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Review

Hepatitis E Virus Mutations: Functional and Clinical Relevance

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ABSTRACT

Hepatitis E virus (HEV) infection is a major cause of acute hepatitis and affects more than 20 million individuals, with three million symptomatic cases and 56,000 recognized HEV-related deaths worldwide. HEV is endemic in developing countries and is gaining importance in developed countries, due to increased number of autochthone cases. Although HEV replication is controlled by the host immune system, viral factors (especially specific viral genotypes and mutants) can modulate HEV replication, infection and pathogenesis. Limited knowledge exists on the contribution of HEV genome variants towards pathogenesis, susceptibility and to therapeutic response. Nonsynonymous substitutions can modulate viral proteins structurally and thus dysregulate virus-host interactions. This review aims to compile knowledge and discuss recent advances on the casual role of HEV heterogeneity and its variants on viral morphogenesis, pathogenesis, clinical outcome and antiviral resistance.

Contents

Abbreviations: HEV, hepatitis E virus; ORF, open reading frame; MeT, methyltransferase; Y, Y-domain; PCP, papain-like cysteine protease; HVR, hypervariable region; X-domain, macro-domain; Hel, RNA helicase; RdRp, RNA-dependent RNA polymerase; PPR, polyproline region; CP, capsid protein; aa, amino acid; vgRNA, viral genomic RNA; sgRNA, subgenomic RNA; CRE, *cis*-reactive element.

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1. Introduction

Hepatitis E virus (HEV) infection is being increasingly recognized in medical research as HEV infection has reached industrialized countries. Although HEV was discovered in 1983 (Balayan et al., 1983) and subsequent experimental analyses were initiated since 1990/1991 on HEV isolates (Reyes et al., 1990), there exists a considerable lack of understanding and knowledge of transmission routes, life-cycle, pathogenesis, genome variability and viral evolution.

Substantial epidemics and sporadic outbreaks of hepatitis E occur in tropical and sub-tropical countries (e.g., in India, Uganda, Sudan, and Mexico), with up to tens of thousands affected (Dalton et al., 2013; Kamar et al., 2012). Approximately two billion people (one-third of the world population) live in areas endemic for HEV and are at risk (Perez-Gracia et al., 2013). HEV infections are less frequently documented in industrialized countries, as it is believed to be associated with travel to HEV-endemic countries. However, by the end of the millennium, the numbers of autochthone cases were rising exponentially. HEV infections in Western Europe have been reported (Dalton et al., 2013; Kamar et al., 2012; Pischke et al., 2014). Reasons for discrepancies of HEV presentation between developing and developed countries are diverse. The possible likelihood refers to the route of transmission and the different distribution of HEV genotypes (Pauli et al., 2015; Sayed et al., 2015). In developing countries, HEV infection is transmitted mainly as waterborne/fecal-oral due to poor hygiene conditions, whereas in developed countries HEV is transmitted mainly foodborne due to zoonotic transmission by consumption of undercooked meat and bowels (Mansuy et al., 2016). In this regard, HEV is unique, as the only hepatitis virus with an animal reservoir.

HEV variants are viral factors that are known to be associated with transmission dynamics and pathogenicity (Kamar et al., 2012, 2014a; Lee et al., 2016; Meng, 2011). HEV mutations occur under selective pressure imposed by the host immune system and by antivirals. HEV heterogeneity shall contribute towards HEV physiology, pathogenesis and transmission patterns (Lhomme et al., 2014a). In this review, we aim to compile knowledge and discuss recent advances on the casual role of HEV heterogeneity and its variants on viral morphogenesis, pathogenesis, clinical relevance and antiviral resistance.

2. Clinical Course and Pathogenesis of HEV Infection

Although the majority of HEV infections are asymptomatic, the clinical course of symptomatic infections includes acute and chronic hepatitis E, fulminant liver failure and extrahepatic symptoms (Debing et al., 2016a; Hoan et al., 2015). Acute hepatitis E is usually defined as a self-limiting disease and lasts approximately 8 weeks and the symptoms are typically unspecific and mostly indistinguishable from other types of acute viral hepatitis (Wedemeyer et al., 2012). HEV-RNA can be detected in both serum and stool before the onset of clinical symptoms and lasts less than a month after symptom onset in serum but may persist longer in the stool (Krain et al., 2014). A severe form of acute hepatitis (fulminant hepatic failure) has been observed in patients with pre-existing liver diseases and in pregnant women (Dalton et al., 2007; Navaneethan et al., 2008). The severity of HEV infection in pregnant women may be associated with the hormonal balance and immunologic complexity during pregnancy (Bose et al., 2011; Navaneethan et al., 2008). HEV replication occurring in the human placenta may lead to poor pregnant outcomes, including HEV transmission from mother to newborn and abortion (Bose et al., 2014; Navaneethan et al., 2008).

Chronic hepatitis E is defined by the persistence of HEV-RNA and/or *anti*-HEV IgM for more than six months with elevated alanine aminotransferase (ALT) levels. Chronic HEV infection has been reported primarily in immunocompromised individuals, in organ transplant recipients, patients under chemotherapy, and HIV-infected patients (Dalton et al., 2009; Kamar et al., 2008). Chronic hepatitis E has been associated with the development of fibrosis and/or cirrhosis in patients with solid-organ-transplantation (Kamar et al., 2008). Chronic HEV infection largely depends on the host immune responses, and thus the suppressed immunity in those specific groups of patients enables the virus to persist and establish chronic infection. The impairment of HEV-specific T-cell responses is likely associated with the development of chronic hepatitis E (Suneetha et al., 2012). However, rare cases of chronic and/or persistent HEV infection have also been reported in healthy, immunocompetent individuals (Gonzalez Tallon et al., 2011).

HEV may also contribute to various extrahepatic manifestations, including pancreatitis, hematological disorders (thrombocytopenia and anemia), kidney disorders and neurological complications (Guillain-Barré syndrome and meningoencephalitis) (Singh and Gangappa, 2007; Thapa et al., 2009; Wedemeyer et al., 2012). The discovery of HEV quasispecies in serum and cerebrospinal fluid additionally suggest a possible role in neurological disorders and relate to the emergence of neurotropic HEV variants (Kamar et al., 2010). The extrahepatic manifestation mechanism can be explained by HEV replication in the extrahepatic tissues/organs and cause local tissue damage and inflammation. This is supported by recent findings, which showed HEV replication in the human placenta and neuronal-derived tissues (Bose et al., 2014; Drave et al., 2016). Other mechanisms such as cross-reactive immune responses, generation of immune complexes, and secondary infections have been proposed (Feng, 2016). However, the exact underlying mechanism of extrahepatic manifestations by HEV warrants further investigation.

3. HEV Biology and Molecular Virology

HEV is a small RNA, non-enveloped virus, 32–34 nm in diameter and belonging to the genus *Orthohepevirus* of the *Hepeviridae* family (Kamar et al., 2012). The HEV genome is a positive-sense single-stranded RNA molecule of 7.2 kb containing three open reading frames (ORF1, ORF2, and ORF3), 5′- and 3′-untranslated regions (UTRs), and a polyA-tract at the 3′-end (Kamar et al., 2012) (Fig. 1). ORF1 encodes the non-structural proteins and enzymes including methyltransferase (MeT), RNA helicase (Hel) and RNA-dependent RNA polymerase (RdRp) required for RNA replication. ORF2 expresses the capsid protein. ORF3 overlaps partially with ORF2 and encodes a multifunctional phosphoprotein that can modulate cellular signaling and is related to particle secretion (Parvez and Al-Dosari, 2015). A novel ORF4 of 158 amino acids within ORF1 has been described recently for HEV-1. ORF4 is involved in HEV replication by interacting with multiple viral proteins (helicase, RdRp and X) and host factors such as eEF1α1 (eukaryotic elongation factor 1 isoform-1) and β-tubulin (Nair et al., 2016). However, the presence and functional role of ORF4 in other HEV genotypes need to be explored. Additionally, two *cis*-reactive elements (CRE) located at the junction (between ORF1 and ORF3) and at the 3′-end of the ORF2 and 3′-UTR are essential for HEV replication and promoter activity for the subgenomic viral RNA (Emerson et al., 2001).

Although the HEV life-cycle relates to other ssRNA viruses, it warrants further investigation (Fig. 2). HEV attaches the cells via the interaction of ORF2 with attachment receptors such as heparan sulfate proteoglycans (HSPGs) and heat shock cognate protein 70 (HSC70) and enters the cells through dynamin-2, clathrin, membrane cholesterol and actin dependent endocytosis (Holla et al., 2015; Kalia et al., 2009). After entry, the virion uncoats and releases the viral RNA into the cytoplasm. The virus utilizes the host translation machinery to translate the ORF1 polyproteins which include viral enzymes. The viral genomes are replicated by the viral RNA helicase and RdRp, the ORF2 and ORF3 proteins are also translated from the viral subgenomic RNA (Debing et al., 2016a). The replication complex of HEV is likely positioned at the ER-Golgi intermediate compartment, where the viral proteins and positive single-stranded RNA could be localized (Perttila et al., 2013; Rehman et al., 2008). The assembly of RNA and ORF2 protein forms the progeny viral particles, which are then released from the host cells

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