REVIEW

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The Egress of Herpes Simplex Virus from the Infected Cell

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ABSTRACT

Herpes virus is amongst the most complex viruses. It is composed of more than 30 viral as well as cellular proteins. Infection of herpes virus can commonly be observed on genitals and mouth but can appear on other body parts as well. Due to its contagious nature, it can transmit from one person to another through direct contact. Its structure consists of four parts which are morphologically distinct including core, capsid for the protection of viral genome, tegument facilitating the replication of DNA, and envelope for the protection of viral genome. Mostly after the entry of herpes virus into the nucleus of a cell, virus filled up their capsid while being inside the nucleus, and then export or passes their macromolecule outside the nucleus through nuclear pores into the cell's cytoplasm. Various viral and cellular proteins are responsible for the complex process of envelopment and de-envelopment of the herpes virus inside the nucleus, and by fusion with other nuclear membranes. Many viral proteins, as well as cellular proteins, are involved in its regulation process. The current review is aimed to highlight the role of various viral and cellular proteins and their interaction in the egress of the herpes virus facilitating its transmission and thus pathogenicity.

Keywords: Egress; Herpes Simplex Virus, Tegumentation Proteins; Emerin.

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INTRODUCTION

Egress is a process of production of new viruses inside the infected cells of the host and its release from the cell resulting in its spread within the body and also its transmission to the new host (1). Herpes virus is among the common viral infections (2). If a person has ever suffered from a cold sore or fever, they have chances of acquiring infection from the Herpes virus (3). Symptoms of HSV1 include cold sore, oral herpes, and mouth herpes. Hosts of herpes virion include mollusks and humans (4). 30 diverse viral, as well as cellular proteins, constitute the Herpes virus (5). Herpes virus is composed of 4 distinct structural parts in terms of morphology including core containing the genome, capsid for the protection of genetic material, tegument for aiding in viral replication, and envelope for viral protection (6).

There are various mechanisms of viruses that facilitate their replication and transmission into new host resulting in enhanced virulence (7). Most infections spread from cell to cell, for the virus it is very important to release at that site that is close to the entry area. Every virus is unique in its perspective (8). HSV 1 is a large family of viruses that have double-stranded DNA (dsDNA) in their genome, they have enveloped viruses that infect mostly all invertebrates including mollusks (9). Approximately eight human herpes viruses are involved in causing latent infections (8) at which viruses are usually reactive causing illnesses like skin itching, inflammation of the cornea causing watery painful eyes (10). Herpes virus capsid is very large; it cannot easily quit through the nuclear pore (11). For effective quit of amorphous capsid from nucleus defined as nuclear egress. It requires an encoded nuclear egress complex (NEC) (12). Herpes simplex virus after replication assembles its capsids inside the nucleus and releases its products outside the cell via plasma membrane (13). Nuclear pores are very

small which hinders the diffusion of viruses outside the nucleus. So, the capsid escapes using a budding process through the inner nuclear membrane (14). When herpes virus infections may occur, it involves the transcription of virus (15), replication of DNA (16), capsid formations (17), and viral DNA packs inside the nucleus (6). The nuclear egress of the herpes virus is initiated from budding, through which the capsid is surrounded by a cover made up of the inner side of the nuclear membrane (18).

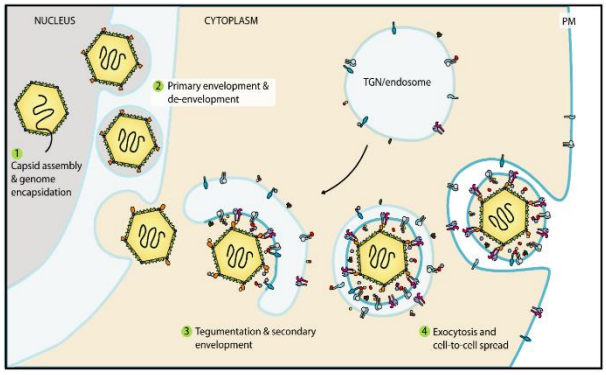

Figure 1.1 Overview of Herpesvirus Egress (19)

Herpes virus can be differentiated into 4 different structural parts (20). The viral set of DNA that is linear and double-stranded is usually surrounded by an icosahedral protein coat which contains four protein coats (21). The nuclear protein coat is inserted in a protein surrounded layer of the tegument that is enclosed by a fat envelope which is derived from the plasma membrane in the process of evolution of virion (22). This outer covering mostly contains glycosylated proteins which are usually encoded by the virus and are responsible for the host's immune response (23). The tegument is divided into two parts that are associated with protein (inner tegument) and cover the central part (outer integument)(24). Different herpes viruses may have different compositions of tegument and are composed of different viral and membrane-enclosed regions (22).

Egress from Nucleus

Budding is the early procedure in the herpesvirus nuclear egression (22). In this procedure, the capsid gains envelope is obtained from the inner part of the nuclear membrane (22).

Before primary development, nucleocapsid encounters the nuclear membrane (25). The movement of the capsid inside the nucleus depends on the actin (26). The contact between the nucleocapsid and nuclear membrane results in softening and partial dissolvement of the nuclear lamina encoded by two viral proteins (27). Two genes UL31 & UL34 genes are involved in this procedure. UL34 gene codes for a membrane protein (Type II c) pUL34 (28). UL31 gene codes for the protein pUL31(29).

In primary envelopment, the formation of the complex of these two proteins is very important. If any of these two proteins is absent the process of egression will be impaired (30). For the phosphorylation of intranuclear lamins, kinases, the cellular protein, are recruited by PUL34 and PUL31 (31). As a result of this phosphorylation, the chromatin and lamin network get dissolved, and by this capsid, it is reached to the inner nuclear membrane (32). Cellular proteins and viral proteins interact in a way that they prepare an environment for primary development (33). To obtain access to the cytoplasm for further process of maturation capsid fuses the primary envelope with nuclear membrane (34).

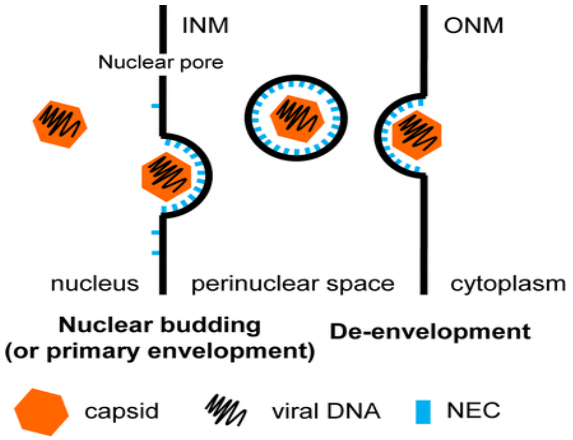

Figure 1.2 Primary Envelopment (Nuclear Budding) (22)

Egress from Perinuclear Space

For the separation of nucleus and cytoplasm, a space known as perinuclear space is located between the inner and outer layer of the nuclear envelope (35). The different steps in the evolution of the herpes virus are sometimes disputed (36). According to model 1, this is suggested for HSV-1 to demonstrate that this perinuclear virion keeps its uniqueness and then quits the cell using the secretory pathway (34). Perinuclear virion contains the complete set of tegument and envelope protein that is an attribute of extracellular virion that is mature (37). One of the other models suggested that the primary envelope intermix with the outwards side of the nucleus envelope and this primary envelope is lost because of this model most probably (38). Central integument of organism and translocation of the coated protein into the protoplasm. At last, into the cytoplasmic compartments, final segmentation and envelopment will occur (39). It has been observed that due to the assemblage of

perinuclear envelope virions mutations may occur that indicate different actions of closely related gene products (40). It was difficult to purify perinuclear virions in homogeneous form and it is not easy to complete the biochemical analysis (41).By using the technique "immunoelectron microscopy" we can distinguish between perinuclear and mature virions (42). No herpes virus is yet to be known to play a role in the intermixing of envelope of virus and cellular membrane resulting in virus egress (43). There are different ways of fusion during egress (44). Most mutations occur in Prv glycoproteins B, in the HSV-1 UL-53 gene product, and glycoprotein-K (45). Two proteins (Prv and HSV-1 US3) are found to play a critical role in the nuclear membrane targeting of UL34 proteins (46). When US3 is present, it increases the perinuclear localization of the protein UL34 (1).

Tegumentation in Cytoplasm

A viral tegument or viral matrix is a network of densely packed proteins in the space between the nucleocapsid and envelopes of herpes viruses that are typically released out into the cytoplasm soon after the infection (47). The teguments formation mostly occurs in the late phase of the infection cycle, most often after the replication of viral genes (48). The proteomics analysis of extracellular HSV-1 virions has identified about twenty-three tegumentation proteins(49), chaperones(50), several host cell enzymes (particularly members of Rab GTPase (51), and Annexin families (52) involved in exocytosis and trafficking) and structural proteins which are integrated into tegument assembly. The determination of the function of each specific protein in the tegument layer has remained difficult to determine owing to the redundancy of their interactions (19). Tegument proteins facilitate various functions in the life cycle of viruses. These include the asymmetrical wrapping of the cytoplasmic capsid to viral membranes during assembly (53), transportation of the virus capsids into the nucleus of a cell during infection which instantly modulates the host cell's environment when entering the cell. Furthermore, suppression of host mRNA transcription, immune response (cellular or extrinsic defenses) evasion by inhibition of immune signals and interferons activation (54), recruitment of host transcription/translation factors, or direct transcription or translation of viral genes (19).

Tegument Formation

Three major events occur in all herpes viruses to ensure accurate glycoprotein assimilation and proper folding of tegument proteins (19). (19)

Incorporation of major UL37 and UL36 tegument proteins

The inner part of the tegument consists of protein UL36 associated with the capsid by UL19-UL25 complex also called as C capsid specific component (CCSC) (55). This complex forms a network with triplexes only located at hexons interfaces or pentons (vertices)(56). Later tegument protein UL37 is added into the tegument layer by binding directly to UL36 (57).

Interaction of UL16 AND UL11 proteins

The Ul16 is crucial for budding, tegument assembly, and viral replication (58). It binds to capsid by recognizing UL11 by an acidic motif, found in the first half of protein (59). The Association of UL11 to the cytoplasmic membrane is helpful in the establishment of a secondary envelope through protein UL16 by bringing capsids to these membranes (34). The interaction of UL16 and UL11 occurs in different herpes viruses such as CMV, HHV-1, and varicella virus UL36 (60).

UL7 and UL51 interaction

The membrane-bounded protein UL51 is essential for recruiting UL7 to the cytoplasm of infected cells. The interaction of tegument proteins UL7 and UL51 interaction is necessary for viral cytoplasmic envelopment and is common for all herpes viruses (61).

Cellular Factors Responsible for Viral Egress

The transport of large nucleocapsids of herpes virus across the nuclear membrane seems to be a complex mechanism, and little is known about its regulation (63). From the infected cells, the egress of the herpes virus involves two different steps: 1. Nuclear budding and 2. Egress from the host cell (64). Initially, it was believed that the budding of the virus is entirely carried out by viral factors but recently it has been reported that cellular factors are also involved in this process (65).

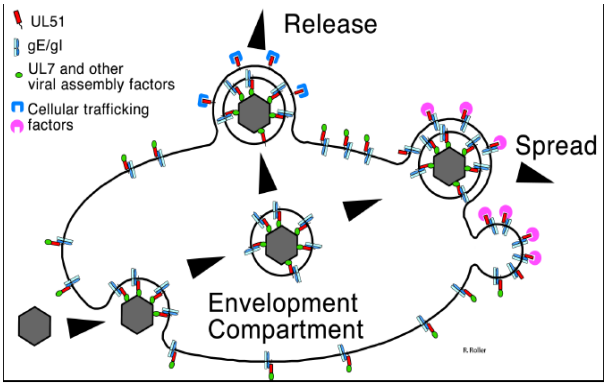

Figure 1.3 UL7 and UL51 interaction (62).

Nucleolin

The egress of HSV-1 is regulated when the viral protein interacts with each other (66). Nucleolin is a marker protein of the nucleolus and is coded by the NLC gene in humans (67). Nucleolin interacts with UL12, and is essential for egress of nucleocapsid in infected cells (63). It might be possible that nucleolin interacts with UL-12 to modulate its role in egress from the nucleus of herpes simplex virus-1 nucleocapsids into the cytoplasm (68). It is generally regarded that nucleolin has role in nuclear egress,

and UL12 may play its role as a cofactor for nucleolin whose mechanism is not yet understood (63). It is also possible that UL12 may have no role in the nuclear egress of nucleocapsids and nucleolin may function independently of UL12 (69). Nucleolin is a protein having multifunction that displays localization in the nucleoplasm, plasma membrane, nucleoli, and cytoplasm (67). It interacts with a diverse variety of viral as well as cellular proteins that affect numerous cellular functions (70). It is also possible that some cellular functions of nucleolin can be involved in the regulation of nucleocapsid egress (71). However, the mechanism of nucleolin interaction and regulation of nuclear egress is still not clear (63).

p32

A major component of HSV-1 NEC is p32, whose important components are UL31 and UL34. p32 regulates the development of HSV-1 during viral egress from the nucleus. It also efficiently disintegrates the nuclear lamina that facilitates the HSV-1 nuclear egress (73). The major viral structural protein interacts with protein p32 of the host cell. It mediates the conscription of p32 into the nuclear envelope in the infected cells (74). ICP34.5 is a viral protein that interacts with p32, a cellular factor and forms a complex (72). This complex is distributed nearly in the nuclear membrane and is linked with the budding of the virus from the nuclei. p32 interacts with ICP34.5 and acts as a mediator for nuclear egress of HSV-1 (73). p32 interacts with pathogen proteins (75). ICP34.5 interacts with p32 and is responsible for the distribution of p32 together with PKCs on the nuclear periphery and forms a complex which phosphorylates the lamina. Consequently, the nuclear lamina disassembles, and viral capsids are released (72).

Emerin and Host Cell Kinases

Protein kinases (PKCs) are known to have a critical role in viral egress (32). In HSV-1 recruitment of PKC-α and PKC-δ occurs into the nuclear membrane (76), indicating the critical role of PKC's recruitment in the egress of Herpes virus (32). Phosphorylation by kinases leads to the breakdown of nuclear lamina (77). In an uninfected cell, emerin remains bound to lamin A & C (78). It is also attached to the inner nuclear membrane by its transmembrane domain. In a cell infected by HSV-1, a complex is made by pUL31 and pUL34. At the inner membrane of the nucleus pUL34 is responsible for attaching a complex through a transmembrane domain (79). This pUL34 and pUL31 complex recruit nuclear membrane sensitive pUS3 and rottlerin (80). Then phosphorylation of lamin A, C, B, and emerin occurs. This phosphorylated emerin detaches from phosphorylated lamin A & C that will result in flexibility due to which the capsid bypasses the lamina and makes its way to the inner membrane of the nucleus. While the inner nuclear membrane is the site of viral envelopment resulting in viral egress from the nuclear membrane (32).

Prolyl Isomerase Pin1

Pin1 is a cellular isomerase that mediates the lamina disassembly by conformational changes of lamins and determines the pathway of nuclear egress (81). The site-specific phosphorylation of lamins is responsible for the disassembly of lamina through a yet unclear mechanism (82). Phosphorylation is proposed to interfere with interactions between lamins and lamin binding proteins, thus leading to lamina disassembly (Liu & Ikegami, 2020). Phosphorylation of lamin can arise by protein kinases of the host cell or herpes virus-encoded or by endogenous kinases. As a result of phosphorylation, Pin1 binds to lamins and mediates isomerization that induces conformational changes in lamins resulting in lamina disassembly. This disassembly is responsible for the process of capsid budding at the inner nuclear membrane (81).

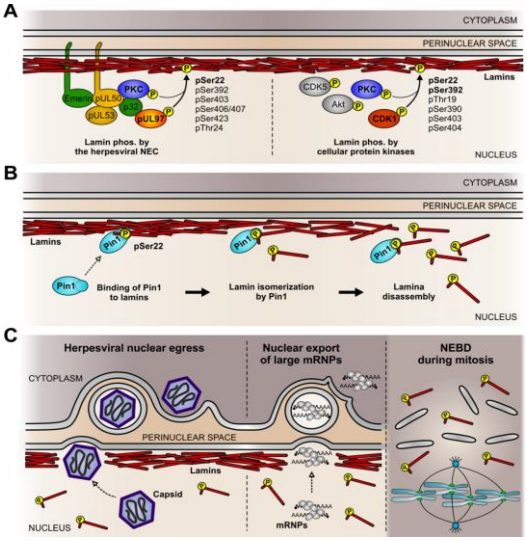

Figure 1.4 Mechanism of Pin1-Induced Nuclear Lamina Disassembly (81).

CONCLUSION

Viruses travel between compartments of the cell during their assembly. Herpes virus assembles in the nucleus and thus migrates into the cytoplasm. Before primary development nucleocapsid interacts with inner nuclear membrane and capsid gain an envelope that results in budding of capsid through INM.

The PEV (primary enveloped virion) is released and its envelope fuses with ONM leading to the release of capsid into the cytoplasm. The cytoplasm is the site for the final tegumentation of the virus. Viral egress is regulated by various cellular and viral factors and their interaction.

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