TOPIC HIGHLIGHT

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Hepatitis D virus infection, replication and cross-talk with the hepatitis B virus

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Abstract

Viral hepatitis remains a worldwide public health problem. The hepatitis D virus (HDV) must either coinfect or superinfect with the hepatitis B virus (HBV). HDV contains a small RNA genome (approximately 1.7 kb) with a single open reading frame (ORF) and requires HBV supplying surface antigens (HBsAgs) to assemble a new HDV virion. During HDV replication, two isoforms of a delta antigen, a small delta antigen (SDAg) and a large delta antigen (LDAg), are produced from the same ORF of the HDV genome. The SDAg is required for HDV replication, whereas the interaction of LDAg with HBsAgs is crucial for packaging of HDV RNA. Various clinical outcomes of HBV/HDV dual infection have been reported, but the molecular interaction between HBV and HDV is poorly understood, especially regarding how HBV and HDV compete with HBsAgs for assembling virions. In this paper, we review the role of endoplasmic reticulum stress induced by HBsAgs and the molecular pathway involved in their promotion of LDAg nuclear export. Because the nuclear sublocalization and export of LDAg is regulated by posttranslational modifications (PTMs), including acetylation, phosphorylation, and isoprenylation, we also summarize the relationship among HBsAg-induced endoplasmic reticulum stress signaling, LDAg PTMs, and nuclear export mechanisms in this review.

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Key words: Hepatitis B virus; Hepatitis D virus; Posttranslational modification; Endoplasmic reticulum stress; Nuclear export

Core tip: Hepatitis D virus (HDV) is a defective virus that depends on hepatitis B virus (HBV) to supply envelope proteins (HBsAgs) for assembling a new virion. The association of the clinical severity of hepatitis with HDV genotypes (HDV-1 to 8) has been reported, but the mechanism is unknown. Whether the combinations of HBV genotypes (A to H) with HDV genotypes cause varying clinical outcomes remains to be explored. This review focuses on HDV replication, the cross-talk between HDV and HBV, and the endoplasmic reticulum (ER) stress induced by HBsAgs in the ER which results in the promotion of large delta antigen export from the nucleus to interact with HBsAgs.

HEPATITIS D VIRUS INFECTION

At least five hepatitis viruses, including the hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV), which can infect humans have been identified and their transmission routes are diverse[1]. These routes can be divided into the oral-fecal route (HAV and HEV) and the blood transmission route (HBV, HCV, and HDV). All hepatitis virus infections cause acute hepatitis; the group that is transmitted through blood can cause both acute and chronic hepatitis[2]. Four hepatitis viruses (HAV, HBV, HCV, and HEV) can infect humans independently, but HDV cannot. HDV either coinfects or superinfects with HBV because it requires the support of HBV to complete its life cycle. Therefore, HDV is known as a defective virus, or a satellite virus of HBV[3-5]. Globally, 350 million people are HBV carriers; among them, more than 15-20 million people are infected by HDV, which is associated with the most severe form of viral hepatitis[6,7]. Although HDV infection has been reported worldwide, its prevalence is not uniform. The regions with a high prevalence of HDV infection are in the northern region of South America, West and Central Africa, and in Mediterranean countries[6,8,9]. According to a survey conducted in the 1980s, the prevalence of HDV infection varied from 0% to 84.9% among HBV carriers world-wide[10]. The prevalence of HDV infection was 1.5% in Far East Asia, and 21.0% in the Middle East. A higher prevalence was discovered in the following countries: Romania (69.5%), the USSR (38.8%), Italy (24.7%), Turkey (23.4%), and France (20.2%)[10]. However, in other European countries, the rate of HDV infection among HBV carriers varied from 8.5% to 11.0%[11]. A remarkably low prevalence (< 5%) of HDV infection in HBV carriers was reported in HBV highly endemic countries, such as Vietnam, certain provinces of China, Hong Kong (China), and South Korea[12-14]. After the HBV vaccination was administered in Italy, the prevalence of HDV infection was reduced from 24.6% (1983) to 8.1% (1997)[15]. Similarly, in Taiwan, an HBV endemic region, the prevalence of HDV also decreased from 23.7% in 1983 to 4.2% in 1995[16]. Thus, the prevalence of HDV infection was efficiently reduced by the prevention of HBV infection in HBV endemic regions.

Clinically, the coinfection of HDV with HBV leads to acute hepatitis, but subsequent chronic infection is rare, whereas the superinfection of HDV in HBV carriers typically induces a severe form of hepatitis and causes chronic infection compared with the effects of HBV monoinfection[6,8]. In addition, HBV suppression is also observed as an outcome of HDV superinfection in HBV carriers, which results in the persistence of HDV infection[17-20]. Although the mechanism of HDV-induced pathogenesis has not been fully clarified, HDV infection is a critical etiological factor for serious liver diseases, such as fulminant hepatitis[6,21-23]. The role of HDV infection as a risk factor in hepatocellular carcinoma (HCC)

remains debatable[23-29]. A report indicated that HDV infection could promote the risk of HCC by nearly three-fold in comparison with HBV monoinfection, which is prevalent in Western European countries[27]. Similar results were also reported in Italy[28], Sweden[24], and Sahelian Africa[23]. A 28-year follow-up study demonstrated that persistent HDV infection promotes cirrhosis and HCC at rates of 4% and 2.8% annually, respectively[26]. Conversely, several reports have indicated that HDV superinfection is not related to the development of HCC in Taiwan[30,31]. Therefore, the role of HDV in the progression of HBV-related liver diseases is a controversial topic.

Previous studies showed that the large delta antigen (LDAg) of HDV might play a role in the HDV-associated pathogenesis because LDAg can activate many eukaryotic promoters to turn on their downstream gene expression[32,33]. It is also reported that the LDAg can modulate tumor growth factor beta (TGFβ)- or c-Jun-induced signal activation[34] and trigger tumor necrosis factor alpha (TNFα)-induced nuclear factor kappa B (NF-κB) nuclear import[35]. Therefore, gene expression or signal activation is considered to contribute to HDV-induced hepatitis. Studies regarding the linkage of HDV-related pathogenesis with HBV are relatively rare. A few studies demonstrated that the LDAg could activate gene expression driven by the pre-S, S and core promoter of HBV[32], but inhibition of that gene expression was mediated by HBV enhancer 1 (Enh1)- and 2 (Enh2).[36] One report showed the X protein of HBV (HBx) induces a synergistic effect on LDAg-activated gene expression[37]. Taken together, these studies might provide some clues to understanding the connection of HDV/HBV-associated pathogenesis. Nevertheless, the contribution of HBV in HDV-related diseases and vice versa remains to be clarified.

The association between the severity of hepatitis and HDV genotypes (HDV-1 to 8) has been reported[6,38-44]; HDV-1 is distributed worldwide and causes hepatitis with a wide range of severity, whereas HDV-2 and HDV-4 infections are distributed only in Japan and Taiwan, and lead to comparatively less severe clinical manifestations[43,45,46]. HDV-3 has been reported to cause a severe form of fulminant hepatitis, which is isolated in the northern region of South America[41,44,47]. HDV-5 to -8 isolates are predominant in Africa, but the relationship between these isolates and the severity of liver diseases requires clarification[38,40,48]. An alternative observation indicated that various combinations of HBV genotypes (A to H) with HDV clades might contribute to the etiology of various clinical outcomes, suggesting that the interaction between HBV and HDV may influence pathogenesis[41,47]. Infection with HBV genotype F has been observed in patients with HDV-3-induced severe hepatitis[49], but a subsequent study demonstrated that HBV genotypes A and D were also isolated in patients with HDV-3-induced hepatitis[41]. Additionally, the influence of the HBV genotype on the replication and assembly of various HDV genotypes has been associated with various clinical outcomes[45,50,51]. The results of previous studies

have indicated that the replication level of various HDV genotypes is not associated with the HBV genotype. In contrast, the assembly of various HDV genotypes is correlated with the expression level of HBsAgs, and not with HBV genotypes[50,51]. Therefore, the relationship between the combinations of HBV-HDV genotypes and the clinical outcome of HDV-induced liver diseases remains obscure.

HEPATITIS D VIRUS REPLICATION

HDV may share the same receptor as HBV for entering hepatocytes because both viruses are enveloped in a phospholipid bilayer embedded with HBsAgs. Several research groups have demonstrated that sodium taurocholate cotransporting peptide[52] and the glycoaminoglycan side chain of heparan sufate proteoglycans are functional receptors for HBV and HDV[53,54]. In addition, purinergic receptors, which are nonhepatocyte-specific receptors, have been suggested to be binding partners of HBV and HDV[55]. Therefore, the exact function of these multiple cell surface receptors for HDV-binding hepatocytes requires further verification. After the HDV attaches to the receptors and enters the hepatocytes, HDV replication requires the assistance of host RNA polymerases for genome amplification and that of HBV surface antigens for new virion assembly. Primarily, HDV replication occurs in the nucleus and new virion assembly occurs in the cytoplasm. Additional details regarding genome amplification and virion assembly are described in the following subsections.

Genome amplification

The HDV genome is a negative-sense, which contains 1.7-kb circular RNA[56-59]. Its genome sequence is separated into the protein-coding region and the viroid-like region[60]. The protein-coding region contains the only open reading frame that can be used to produce hepatitis delta antigens (HDAgs), and the viroid-like region contains the ribozyme sequence required for the monomerization of the HDV genome from the multimer products generated during RNA replication[60,61]. During HDV replication, two types of HDAgs are produced: small delta antigen (SDAg) and LDAg[62,63]. The production of LDAg is mediated through small ADAR-1 (ADAR-1S; adenosine deaminase that acts on RNA), converting the amber stop codon (UAG) of SDAg into the tryptophan codon (UGG). Consequently, the LDAg, depending on various HDV genotypes, contains an additional 19 or 20 amino acids at its carboxyl terminus[64-67]. Both HDAgs have an identical amino acid sequence in the N-terminus, but the additional 19 or 20 amino acids of LDAg results in varying degrees of functionality between the LDAg and SDAg in the process of HDV replication. The SDAg is composed of 194 or 195 amino acids and supports HDV replication, whereas the LDAg consists of 214 amino acids, which inhibit HDV replication[63] and interact with HBsAgs to assemble new virions[68].

Both HDAgs are able to bind to HDV genomic RNA, but lack RNA polymerase or replicase activity[69-71]. Therefore, the genome replication of HDV completely depends on the cellular DNA-dependent RNA polymerases (RNAPs) and occurs in the nucleus[69,72-77]. Three species of host RNAP Ⅰ, Ⅱ, and Ⅲ have been demonstrated to interact with the HDV genome[72,78]. However, the role of RNAP Ⅰ and Ⅲ in HDV replication remains undetermined, unlike that of RNAP Ⅱ[69,75-77]. The role of RNAP Ⅱ in HDV replication involves the *de novo* synthesis of HDV genomic RNA and HDAg-coding mRNA[69,75]. Whether RNAP Ⅰ plays a role in HDV replication is debatable. The studies conducted by Lai and colleagues demonstrated that newly synthesized HDV antigenomic RNA is present after treatment with a specific inhibitor of RNAP Ⅱ, α-amanitin. In contrast, treatment with actinomycin D, an inhibitor of RNAP Ⅰ, decreases the *de novo* synthesis of HDV antigenomic RNA[69,76]. However, Taylor and coworkers provided evidence suggesting that RNAP Ⅱ is the only host RNAP and that it is required for the amplification of both HDV genomic and antigenomic RNA[75,77]. There is no evidence supporting the role of RNAP Ⅲ in HDV replication, except for its interaction with the HDV genome[78].

In vitro transfection studies revealed that SDAg is required for HDV replication[63]. SDAg has been demonstrated to interact with RNAP Ⅱ[76,79,80] and the transcription initiation factor, SL1, of RNAP Ⅰ[61]. Therefore, SDAg-supporting HDV replication is mediated through the interaction with the host RNAPs to drive the replication of HDV[74,79,80]. Because of the rolling circle mechanism, the replication process produces a linear form of multimeric antigenomes or genomes, which is subsequently cleaved by the ribozyme residing in the antigenomic and genomic sequence to form a monomeric circularized unit. The total number of HDV genomes can reach 300000 copies per single cell and the ratio of genome to antigenome is approximately 5-22 in HDV-infected hepatocytes[81]. The HDV genome also serves as a template for making mRNA to produce SDAg. LDAg is subsequently produced, resulting from ADAR-1 editing, and trans-inhibits HDV replication through the interaction with SDAg to reduce the binding specificity between the HDV genome and SDAg[82]. The LDAg interacts with SDAg and genomic RNA to form RNP that can be exported from the nucleus and assembled with HBsAgs. How the amplified HDV genome, but not antigenome, is selected by HDAgs to form RNP is still unclear.

Virion assembly

Several studies have demonstrated that the LDAg alone, or in the presence of HDV RNP, can interact with HBsAgs residing in the endoplasmic reticulum (ER) or Golgi apparatus to form empty viral-like particles or HDV virions[83-85]. The interaction between LDAgs and HBsAgs is dependent on the additional 19 or 20 amino acids at the C-terminus of LDAgs[86]. However, the predominant cellular distribution of LDAgs is in the nucleus, whereas

the major location of HBsAgs is in the cytoplasm[85,87-89]; two questions are thus raised: (1) how the LDAg receives signals to export from the nucleus to the cytoplasm; and (2) how the HBsAgs participates in LDAg nuclear export. Furthermore, the exact location, ER or Golgi, where LDAgs interact with HBsAgs to form particles remains undetermined. The study conducted by Tavanez *et al*[90] demonstrated that the HDV RNP could be shuttled between the nucleus and cytoplasm, suggesting that the interaction between HBsAg and HDV RNP is the consequence of HDV RNP being shuttled from the nucleus to the cytoplasm. The isoprenylation of LDAg is the key event for HDV assembly when HBsAgs interact with HDV RNP[85,89,91]. However, isoprenylated LDAg has been detected inside the nucleus of cells transfected with recombinant LDAg-expressing constructs in the absence of HBsAgs[92]. Thus the role of HBsAgs in the isoprenylation of LDAg remains to be elucidated. Collectively, neither the mechanism of HDV RNP shuttling between the nucleus and cytoplasm nor the cross-talk between LDAg and HBsAg that contributes to the packaging of HDV is fully understood.

POSTTRANSLATIONAL MODIFICATIONS OF LDAG

According to accumulated studies, the posttranslational modifications (PTMs) of HDAgs are required to execute various functions during HDV replication, assembly, and secretion. The isoprenylation, phosphorylation, and acetylation of LDAg have been reported to be associated with the dynamic distributions of LDAg and HDV packages[85,86,91,93,94] For example, the cysteine-211 isoprenylation of LDAg is essential for the association with HBsAgs and HDV secretion[86,91], the deficiency of isoprenylated LDAg leads to the loss of dynamic distribution from nucleoli to nuclear speckles and nuclear export, even in the presence of HBsAgs[84,89]. Although isoprenylated LDAgs have been observed inside the nucleus[89], the location where LDAg isoprenylation occurs is still debatable. The serine-123 phosphorylation of LDAgs is crucial for the nucleolus to SC35 nuclear speckle redistribution and HDV secretion[85]. The deficiency of serine-123 phosphorylation in LDAgs results in SC35 nuclear speckle-specific accumulation and leads to the reduction of LDAgs nuclear exportation and viral particle secretion[85]. The lysine-72 acetylation of LDAgs favors their nuclear retention because the lack of lysine-72 acetylation in LDAgs profoundly increases their cytoplasmic accumulation[93]. Combined, the progression of LDAg nuclear export is closely associated with PTMs. However, how the PTMs of LDAgs are regulated is unclear.

Numerous enzymes involved in the PTMs of various proteins are activated or their cellular localizations are changed under ER stress conditions. In HBV-infected cells and under the ER stress condition, the up-regulation of protein phosphatase 2A (PP2A) has been observed[95]. The dephosphorylation of LDAgs is required for the

dynamic distribution of LDAgs from the nucleoli to the SC35 nuclear speckle[85]. Whether the PP2A or other protein phosphatases participate in the dephosphorylation of LDAgs for various nuclear translocations has not been clarified. In addition to PP2A, p38 MAPK or ERK1/2 is activated in the ER stress condition[96]. ERK1/2 has been reported to phosphorylate SDAg at serine-177[97], and the ERK1/2 recognition sequence is also present in the LDAg. Whether serine-177 of LDAgs is the site phosphorylated by ERK1/2 for LDAg export is still unclear. We hypothesized that various PTMs of LDAg or various amino acid sequences of LDAg encoded by different genotypes may result in different conformations of LDAg resulting in different targeting patterns to various subcellular sites (Figure 1).

ER STRESS INDUCED BY HBSAGS AND TNFα SIGNALING

Three types of HBsAg are encoded by the HBV genome, which are designated as small, middle, and large HBsAgs according to their molecular weight. The presence of a large surface antigen (LHBsAg) in virions has been shown to enhance the infectivity of both HBV and HDV[98]. An *in vitro* HDV package system revealed that the presence of small surface antigen (SHBsAg) is sufficient for completing HDV assembly and secretion[99]. Furthermore, the nuclear export and cytoplasmic retention of HDAgs has been observed to increase in the presence of HBsAgs[83,85,89]. Therefore, this suggests that HBsAgs play a role in the facilitation of HDAg nuclear export because HBsAgs induce ER stress[84].

The HDV RNP shuttles back and forth between the nucleus and cytoplasm[90], but the dynamics of LDAg alone in the absence or presence of HBsAgs is poorly understood. To understand the dynamics of LDAg during HDV assembly and secretion[68,83,85,89], *in vitro* systems have been used in which green-fluorescent protein (GFP) fused with LDAg (GFP-LDAg) is used to trace the location of LDAg under various conditions. In the absence of HBsAg of any type, there is virtually no nuclear export of GFP-LDAg. The highest rate of GFP-LDAg export was detected in the presence of LHBsAg, whereas the lowest rate was observed in the presence of SHBsAg[84] (Figure 2). Together with a study demonstrating that a higher efficiency of HDV packaging was observed in the presence of authentic small HBsAgs than in the presence of nonglycosylated small HBsAgs[100], we hypothesize that the various degrees of glycosylation in the three HBsAgs may result in various capabilities for causing ER stress.

To mimic HBsAg-induced ER stress to facilitate LDAg nuclear export, experiments have been conducted by adding ER stress inducers (brefeldin A and tunicamycin) in the absence of HBsAgs, which resulted in a high amount of GFP-LDAg accumulation in the cytoplasm[84]. The ER stress typically results in activation of NF-κB, which is a transcription factor that facilitates NF-κB
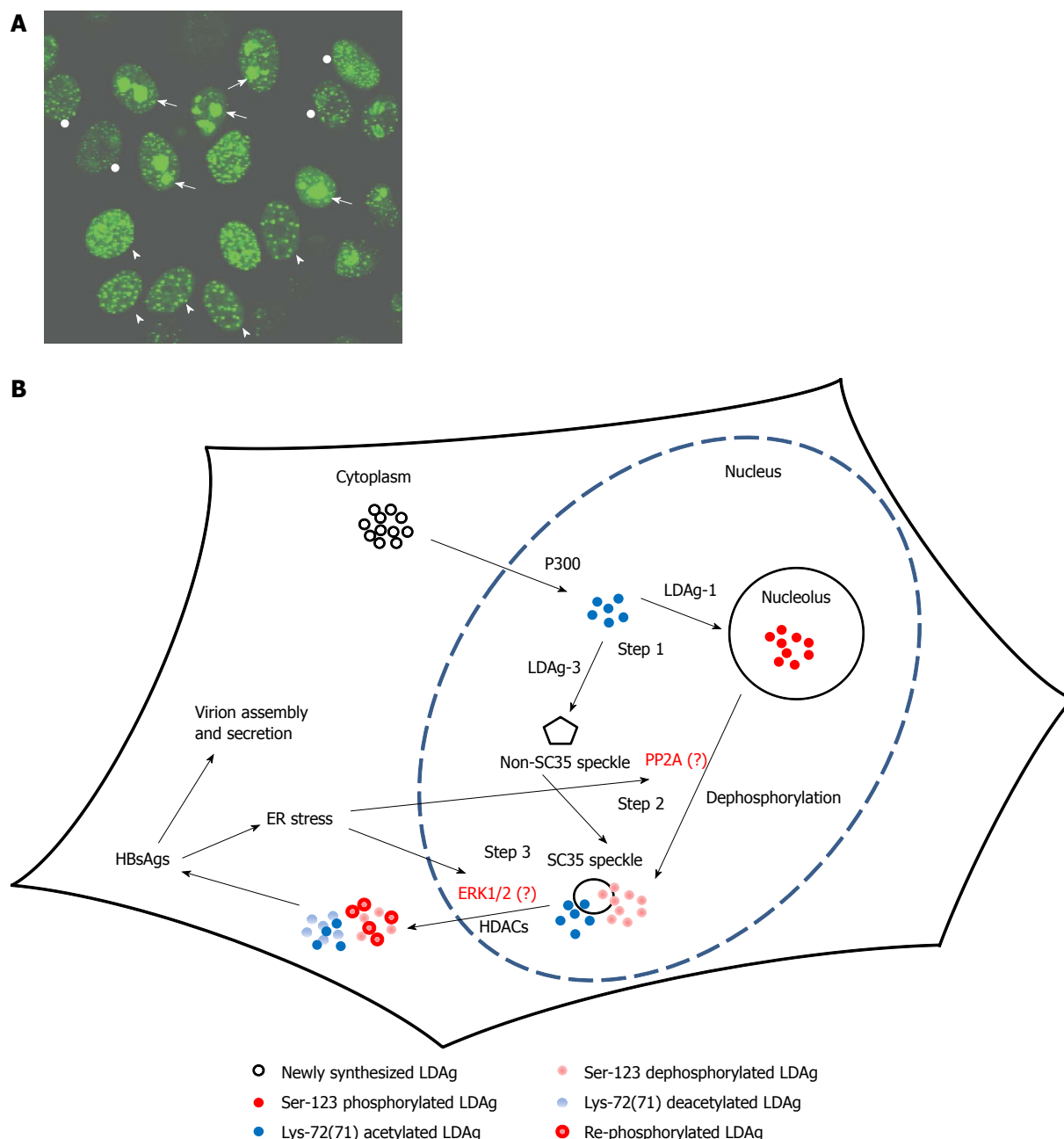
Figure 1 Large delta antigen resulting in different targeting patterns to various subcellular sites. A: Green-fluorescent protein (GFP) fused with LDAg (GFP-LDAg) distribution shown by a fluorescence microscopic image. HeLa cells were transfected with GFP-LDAg expressing construct and the GFP signal was photographed under a fluorescence microscope. The distribution of GFP-LDAg is in different nuclear compartments indicated by the GFP signal. Three predominant locations of GFP-LDAg in GFP positive cells are nucleolus (Nu), nuclear speckles (SC35) and non-SC35 nuclear speckles (NS). The cells marked with arrow, arrowhead and circle indicate the most GFP signals in Nu, SC35 and NS, respectively; B: A schematic model of HBsAgs-induced LDAg nuclear exportation. The newly synthesized LDAg is acetylated by p300 (a type of acetyltransferase) followed by targeting to the nucleolus (genotype 1) or non-SC35 speckles (genotype 3). It is unclear whether there is a direct association between acetylation and/or serine-123 phosphorylation and LDAg localization to the nucleolus or nuclear speckles. Nevertheless, in both hepatitis D virus genotypes, LDAg moves to the SC35 speckles later (step 2) and it is speculated that phosphatase (PP2A) might contribute to the dephosphorylation of LDAgs. Afterwards, LDAg is deacetylated by histone deacetylases (HDACs) and exported out of the nucleus (step 3) and the ERK1/2 might participate in the re-phosphorylation of LDAgs. Finally, in the cytoplasm, the LDAg interacts with hepatitis B virus supplying surface antigens (HBsAgs) to assemble into empty viral particles or virions.

down-stream gene expression[101]. Although three types of HBsAgs individually induce varying degrees of NF-κB activation with various results in LDAg nuclear export, the study conducted by Huang *et al*[84] may provide a line of evidence that cross-talk occurs between HBV and HDV, *via* signaling through NF-κB activation.

During the course of infection, numerous cyto-kines, including tumor necrosis factor alpha (TNFα), interferon, and interleukins, are up-regulated in HBV patients; the up-regulated TNFα and IFNγ derived from the T cells limit HBV replication in hepatocytes[102]. The TNFα-activating signal transduction participates in the disruption of HBV capsid integrity *via* activation of NF-κB[103]. In the absence of HBsAgs, TNFα is reported to
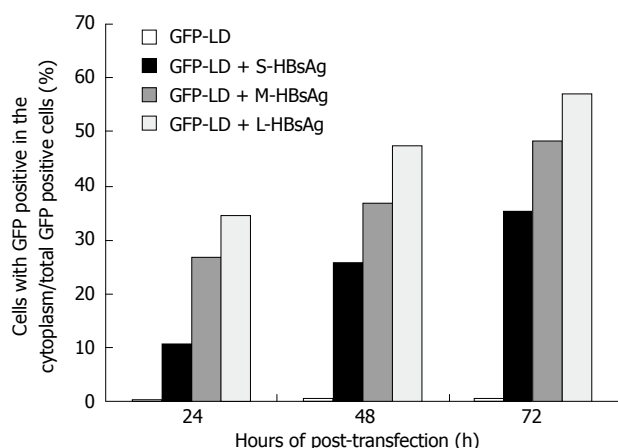
Figure 2 Distribution ratio of cytoplasmic green-fluorescent protein-large delta antigen in the presence of hepatitis B virus supplying surface antigens (modified from the results in reference 84). The green-fluorescent protein fused with large delta antigen (GFP-LDAg) (genotype 1) expressing construct was co-transfected alone or with various hepatitis B virus supplying surface antigens (HBsAgs) expressing plasmids into HuH-7, a human hepatoma cell line. The S-HBsAg, M-HBsAg, and L-HBsAg represent the small HBsAg, middle HBsAg and large HBsAg, respectively. The distribution of GFP-LDAg was observed with a fluorescence microscope at different post-transfection times. The percentage of GFP-LD distributed in the cytoplasm is shown. Results conclude that the GFP-LD remains inside the nucleus in the absence of HBsAg. In contrast, in the presence of various forms of HBsAg, the amount of GFP-LD translocation from the nucleus to cytoplasm is time-dependent.

significantly increase LDAg nuclear export[84] However, the efficiency of LDAg nuclear export induced by TNFα treatment is unaffected by cycloheximide, a translation inhibitor[84], suggesting that the LDAg nuclear export is not dependent on *de novo* translation when the signals are induced by TNFα. Both TNFα and HBsAgs-induced ER stress are linked to the activation of NF-κB. However, the link between enzymes that modify LDAgs (PP2A and ERK1/2) and the downstream molecules either activated or suppressed by NF-κB remains unclear.

CONCLUSION

Coinfection and previous infection with the HBV is necessary for HDV to complete its life cycle and enter uninfected hepatocytes. Few studies have described how the two viruses cross-talk. In this review, we present two possible cross-talk pathways between HBV and HDV: one is through ER stress induced by HBsAgs and the other is through TNFα secreted from immune cells, which respond to HBV infection. Both HBV-dependent pathways can activate NF-κB, and the activation of NF-κB correlates with LDAg nuclear export and HDV particle secretion. Because various states of LDAg PTMs are also closely related to LDAg cellular distribution, identifying the target molecules of NF-κB that play a role in LDAg modifications will be necessary in order to understand the HBV-HDV cross-talk. Additional effort should be invested in studying the cross-talk between HDV and HBV to develop new regimes to control HDV replication and infection, and the resulting clinical complications caused by this virus.

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