Virus Research 161 (2011) 59–64

Contents lists available at ScienceDirect

Virus Research

journal homepage: www.elsevier.com/locate/virusres

Review

Structure of hepatitis E viral particle

Yoshio Mori[a,b], Yoshiharu Matsuura[a,*]

[a] Department of Molecular Virology, Research Institute for Microbial Diseases, Osaka University, 3-1 Yamada-oka, Suita, Osaka 565-0871, Japan
[b] Department of Virology III, National Institute of Infectious Diseases, Tokyo, Japan

ARTICLE INFO

Article history:
Available online 1 April 2011

Keywords:
Hepatitis E virus
Capsid protein
Crystal structure
Particle assembly

ABSTRACT

Hepatitis E is acute hepatitis caused by infection of hepatitis E virus (HEV) via a fecal-to-oral or zoonotic route. HEV is a small, non-enveloped virus containing positive strand RNA as a genome. Recently, the three-dimensional structures of the HEV-like particles and spike domain protruded from the surface of the particle expressed by recombinant baculovirus or bacteria have been revealed. Based on these reports, the structural features of the HEV capsid subunit and viral particle are reviewed to give insights to the mechanisms underlying the particle assembly, antigenicity, host cell attachment and native virion packaging.

Contents

1. Introduction

Earlier studies using immuno-electron microscopy revealed that hepatitis E virus (HEV) obtained from human fecal specimens was a nonenveloped icosahedral particle with indentations on the surface (Balayan et al., 1983; Bradley et al., 1988; Sreenivasan et al., 1984). Particles purified by sucrose gradient centrifugation had a diameter of 320–340 Å (Bradley et al., 1988). Based on observation by electron microscopy, the morphology of HEV was similar to those of "small round viruses" in feces samples, such as Norwalk virus (the family *caliciviridae*) and hepatitis A virus (the family *picornaviridae*). Like other hepatitis viruses, HEV could not efficiently replicate in cell culture until recently. Therefore, almost of detailed structural analyses regarding HEV particles relied upon recombinant proteins by baculoviral or bacterial expression system.

HEV is the sole member of the genus *hepevirus* within the family *hepeviridae* (Panda et al., 2007). This virus has a single, positive-stranded RNA genome of 7.2 kb in length, which is capped with m7G and polyadenylated at the 5′- and 3′-termini, respectively (Okamoto, 2007). The genome contains three open reading frames (ORF), ORF1, ORF2 and ORF3. The viral capsid protein encoded by ORF2 works for particle assembly, binding to host cells, and eliciting of neutralizing antibodies. Expression of truncated capsid protein in insect cells by baculovirus expression system resulted in self-assembly of the capsid protein and production of two types of HEV-like particle (HEV-LP) with different diameters (Li et al., 1997, 2005, 2007; Xing et al., 2010). In this review, the small and large HEV-LPs were designated as HEV-LP/$T=1$ and HEV-LP/$T=3$, respectively, based on difference of packaging of the capsid protein

Abbreviations: HEV, hepatitis E virus; HEV-LP, HEV-like particle; HSPGs, heparan sulfate proteoglycans; NOB, neutralizing-of-binding; ORF, open reading frame.

* Corresponding author. Tel.: +81 6 6879 8340; fax: +81 6 6879 8269.
E-mail address: matsuura@biken.osaka-u.ac.jp (Y. Matsuura).

0168-1702/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.virusres.2011.03.015

Table 1
Structural properties of HEV-LPs and HEV virion.

	HEV-LP/T = 1	HEV-LP/T = 3	HEV virion
Diameter	270 Å[a]	410 Å[b]	320–340 Å[c]
Amino acid residues forming particle	ORF2 aa126–601 (as a minimum requirement)[d]	ORF2 aa112–608?[b]	ORF2 aa1–660?
Number of capsid subunit	60[a]	180[b]	180?
Triangulation number	T = 1[a]	T = 3[b]	T = 3?
RNA packaging	No[a]	Yes[b]	Yes

[a] Xing et al. (1999).
[b] Xing et al. (2010).
[c] Bradley et al. (1988).
[d] Li et al. (2005).

(Table 1 and see below). The structural analyses of HEV-LP/T = 1 preceded those of HEV/T = 3 because of simplicity of purification of the former from the cell supernatant. In the first structural study using a low-resolution (22 Å) cryoelectron microscopy, it was shown that the genotype 1 HEV-LP/T = 1 formed T = 1 icosahedral particle composed of 60 copies of the truncated capsid protein (Xing et al., 1999). HEV-LP/T = 1 appeared to be empty due to no significant density of RNA inside and exhibited 270 Å in diameter, which is less than the diameter of partially purified native virions. However, HEV-LP/T = 1 displayed similar properties to the native HEV particles in terms of antigenicity and surface substructure (Li et al., 2004; Xing et al., 1999). Thus, HEV-LP/T = 1 is thought to be a good material to approach a three-dimensional structure of the native HEV. Until now, three laboratories, including us, succeeded to resolve the crystal structures of HEV-LP/T = 1 of genotypes 1 (Xing et al., 2010), 3 (Yamashita et al., 2009) and 4 (Guu et al., 2009). Meanwhile, a cryoelectron microscope structure of HEV-LP/T = 3 has been reported very recently (Xing et al., 2010), suggesting the more plausible packaging of the HEV virion. In addition, another study using a bacteria expression system illustrated the more detailed structure of the protruding spike domain of HEV (Li et al., 2009). Here, the accumulating information from mainly these reports is reviewed to understand the structural basis regarding the particle assembly, antigenicity, host cell binding and the native virion packaging.

2. Primary structure of the HEV capsid protein

ORF2 encodes the major capsid protein composed of 660 amino acid residues (Fig. 1). Among four major mammalian HEV genotypes, genetic homology of amino acid residues of the capsid

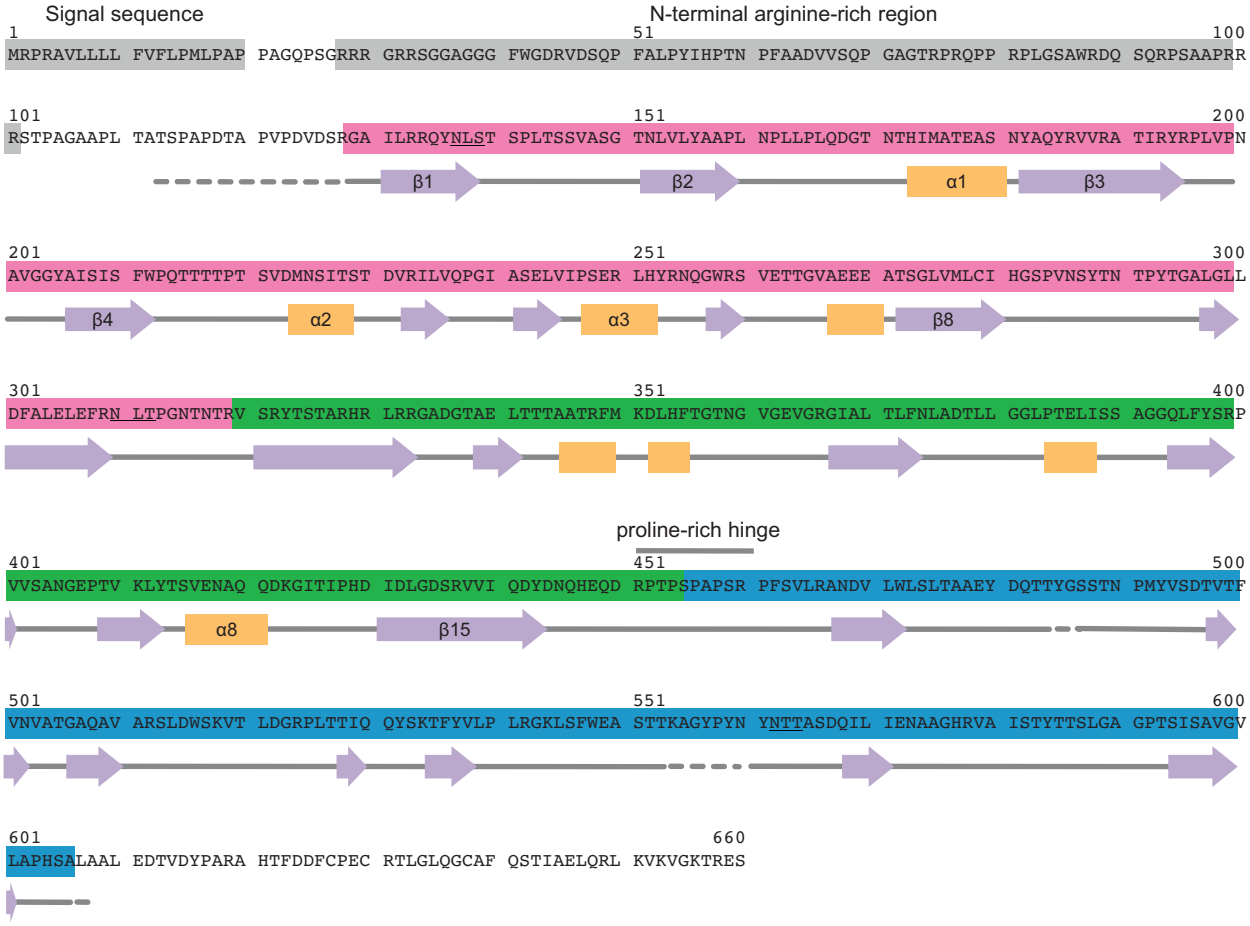

Fig. 1. Secondary structure assignment of the capsid protein of HEV-LP. It is represented based on the data from the crystal structure of HEV-LP of the genotype 3 2712 strain (PDB ID, 2ZTN). The truncated form of the amino acid residues 112–608 is used for production of HEV-LP. The S, M and P domains are shown in pink, green and blue, respectively. α-Helices, β-sheets and loops are indicated as orange rectangles, purple arrows and thick lines, respectively. Disorder regions are shown by dotted lines.