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

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ABSTRACT

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.
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.
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.

Contents

☆ Asian AOMS: Asian Association of Oral and Maxillofacial Surgeons; ASOMP: Asian Society of Oral and Maxillofacial Pathology; JSOP: Japanese Society of Oral Pathology; JSOMS: Japanese Society of Oral and Maxillofacial Surgeons; JSOM: Japanese Society of Oral Medicine; JAMI: Japanese Academy of Maxillofacial Implants.

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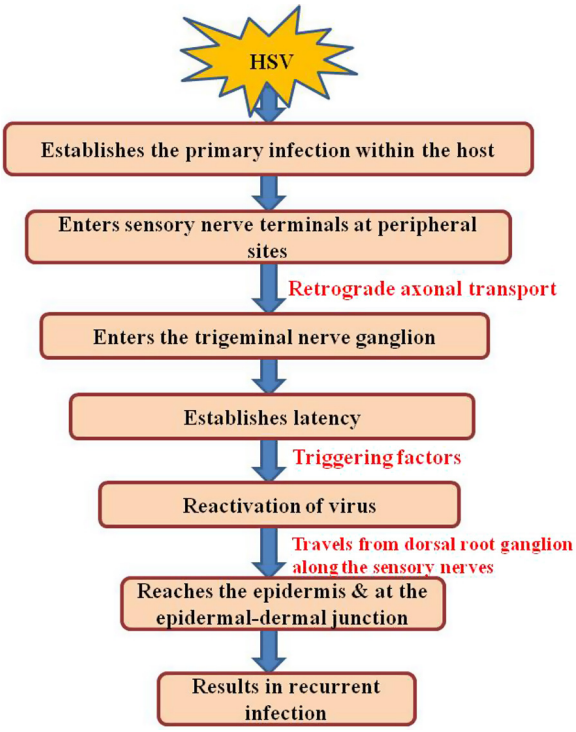

Fig. 1. Lifecycle of herpes simplex virus infection.

1. Introduction

Herpes simplex virus (HSV) is a double-stranded DNA virus which is a member of the Alphaherpesvirinae, a subfamily of the Herpesviridae family [1]. The name "herpes" is derived from a Greek word meaning "to creep". HSV has the subtypes herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) which causes lesions in the oral cavity and genitalia respectively [1]. The worldwide prevalence rate of HSV infection is estimated to be about 65–90% [2]. Herpes simplex virus type 1 is considered to be a ubiquitous and highly contagious human pathogen which has high capacity in subverting host cell functions for its own benefit [3]. Blockage of the expression of cellular proteins and efficient synthesis of viral proteins are effectively done by HSV-1 [4].

2. Pathogenesis of herpes simplex virus infections

There are widespread infections in the oro-facial region caused by the herpes simplex virus [5]. The infectious cycle of HSV-1 is highly interesting which includes a primary orolabial infection mainly occurring on non-keratinized mucosa such as the labial mucosa and buccal mucosa, less likely developing on keratinized surfaces like gingiva, hard palate, dorsum of tongue [6]. Following the primary infection, the virus ascends the sensory nerve axons and establishes chronic, latent infection in trigeminal ganglia. The dormant virus will be reactivated by various triggering factors which will then establish the recurrent lesions at the site of primary infection [7,8] (Fig. 1). HSV is more exposed to sensory neurons innervating the outer layers of skin and mucosa [9]. This is the reason why recurrent infections are exclusively seen on keratinized surfaces of skin and mucous membrane [6].

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