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Contents

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Innate immune recognition and modulation in hepatitis D virus infection

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Abstract

Hepatitis D virus (HDV) is a global health threat with more than 15 million humans affected. Current treatment options are largely unsatisfactory leaving chronically infected humans at high risk to develop liver cirrhosis and hepatocellular carcinoma. HDV is the only human satellite virus known. It encodes only two proteins, and requires Hepatitis B virus (HBV) envelope protein expression for productive virion release and spread of the infection. How HDV could evolve and why HBV was selected as a helper virus remains unknown. Since the discovery of Na^+-taurocholate co-transporting polypeptide as the essential uptake receptor for HBV and HDV, we are beginning to understand the interactions of HDV and the immune system. While HBV is mostly regarded a stealth virus, that escapes innate immune recognition, HBV-HDV coinfection is characterized by a strong innate immune response. Cytoplasmic RNA sensor melanoma differentiation antigen 5 has been reported to recognize HDV RNA replication and activate innate immunity. Innate immunity, however, seems not to impair HDV replication while it inhibits HBV. In this review, we describe what is known up-to-date about the interplay between HBV as a helper and HDV's immune evasion strategy and identify where additional research is required.

Key words: Hepatitis D virus; Hepatitis B virus; Innate immunity; Pathogen-associated molecular pattern molecules; Immune evasion; Immunosuppression

Core tip: Hepatitis D virus (HDV) is the only known human satellite virus requiring hepatitis B virus (HBV) coinfection for productive viral release. However, it was recently shown that HDV can be disseminated by viruses other than HBV in experimental setups, so it remains unexplained why HDV chose HBV as a helper virus.

As HDV might possibly profit from HBV mediated immunosuppression, we first focus on recent findings on HDV recognition by the innate immune system. Later on, we summarize partially controversial data on immunomodulatory mechanisms of both, HBV and HDV.

INTRODUCTION

First identified in 1977 by Rizzetto *et al*[1], Hepatitis D virus (HDV) represents a unique pathogen that defines it's stand-alone genus Deltavirus. Eight genotypes of HDV varying in their RNA-genome sequences have been described. As a satellite RNA virus, HDV does not encode its own envelope proteins for packaging of its ribonucleoprotein (RNP) and therefore depends on the envelop glycoproteins of the hepatitis B virus (HBV) for virion assembly, envelopment and transmission. HDV has a broad cell and host tropism and, theoretically, several virus genera can provide help by enveloping the HDV RNP[3]. Clinically, however, HDV infection has so far only been described as coinfection with HBV or as a superinfection of chronic HBV carriers. Both, co- and superinfection may lead to HDV persistence and inflammatory liver disease, called hepatitis D. Currently, World Health Organization estimates that 15-20 million people are infected with HDV worldwide, while others predict up to 70 million carriers.

The pathogenesis of hepatitis D has been recently summarized by Koh *et al*[6]. Coinfection with HBV and HDV tends to result in both, acute hepatitis B and D at the same time, leading to most severe disease. In a superinfection scenario, HDV profits from pre-existing hepatitis B surface antigen (HBsAg) expression for progeny virus production but at the same time decreases HBV replication rates[7,8]. Chronic hepatitis D is the viral hepatitis form that is most likely to lead to liver cirrhosis and it is associated with a significant risk of hepatocellular carcinoma development and high mortality rates[6]. The reasons for more severe disease progression in HBV-HDV infection compared to HBV monoinfection have not been ultimately resolved. Chimpanzee studies indicate that liver damage by HBV is immune mediated whereas in HDV infection it is mainly cytopathic[9,10]. Direct cytopathic effects and induction of liver fibrosis by HDV antigen (HDAg) were also indicated in *in vitro* studies[11-14].

Current treatment options rely on interferon alpha and are largely unsatisfactory leaving chronically infected at high risk to develop liver cirrhosis and hepatocellular carcinoma. New treatment options include interferon lambda, a farnesyl transferase inhibitor (Lonafarnib), the entry inhibitor peptide Mycludex B (Bulevirtide), nucleic acid polymers (*e.g.* REP 2139-Ca) that are applied alone or in combination with interferon and show promising results in phase II clinical trials[6].

HDV

The viral genome of HDV is a single-stranded, circular, negative sense RNA with a length of approximately 1680 nucleotides. Due to broad base pairing within the RNA molecule, the genome appears as a double stranded, rod-like structure resembling a plant viroid. During HDV replication, exclusively taking place in the nucleus, three distinct RNAs, which includes the genome, the positive-stranded antigenome, and viral mRNA, are generated by host RNA polymerases. RNA-Pol I drives the transcription of genome to antigenome in the nucleolus, whereas RNA-Pol II is responsible for genome replication using the antigenome as template on the one hand and for transcription of mRNA in the nucleoplasm on the other hand. Genome replication functions *via* a double rolling-circle mechanism. RNA oligomers of genomic and antigenomic orientation are generated, followed by self-cleavage into monomers through genome and antigenome intrinsic ribozyme activity, respectively.

Although there are several open reading frames within the HDV genome, only a single one is actively transcribed leading to the expression of two isoforms of HDAg. The small HDAg (S-HDAg) is composed of 195 amino acids, and the large HDAg (L-

HDAg) is comprised of 214 amino acids. Initially, only S-HDAg is expressed because a termination codon prevents protein translation of L-HDAg. In order to produce the large isoform, the stop-codon (UAG) within the antigenome is mutated into a tryptophan codon (UGG) by the cellular enzyme Adenosine Deaminase Acting on RNA (ADAR1). ADAR1 is an "RNA editor" induced by interferon. Transcription of this modified genome into mRNA extends the open reading frame until the next stop codon is reached, resulting in the translation of L-HDAg harbouring an additional 19 C-terminal amino acids[23,24].

For both isoforms, post-translational modifications play an important role. For S-HDAg it has been shown that phosphorylation of a serine residue enables interactions with the cellular RNA-Pol II, which is essential for HDV replication. Due to its C-terminal elongation, L-HDAg incorporates a nuclear export signal and a prenylation site, which allows farnesylation. The farnesylated form of L-HDAg inhibits HDV replication by masking a conformational epitope present in S-HDAg that is essential for trans-activating HDV RNA replication. The farnesylated L-HDAg is also crucial for virion assembly through its promotion of the interaction of the viral genome with a tryptophan-rich domain in the cytosolic loop of HBsAg. Common arginine rich motifs within S- and L-HDAg allow their mutual binding to RNA, leading to the formation of the so-called RNP complex, which consists of HDV genomic RNA and both HDAg isoforms. The RNP is subsequently exported into the cytoplasm, where virion assembly takes place. Export is likely mediated by nuclear export factor 1 and the cellular RNA export factor REF/Aly. During these different steps of viral replication, HDV induces a pronounced cytokine response and activates a broad range of host defence mechanisms[31-33]. This review focuses on the mode of HDV-detection by cellular pattern recognition receptors (PRRs) and selective modulatory properties of the HDV antigens. Additionally, immune-evasive and immuno-suppressive strategies of HDV, and its coexisting host virus HBV, are discussed.

PATTERN RECOGNITION OF VIRUSES

The immune system of vertebrates acts as protective mechanism against damage on cellular and organism level, and is subdivided into two branches, the innate and the adaptive immune systems[34]. Innate immunity, as the evolutionary older system, is the frontline of host defence which upon infection with a pathogen initiates and fine-tunes pathogen-specific adaptive immunity. For this purpose, innate immunity possesses the capacity to distinguish between self and non-self, as well as different classes of pathogens by recognizing certain structural patterns. This function is enabled by the expression of PRRs that detect distinct pathogen associated molecular patterns, also referred to as "PAMPs", such as unusually structured or located nucleic acids or characteristic bacterial proteins which are not found in a given cellular compartment under physiological conditions. In the case of viral infections, innate immune sensing mostly depends on characteristic modifications of viral genomes or genome-replication intermediates and mRNA as well as special RNA structures which are normally absent in eukaryotic cells.

Extensive studies have narrowed viral RNA detection down to two families of PRRs: Endosomal Toll like receptors (TLRs) and cytosolic RIG I like receptors (RLRs) (Figure 1). The latter consists of two activating PRRs, retinoic acid inducible gene 1 (RIG I) and melanoma differentiation associated gene 5 (MDA5), as well as a third signalling-incompetent accessory molecule termed laboratory of genetics and physiology 2. Double-stranded RNA regions are both required for RIG I and MDA5 activation, although MDA5 was reported to bind longer double-stranded RNA whereas RIG I activation is mostly thought to be triggered by shorter double-stranded RNA or hairpin structures with a 5' phosphorylation. Interaction of RLRs with their specific RNA patterns results in intramolecular conformational changes, exposing their "Caspase activation and recruitment domain" site for interaction with the mitochondrial antiviral signalling (MAVS) protein[37]. Subsequently, MAVS functions as a scaffold and initiates two divergent immune signalling pathways: (1) Proinflammatory cytokine release is provoked in a nuclear factor "kappa-light-chain-enhancer" of activated B-cells (NF-κB) dependent manner; and (2) Phosphorylation and nuclear translocation of "Signal transducer and activator of transcription" (STAT 1/2) induces production of interferon (IFN). IFN signalling activates the expression of interferon-stimulated gene (ISGs) by modulating cellular homeostasis in both autocrine and paracrine manners, resulting in an antiviral state that protects both infected and noninfected cells and suppresses viral replication and progeny virus production.
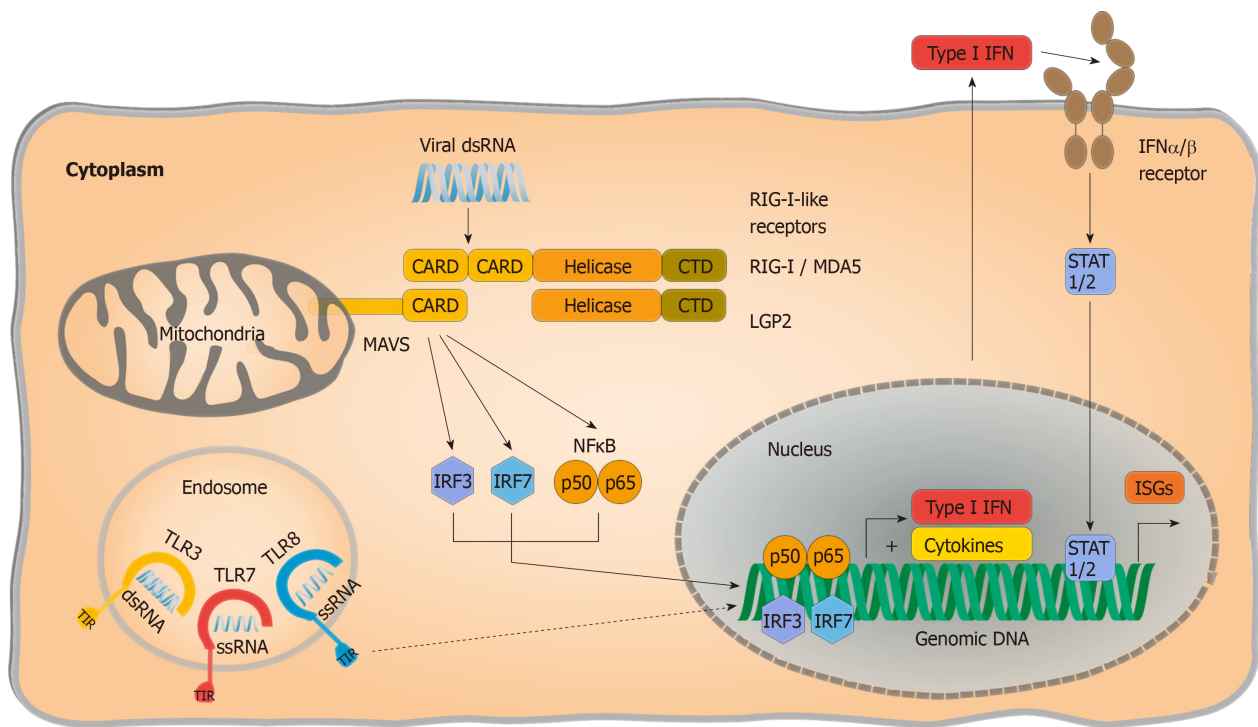
Figure 1 RNA-sensing by pattern recognition receptors. Intracellular pathogenic RNA is sensed by endosomal Toll-like receptors (TLRs) and retinoic acid inducible gene I (RIG I) like receptors. TLR3 detects double-stranded RNA (dsRNA), whereas TLR7 and TLR8 detect single-stranded RNA in a sequence-specific manner and signal *via* their Toll/interleukin-1 receptor homology domains. RIG I and melanoma differentiation antigen 5 bind cytoplasmatic dsRNA structures and activate conformational changes leading to the exposure of Caspase activation and recruitment domains (CARDs). Signalling-deficient laboratory of genetics and physiology 2 only consists of a helicase and a C-terminal domain and functions as an accessory receptor. This enables interaction of CARDs with mitochondrial antiviral signalling protein (MAVS), resulting in subsequent signalling cascades that release nuclear factor "kappa-light-chain-enhancer" of activated B-cells inducing a proinflammatory cytokine response. MAVS also activates interferon regulatory factor 3/7 signalling and signal transducers and activators of transcription 1/2-dependent type I interferon production and antiviral state with upregulation of interferon-stimulated genes in the host cell. TLRs: Toll-like receptors; RIG I: Retinoic acid inducible gene I; LGP2: Laboratory of genetics and physiology 2; ssRNA: Single-stranded RNA; CTD: C-terminal domain; RLRs: RIG I like receptors; NF-κB: Nuclear factor "kappa-light-chain-enhancer" of activated B-cells; MAVS: Mitochondrial antiviral signalling protein; TIR: Toll/interleukin-1 receptor; dsRNA: Double-stranded RNA; MDA5: Melanoma differentiation antigen 5; CARDs: Caspase activation and recruitment domains; IRF: Interferon regulatory factor; STAT1/2: Signal transducers and activators of transcription 1/2; Type I IFN: Type I interferon; ISGs: Interferon-stimulated genes.

PATTERN RECOGNITION OF HDV

Partial dependence on RLR signalling has been reported by Suárez-Amarán *et al*[38] in immune pattern recognition of HDV. The authors used adenovirus-associated virus (AAV) to deliver HBV and HDV genomes (AAV-HBV and AAV-HDV) into murine liver cells to circumvent species-specific limitations of viral entry. Both wildtype (wt) and MAVS-knockout (MAVS-ko) mice showed HDV gene expression and replication, but the innate immune response to HDV infection was diminished in MAVS-ko cells. HDV-induced immune activation resulting in type I and type III IFN production was later found to be dependent on MDA5 in both primary human hepatocytes and hepatoma-cell lines[32]. While pattern recognition of HDV RNA is considered the primary source of immune activation, direct induction of IFN-signalling by L-HDAg has also been reported[39]. Nevertheless, pattern recognition of HDV infection has not been conclusively resolved. As residual IFN-responses are still detectable in the absence of RLR-signalling[38], the impact of synergic immune activating pathways require further investigation. Additionally, the nature of HDV-specific molecular patterns that activate PRRs and changes in HBV-induced cellular immunoregulatory pathways are still poorly characterized. Considering that HDV only occurs as a satellite virus and chose HBV as a helper under natural conditions although theoretically a broad variety of viruses could provide their envelops[3], the detailed characterization of pattern recognition should regard potential confounding effects of HBV coinfection.

IMPACT OF HBV COINFECTION

The impact of HBV infection on innate immunity has been subject to numerous

studies and discussions. Numerous studies proved that HBV is sensitive to interferons and other antiviral cytokines *in vivo* in the liver[40,41], in primary hepatocytes or in HepaRG cells that have maintained their sensitivity to innate immune stimulation[42,43]. Cytokines can block HBV replication at transcriptional and posttranscriptional steps (Summarized in: Xia *et al* 2017) and affect cccDNA stability by inducing the enzymes that edit and subsequently digest it[45,46]. Up to date, the discussion is ongoing whether HBV can actively interfere with or suppress innate immunity, and thus support HDV persistence.

HBV is primarily regarded a stealth virus, neither activating nor inhibiting an innate immune response during virus replication[47-49]. Macrophages may, however, recognize virus particles early during infection[50,51]. This may be responsible for suppression of HBV replication shortly after infection and allow to prevent early activation of adaptive immunity. Several HBV proteins have been reported to have distinct features resulting in active interference with immune recognition or immune suppression. A number of these studies were done in settings where HBV proteins were overexpressed resulting in controversial discussions about the physiological relevance of the results[42,52-55]. An inhibition of interferon responses by HBV, however, has also been described in mice with humanized livers[56]. An inhibition of interferon responses by HBV, however, has also been described in mice with humanized livers. One would expect these livers to be close to the human physiological situation although HBV replication levels may be higher due to the lack of adaptive immunity and a cross-talk between human hepatocytes and murine non-hepatocytes.

A recent publication showed that HDV can be efficiently disseminated by helper viruses other than HBV from different genera, including flavivirus, vesicular stomatitis virus and the hepatitis C virus *in vitro* and in mice[3]. HDV particles packaged within a vesicular stomatitis virus envelope were able to overcome liver specificity conferred by the HBV envelope proteins and efficiently infect human embryonic kidney cell derived 293 cells[3]. In the context of tissue-specific pattern recognition, liver tropism may only confer a minor advantage for HDV since dsRNA-detecting TLR3, RIG I and MDA5 functions have been verified despite low protein expression levels *in vitro*[42,57,58] and *in vivo*[59].

From an evolutionary standpoint, one would argue that coinfection with HBV must be favourable for HDV, leading to the question of what benefit this confers. One possible explanation could be that HBV does indeed prevent or block innate immunity and that HDV profits from this. Regarding HDV recognition by MDA5, downregulation of MAVS-induced signalling by HBV-encoded X-protein has been proposed[60-64]. Interference has also be reported by the HBV polymerase[65] or by HBV induced microRNA146a[66] – all of which could support the survival of HDV infected cells. Proving this, however, requires additional studies using infection models because there are potential confounding effects from overexpression of HBV proteins in these experiments. The impact of HBV infection on downstream immune pathways also remains controversial. Direct blocking of interferon-signalling by HBV polymerase[52,54,67], HBV envelope protein[68], X-protein[69,70] or microRNA 146a[71] has been reported, which could also benefit HDV infection. These effects may well be subtle as HDV envelopment requires a certain level of interferon activity to allow induction of expression of the interferon-stimulated ADAR1 that is essential for L-HDAg expression. Regardless of the exact mode of HBV-induced immuno-suppression, dependency of HDV on help to survive innate immunity seems likely, given that it only encodes for a single protein.

SENSITIVITY OF HDV TO ANTIVIRAL CYTOKINES

In addition to exploiting immunosuppressive and immune-evasive mechanisms, HDV possesses some resistance to interferon-mediated antiviral effects. In contrast to HBV, HDV induces interferon signalling in both cell lines and mice without viral replication being affected[31,32,38]. The most prominent interferon-induced protein in HDV infection is ADAR1, which both inhibits viral replication and promotes RNA packaging. ADAR1 exists in two isoforms, constitutively expressed short ADAR1p110 present in the nucleus and IFN-inducible long ADAR1p150 which is both present in the cytoplasm and nucleus. In untreated Huh7-cells, non-inducible ADAR1p110 is mainly responsible for L-HDAg expression, whereas ADAR1p150 can enhance HDV-RNA editing rates up to one-third upon IFN-treatment[24,74,75]. Though ADAR1p150 editing was hypothesized to be partially responsible for the antiviral effects of interferon-α therapy, this effect seems to be limited due to additional regulatory mechanisms.

HDV production appears to remain unaffected or even promoted during

proinflammatory cytokine responses. Various groups have reported L-HDAg enhanced NF-κB translocation to the nucleus and the upregulation of proinflammatory genes in response to transfection of HDV-encoding plasmid[76-78]. This might be necessary for viral assembly as L-HDAg translocation from nucleus to cytoplasm was reported to be induced by NF-κB activation. However, all these experiments were performed as transient HDAg overexpressions, which could also induce unfolded protein response in the endoplasmatic reticulum, leading to NF-κB activation[80,81]. These circumstances were caused by unavailability of HDV-susceptible cell lines until the identification of Na+-taurocholate co-transporting polypeptide (NTCP) as an essential factor for HBV/HDV infection[82]. Newly developed infection systems utilizing AAV-HDV, as well as NTCP-expressing cell lines and mouse models, should be used to strengthen previously published results on antiviral activity of cytokines against HDV.

IMMUNE EVASION BY HDV

Despite the very limited coding capacity of its genome, HDV has evolved mechanisms to escape immunity (Figure 2). First of all, the HDV genome avoids direct contact with cytoplasmic or endosomal PRRs by replicating in the nucleus, taking advantage of cellular compartmentalization. Furthermore, it forms a circular RNA genome without "open" 5' or 3' ends to prevent PRR binding, as circular RNA has been reported not to activate RIG I[83], and an RNP complex reducing the binding of PRRs to virus-characteristic structures. Transfection of HDV-cDNA and HDV-encoding plasmid pSVL(D3) in Huh7 cells reduced STAT-signalling and expression of ISGs in response to IFN-α treatment and inhibited phosphorylation and nuclear translocation of STAT-proteins. This direct inhibition of interferon signalling was hypothesized to account for poor responsiveness to IFN treatment in infected patients. However, these results have not been reproduced in HDV-infection so far and, contradictory to the complete blocking of IFN signalling observed in this study, HDV triggers immune activation *via* MDA-5[32]. Whether HDV immune recognition by alternate PRR plays a role and which HDV-RNA structures trigger HDV-immune recognition still needs to be identified. It also remains ambiguous if HDV initiates IFN production in infected patients, since as to the authors' knowledge no data exist on this so far. HDV also offers little for adaptive immunity to attack since there is only two proteins expressed, and S-HDAg and L-HDAg largely overlap in their protein sequence. Thus, few HDV-derived peptides can be presented on infected cells and recognized by T cells. In a systematic screen to define CD8 epitopes, the overall number of epitopes identified was very low compared to other hepatotropic viruses[85]. When sequences of HDV RNA and HLA class I alleles that present epitope peptides to CD8+ T cells in patients with persistent HDV infection were analyzed, HDV variants were identified that can escape T cell-mediated immunity[85,86]. As an RNA virus, HDV genomes are mutated during virus replication allowing immune escape variants to emerge. Hereby, HDV escape from the immune response was associated with uncommon HLA class I alleles, indicating that HDV has evolved, at the population level, to evade recognition by common HLA class I alleles[86,87]. T cell exhaustion doesn't seem to be a major reason for failure to clear HDV. Activated HDV-specific CD8+ T cells target conserved epitopes and seem to contribute to disease progression. Even memory-like HDV-specific CD8+ T cells remain functional but are unable to clear HDV because of the presence of escape variants[86,87]. Thus, HDV mainly escapes adaptive immunity because there are so few epitopes that may be presented by human HLA haplotype repertoire and recognized by T cells.

CONCLUSION

As the only known satellite virus known in humans, HDV has chosen HBV as a helper virus although HDV per se is promiscuous. HDV seems to profit from the co-existence of HBV. Whether the advantage conferred is the strict liver tropism of HBV where pattern recognition is tuned down due to the constant exposure to bacterial components, or whether active HBV-induced immunosuppression contributes remains open. HDV shows some capabilities to escape immune responses and also a certain degree of resistance to interferon activity. Detailed studies on the mode of HDV-induced immune regulation and immune activation could contribute valuable key information to target this virus and develop new therapies against this fatal disease.
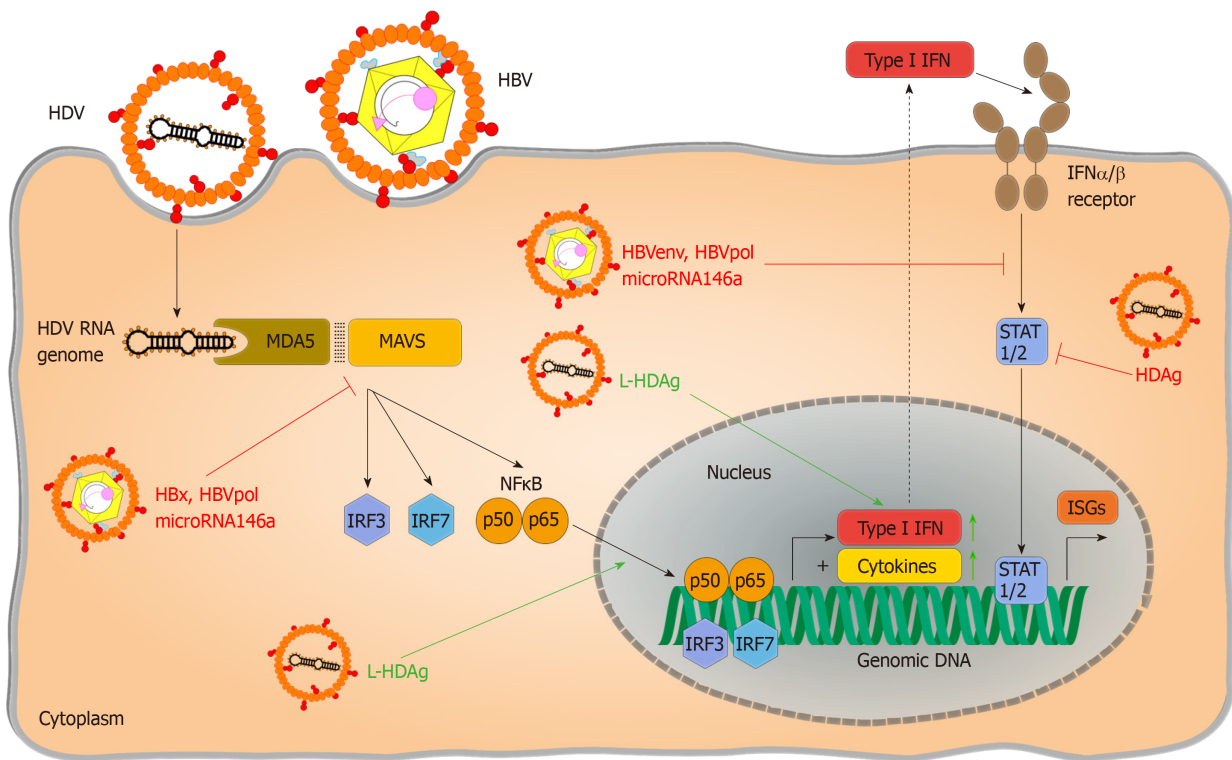
Figure 2 Immune evasion and immunomodulation in hepatitis D virus infection. Pattern recognition of hepatitis D virus RNA was reported to be both inhibited by hepatitis B virus (HBV) specific proteins like HBV X protein, HBV envelope proteins, HBV polymerase as well as the hepatitis delta antigen and in particular its large variant. Inhibitions of major pathways are indicated with red flat arrows, activation of cytokine response is indicated in green pointed arrows. HBV: Hepatitis B virus; HDV: Hepatitis D virus; HBx: Hepatitis B virus X protein; HBV env: Hepatitis B virus envelope proteins; HBV pol: Hepatitis B virus polymerase; HDAg: Hepatitis delta antigen; L-HDAg: Large hepatitis delta antigen; TLRs: Toll-like receptors; RIG I: Retinoic acid inducible gene I; LGP2: Laboratory of genetics and physiology 2; ssRNA: Single-stranded RNA; CTD: C-terminal domain; RLRs: RIG I like receptors; NF-κB: Nuclear factor "kappa-light-chain-enhancer" of activated B-cells; MAVS: Mitochondrial antiviral signalling protein; TIR: Toll/interleukin-1 receptor; dsRNA: Double-stranded RNA; MDA5: Melanoma differentiation antigen 5; CARDs: Caspase activation and recruitment domains; IRF: Interferon regulatory factor; STAT1/2: Signal transducers and activators of transcription 1/2; Type I IFN: Type I interferon; ISGs: Interferon-stimulated genes.

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