Springer

Asian Pac J Trop Med
2008;1(2):61-64

Review article

Replication of human herpes virus 1 (HHV-1) as a ubiquitous virus: A mini review

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Abstract

Human herpes viruses cause a range of human disorders including cold sores, roseola, genital warts and most importantly, tumours. These viruses cause chronic, latent and recurrent infections. Among them HHV-1, an alpha-herpesvirus could become latent after a primary infection, becoming reactivated after later provocation. Epidemically, they are found everywhere and are neurotropic. They also have a rapid and highly regulated replication cycle and usually a broad host and cell range. This article summarizes and focuses on replication strategies of the virus.

Keywords: human herpes virus 1; replication; infection

STRUCTURE AND CLASSIFICATION OF HERPESVIRUSES

The herpes viruses are a family of double-stranded DNA viruses who share basic structural features and characters of genomic organization. They are divided into subfamilies separated by sequence and biological features such as speed of replication host cell range and manner in which persistent infections may be established. Biological properties are becoming superseded by sequence analysis as a tool for classification. The current classification of the family is shown in table 1, which also lists the genome sizes of each class and generic biological properties.

Human herpes virus 1 (HSV-1 or herpes simplex virus 1) is classified in the subfamily Alphaherpesvirinae of the family Herpesviridae. The basic structure of all herpes viruses is illustrated with reference to HHV-1 in Figure 1; the HHV-1 capsid is an icosahedral shell 15 nm thick and 125 nm in diameter that 162 capsomers (12 pentons and 150 hexons) forms its structure. The capsomers lie on a T = 16 icosahedral lattice and are connected in groups of three by trivalent structures, called triplexes, that lie above the capsid level and fix the capsomers. There are a total of 320 triplexes in the capsid[1]. The capsid in HSV-1 and HSV-2 contain seven polypeptides that are called NC-1 through NC-7 and their molecular weight varies from 154,000 to 12,000 Da [154K (NC-1), 50K (NC-2), 40K (NC-3), 38K (NC-4), 33K (NC-5), 26K (NC-6), and 12K (NC-7)], and among them two polypeptides, NC-1 and NC-7, had similar peptide profiles[2]. 6 main proteins of the capsid; VP5, VP19c, VP21, VP23, VP24, VP26 are encoded by UL19, UL38, UL26, UL18, UL26.5, UL35 genes of the virus. Proteins encoded by UL4, UL11, UL13, UL21, UL25, UL36, UL37, UL46, UL49, UL56, US3, US9, US10 and US11 form the tegument layer (a shapeless layer of viral proteins, localized between the viral capsid and envelope).

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Table 1 Human herpesviridae family

Classification of Human Herpes Viruses				
Subfamily	Viruses	Synonym name	Genome (Kbp)	Biological Properties
α	Human Herpes Virus 1	Herpes simplex virus 1	152	Rapid replication, broad host cell range, Latent infection in neural tissue
	Human Herpes Virus 2	Herpes simplex virus 2	152	
	Human Herpes Virus 3	Varicell-zoster virus	125	
β	Human Herpes Virus 6A	-	159	Slower replication, restricted host cell range, Persist in lymphoid tissue
	Human Herpes Virus 6B	-	162	
	Human Herpes Virus 5	cytomegalovirus	248	
γ	Human Herpes Virus 4	Epstein-Barr virus	172	Very slow replication, host range limited to one or two cell types, Persist in lymphoid tissue
	Human Herpes Virus 8	Kaposi´s sarcoma associated herpes virus	170	

HHV-1 REPLICATION

The Herpesviridae show tight regulation of gene expression by means of transcriptional control [3]. Although recent use of genomic technology has revealed that some genes are transcribed to greater or lesser extents throughout infection, it remains generally true that transcription occurs in three waves. The infection begins by the fusion of viral envelope with the plasma membrane following attachment to the cell surface by specific interaction with one of several cellular receptors termed HVEM (herpes virus entry mediators). In the case of HHV-1, glycoproteins B (gB) and glycoproteins C (gC) are known to be involved in binding to the cell at the heparan sulfate receptors [4-6]. Another factor that is implicated in attachment is basic fibroblast growth factor receptor (FGFR) [7]. After binding to the cell, glycoprotein D (gD) plays the most important role for viral entry into the cells [8]. Penetration into the cell occurs at the plasma membrane using gD as the main fusion protein. This also requires the action of a number of other viral glycoproteins including gB, gH, gI, and gL [9]. The viral capsids and some tegument proteins enter the cell; the capsids migrate to nuclear pores along cellular microtubules. Tegument protein vhs (virion host shutoff) inhibits host cell protein synthesis by initiating degradation of cellular mRNAs in the cytoplasm [10]. α-TIF (α gene trans-inducing factor, VP16) is moved to the nucleus to stimulate the first round of virus mRNA transcription. This is termed α or immediate-early (IE) phase and genes expressed at this time comprise the major transcriptional regulatory proteins required for the transcription of the and gene classes.

The transcription of α genes is induced by α-TIF which interacts with host transcription factor, Oct-1 [11;12], but the transcription itself is performed by cellular RNA polymerase II [13]. Five α mRNAs are synthesized from 5 genes (α 4-ICP4, α 0-ICP0, α 27-ICP27/UL54, α 22-ICP22/US1, and α 47-ICP47/US12), transported into the cytoplasm and translated to make proteins [3]. The proteins are then transported into the nucleus where a new round of transcription synthesizes the β proteins. Some 31 proteins are synthesized in the β phase of protein synthesis, among them DNA polymerase (UL30), DNA binding proteins (UL42 and UL29 or ICP8), origin binding protein (OBP) (UL9), and the helicase/primase complex (UL5, 8, and 52) are necessary for viral DNA replication [12]. In the next step, a new round of transcription/translation occurs and results in synthesis of the γ proteins. In this step β proteins are necessary for transcription of late (γ) mRNAs, most of these specify structural proteins and lead to capsid formation. Three classes of herpesvirus capsids, designated A, B and C have been identified [14]. Type A capsids are empty and are

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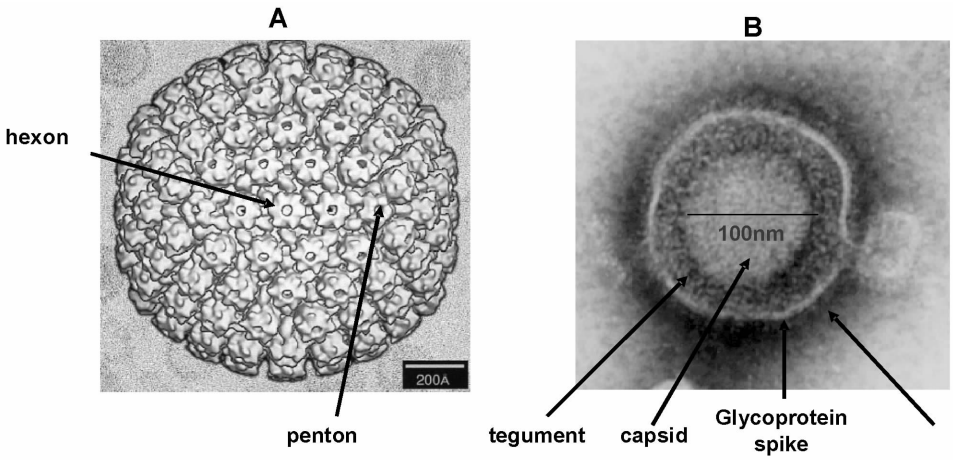

Figure 1 Human herpes virus 1 structure. Reconstructed structure (A) and electron micrograph (B) of HSV-1. The herpes virus capsid is an icosahedron of triangulation number T = 16. There are 12 pentavalent capsomers (one at each apex) and 150 hexavalent capsomers. Each capsomer has a deep central indentation. A lipid envelope derived from the host cell surrounds the nucleocapsid.

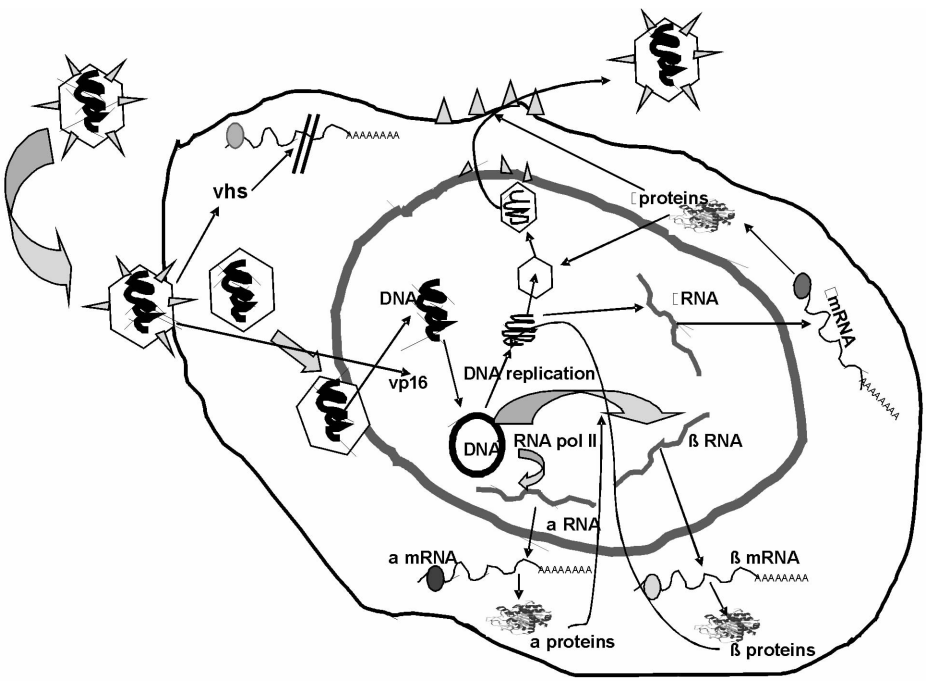

Figure 2 Schematic representation of HHV-1 replication. HHV-1 virion attaches to host cell with the envelope glycoproteins onto heparan sulphate then the viral envelope fuses to the plasma membrane. This releases both the nucleocapsid and the proteins of the tegument into the cytoplasm. Virus protein vhs (virus host shutoff) reduces translation of cellular proteins, whilst transcription activator VP16 is moved into the nucleus. The capsid travels along the cytoskeleton to a nuclear pore where the viral DNA is released, enters the nucleus and is circularized. Once in the nucleus, the viral DNA is transcribed into mRNA by cellular RNA polymerase II, a process stimulated in the first instance by VP16. Transcription follows three stages of gene activation, alpha genes (mainly activators), beta genes (mainly enzymes for nucleic acid metabolism) and gamma genes (mainly structural components required to assemble new progeny). However, some genes in each class are transcribed throughout infection. After transcription in the nucleus, all mRNA transcripts are translated into proteins in the cytoplasm, some products being imported to the nucleus. Capsid proteins assemble in the nucleus to form empty capsids. Full-length viral DNA is packaged within to form nucleocapsids. The nucleocapsids exit the cell by a process of envelopment/de-envelopment: the nucleocapsids enter the nuclear inter membrane space through the inner nuclear membrane and the primary envelope is formed. This envelope is lost when the capsid fuses with the outer nuclear membrane and enters the cytoplasm. Final envelopment is occurred in cytoplasm by budding into exocytotic vesicles. Ultimately the vesicle membrane fuses with the plasma membrane and the mature virion is released (detail of release not shown).

believed to be a dead end assembly product. Type B capsids have an electron lucent core and contain various virion scaffold proteins. These must be expelled and replaced with virus DNA forming type C capsids, which are thought to be the precursors to mature virions. At least three proteins of HHV-1 have been shown to have a role in DNA packaging inside the capsid; UL17, UL25 and UL6. Among them UL17 protein seems to play a major role [15]. After packaging of DNA, capsids are surrounded by the primary tegument protein, a nuclear phosphoprotein specified by gene UL31. This protein has an important role in the budding of the mature capsids through the inner nuclear membrane to the inter nuclear membrane space.

In the inter nuclear membrane space the UL31 and UL34 gene products (type II C-terminally anchored membrane protein) are added to the capsid, and the primary envelope is formed [16;17]. These capsids then fuse with the outer nuclear membrane losing their temporary envelope. In the cytoplasm, at least 15 tegument proteins associate with the cytoplasmic capsids (among them are α-TIF and vhs that is thought to be involved in final envelopment). Final envelopment of the tegument capsid is proposed to occur in cytoplasm by budding into exocytotic vesicles of the trans-Golgi network, which contain all the glycoproteins associated with the mature virions. Eventually the vesicle membrane fuses with the plasma membrane and leads to release of mature virions [18]. The schematic illustration of HHV-1 replication process is shown in figure 2.

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