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Subversion of RNA Processing Pathways by the Hepatitis *delta* Virus

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1. Introduction

Viruses are the most opportunistic pathogens, since they extensively use host cell components for their replication. Among the various host factors usurped by viruses, proteins involved in RNA processing pathways are frequently used to regulate their own replication and to affect host protein expression (Lai, 1998). Over the years, the study of viral replication led to discoveries on how cellular RNA processing pathways are complex and how each step is crucial and extremely regulated. In addition to provide a better understanding of viral pathogenesis, investigation of viruses continue to be used as tools to understand the normal cellular RNA processing pathways and to identify new actors or new functions of known components.

The hepatitis *delta* virus (HDV) is a fascinating model. This virus is the smallest known pathogenic RNA capable of infecting human cells, and has to rely more heavily than any other viruses on host proteins for its replication (for general reviews of HDV biology and replication, see (Lai, 2005; Taylor, 2006, 2009; Tseng & Lai, 2009; Pascarella & Negro, 2011)). In this chapter, we present the current knowledge of the use of host proteins involved in RNA processing pathways by HDV, from RNA synthesis to RNA maturation. In addition, we discuss the potential contribution of these proteins to the life cycle of HDV, and possible impacts these interactions might have on natural host processes during an HDV infection.

2. The hepatitis *delta* virus

HDV is a defective RNA virus that requires the hepatitis B virus (HBV) envelope proteins for encapsidation and dissemination (Rizzetto et al., 1977). Co- and super-infection of HBV carriers by HDV causes acute exacerbation of the disease and subsequent chronic hepatitis. People with HDV superinfection have a much greater risk of developing fulminant hepatitis, hepatocellular carcinoma, cirrhosis, and liver failure than people infected with HBV alone (Fattovich et al., 2004; Su et al., 2006; Taylor, 2006; Romeo et al., 2009).

As stated above, HDV is the smallest known human RNA pathogen. It consists of a circular negative single-stranded RNA of about 1,680 nucleotides. This RNA can fold on itself using 74% intra-molecular base-pairing to form an unbranched, rod-like structure that can be divided into two domains (Fig. 1; reviewed by (Chen et al., 1986; Lai, 2005; Taylor, 2006, 2009; Tseng & Lai, 2009)). The left-terminal domain (~360 nt) includes both genomic and

antigenomic self-cleaving motifs (i.e. *delta* ribozymes or δRz). The right-terminal domain contains a single open reading frame (ORF) encoding two viral proteins produced alternatively: the small HDAg (HDAg-S) and the large HDAg (HDAg-L; Weiner et al., 1988). The difference between these two proteins is that HDAg-L contains 19 additional amino acids at its C-terminus. During replication, post-transcriptional editing of HDV antigenomic RNA results in transcriptional read-through from the HDAg-S gene (24 kDa; 195 amino acids) and to the production of HDAg-L (27 kDa; 214 amino acids; Casey et al., 1992; Casey & Gerin, 1995; Wong & Lazinski, 2002). Although they are mostly identical, each protein has a distinct function. HDAg-S is essential for HDV replication (Kuo et al., 1989; Yamaguchi et al., 2001), while the HDAg-L is necessary for virion assembly and is reported to be a dominant negative inhibitor of replication (Chao et al., 1990; Chang et al., 1991; Ryu et al., 1992; Sureau et al., 1992; Lee et al., 1995).

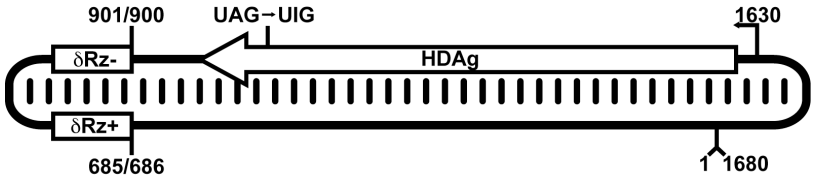

Fig. 1. The Hepatitis *delta* virus RNA genome. The HDV genome is depicted as a superposition of both genomic and antigenomic polarities. The *delta* ribozyme motifs (δRz) and their respective cleavage sites are indicated. The post-transcriptional editing performed by ADAR-1 is also indicated on the top stand. The arrows indicate the proposed HDAg mRNA initiation site. Numbering is in accordance with (Kuo et al., 1988).

HDAgs are RNA binding proteins that associate with HDV genomic RNA to form ribonucleoprotein (RNP) complexes in the HDV-containing HBV virion and in transfected cells (Chang et al., 1988; Niranjanakumari et al., 2002; Chang et al., 2008). This binding is likely facilitated by the rod-like structure adopted by the HDV RNA genome. In addition, HDAg-S can function as an RNA chaperone and modulate the ribozyme activity of HDV RNA (Wang et al., 2003), and is proposed to shuttle HDV RNA to the nucleus for replication, to the cytosol for packaging and export (Ryu et al., 1993; Lai, 2005; Taylor, 2006), and to modulate both HDV transcription and replication (Yamaguchi et al., 2001). Both HDAgs are post-translationally modified (i.e. serine and threonine phosphorylation (Chang et al., 1988; Mu et al., 1999; Mu et al., 2001), arginine methylation (Li et al., 2004), lysine acetylation (Mu et al., 2004), and cysteine farnesylation (Glenn et al., 1992; Otto & Casey, 1996)). These modifications regulate intermolecular interactions affecting subcellular localization of HDAgs and HDV RNA synthesis (Mu et al., 2001; Li et al., 2004; Mu et al., 2004).

Replication of HDV RNA is considered to take place in the nucleus of the infected cells using a symmetrical rolling cycle mechanism (Fig. 2; Taylor, 2009). Replication of the infectious circular RNA monomer (which is assigned genomic polarity by convention and accumulates to a greater intracellular abundance than the antigenomic species) produces linear, multimeric strands which are subsequently cleaved by endogenous ribozymes and ligated, yielding antigenomic circular RNA monomers (~30,000 copies). Using the latter RNAs as templates, the same three steps are repeated to generate the genomic RNA progeny (~300,000 copies). A third RNA also accumulates during replication, which corresponds to the unique HDV mRNA (~600 copies).

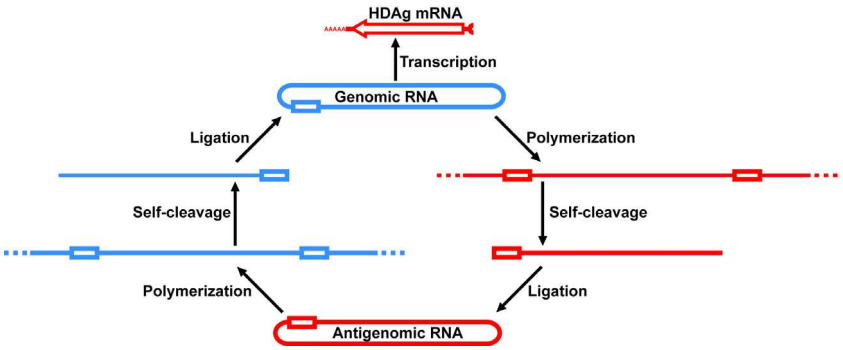

Fig. 2. Symmetrical rolling cycle mechanism used by HDV to replicate its RNA genome. Genomic RNA (blue) serves as a template for the synthesis of antigenomic RNA (red) multimers, which self-cleave and are ligated to form circular antigenomic RNA monomers. The antigenomic RNA monomers are used to synthetize circular genomic RNA monomers using the same steps. Genomic RNA also serve as a template for the transcription of HDAg mRNA.

3. The pathogenesis of hepatitis *delta* virus

Despite its apparent simplicity, HDV causes one of the most serious and rapidly progressive viral hepatitis. It provokes severe acute and chronic liver diseases, and it is associated with the development of hepatocellular carcinoma (Fattovich et al., 2004; Su et al., 2006; Taylor, 2006; Romeo et al., 2009). Interestingly, it was found that HBV replication is repressed in the presence of HDV (Krogsgaard et al., 1987; Farci et al., 1988), suggesting that the induced liver damage is likely caused by HDV replication rather than by HBV.

Since the genome of HDV can replicate in animal cells independently of HBV, many experimental systems using transfection of mammalian cells have examined the impact of the accumulation of HDAg and/or HDV RNA on the phenotype of cells in culture. It has been suggested that expression of HDAg-S or HDAg-L in mammalian cells might cause HDV pathogenesis (Cole et al., 1991; Cole et al., 1993). In contrast, some reports have shown that HDV RNA replication, rather than expression of the HDAgs, might be responsible for the cytopathic effects (Wang et al., 2001). At low concentrations of HDAg-S and without HDAg-L, low levels of HDV genome replication was reported to be able to proceed for at least 2 years without any deleterious effects on the host cell (Chang et al., 2005). When higher level of HDV RNA was induced, cell-cycle arrest in G1/G0 was observed followed by cell death (Chang et al., 2005). Using such systems, experiments have shown that when HDAg and/or HDV RNA are over-expressed, host proteins involved in regulation of cell metabolism and energy pathways, nucleic acid and protein metabolism, transport, signal transduction, apoptosis, and cell growth and maintenance are differentially produced (Mota et al., 2008; Mota et al., 2009). During viral replication, interaction of host factors with both HDAg and the HDV RNA genome might thus affect normal cellular activities.

4. Hijacking of cellular RNA processing machinery by HDV

Because HDV has an extremely limited protein coding capacity, it is completely dependent on its host cell for its replication. HDV has to interact and divert several proteins during its

life cycle, including those in the nucleus involved in both viral replication and transcription and those in the cytoplasm that are required for the production of HDAgs. The high accumulation of HDV RNA in infected cells (Chen et al., 1986) suggests that the interaction of HDV RNA with host factors might interfere with several of the normal cellular functions, thereby eliciting the virus' pathogenic effect. Over the last few years, studies have investigated cellular proteins that might interact with either HDAgs or HDV RNA. Several of these proteins are involved in RNA processing, including RNA polymerase subunits, heterogeneous ribonucleoproteins (hnRNPs), RNA helicases, RNA-binding proteins, and both transcription and splicing factors (for a review, see (Greco-Stewart & Pelchat, 2010)). However, the physiological significance of the interaction of most of these proteins remains enigmatic and the identification of additional host factors involved in viral replication is still required to gain a better understanding of both HDV replication and the associated pathogenicity.

4.1 HDV uses host RNA polymerase(s) for both its replication and transcription.

Because HDV does not encode its own replicase, host DNA-dependent RNA polymerases (RNAPs) are considered to be involved in the replication and transcription of HDV RNAs. Several approaches have been used to identify the host RNAP(s) involved in HDV replication/transcription and to study how this redirection from DNA to RNA templates occurs. However, it is largely unknown how the RNA-dependent RNA synthesis of HDV proceeds and there is still controversy on the identity of the RNAP(s) involved in HDV replication.

Many studies using cultured cells and cell extracts have provided evidence of the involvement of RNAP II in HDV replication based on the sensitivity of the accumulation of HDV mRNA and processed unit-length genomic HDV RNAs to low levels of α-amanitin, a mycotoxin that inhibits DNA-dependent RNA synthesis by RNAP II (MacNaughton et al., 1991; Fu & Taylor, 1993; Filipovska & Konarska, 2000; Moraleda & Taylor, 2001; Chang et al., 2008). These results were substantiated by experiments using cells containing an α-amanitin-resistant allele of the largest subunit of RNAP II, which partially relieved transcription inhibition by α-aminitin (Filipovska & Konarska, 2000). RNAP II is furthermore speculated to be involved in the transcription of the HDAg mRNA because, *in vivo*, this mRNA was shown to be post-transcriptionally processed with a 5'-cap and a 3'-poly(A) tail, which are typical features of transcripts generated by RNAP II (Gudima et al., 1999).

Synthesis of complementary strands was possible in transcription assays using nuclear extract (NE) from HeLa cells and RNA derived from the left terminal stem-loop domain of antigenomic HDV RNA (Filipovska & Konarska, 2000). Accumulation of this RNA product was highly sensitive to α-amanitin. This sensitivity was partially abrogated in experiments conducted in NE from cells containing an α-amanitin-resistant allele of the largest subunit of RNAP II, suggesting the involvement of RNAP II in this reaction. Interestingly, the transcription did not proceed by *de novo* initiation, but rather by cleavage of the RNA template followed by extension of the new 3' end, generating a chimeric template/transcript RNA product. In addition, transcription stopped after the elongation of only 41 nucleotides, and addition of HDAg-S allowed the RNA synthesis to resume (Filipovska & Konarska, 2000). Although not believed to be required for the initiation of RNA synthesis, HDAg-S was suggested to be implicated in the regulation of the elongation reaction through direct binding to RNAP II and displacement of the elongation repressors NELF and DSIF

(Yamaguchi et al., 2001; Yamaguchi et al., 2007). Interestingly, HDAg has been shown to affect transcription from numerous bacterial and eukaryotic promoters (Brazas & Ganem, 1996; Lo et al., 1998; Wei & Ganem, 1998). For example, transcription from the serum response element (SRE) pathway was reported to be stimulated by HDAg-L in a manner independent of the binding of the serum response factor (SRF) protein (Goto et al., 2000; Goto et al., 2003). Because HDAg directly binds RNAP II and stimulates transcription elongation (Yamaguchi et al., 2001), it is possible that this protein affects the rate of host mRNA transcription, and consequently some RNA processing events.

Recently, RNAP II was reported to interact with HDV-derived RNAs at sites located within the terminal stem-loop domains of both polarities of HDV RNA (Greco-Stewart et al., 2007; Abrahem & Pelchat, 2008; Chang et al., 2008). Mutagenesis near these tips of the rod affects both HDV accumulation in cells and RNAP II binding *in vitro* (Beard et al., 1996; Greco-Stewart et al., 2007; Abrahem & Pelchat, 2008). To obtain insights into the recognition of HDV RNA promoter by RNAP II, an RNA fragment derived from the right terminal stem-loop region of genomic HDV RNA was used. This RNA fragment includes the reported initiation site for HDAg mRNA transcription (i.e. position 1630; Gudima et al., 2000) and it has been used in several investigations as templates for *in vitro* transcription using NE (Beard et al., 1996; Abrahem & Pelchat, 2008). Inhibition of HDV transcription by an antibody raised against the C-terminal domain of RNAP II, and direct binding of the RNA polymerase II confirmed that this HDV-derived RNA acts as a promoter for RNAP II (Abrahem & Pelchat, 2008). Using RNA affinity chromatography, it was established that an active RNAP II pre-initiation complex forms on this RNA promoter, and that this complex contains the same RNAP II subunits as those found on a typical DNA promoter during promoter recognition (i.e. RNAP II, TFIIA, TFIIB, TFIID, TFIIE, TFIIF, TFIIH, and TFIIS; Abrahem & Pelchat, 2008). In addition, analogous to what is observed to occur on DNA promoters during transcription (Yudkovsky et al., 2000), it was found that a re-initiation complex (i.e. TFIIA, TFIID, and TFIIE) might remain on the RNA promoter following transcription initiation (Abrahem & Pelchat, 2008). Furthermore, the direct binding of the TATA-binding protein was demonstrated, and it was suggested that this protein might be required to nucleate the RNAP II pre-initiation complex on the RNA promoter (Abrahem & Pelchat, 2008). Finally, the tertiary structure of purified RNAP II engaged in transcription on an HDV-RNA promoter has been reported (Lehmann et al., 2007). Superposing the DNA and RNA template-product crystal structures on the RNAP II transcription active site showed that they both occupied the same site. This finding suggests that RNAP II is recognizing RNA and DNA templates in similar way.

In contrast to the genomic RNA and HDAg mRNA, the synthesis of the antigenomic species has been shown to be resistant to higher doses of α-amanitin and to take place in the nucleolus, suggesting the involvement of another yet unknown RNAP in the life cycle of HDV (Modahl et al., 2000; Macnaughton et al., 2002; Li et al., 2006). It has been hypothesized that RNAP I or an RNAP I-like polymerase might be involved in HDV replication, because *in vitro* antigenomic HDV RNA synthesis is significantly decreased upon immunodepletion of the NE with an α-SL1 antibody (Li et al., 2006), and both polarities of HDV RNA were shown to associate with RNAP I in cells replicating HDV RNA (Greco-Stewart et al., 2009). Similarly, a role for RNAP III was also suggested based on its association with the HDV RNA genome in cells replicating HDV (Greco-Stewart et al., 2009). However, whether or not these associations are relevant for HDV replication is uncertain.

4.2 Interaction of host proteins with HDAgs.

Several RNA helicases were found to interact with HDAgs, including nucleolin, nucleophosmin, DDX1 and DHX15 (Lee et al., 1998; Huang et al., 2001; Cao et al., 2009). Nucleolin is a multifunctional nuclear phosphoprotein with both DNA/RNA helicase and ATPase activities, and is involved in several processes, including synthesis and maturation of the ribosome, cell proliferation and growth, nuclear trafficking, cytokinesis, nucleogenesis, transcriptional repression, replication, signal transduction, and chromosome remodelling (Tuteja & Tuteja, 1998). The nucleolin-binding domain of HDAgs is conserved among HDV variants, and it was shown that this domain is required for nucleolar targeting and accumulation of HDV RNA. Like Nucleolin, nucleophosmin is another multifunctional nuclear phosphoprotein that has been shown to interact with both HDAg-S and HDAg-L (Huang et al., 2001). This protein is involved in cell growth and proliferation, nuclear shuttling, and ribosome biogenesis. Nucleophosmin was reported to be upregulated in cells replicating HDV and to co-localize with HDAg in the nucleolus (Okuwaki, 2008). Both DDX1 and DHX15 are ATP-dependent RNA helicases involved in cellular processes such as alteration of RNA secondary structure during translation initiation, splicing, and both ribosome and spliceosome assembly (de la Cruz et al., 1999; Wen et al., 2008). Although the function of all these RNA helicases in HDV replication is unknown, their levels correlates with the amount of HDV RNA present in cells (Huang et al., 2001; Cao et al., 2009), suggesting that they might enhance HDV replication by affecting the localization of HDV RNPs. Alternatively, they might assist to the refolding of the HDV RNA genome during viral replication (Ghisolfi et al., 1992; Tuteja & Tuteja, 1998). However, it is possible that their interaction with HDAgs might be indirect since all the interactions were also observed in the absence of HDV replication (Hiscox, 2002; Cao et al., 2009; Han et al., 2009).

HDAg-S was also found to interact with many proteins capable of associating with the Argonaute (Ago) proteins, and suspected to be involved in miRNA-mediated silencing (Haussecker et al., 2008; Cao et al., 2009). Using a combined proteomic-RNAi screen, several RNA-binding proteins (IMP2, IMP3, RALY, RBM14, ILF2, and ILF3), the polyadenylate-binding protein 4 (BABPC4), and the putative RNA helicase MOV10 were found to be required for efficient HDV replication (Haussecker et al., 2008; Cao et al., 2009). Interestingly, HDV accumulation was found to be diminished only when Ago4 expression wass prevented, but not in the absence of Ago1-3 (Haussecker et al., 2008). Although the precise function of all these proteins for HDV is unclear, it was suggested that some uncharacterized downstream effectors in the microRNA (miRNA) interference pathway might remodel HDV RNA and facilitate HDV replication/transcription (Haussecker et al., 2008). It is also possible that during HDV replication, specific miRNA pathways might be deregulated.

4.3 Interaction of host proteins with the HDV RNA genome.

An essential host protein for the progression of HDV infection is the adenosine deaminase that acts on RNA (ADAR). This enzyme is involved in site-selective RNA editing, by changing specific adenosine residues to inosine (Fig. 1; Casey et al., 1992; Casey & Gerin, 1995). The small isoform of adenosine deaminase acting on RNA (ADAR-1) performs the post-transcriptional RNA editing of the HDV antigenome leading to the production of HDAg-L (Wong & Lazinski, 2002). Specifically, during HDV replication, the UAG amber termination codon of HDAg-S is converted to UIG on the antigenomic RNA genome. When genomic RNA is generated from the modified antigenome, inosine is read as guanine

yielding a codon for tryptophan instead of a stop codon. This modification is retained in subsequent rounds of replication and results in translational readthrough which produces HDAg-L. HDAg-S was shown to inhibit this editing event (Polson et al., 1998), thus delaying HDAg-L production and regulating HDV life cycle. As stated above, HDV RNA accumulating at high levels was shown to be pathogenic to the cell (Chang et al., 2005). Thus, it is possible that during a typical HDV infection, HDV RNA-editing by ADAR-1, with the appearance of HDAg-L and the resulting down-regulation of viral RNA replication might have been selected to insure cell survival.

Recently, several approaches were used to identify additional host proteins that might be involved in HDV replication using HDV-derived RNA fragments as baits (Sikora et al., 2009). These studies led to the identification of SC35, ASF/SF2, the heterogeneous ribonucleoproteins L (hnRNP-L), the polypyrimidine tract-binding (PTB) protein-associated splicing factor (PSF), p54nrb, the glyceraldehyde 3-phosphate dehydrogenase (GAPDH), and the eukaryotic translation elongation factor 1 alpha 1 (eEF1A1). Due to their specific interactions with both polarities of HDV RNA (Sikora et al., 2009), it is possible that these RNA processing proteins could play a role in HDV RNA biology.

SC35, ASF/SF2 and hnRNP-L are abundant nuclear proteins playing important roles in pre-mRNA splicing and various RNA metabolism pathways (Hastings & Krainer, 2001). Both ASF/SF2 and hnRNP-L have also been shown to enhance cytoplasmic accumulation of an intronless mRNA (Liu & Mertz, 1995; Huang & Steitz, 2001). For example, hnRNP-L was reported to enhance cytoplasmic export of the herpes simplex virus thymidine kinase intronless mRNA by binding to the pre-mRNA processing enhancer (PPE; Liu & Mertz, 1995). Although SC35, ASF/SF2 and hnRNP-L have the ability to bind to the HDV RNA genome (Sikora et al., 2009), the functions of these proteins in the HDV life cycle is unknown. One possibility is that they might have a role in HDV RNA cellular localization, since HDV RNA is intronless. Furthermore, because hnRNP-L can also interact with HDAg-S (Cao et al., 2009), a complex of these two proteins might modulate HDV RNA shuttling in the cell. HDV RNA was shown to transiently co-localize with SC35 in nuclear speckles, and SC35 was reported to be binding HDV RNA during active transcription by RNAP II (Bichko & Taylor, 1996; Abrahem & Pelchat, 2008). It is thus possible that SC35 might have a role in HDV RNA transcription. The interaction of HDV RNA with these proteins might also give clues to HDV pathogenesis. Dysregulation of the splicing pathways have been associated with cell transformation and tumorogenesis (Castiglioni et al., 2006; Lee et al., 2006; Pospisil et al., 2006). ASF/SF2 is also involved in the maintenance of genome integrity. It was reported that stable RNA-DNA hybrids (R-loops), that form between nascent RNA transcripts and template DNA, accumulate in ASF/SF2-depleted cells (Li & Manley, 2005; Li et al., 2005). Although not tested, it is possible that under high HDV RNA accumulation, ASF/SF2 might be diverted from protecting chromosomal DNA, which in turn could lead to accumulation of R-loops, ultimately leading to genomic instability, a characteristic of almost all human cancers.

Two additional host proteins known to be involved in splicing were also found to bind HDV RNA: PSF and p54nrb (Greco-Stewart et al., 2006; Sikora et al., 2009). PSF is a multifunctional protein involved in many processes such as splicing, polyadenylation, transcriptional regulation, retention of defective RNAs, nucleic acid unwinding and annealing, nuclear shuttling, and pH homeostasis (Shav-Tal & Zipori, 2002). P54nrb is related to PSF, and both proteins share homology within their C-terminal portions (Dong et

al., 1993). PSF forms a heterotetramer with p54nrb, and together they were shown to interact with the C-terminal domain (CTD) of RNAP II during both transcription initiation and elongation (Emili et al., 2002). It is also suggested that PSF might be able to interact with RNA and the CTD of RNAP II simultaneously (Emili et al., 2002). Using co-immunoprecipitations and electrophoretic mobility shift assays of a series of HDV-derived RNAs with purified, recombinant hexahistidine-tagged PSF, it was determined that PSF binds directly to terminal stem-loop domains of both polarities of HDV RNA at locations corresponding to the regions bound by RNAP II (Greco-Stewart et al., 2006), including a section of the HDV RNA genome reported to have RNA promoter activity (Beard et al., 1996; Abrahem & Pelchat, 2008). Recent results indicate that RNAP II interaction with HDV RNA might require both the PSF-HDV RNA interaction and the RNAP II-PSF interaction (Greco-Stewart and Pelchat, unpublished data). This suggests that PSF might provide a direct physical link between HDV RNA and RNAP II to promote initial binding of RNAP II and subsequent transcription on an HDV RNA template. The interaction of PSF with HDV RNA might also provide a mechanism for HDV pathogenesis. PSF mutations have been identified in both cervical cancer and papillary renal carcinoma cell lineages, and PSF dysregulation is associated with induction of several oncogenes (Clark et al., 1997; Benn et al., 2000; Song et al., 2004; Song et al., 2005; Li et al., 2009; Wang et al., 2009). More importantly, it was shown that noncoding RNAs can bind PSF and reverse PSF-mediated repression of several proto-oncogenes, thus promoting cell proliferation and oncogenesis (Song et al., 2004; Song et al., 2005). Thus, it is possible that the interaction of PSF with HDV RNA can reverse PSF repression and promote liver tumor development.

GAPDH was found to bind to the extremities of both polarities of the HDV RNA genome (Lin et al., 2000; Sikora et al., 2009). GAPDH is an enzyme historically known to be involved in glycolysis. In addition to this metabolic role, GAPDH is a multifunctional protein involved in apoptotic cell death, DNA proofreading, nuclear fusion, telomere maintenance, nuclear translocation, cell entry into S-phase, and hyperglycemic stress (Sirover, 2005). GAPDH might also be involved in transcriptional regulation, as it associates with Schizosaccharomyces pombe RNAP II (Mitsuzawa et al., 2005), stimulates RNAP II transcription in Xenopus laevis oocyte (Morgenegg et al., 1986), and was reported to transcriptionally activate histone H2B (Zheng et al., 2003). Although the precise function of GAPDH in HDV biology is still unknown, this protein was reported to facilitate the shuttling of HDV RNA to the nucleus, and to act as a molecular chaperone enhancing *delta* ribozyme activity almost two-fold (Lin et al., 2000). Interestingly, GAPDH can also bind both the 5′-UTR (+) of the hepatitis A virus and the 3′-UTR (+/-) of the human parainfluenza virus-3 (De et al., 1996; Schultz et al., 1996). These interactions were suggested to have a role in RNA-dependent viral RNA synthesis of these two viruses. Because GAPDH plays essential roles in several cellular processes, it is possible that the high level of HDV RNA occurring during infection might affect one or more GAPDH activities and contribute to liver disease.

Recently, the eukaryotic translation elongation factor 1 alpha 1 (eEF1A1) was reported to interact with both polarities of the HDV RNA genome (Sikora et al., 2009). eEF1A1 is mostly known for its role in translation where it binds and delivers aminoacyl-tRNA to the ribosome (Brands et al., 1986). Interestingly, eEF1A1 is one of the protein repetitively reported to be involved in viral RNA synthesis. eEF1A1 associates and enhances the RNA-dependent RNA polymerase activities of poliovirus, vesicular stomatitis virus, turnip yellow mosaic virus, and West Nile virus (Joshi et al., 1986; Harris et al., 1994; Blackwell & Brinton, 1997; Das et al.,

1998). eEF1A1 has also been reported to be involved in the recruitment of HIV RNA to RNAP II using the HIV TAR element (Wu-Baer et al., 1996). More importantly, eEF1A1 was recently shown to interact with the peach latent mosaic viroid (Dube et al., 2009). Viroids are RNA pathogens very similar to HDV, because they have no replicase and have to rely heavily on their hosts. They are a small, single-stranded, circular RNA pathogens able to infect plants and do not encode any proteins (Flores et al., 2011). Although the function for eEF1A1 interaction with HDV RNA is still unknown, based on its involvement in viral RNA synthesis, it is tempting to speculate that this protein might enhance the RNAP II-mediated replication of HDV RNA. Interaction of HDV RNA with eEF1A1 might also give clues to HDV pathology. In addition to its main role in cellular translation through the binding of tRNAs (Brands et al., 1986), eEF1A1 also binds other highly-structured single-stranded RNA, such as the non-coding RNA HSR1. The eEF1A1-HSR1 complex activates the heat shock transcription factor 1 (HSF1), which binds to DNA elements and induces the expression of heat shock proteins. Although not studied, it is possible that HDV RNA might compete with HSR1 for eEF1A1 binding and block a heat shock response. In agreement with this hypothesis, hsp105, which belongs to the heat shock protein 70 family which is regulated by HSF1, was found to be downregulated in Huh7 cells expressing HDV mRNA (Mota et al., 2008).

5. Conclusion

The mechanisms by which HDV infection contributes to clinical hepatitis are poorly understood. HDV is unique among human viral pathogens in that it has a very limited coding capacity and must rely heavily on host proteins for its life cycle. Over the last few years, several host proteins have been shown to interact with either HDAgs or HDV RNA. Similar to what is observed for other RNA viruses, normal cellular components associated with RNA-processing pathways appear to be exploited by HDV. However, it is likely that several of these proteins interact indirectly with the HDV components, either through host RNA or protein interaction.

Although the normal functions of these proteins are frequently linked to viral replication and/or transcription, their precise roles in both HDV biology and HDV-mediated pathogenesis still need to be clarified. However, their interaction with the HDV RNA genome is consistent with their known biological properties. Several of these proteins are very abundant and are often referred as housekeeping proteins. Nonetheless, it is possible that the high level of HDV RNA occurring during infection could divert some of these proteins from their normal cellular functions, and produce ill effects. Further investigation on these interactions is needed in order to improve our understanding of the mechanisms of both HDV replication and pathogenesis.

6. Acknowledgment

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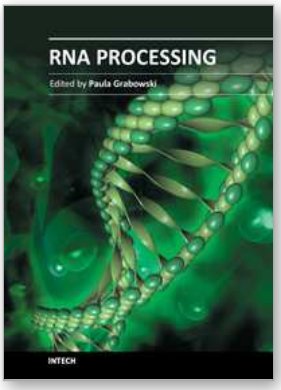

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RNA functions broadly as informational molecule, genome, enzyme and machinery for RNA processing. While these functions reflect ancient activities, they also remain vital components of contemporary biochemical pathways. In eukaryotic cells RNA processing impacts the biogenesis of RNA molecules of essentially every shape and function. The collection of articles in this volume describes the current state of understanding of the broad array of RNA processing events in animal and plant cells, key unanswered questions, and cutting edge approaches available to address these questions. Some questions discussed in this volume include, how viruses subvert the RNA processing machinery of the host cell, how the coordination of co-transcriptional RNA processing is regulated at the level of chromatin, the status of RNA processing in plant organelles, and how micro RNA machinery is biosynthesized and regulated.

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