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Recent Understanding of the Classification and Life Cycle of Herpesviruses: A Review

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Abstract

Herpes viruses are widely distributed in nature. The number of the herpes viruses that have been isolated exceeds 200. The core of a typical herpesvirus particle consists of genomic linear double stranded DNA which is wrapped in an icosahedral capsid of T=16 symmetry and has an approximate diameter of 100 to 110 nm. Herpes virus genomes vary in length from 120 to 250 kilobase pairs (kb) and encode between 70-220 open reading frames (ORFs) although the recent characterization of clinical human cytomegalovirus (HCMV) strain suggests that the viral genome has 252 ORFs that may encode potential proteins. The life cycle of herpes viruses is divided into two different stages in the host; the lytic stage and the latent stage. The first step in the typical lifecycle of the herpes viruses is the entry into the host cell. Most of the herpesviruses enter into the host cell by fusion but some also use the endocytic pathway for viral entry. The glycoproteins present in the viral envelope interact with the target molecules present on the host cell membrane and allow the viral capsid and tegument proteins to enter into the cytoplasm of the host cell. The process of HSV virion attachment on the host cell surface involves the interaction of five different glycoproteins. Transcription of herpes virus's genes occurs via a highly regulated expression cascade. The objective of this review was to describe the recent understanding of the classification and life cycle of herpesviruses.

Introduction

Herpesviruses are widely distributed in nature. A large number of animal species have been shown to be infected with at least one, and sometimes several distinct herpesviruses [1, 2]. The number of the herpesviruses that have been isolated exceeds 200 [1]. Despite this knowledge, the majority of potential animal hosts for herpesviruses have so far not been investigated [3]. Herpesviruses have co-evolved with their hosts and have changed from a common ancestor, in a manner mediating co-speciation of herpesviruses with host species, through species-specific latent infections [4, 5]. Herpesviruses have some common biological properties, including shared expression of different enzymes important for DNA/RNA metabolism (thymidine kinase), DNA synthesis (DNA helicase) and regulation of proteins (protein kinase). Herpesvirus replication and assembly occur in the nucleus. All known herpesviruses are able to establish and maintain latency in the host cell. In the infected cell, the viral genome is present in an episomal and circular form during latency, and only a few of viral genes show their expression [1]. The latent virus is able to reactivate following cellular stress and resumes viral replication and new infectious virion production. This review article is an attempt to describe the recent understanding of the classification and life cycle of herpesviruses.

Herpesvirus structure

A typical herpesvirus particle consists of a core containing genomic linear double stranded DNA which is wrapped in an icosahedral capsid of T=16 symmetry and has an approximate diameter of 100 to 110 nm (Fig. 1). The viral capsid is surrounded by a loosely organized protein structure termed the tegument. The tegument contains many viral proteins which play important roles in host cell infection initiation, expression of viral genes and help in the transport of viral proteins and regulating the packaging of viral DNA [6, 7]. An envelope derived from the patches of altered host cell membrane surrounds the tegument. The viral envelope also contains embedded virally encoded glycoproteins, which vary in number and relative amount, for example, herpes simplex virus-1 (HSV-1) encodes at least 11 glycoproteins [8]. The size of the virion increases from 120 nm to approximately 300 nm after the inclusion of the tegument and envelope [9].

Herpesvirus genome

Herpesvirus genomes vary in length from 120 to 250 kb and encode between 70-220 open reading frames (ORFs) [9, 10], although the recent characterization of clinical human cytomegalovirus (HCMV) strain suggests that the viral genome has 252 ORFs that may encode potential proteins [11]. The current estimate is that 43 ORFs are core genes and are conserved throughout the herpesvirus family. The core genes include capsid proteins, tegument proteins, and components involved in DNA replication. The remaining ORFs are unique and vary between sub-families (alpha, beta, and gamma) species and genus. In addition to protein coding regions, there are several regions within herpesvirus genomes which either do not encode for any protein or encode non-coding RNAs [12]. Furthermore, microRNAs (miRNA) have also been identified in most of the herpesviruses [13-15].

Herpesvirus genome contains internal and terminal repetitive (reiterated) sequences through extensive regions. The genome length can vary depending on the copy numbers of these repeat sequences. Herpesviruses are grouped into six categories A – F, on the basis of repeat regions on the terminus. A diagrammatic representation of the sequence arrangements of each group is shown in Fig. 2. In the viruses in group A, a large sequence is repeated on both terminals of the genome. These regions are named as a left terminal repeat (LTR) and right terminal repeat (RTR). In group B viruses (e.g., herpesvirus saimiri (HVS), the genomes possess a variable number of directly repeated sequences at either of the termini. The grouping of group C virus (e.g., Epstein-Barr virus (EBV) genomes is similar to that of group B with the exception that the direct

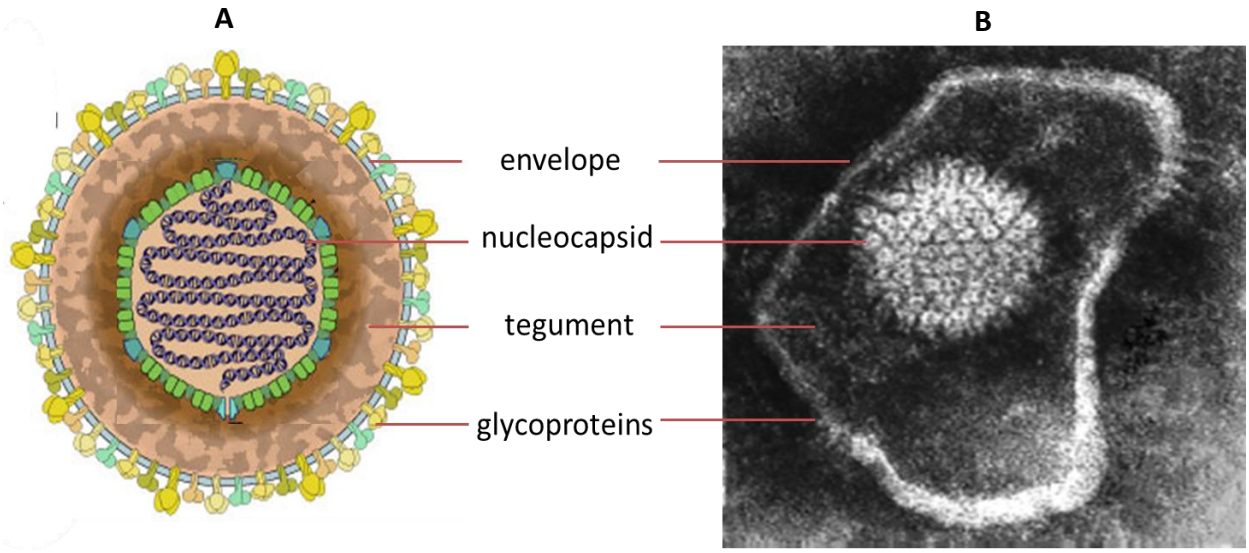

Fig. 1 A typical herpesvirus virion. (**A**) Diagrammatic representation showing the major structural components (image adapted from http://viralzone.expasy.org/all_by_species/526.html), (**B**) electron micrograph of herpes simplex virus (image adapted from http://pathmicro.med.sc.edu/mhunt/dna1.htm).

repeat sequences are fewer in number in comparison with group B. Additionally, group C unique genome sequences are further divided by other directly repeated, though unrelated, genome sequences of more than 100 bp. In the group D virus genomes (e.g., varicella-zoster virus, VZV), the unique sequences are grouped into long repeat (UL) and short repeat (US) regions. In this group, the repeat sequence present on one terminus is also present internally in an inverted orientation. The US domain is flanked by those inverted repeat sequences. The genomes of group E viruses (e.g., HSV and HCMV) are also divided into UL and US domains. However, the difference is the presence of its own inverted repeat sequence on the flanks of each domain. These sequences are called RL (long or large) and RS (short or small) repeat. Quite similar to US domains of group D viruses, in the viruses of group E, UL and US domains can invert to each other resulting in four possible isomers. The genomes of group F (e.g., tupaia herpesvirus) do not contain any repeat sequences (Fig. 2).

Herpesvirus classification

The members of *Herpesviridae* family are divided into three subfamilies: *Alphaherpesvirinae*, *Betaherpesvirinae*, and *Gammaherpesvirinae*. Herpesvirus classification is based on biological properties, DNA sequence homology, similarities in the genome sequence arrangements and similarities in the functions of important viral proteins (Fig. 3).

Alphaherpesviruses

Alphaherpesviruses have a wide host range, efficient and short reproductive cycles and establish latency in sensory neuronal cells. This subfamily is divided into four genera: *Simplexvirus*, *Varicellovirus*, *Mardivirus*, and *Iltovirus* (Table 1). HSV-1 and HSV-2 were the first discovered human herpesviruses and are the most investigated of all viruses. HSV generally causes genital or oral infections, which can result in a wide range of clinical conditions, from mild cutaneous lesions to fatal encephalitis. Primary infection of HSV is generally asymptomatic. After transmission through the epithelial mucosa of mouth or genitals, the virus establishes latent infection in the sensory ganglia which are innervating the site of infection. Reactivation of the virus may occur as a result of stress. Symptoms related to HSV reactivation (typically cold sores) include small, grouped vesicles or blisters on the epithelial surfaces which then pustulate, ulcerate and later form a crust. Vesicles are

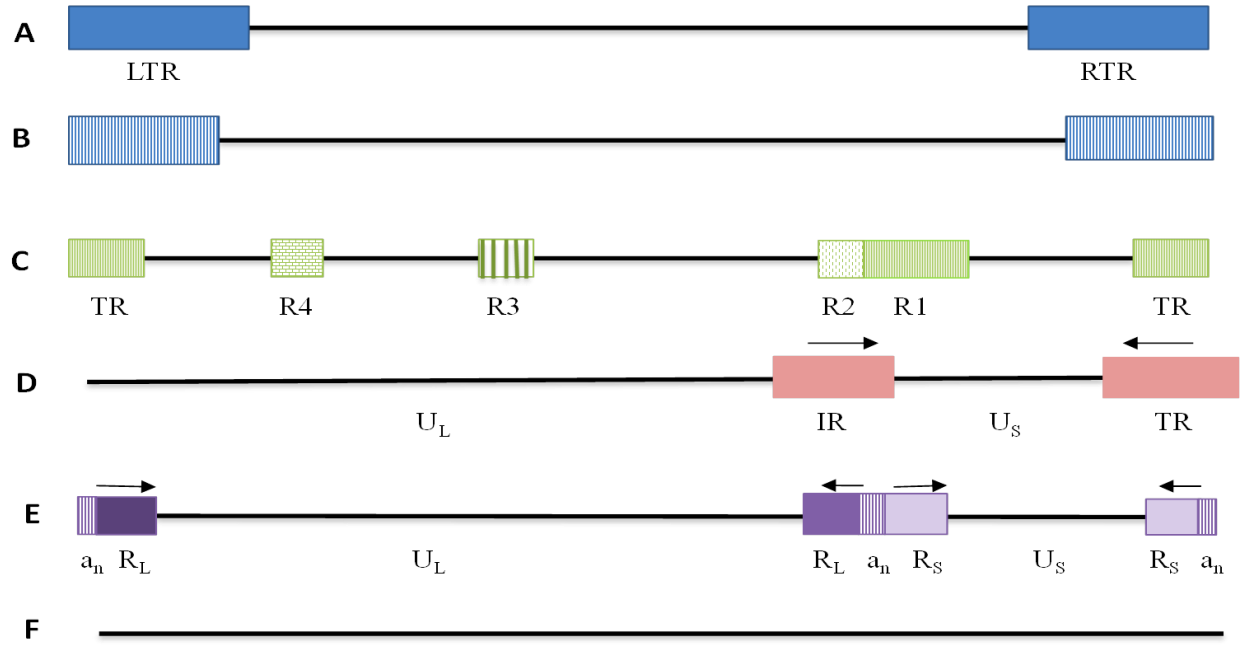

Fig. 2 Schematic diagram depicting the sequence arrangement of six classes (A-F) of viral genome of the herpesvirus family.

The genomes A, B, C, D, E, and F are exemplified by the channel catfish herpesvirus, herpesvirus siamiri, Epstein-Barr virus, varicella zoster virus, herpes simplex viruses, and tupaia herpesvirus, respectively. The relative orientations of repeat sequences are indicated with arrows. The genomes of group A viruses contain a large sequence from one terminus directly repeated at the other terminus. The genomes of group B viruses contain a variable number of directly repeated sequences at both termini. The genomes of group C viruses contain both terminal repeats and other unrelated repeat sequences that subdivide the unique sequence. The unique regions of the genomes of group D viruses are divided into two segments separated by an inverted repeat of the terminal region from the short (U_S) segment. The unique regions of the genomes of group E viruses are similarly divided with inverted repeats flanking both the long U_L and U_S regions. On one terminus there are n copies of sequence 'a' next to a larger sequence designated as 'R_L'. The other terminus has one directly repeated 'a' sequence next to a sequence designated as 'R_S'. The terminal repeat 'R_La' and 'R_Sa' sequences are inserted in an inverted orientation. Terminal reiterations in the genome of group F have not been described. The figure was adapted from Roizmann et al. [9].

filled with newly produced infectious virions. HSV-1 can also cause more severe clinical symptoms, including vision loss, serious complications of atopic eczema, neurological impairment, and death in neonates [16]. Early events in HSV-1 infection reactivate the latent human immunodeficiency virus, Epstein Barr virus, and human papillomavirus in the presence of acyclovir (ACV). The common use of nucleoside analog medications, such as ACV and pencyclovir has resulted in the emergence of drug resistant HSV-1 strains in clinical therapy [59]. Varicella Zoster virus (VZV) is another widespread, human pathogen. It is efficiently transmissible, usually during childhood, through the skin to skin contact and inhalation of infected droplets. VZV causes chickenpox (varicella) which is characterized by the appearance ofwidespread skin lesions [17-19]. VZV establishes latency in sensory ganglia and its reactivation remains limited, generally once in a lifetime, resulting in a localized vesicular rash (herpes zoster). Reactivation can be frequent in immune suppressed systems. VZV can also cause serious infections such as pneumonia, liver failure, varicella encephalitis, cerebellar ataxia and thrombocytopenia in immunosuppressed individuals [20].

Marek's disease virus (MDV) is a member of *Mardivirus* genus and is the cause of Marek's Disease (MD). In poultry, MDV initially infects B lymphocytes, although latency is established in T (CD^{4+}) lymphocytes [21]. It was reclassified as an alpha herpesvirus due to its sequence similarities and

gene organization as against its classic classification as a gammaherpesvirus [9]. It is highly contagious and has identical early stages of replication to other members of the *Alphaherpesvirinae* [22].

Betaherpesviruses

Unlike alphaherpesviruses, betaherpesviruses have a restricted host range and a long reproduction cycle. Betaherpesvirus infection slowly progresses in tissue culture and the infected cells become larger rather than lyse [9]. Latent infection is established predominantly in monocytes or macrophages. The viruses in this sub-family are subdivided into four genera (*Cytomegalovirus*, *Muromegalovirus*, *Roseolovirus*, and *Proboscivirus*) comprising 14 species (Table 1) [23, 24]. HCMV is a pathogen in immune compromised individuals. Primary infection typically starts with the replication of the virus in the mucosal epithelium as a result of direct contact with infectious secretions from an infected individual. Asymptomatic infection occurs after primary infection generally but occasionally can lead to the development of prolonged fever and mild hepatitis (similar to gammaherpesvirus EBV mononucleosis) [25]. In a natural infection, HCMV establishes latency in monocytes, macrophages, and their progenitors while reactivation may occur with the shedding of the virus from mucosal sites [26]. Severe clinical conditions of HCMV virus are usually only observed in neonates and immunosuppressed individuals. Congenital HCMV infection can result in purpura, hepatosplenomegaly, microcephaly and sensorineural hearing loss in neonates [27]. HCMV more rarely presents with multisystem manifestations, in immunocompetent individuals, with symptoms ranging from fever, rash, anemia, and thrombocytopenia to retinitis, encephalitis, pneumonitis, hepatitis and pancreatitis [28]. Organ and stem cell transplantation may involve complications, including HCMV infection leading to fatal pneumonitis [29, 30].

Gammaherpesviruses

The members of the subfamily *Gammaherpesvirinae* have a limited host range (Table 1). Gammaherpesviruses replicate in lymphocytes. Unlike alpha- and betaherpesviruses, gammaherpesviruses establish and maintain latency in either T or B cell [31]. In addition to the genes conserved between herpesviruses, each gammaherpesvirus also contains a set of unique genes which are usually present at the terminal regions of the genome and which are important for viral pathogenesis. In addition, gammaherpesviruses have more cellular homolog genes than the members of the other two sub-families. The viruses in this sub-family are subdivided into 4 genera (*Lymphocryptovirus, Rhadinovirus, Macavirus, and Percavirus)* comprising 34 species [23, 24]

EBV is the most studied virus in the genus *Lymphocryptovirus*. EBV is a strictly human pathogen and in most cases transmitted through saliva [32]. Primary infection occurs usually in infants and has an asymptomatic course. In contrast, in adolescents, it leads to infectious mononucleosis [33]. Primary infection occurs in epithelial cells of the oropharynx and after replication at the infected site, latency is established by targeting the naïve B cells in such a manner that the immune response of the host is not activated [34, 35]. EBV has also been linked to numerous lymphomas in immunodeficient individuals; Burkitt's lymphoma (BL), Hodgkin lymphoma (HD), nasopharyngeal carcinoma (NPC) and post-transplant lymphoproliferative disease (PTLD). Immunocompetent individuals may develop EBV associated cancers due to the host genetic background/ contributing environmental factors in the growth of EBV, in certain geographical locations. Kaposi's sarcoma-associated herpesvirus (KSHV) is a *Rhadinovirus* and humans are the only known hosts of the virus. There are currently three proliferative diseases associated with KSHV infection; Kaposi's sarcoma (KS), primary effusion lymphoma (PEL) and multicentric Castleman's disease (MCD). These lymphomas are most frequently identified in immunosuppressed individuals, particularly patients with AIDS [36, 37]. KSHV transmission occurs mostly through saliva. The site of KSHV lytic replication is the oro-pharynx in B cells of tonsil or

Table 1 Herpesviruses of humans and other animals.

Types of virus	Animals infected	Disease / symptoms
Alpha herpes virus		
1. Herpes simplex virus 1 (human herpesvirus 1).	Humans	Cold sores, occasional, brain infection.
2. Herpes simplex virus 2 (human herpesvirus 2).	Humans	Genital infections
3. Varicella-Zoster virus (human herpesvirus 3)	Humans	Chicken pox, Shingles
4. Gallid herpesvirus 1	Birds	Infectious laryngotracheitis
5. Marek's disease virus (Gallid herpesvirus 2)	Birds	Marek's disease
6. Cercopithecine herpesvirus-1, (monkey B virus)	Macaque monkey	Encephalomyelitis.
7. Bovine herpesvirus 1	Bovines	Infectious bovine rhinotracheitis, vaginitis, balanoposthitis
8. Bovine herpesvirus 2	Bovines	Mammillitis and pseudo-lumpy skin disease
Beta herpesviruses		
1. Human *Cytomegalovirus* HCMV (human herpesvirus 5 or HHV-5	Humans	Infectious mononucleosis-like syndrome, retinitis
2. Porcine herpesvirus 2	Porcine	Inclusion body rhinitis
Gamma herpesviruses		
1. Epstein-Barr virus (human herpesvirus 4)	Humans	Infectious mononucleosis, Burkitt's lymphoma, CNS lymphoma, post-transplant lymphoproliferative syndrome (PTLD), nasopharyngeal carcinoma
2. Kaposi's sarcoma-associated herpesvirus (Human herpesvirus 8)	Humans	Kaposi's sarcoma, Primary effusion lymphoma, Multicentric Castleman's disease
3. Murid herpesvirus 68	Mouse	Zoonotic importance
4. Ovine herpesvirus 2 (OvHV-2) and alcelaphine herpesvirus 1 (AlHV-1)	Cloven Hoofed Animals	Malignant Catarrhal Fever
5. Bovine herpesvirus 4	Bovines	Endometritis, vulvovaginitis and mastitis

other pharyngeal lymphoid issues [38]. Latency is established in B-cells and in latent infection the linear viral genome maintained as an episome autonomously in the nucleus. Viral gene expression is sharply restricted in latency and there is no cytotoxicity and no virus particles are produced [39].

Murine gammaherpesvirus 68 (MHV-68) is another member of the genus *Rhadinovirus*. MHV-68 was originally isolated from the bank vole (*Cletrinomys glariolus*) in Slovakia. HSV has been detected in the urethral swabs and first-voided urine (FVU) specimens collected from men suffering from acute urethritis without visible herpetic lesions [40]. MHV-68 appears to be widespread among rodent populations and MHV-68 infection of laboratory mice also represents a model system for understanding gammaherpesvirus pathogenesis. Oncolytic herpes simplex virus 1716 (HSV1716) can specifically inhibit pHGG and DIPG migration and invasion, highlighting a novel mechanism of action for an OV against a principal hallmark of cancer [41]. Transmission of MHV-68 occurs through the intranasal route. Lytic infection occurs in the alveolar epithelial cells in the lungs [42]. Latently infected B lymphocytes reside and maintain latency in the spleen. Initially, those cells undergo expansion which results in splenomegaly, followed by an infectious mononucleosis-like syndrome, and lymphoproliferative disease [42-44].

Herpes virus saimiri (HVS), a T lymphotropic virus is the classical prototype of the genus *Rhadinoviruses*. The natural host for HVS is squirrel monkeys (*saimiri sciureus*) and these are found to be persistently infected with this virus. Methods commonly and currently used for quantification of viruses suitable as standards in qPCR comprise quantification of Virus particles by using electron microscopy and particle counters and determination of plasmid and oligonucleotide equivalents [45]. Certain strains of HVS, e.g., C488 have the ability to transform human T-lymphocytes to continuous growth without the need of re-stimulation by an antigen or a mitogen, providing for the first time a means of human T-lymphocyte immortalization in

cell culture [46]. Ovine herpesvirus 2 (OvHV-2) and alcelaphine herpesvirus 1 (AlHV-1) are members of genus *Macavirus*. Both viruses have been shown to cause a fatal lymphoproliferative disease (malignant catarrhal fever (MCF) in cloven-hoofed animals [47, 48].

Herpesvirus life cycle

The life cycle of herpesviruses is divided into two different stages in the host; the lytic stage and the latent stage. The lytic stage involves virus replication and release of infectious virus particles from the infected cell. In the latent stage, the virus genome remains in the infected cell as an episome with very little virus gene expression and no infectious progeny is produced. The latent virus is able to reactivate following a number of stimuli including cellular stress, UV, immunosuppression or tissue damage and resumes viral replication and new infectious virion production.

Attachment and entry

Most of the herpesviruses enter into the host cell by fusion but some also use the endocytic pathway for viral entry [49, 50]. The glycoproteins present in the viral envelope interact with the target molecules present on the host cell membrane and allow the entry of viral capsid and tegument proteins into the host cell cytoplasm. The process of HSV virion attachment involves the interaction of five glycoproteins: gB, gC, gD, gH-gL heterodimer with the host cell surface [51]. Initial interactions occur between gC and gB (to a lesser extent) with the glycosaminoglycan (GAG) molecules present on the host cell membrane. This interaction brings the cellular and viral membranes into close apposition. Heparin sulphate proteoglycan is the predominant GAG molecule involved in this interaction. In the group of herpesvirus antivirals, the focus is on acyclovir, penciclovir, ganciclovir, and their respective prodrugs valacyclovir, famciclovir, and valganciclovir, respectively [52]. Though, other molecules like chondroitin sulphate can also be used in its absence. The process of penetration starts after attachment to the cell membrane, which mostly depends on the type of host cell and mode of entry [53]. In HSV, gD interacts with one of several specific cell membrane receptors: nectin-1, nectin-2 herpesvirus entry mediator (HVEM) or 3-O sulfated heparin sulphate (3-O HS) [54]. The binding of gD to its receptors causes conformational changes in gD that cause the formation of a multi-glycoprotein complex of gB, gD, gH-gL [55, 56]. Nectins and 3-O HS) have a wide tissue distribution and can mediate entry of all HSV-1 strains tested. Soluble forms of gD and its receptors can trigger fusion of HSV with the host plasma membrane which indicates that gD has a role in the attachment and fusion for entry of HSV [57]. EBV interacts with the B cells through the interaction of EBV envelope glycoprotein gp350/220 with the cellular complement receptor type 2 (CR2 or CD21) [58-60]. K8.1 of KSHV and gp [97] of MHV-68 are thought to be the homologies of gp350/220 and carry out the initial attachment of these viruses [61]. It has also been shown that a complex of three glycoproteins gp85 (homolog of gH), gp25 (homolog of gL) and gp42 are essential for virus penetration into host cells. Attachment of EBV to host cells is not sufficient to trigger fusion; instead a complex formed of gp25-gp42-gp85 (three-part complex) mediates the interaction by binding gp42 to the human leukocyte antigen class II (HLA class II) on target B cells, whereas entry into epithelial cells which lack HLA class II requires a glycoprotein complex without gp42 (two-part complex) [62]. To accommodate infection of both epithelial and B cells EBV virions carry both two and three part complexes and the ratio of the two of the virus particles also influences the cell tropism of the virus [63]. Deletion of gp42 or addition of gp42 can produce a virus that can infect only epithelial cells or only B lymphocytes respectively [62].

The HSV and EBV receptor-binding activities described above can trigger fusion but are not sufficient for the completion of this process. To initiate the core fusion machinery, a glycoprotein complex in HSV (gB and gH-gL) and EBV (gB and gp85-gp25) is required. gB is a conserved

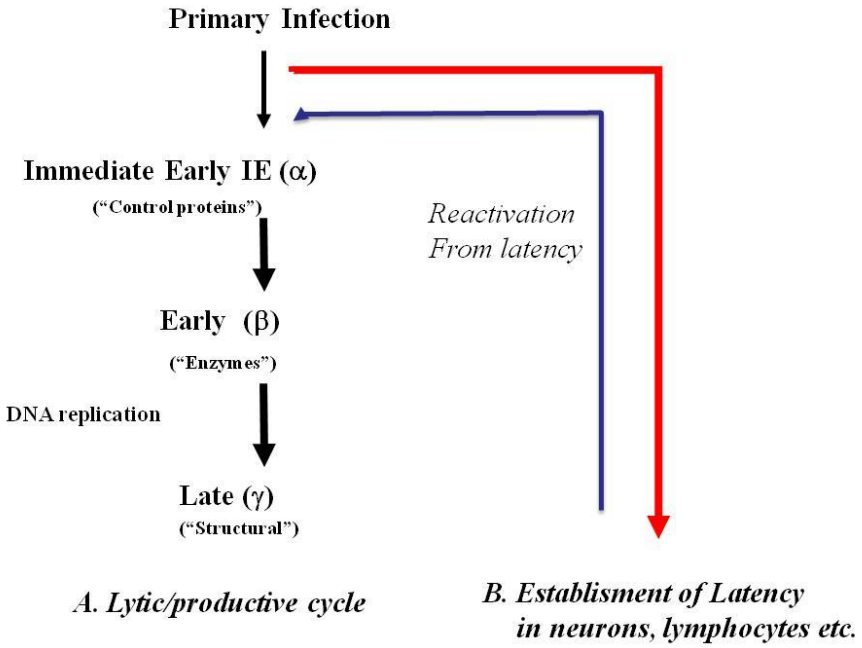

Fig. 3 Schematic diagram of the lifecycle of a typical herpesvirus.

herpesvirus fusion protein and has been shown to have a key role in virus attachment to host cells and fusion of the envelope with the host cell membrane [64]. Viral fusion proteins are inserted into the host cell membrane and undergo large conformational changes by refolding, which draw viral and host cell together [59]. As a result formation of a pore occurs which allows the mixing of cytoplasmic and viral contents. This step delivers the viral tegument and nucleocapsid into the cytoplasm [51]. At the cell membrane level, fusion occurs in a pH-independent manner [54]. EBV uses endocytosis to enter into the normal B cells. Many changes occur in the fusion proteins due to low pH and lead to the fusion of the HSV-1 envelope with the membrane of the vesicle releasing the viral contents into the host cell cytoplasm [65]. In HSV-1, outer tegument is released during entry into the cytoplasm and is due to the involvement of UL13 (viral tegument protein) through phosphorylation [66]. Inner tegument proteins; UL36 and UL37 remain associated with the capsid and are transported along with the nucleocapsid to the nucleus. UL36 assists in the transfer of the viral genome into the nucleus through the nuclear pore [70]. Upon entry into the nucleus, the genome circularizes without prior viral protein synthesis and lytic replication.

Lytic replication

Transcription of herpes virus's genes occurs via a highly regulated expression cascade. Soon after HSV infection (about 2 to 4 hours post-infection), the viral immediate early (IE) genes (also referred to as alpha or α) are expressed. The peak expression of the next set of genes; early (E) genes (also referred to as beta or β) occurs between about 4 to 8 hours post-infection. The third set of genes is late (L) genes (also referred to as gamma or γ), whose peak expression occurs between about 7-15 hours post-infection. The transcription of IE genes does not require *de novo* protein synthesis. VP16 an HSV-1 tegument protein plays a key role in promoting the expression of IE genes. VP16 is synthesized during the late phase of HSV-1 replication and is packaged into the tegument during virion assembly. During infection of the host cells, this protein is released and stimulates transcription of HSV-1 IE genes. It acts in a complex with the cellular proteins; Octamer binding protein Oct-1 (Oct-1) and host cell factor-1 (HCF-1) to

activate RNA polymerase II-dependent transcription of the viral IE genes (ICP0, ICP4, ICP22, ICP27 and ICP47) promoters through their TAATGARAT motifs [71]. The vp16-hcf-1 complex is formed in the nucleus where it binds to Oct-1 bound to IE gene promoters allowing the IE genes to transcribe and initiate the viral gene cascade.

In EBV, the proteins encoded by IE genes BZLF-1 (Zta) and BRLF-1 (replication and transcription activator (RTA) is a key element in initiating lytic gene expression. In B cells, the expression of BZLF-1 and in epithelial cells, the expression of BZLF-1 or BRLF-1 is sufficient to trigger the induction of EBV lytic infection [67]. The Rta protein is analogous to other gammaherpesvirus trans activators; ORF50 of HVS, KSHV and MHV-68 [68, 69] which are also capable of driving lytic replication in latently infected cells [70, 71]. EBV Rta, has been shown to activate its own expression, as well as the transcription of a number of viral IE genes, including other trans activators such as Zta and BMLF-1, also referred as Mta. In the gammaherpesvirus, Mta and its homologs encoded by ORF57 are capable of both post-transcriptional activation and repression of a number of viral genes and the shuttling of intron less viral mRNAs [72-74]. KSHV ORF50 and HVS ORF50a have also been shown to induce ORF57 gene expression [69, 75].

The IE genes products initiate E genes transcription. Many E genes are responsible for viral DNA replication, such as DNA polymerase (e.g., EBV BALF-5, OvHV-2 ORF9), SS-DNA binding proteins (e.g., EBV BALF-2), ribonucleotide reductase (e.g. EBV BORF-2 and BORF-1, OvHV-2 ORF60 and ORF61) and thymidine kinase (e.g., EBV, BXLF-1, OvHV-2 ORF21) [8]. The products of some of the E genes cluster at the origin of replication of the viral genome (Fig. 3). It has been proposed that herpesvirus DNA synthesis is initiated by a theta mechanism and at some point theta replication switches to the rolling circle replication, which is the predominant mode of herpesvirus DNA replication and results in the formation of long concatamers of viral genomic DNA being produced.

Newly synthesized viral DNA genomes are used as templates for L gene transcription, and the late mRNAs produce viral structural proteins necessary for the assembly of progeny virions inside the nucleus [76]. Cleavage and packaging of DNA occur in newly formed capsids. It is a tightly coupled process in which the cleavage of the genome concatamers occurs at the terminus of one unit length as they are packaged into the capsid. Before the insertion of viral DNA, a protein scaffold is formed to support the capsid. EBV BDRF1 acts as a scaffold on which other late structural capsid proteins BCLF1, BFRF3, BORF1 and BDLF1 form a spherical procapsid. BVRF2 cleaves the BDRF1 scaffolding as the newly replicated viral DNA is packed inside and form a mature icosahedral nucleocapsid [77].

The completed nucleocapsid is released from the nucleus through a two stage enveloping process. The first envelope is made through budding at the inner nuclear membrane. De-envelopment of the first envelope occurs by fusion with the outer nuclear membrane [78] and de-enveloped nucleocapsids are delivered to the cytoplasm in association with tegument proteins. The second envelope is acquired during rebudding into the trans-Golgi network. The newly formed virions are then shifted to the cell membrane and are released by exocytosis [66, 78].

In HSV-1, two of the herpesvirus conserved proteins UL31 and UL34 are involved in embedding the nucleocapsid into the inner nuclear surface. The UL13 protein affects the stability of the nuclear surface for the entrance of the nucleocapsid into the perinuclear space. In the Golgi, the proteins UL36 and UL37 have been shown to make the first layer of the tegument and proteins UL11, UL16, and UL21 make the outer tegument layer [76, 79]. In EBV, gB is present is higher level in the nuclear membrane and is thought to have a role in the initial envelopment of the nucleocapsid [66]. In addition, gB also plays a role in a nuclear release. EBV GH and gp350/220 (most abundant virus proteins) are found in the Golgi and on the cell membrane of host cells. It is thought

that during the re-envelopment process at the plasma membrane level, the virus receives an envelope rich in gp350/220. Mature progeny virions reach to the surface by vesicular movement via the Golgi apparatus and are exported into the extracellular space by exocytosis.

Herpesvirus latency

In latency, the virus enters a state where there is a limited gene expression and no replication occurs. In this stage of the herpesvirus life cycle, the nucleosomes become relatively more stable and dense [77, 80]. The expression of genes during latency varies considerably among herpesviruses. Consistent with the previous section, in this section, the strategies of HSV-1 and EBV will be discussed. The LATs are the only viral transcripts which are detected frequently in HSV-1 latency [81, 82]. The LAT gene does not form any protein and complementary to an α gene, ICP0. LAT overlaps the ICP0 transcript and it has been suggested that LAT stops expression of ICP0 gene [83-85]. Various reports have reported that LAT expression plays a role in the establishment of latency or reactivation of virus from latency [82, 86, 87]. Ahmad et al. [88] reported that a region (of nearly 2 kb) of the LAT was involved in inhibiting apoptosis. LAT stops apoptosis and latency remained maintained, which promotes the survival of infected neurons [89], possibly by down-regulation of the transcripts of α genes involved in lytic replication such as ICP0. It has also been shown that lower lytic gene expression during latency was due to HSV encoded miRNAs in latently infected cells [90-94]. LAT region encodes for more than 50% of HSV-1 miRNAs which are expressed abundantly during latency [90, 95]. In transient transfection assays, HSV-1 LAT region encoded miRNA, miR-H2, can repress expression of ICP0.

In gammaherpesviruses, homologs of EBV EBNA-1 or KSHV LANA are considered to play a key role in the maintenance of latency. During latency as many as eleven EBV genes are expressed; six EBV nuclear antigens: EBNA1, EBNA2, EBNA3A, EBNA3B, EBNA3C and EBNALP; three latent membrane proteins: LMP1, 2A and 2B; transcripts from the *Bam*HIA region (BART) of the viral genome and small, non-polyadenylated, non-coding RNAs: EBER1 and EBER2 [96]. It has been shown that there are three types of latency (I, II, III) that can occur in EBV virus on the basis of viral transcripts present [97]. Latency type I is seen in Burkitt's lymphoma and during this EBNA-1 viral transcripts, BARTs, EBER1, and EBER2 are found. Activation of a Qp promoter initiates the transcription of EBNA-1 and it is the only virus protein expressed in type I latency. Latency type II can be seen in Hodgkin's lymphoma, T cell lymphomas, and nasopharyngeal carcinoma. In latency type II, LMP-1, LMP-2A and LMP-2B along with other latency I associated viral transcripts are expressed. Activation of one or more LMP promoters leads to the expression of LMPs. LMP-1 have a role in preventing apoptosis by inducing the expression of bcl-2, while LMP-2A and LMP-2B proteins inhibit the B cell activation required for lytic replication. In addition to the viral transcripts expressed in latency type II, latency type III cells express five more EBNA transcripts: EBNA2, EBNA3A, EBNA3B, EBNA3C and EBNALP. They perform various functions in both up and down regulation of viral gene expression. This state of EBV latency has been seen in cultured human EBV infected B cells and cells derived from B cell lymphomas. It has been reported that EBV encoded miRNAs played important role EBV latency [98]. B cells, which are in latency can also be stimulated occasionally and reactivate to produce new virions, which can infect new B lymphocytes and epithelial cells [99]. The precise stimuli which trigger the reactivation *in vivo* are not clearly understood. The presumption is that the reactivation occurs as a result of B cell response to foreign or unrelated infections because, in B-cell lines, B-cell receptor stimulation can trigger reactivation [99].

Conclusions

Herpesvirus infections of humans and animals are of great importance, especially because herpesviruses

have developed sophisticated strategies to persist in susceptible populations of restricted size. All herpesviruses have one property in common in their life cycle, i.e., latency which allows them to remain in their host. The mechanisms of establishment and maintenance of latency and reactivation from latency, pathogenicity and the lifecycle of herpesviruses are not yet fully elucidated. The molecular studies and new approaches are in progress to understand diseases caused by herpesvirus infections including from mild infections like cold sores to acute infections and cancer.

Conflict of interests

The authors declare that they have no competing interest.

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