Oral Medicine/Review article

Pathogenesis and life cycle of herpes simplex virus infection—stages of primary, latency and recurrence

Sreeja P. Kumar\textsuperscript{a,}\textsuperscript{*}, Marina Lazar Chandy\textsuperscript{b}, Muhammad Shanavas\textsuperscript{b}, Saba Khan\textsuperscript{c}, K.V. Suresh\textsuperscript{d}

\textsuperscript{a} Department of Oral Medicine & Radiology, Amrita School of Dentistry, Cochin, India
\textsuperscript{b} Department of Oral Medicine & Radiology, Mehe Institute of Dental Sciences & Hospital, Puducherry, India
\textsuperscript{c} Department of Oral Medicine & Radiology, Darshan Dental College, Udaipur, India
\textsuperscript{d} Department of Oral Medicine & Radiology, Segi University, Kuala Lumpur, Malaysia

\textbf{A R T I C L E   I N F O}

Article history:
Received 24 September 2015
Received in revised form 29 November 2015
Accepted 28 January 2016
Available online 3 March 2016

Keywords:
Herpes simplex virus
Herpes labialis
Virus host shut off protein

\textbf{A B S T R A C T}

\textit{Aims and objectives:} (1) To understand the molecular level mechanism involved in immune evasion leading to primary HSV infection. (2) To explain the neuronal latency of herpes simplex virus. (3) To explain the reason for the specificity in the sites of primary and recurrent HSV lesions.

\textit{Methods:} A systematic review was done to understand the molecular level mechanism involved in primary, latency and recurrent herpes simplex infections. We prepared this article by compiling the data from various textbooks, literatures and PubMed, Embase, and EBSCOhost databases.

\textit{Results and conclusion:} Herpes simplex virus is a highly contagious human pathogen that has widespread infections in the oro-facial region which is associated with HSV-1. This single review article can provide the entire knowledge about the pathogenesis, its interesting property of latency and clinical features of HSV infection under one tree. Thus, this article enlightens the dental professionals with an adequate knowledge about the pathogenesis, clinical manifestations and specific sites of primary and recurrent lesions which will highly help them in timely diagnosis, management and also for controlling the spread of infection.

© 2016 Asian AOMS, ASOMP, JSOP, JSOMS, JSOM, and JAMI. Published by Elsevier Ltd. All rights reserved.

\textbf{Contents}

1. Introduction .......................................................................................................................... 351
2. Pathogenesis of herpes simplex virus infections ................................................................. 351
   2.1. Establishment of primary infection ............................................................................... 351
       2.1.1. Role of virion host shut off protein (vhs) ................................................................. 351
       2.1.2. Mechanism of immune evasion ............................................................................. 351
   2.2. State of latency ............................................................................................................... 351
   2.3. Reactivation of virus and recurrent lesions ................................................................. 352
   2.4. Site specificity for primary and recurrent lesions – role of keratin ............................ 352
3. Conclusion .......................................................................................................................... 352
   Competing interest .............................................................................................................. 353
   References .......................................................................................................................... 353

\textsuperscript{*} Corresponding author. Tel.: +34 9947320443; fax: +34 976 761767.
\textsuperscript{*} E-mail addresses: sreejapk@gmail.com (S.P. Kumar), marinalazarchandy@gmail.com (M.L. Chandy), dr.shanavas.kp@gmail.com (M. Shanavas), dr.sabakhan23@gmail.com (S. Khan), dr._suresh@yahoo.co.in (K.V. Suresh).

http://dx.doi.org/10.1016/j.joms.2016.01.006
2212-5558/© 2016 Asian AOMS, ASOMP, JSOP, JSOMS, JSOM, and JAMI. Published by Elsevier Ltd. All rights reserved.
2.1. Establishment of primary infection

There is a spectrum of clinical manifestations caused by HSV-1 infection which can even lead to considerable morbidity and mortality in humans [10]. Primary infection mostly occurs in children and teenagers. Oral lesions develop following a prodrome of fever, loss of appetite, malaise and myalgia. The clinical presentation of oral lesions will be in the form of clusters of vesicles and ulcers which appear on both keratinized and non-keratinized mucosa. Vesicles formed will rupture to form ulcers having a scalloped border and marked surrounding erythema. The disease is self-limiting and resolves within 10–14 days [11]. The susceptibility to clinical HSV-1 infection is modulated by polymorphism in genes encoding HLA class I with combinations of KIR and CD16A molecules. These molecules are involved in controlling the effector functions of cytotoxic T and NK lymphocytes [12]. It was observed that HLA class I B*18 allele was significantly less common among herpetic patients, whereas B35 allele provides protection against HSV-1 [13]. The severity of primary viral infection with HSV is determined mainly by the status of the host’s immune response and its interaction with the attacking viral genes [14]. Establishment of primary HSV infection is mainly initiated by the Virion host shutoff protein and by the destruction of complement proteins, natural killer cells, major histocompatibility complex class I or II molecules and antibodies of the host immune system [15]. At cellular level, herpes simplex virus 1 infection affects the metabolism of host cells by dramatically decreasing the levels of NAD [16].

2.1.1. Role of virion host shutoff protein (vhs)

Virion host shutoff (Vhs) protein is the most important primary protein that initiates an earliest attack on cellular gene expression. Vhs is a crucial factor in the pathogenesis, virulence and replication of HSV. Vhs protein is an endoribonuclease which is encoded by UL41 gene, is part of the tegument and is synthesized mainly in the immediate-early and early phases of infection [8,17,18]. Vhs protein is capable of degrading all types of RNA, but in infected cells vhs destroys only the mRNA [19,20]. The degradation of cellular mRNA will decrease the viral competition for cellular translation machinery thus easily establishing and promoting the progression of viral infection. In contrast, the viral mRNA is highly stabilized by Vhs through the stabilization of the gE/gI complex which is necessary for cell-to-cell spread [21]. Vhs reduces the synthesis of innate and adaptive immune response proteins and thereby blocks the type I interferon system, dendritic cells and reduces the production of proinflammatory cytokines and chemokines [22–24] (Fig. 2).

2.1.2. Mechanism of immune evasion

To invade the host immune system and to establish the primary infection, the herpes simplex virus must overcome all the mucosal barriers. As a part of evolution, a multitude strategies have been developed which help HSV to hide from immune evasion [25]. HSV evades the host immune response by targeting components such as complement proteins, natural killer cells, major histocompatibility complex class I or II molecules and antibodies [26]. Glycoprotein C binds with C3b and gE binds with the IgG Fc domain thus blocking complement activation and antibody-dependent cellular cytotoxicity. HSV expresses the viral gene ICP0, which produces high resistance to interferon system of the host [27].

2.2. State of latency

Latency is described as a state in viral infection which is characterized as the non-replicating, non-pathogenic, silent persistence of the virus in the body [28]. It can become active intermittently in presence of certain triggering factors. The sites of latency vary according to the types of herpes virus. Gammaherpesvirinae which includes EBV remains latent within the lymphocytes [29]. Betaherpesvirinae including the murine cytomegalovirus establishes latency in salivary gland cells and in spleen lymphocytes [30]. Alphaherpesvirinae such as HSV possess a nervous site of latency especially the trigeminal ganglion whereas other members
Recurrent HSV infection is generally not associated with systemic signs and symptoms. Recurrent/recrudescence HSV infection mostly occurs on the mucocutaneous junction of the lip in the form of cold sores which is also called as recurrent herpes labialis which affects approximately 16–38% of the population [41]. Intraoral lesions are rare in recurrent infection and if it occurs, they usually develop within keratinized mucosa of the hard palate, gingiva and dorsum of the tongue. Recrudescence lesions are associated with a prodrome of tingling, itching and burning sensation in 50% of cases. These prodromes will be followed by the development of papules, vesicles, painful ulcers, crusting and then healing of lesions [11].

Lifetime persistence of virus in the body of the host with periodic reactivation is an important characteristic feature of HSV. Viral shedding may be present even from mucosal surfaces without any visible lesions. Recurrent lesions highly differ from the primary lesions in their smaller vesicle size and by the close grouping feature, and in the usual absence of constitutional symptoms.

2.4. Site specificity for primary and recurrent lesions – role of keratin

Basically, there are two types of epithelial cells within the oral cavity-keratinized cells and non-keratinized cells. Keratinized cells can produce keratin which will then coats the cell surface. Keratinized cells are found in the mucocutaneous junction on the lip, hard palate, gingiva and dorsum of tongue [6]. Primary lesions of HSV occur mostly on non-keratinized tissues such as buccal mucosa and labial mucosa. But primary lesions can also develops on keratinized tissues like gingiva and the dorsum of tongue [42]. The involvement of both keratinized and non-keratinized tissues of oral cavity can be explained by the role of keratin coating on the cells. In case of keratinized cells, strong keratin coat over the cell surface will prevent the easy penetration of virus into the tissue surface. The common site of involvement for the primary infections is the non-keratinized tissues of the oral cavity where the virus likely enters easily from basolateral surfaces [43]. The lesions on the keratinized tissues occur only when virus enters through minute breaks in the keratin coat where the infection starts from the basal layers of the replicating epithelium.

In contrast to the primary lesions developing on both keratinized and non-keratinized coated tissues, recurrent lesions are highly restricted to the keratinized epithelial tissues [6]. This site specificity of the recurrent lesions can be interestingly explained by the pathogenesis of HSV. The reactivated virus from the dorsal root ganglion enters tissues from sensory nerves which are located within the epidermis and at the epidermal-dermal junction which will be well below the superficial keratin layer. Thus, in case of recurrent lesions the virus is already present within the ganglion and then it travels along the sensory nerves and reaches the tissues. Here the initial penetration through the cell surface is not required because the virus is already present within the nerve ganglion after the primary infection. So the recurrent HSV lesions occur mostly on the keratinized tissues especially the mucocutaneous junction of lip. Because in case of recurrent lesions of HSV, keratin has a protective role which safeguards the virus from immune responses [6].

3. Conclusion

Herpes simplex virus leads a double life: in epithelial cells HSV performs lytic replication, however in sensory neurons the virus is able to enter latency and persist indefinitely in this state. HSV latency is marked by genetic silence, yet upon receiving a stress stimulus the virus is able to reactivate and replicate to form infectious progeny. This specialized infectious cycle is the product of a complicated interaction between HSV and the neuronal system.
environment, which features several levels of regulation. HSV has evolved to exploit the specific environment of the neuron, a cell with a distinctive pool of transcription factors and availability of regulatory mechanisms, to establish a latent reservoir that ultimately fosters the spread and survival of this virus within the human population. Clinicians should have a clear picture of HSV pathogenesis, difference in clinical manifestations and specific sites of primary and recurrent lesions. This will enable them for a timely diagnosis, management of HSV infections and also helpful in controlling the spread of infection.

Competing interest
Nil.

References
[18] Kwong AD, Frenkel N. Herpes simplex virus-infected cells contain a function(s) that destabilizes both host and viral mRNAs. Proc Natl Acad Sci U S A 1987;84:1926–30.