to bind to CpG islands of the viral cccDNA, the template for HBV replication, and was associated with increased viral replication [247]. In addition, HBc has been described as directly binding to regulatory elements of genes coordinating the innate immune response, especially ISGs. This mechanism causes reduced expression of ISGs, including the GTPase MxA, which is known to possess antiviral activity against a broad set of viruses [248]. Epigenetics should also be considered in treatment strategies of viral hepatitis. IFN-α, either secreted by infected cells or administered as IFN-α or PEG-IFN-α as an antiviral, has been shown to hamper viral replication. As described above, cccDNA as the template for viral replication is an important target for epigenetic modulation. IFN-α2b was able to mediate de-2-hydroxyisobutyrylation of the histone H4K8 on the cccDNA minichromosome [249]. This form of deacetylation was facilitated by the class I deacetylase HDAC3, which is known to decrease HBV replication via the miR-29a-3p/NFAT5 pathway [250]. Histone modification on HBV DNA, especially PTM H3K4me3, was investigated in chronic HBV patients and linked to HBV transcription levels [251].Although various epigenetic modulations of HBV genome replication have been described, the interpatient variability of its occurrence makes it challenging to draw conclusions and to provide reliable information [251]. Another obstacle in determining the effects of epigenetic modulation on HBV replication and the resulting immune response

is that, at the moment, HBV/HDV in vitro models are insufficient for representing the epigenetic landscape found in patients [251]. Therefore, to answer these questions, patient liver biopsies are indispensable. Nevertheless, because epigenetic imprinting is highly prone to modifications, it represents a highly attractive target for drug development and therefore should be a focus of further research efforts.

In the past decade, novel techniques like metabolomic and fluxomic technologies have enabled researchers to investigate the close connection between cellular metabolism and the innate immune response. HBV and HDV are both hepatotropic viruses. Since hepatocytes are cells that function as crucial regulators of the body's metabolic homeostasis and therefore modulate the level of glucose, lipids, and cholesterol, research has primarily focused on alterations in the metabolism of these compounds and their cross-talk with key signaling pathways of the innate immune system. HBV infection has been described to increase both glycolysis and fatty acid oxidation to promote energy supply and to stimulate the pentose phosphate pathway to increase nucleotide synthesis for viral replication [252,253]. HBV is capable of inducing the Warburg effect in hepatitis-infected cells [254]. This means that glycolysis and subsequent lactate secretion take place at high rates, even in situations where enough oxygen for aerobic metabolism is present. This mechanism provides a rapid supply of energy, which is especially important in the early stages of HBV replication. Along with the increase in glycolysis, synthesis of nucleotides, amino acids, and lipids, all of which are necessary for viral replication, is increased. Increase in glycolysis leads to enhanced secretion of lactate into the extracellular space. Lactate has been studied most intensively in the context of cancerous diseases, since tumor cells often display high levels of glycolysis. One important mode of action of lactate is the downregulation of the nuclear factor of activated T cells (NFAT), which affects both T and NK cells [255]. This is facilitated by increased uptake of lactate, or intracellular acidification, which leads to reduced IFN-γ production and at higher doses results in immune cell apoptosis [255]. As tumors represent ongoing chronic inflammatory responses, such as those found in chronic hepatitis, immune-suppressive effects of increased glycolysis should be also applicable to viral situations. In addition to its direct detrimental effect on the primary cytotoxic innate immune effector cells, $\gamma\delta$ T cells and NK cells [255,256], lactate has also been described as inducing the formation of immunosuppressive cells such as M2 macrophages, myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs) [257]. These cells are known to hamper $\gamma\delta$ T and NK cell function through their expression of immune-checkpoint ligands such as PD-L1, the depletion of essential nutrients such as arginine and cysteine, the release of immunosuppressive molecules including kynurenine and adenosine, and the production of reactive oxygen species [258–260]. In addition, MDSCs and Tregs can suppress the activation of the adaptive immune system by impairing antigen presentation of DCs [261]. While research on MDSCs and Tregs has been primarily performed in the context of cancer, MDSCs and Tregs have gained more and more attention in recent years due their implication in the pathogenesis of HBV through metabolic regulation [262]. Besides glucose, free fatty acids are an important influence on the innate immunity in hepatitis infection. Free fatty acids can activate TLR4 signaling, which counteracts HBV infection [263]. The HBV-mediated increase in their breakdown may be a potential mechanism how HBV-induced changes in infected cells' metabolism impair the innate immune response [256]. In late-stage HBV patients with progressive liver cirrhosis, acute-on-chronic liver failure (ACLF) syndrome can occur, which is a severe condition with a high short-term 28-day mortality of 33% [264]. In contrast to acute decompensation (AD) of the liver due to cirrhosis, ACLF is a recently defined syndrome that is characterized by multiple organ failure involving the liver, kidney, brain, coagulation, respiratory system, and circulation [264]. While the exact pathophysiology is not clear, macrophages recruited to the liver and activated by HBV-induced accumulation of free fatty acids obtain an immunosuppressive phenotype, characterized by increased secretion of IL-10 and expression of CD206 [265]. This is intriguing, since in ACLF the degree of tissue inflammation due to innate immune cells facilitating an immunosuppressive environment seems to be lower compared to other

affected organs. This highlights metabolomic effects on the innate immune system as an important part in the pathogenesis of this disease, which needs future attention. Cholesterol has been shown to be indispensable in the viral envelope of the HBV to enable it to infect hepatocytes [266]. Also, small-molecule inhibitors of lipid synthesis have been shown to drastically reduce HBsAg levels in in vitro cultures of HepG2–hNTCP cells [267]. While in HBV infections, total cholesterol and low-density lipoproteins (LDLs) were increased, high-density lipoproteins (HDL) were lowered [268,269]. This increase in the LDL/HDL ratio not only contributes to cardiovascular diseases but also affects the innate immune response. Although LDLs promote NK cell activity at low concentrations, NK cell functions are drastically impaired when LDLs are accumulating. Similar observations have been described for γδ T cells [270,271]. Taken together, both epigenetic alterations and metabolic changes can contribute to HBV/HDV pathogenesis. Overall, the data discussed indicate that pursuing and harnessing these options could benefit hepatitis patients' outcomes.

10. Perspectives

While nearly absent in HBV infection, the innate immune cell response, which involves the cell-intrinsic IFN response, induction of ISGs, as well as subsequent innate immune cell activation and recruitment, plays a major role in controlling viral spread in HBV/HDV co-infections. Thus, dysfunction of the innate immune system in acute HBV/HDV infection due to viral escape mechanisms, which have been extensively reviewed recently [272,273], support the establishment of chronic viral infection with HBV and HDV. Despite the fact that innate immune cells contribute to viral clearance, activation of these cells also contributes to collateral liver damage, which is important to consider when developing therapeutic strategies against HBV and HDV that target innate immune cells. Therefore, further research should focus on developing immunotherapeutic strategies that optimally activate immune cells to achieve viral clearance while avoiding liver damage. In addition, novel tools to analyze the spatial distribution of immune cells in tissue samples such as spatially resolved transcriptomics and proteomics are needed for a deeper understanding of the distribution and function of intra-hepatic immune cells and their role in anti-viral responses against HBV and HDV. Due to the strong therapeutic benefit of the entry inhibitor bulevirtide for treatment of HBV/HDV infection, current research primarily focuses on optimizing viral entry inhibitors as well as on targeting different steps of the viral life cycle to inhibit viral spread [272]. Considering the important role of the innate immune response on viral clearance and liver fibrosis, modulation of the functionality of innate (-like) immune cells represents a promising additional approach to expand the therapeutic options for patients infected with HBV/HDV.

Author Contributions: C.G.: writing, review, and revision of the manuscript and figures. S.W.: preparation of figures and review of the manuscript. G.E.G., K.B. and A.C.: review of the manuscript and figures. All authors have read and agreed to the published version of the manuscript.

Funding: The project was supported by the German Research Foundation: TRR179 (Project No. 272983813; TP07 to A.C., TP06/TP25 to K.B., TP15 to G.E.G.), SFB1366 (Project No. 394046768-SFB 1366; C02 to A.C.), SPP 1937 (CE 140/2-2 to A.C.), SFB-TRR156 (B10N to A.C.), RTG2727–445549683 (B1.2 to A.C.), RTG 2099 (Project No. 259332240-RTG2099; P9 to A.C.), and ExU 6.1.11 (to A.C.), and by the German Cancer Aid translational oncology program "NK fit against AML" (74114180) (to A.C.).

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

AAVS1	adeno-associated virus safe harbor integration site 1
ACLF	acute-on-chronic liver failure
AD	acute decompensation
ADAM17	disintegrin and metalloprotease 17
ADAR1	adenosine deaminases acting on RNA 1
APC	antigen-presenting cells
BRD	bromodomain
CARD	caspase activation and recruitment domain
cccDNA	closed circular DNA
cDC	conventional dendritic cell
cNK	conventional NK cell
CTD	carboxy-terminal domain
DAMPs	damage-associated molecular pattern molecules
DC	dendritic cell
DNMT	DNA methyltransferase
EGFR	epidermal growth factor receptor
Enh	enhancer
gRNA	genomic RNA
HBc	HBV core protein
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HBx	hepatitis B virus X protein
HCC	hepatocellular carcinoma
HD	healthy donors
HDAC	histone deacetylase
HDL	High-density lipoprotein
HDM	histone demethylase
HDP	hepatitis D virus
HAT	histone acetyltransferase
HAT	histone acetyltransferase
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HLA	human leukocyte antigen
HLC	hepatocyte-like cell
HMT	histone methyltransferase
HS	heparan sulfate
HSC	hepatic stellate cell
HSPG	heparan sulfate proteoglycan
HSV	herpes simplex virus
IL	interleukin
ILT2	immunoglobulin-like transcript 2
iKIR	inhibitory killer-cell immunoglobulin-like receptor
iNKT	invariant natural killer T
IPP	isopentenyl pyrophosphate
ISG	interferon-stimulated gene
LGP2	laboratory of physiology and genetics 2
LDL	low-density lipoprotein
L-HDAg	large hepatitis D antigen
LPE	lysophosphatidylethanolamine
LSEC	liver sinusoidal endothelial cells
m^6A	N6-methyladenosine
MAIT	mucosal-associated invariant T
MAVS	mitochondrial antiviral signaling
MCMV	mouse cytomegalovirus
MDA5	melanoma differentiation-associated gene 5
MDSC	myeloid-derived suppressor cell
MR1	MHC-related protein-1

m6A	N6-methyladenosine
NAP	nucleic acid polymer
NFAT	nuclear factor of activated T cells
NK cell	natural killer cell
NKG2D	natural killer group 2 member D
NTCP	sodium taurocholate co-transporting peptide
OXPHOS	oxidative phosphorylation
PAMP	pathogen-associated molecular pattern molecule
PBMC	peripheral blood mononuclear cell
PEG	pegylated
pgRNA	pregenomic RNA
PHH	primary human hepatocyte
pAg	pyrophosphate antigens
pDC	plasmacytoid dendritic cell
RIG-I	retinoic acid-inducible gene I
RLR	RIG-I-like receptor
RNP	ribonucleoprotein
ROS	reactive oxygen species
S-HDAg	small hepatitis D antigen
SOCS	suppressor of cytokine signaling
T-bet	T-box transcription factor
TCR	T cell receptor
Treg	regulatory T cells
TRAIL	tumor necrosis factor-related apoptosis-inducing ligand

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