Herpes Simplex Type 1

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Herpes simplex type 1 (HSV-1) is a neurotropic virus that infects the peripheral and central nervous systems. Primary infection takes place in epithelial cells and the virus is transmitted to new hosts via saliva. In this stage, HSV-1 typically causes labial and oral lesions. After primary infection in epithelial cells, HSV-1 spreads retrogradely to the peripheral nervous system (PNS), where it establishes a latent infection in the trigeminal ganglia (TG). The virus can reactivate from latency, traveling anterogradely along the axon and replicating in the local surrounding tissue. Occasionally, HSV-1 may spread trans-synaptically from the TG to the brainstem, from where it may disseminate to higher areas of the central nervous system (CNS). HSV-1 can cause severe pathologies such as encephalitis or keratoconjunctivitis. Herpes simplex encephalitis (HSE) mostly affects the frontal and temporal lobes and the limbic system. It is not completely understood how HSV-1 reaches the CNS, although the most accepted idea is retrograde transport through the trigeminal or olfactory tracts. Once in the CNS, HSV-1 may induce demyelination, either as a direct trigger or as a risk factor, modulating processes such as remyelination, regulation of endogenous retroviruses, or molecular mimicry.

Keywords: HSV-1 ; Nervous system infections ; Neurotropic viruses ; Demyelination

1. Definition

Herpes simplex type 1 (HSV-1) is a neurotropic virus that infects the peripheral and central nervous systems. After primary infection in epithelial cells, HSV-1 spreads retrogradely to the peripheral nervous system (PNS), where it establishes a latent infection in the trigeminal ganglia (TG). The virus can reactivate from the latent state, traveling anterogradely along the axon and replicating in the local surrounding tissue. Occasionally, HSV-1 may spread trans-synaptically from the TG to the brainstem, from where it may disseminate to higher areas of the central nervous system (CNS). It is not completely understood how HSV-1 reaches the CNS, although the most accepted idea is retrograde transport through the trigeminal or olfactory tracts. Once in the CNS, HSV-1 may induce demyelination, either as a direct trigger or as a risk factor, modulating processes such as remyelination, regulation of endogenous retroviruses, or molecular mimicry.

2. Introduction

Several neurotropic viruses may reach and infect the central nervous system (CNS) [1][2][3][4], including herpesviruses (herpes simplex virus type 1 (HSV-1), HSV-2, human cytomegalovirus (HCMV), and varicella zoster virus (VZV)), several arboviruses (West Nile, Japanese encephalitis, and chikungunya viruses), enteroviruses, henipaviruses, Ebola virus, and rabies virus [5]. These pathogens can cause a variety of nervous system diseases, such as encephalitis, flaccid paralysis, inflammatory immune disorders, or meningitis. Regarding the aetiology of demyelinating diseases (i.e., multiple sclerosis (MS)), several infectious agents, including viruses, bacteria, and protists, have been associated [6][7][8][9], in particular many viruses from the family Herpesviridae [10][11][12][13]. Epstein–Barr virus (EBV), human herpesvirus 6 (HH6), and HSV-1 have been linked to demyelinating diseases, although their role in these pathologies, and particularly in MS, is difficult to determine given their almost ubiquitous nature [11]. HSV-1 has also been involved in neurodegenerative disorders of the CNS [14][15][16][17].

It is not fully understood how HSV-1 reaches the CNS, although the most feasible explanation is retrograde transport through the olfactory or trigeminal tracts. It is also unknown whether herpes simplex encephalitis (HSE) is caused by the reactivation of the latent virus or primary infection, as both seem to be possible. Nevertheless, the poor correlation of HSE with primary infection suggests that HSE is more likely due to viral reactivation than to primo-infections [18]. However, latent HSV-1 has been demonstrated within several structures of the CNS, and the effects of infection with this virus in oligodendrocytes (OLs), the myelin-forming cells of the CNS, has also been reported.

3. Herpes Simplex Type 1

HSV-1 is a double-stranded DNA herpesvirus belonging to the Alphaherpesvirinae subfamily [19]. It is an important neurotropic human pathogen that can infect also other species, especially non-human primates [20], as well as numerous cell types in vitro, although humans are the natural hosts [21]. HSV-1 is one of the most widely spread human viral pathogen, and around 67% of the global population have antibodies to this pathogen [22]. Primary infection takes place in epithelial cells and the virus is transmitted to new hosts via saliva. In this stage, HSV-1 typically causes labial and oral lesions, and although it may also cause genital herpes, the most common sexually transmitted type is herpes simplex virus type 2 (HSV-2) [23][24][25]. In addition, HSV-1 can cause severe pathologies such as encephalitis or keratoconjunctivitis [26]. HSE includes severe brain damage with hemorrhage, edema, and necrosis, and mostly affects the frontal and temporal lobes and the limbic system. It is generally considered that HSV-1 primary infections utilize oral routes of entry, given the common presentation of oral lesions. However, it has been argued that the acute oral lesions of human HSV-1 infections do not necessarily reflect oral host entry, and that the routes used for primary infection and reactivation are not necessarily the same [18].

After infection of epithelial cells, HSV-1 spreads to the peripheral nervous system (PNS), entering sensory neurons by fusion with the plasma membranes of their sensory terminals. Then, HSV-1 travels retrogradely to the cell body and establishes a latent infection in the trigeminal ganglia (TG) [27]. However, latent virus may also locate to CNS structures such as the olfactory bulb (OB), brainstem, or temporal cortex. During latency, the virus persists in the cell nucleus as an episome; the expression of lytic genes is repressed, and conversely the expression of latency-associated transcripts (LAT) begins. Periodically, HSV-1 may leave the latent state and reactivate, either spontaneously or in response to stimulation from immunosuppression, fever, ultraviolet light exposure, or injury to the tissues innervated by latently-infected neurons [19]. This process may lead to a recurrent lesion, but it may also proceed asymptomatically. Although reactivation is a complex process triggered by causes that are not fully understood, it has been demonstrated that the immune system plays a critical role, and in this regard host stress may lead to HSV-1 reactivation by increasing regulatory T cell (Treg) control of CD8+ T lymphocytes [28]. The roles of Tregs in the context of viral infections seem to be highly complex; Tregs may exert radically different roles depending on the infectious agent, the disease phase, or the genetic profile of the host, both suppressing antiviral immune responses and contributing to viral spread and establishment of latency, or conversely contributing to virus control [29]. Latency is also an epigenetically controlled process [19] in which changes induced by different stressors may trigger viral reactivation [30][31]. During reactivation, the virus travels anterogradely along the axon, replicating in the tissue of the dermatome innervated by the sensory neuron in which the virus established latency.

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