HERPESVIRUS REPLICATION: FROM SIMPLE TO COMPLEX

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In clinical practice, physicians of various specialties frequently encounter diseases caused by viruses of the Herpesviridae family. Currently, eight antigenic serotypes of herpesviruses are known: herpes simplex virus types 1 and 2, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, and human herpesviruses 6, 7, and 8. Herpesviruses are widely prevalent in the human population and are capable of affecting almost all organs and systems of the host organism, causing latent, acute, and chronic forms of infection. It should be noted that these viruses may play a role in the development of neoplastic processes, such as cervical cancer and prostate cancer, and in the induction of atherosclerosis, where herpes simplex virus may act in association with cytomegalovirus. They can also have adverse**,** and sometimes fatal, effects on pregnancy and childbirth, as well as neonatal pathology.

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Studies of the pathogenesis of viral infections, including herpes, have shown that the interaction between a virus and its host can vary depending on the duration of viral persistence. First, when the virus is present for a short period, the infectious process may manifest either as an acute form (with a short incubation period followed by the development of characteristic symptoms) or as an inapparent (asymptomatic) form. The second type of interaction is associated with long-term viral persistence in the host and can manifest in three main forms of infection:

1. Latent infection – asymptomatic persistence of the virus, during which the full replication cycle is interrupted, and the virus exists in host cells in the form of subviral structures. It is believed that mature viral particles may occasionally be produced and released.
2. Chronic infection – viral persistence is accompanied by clinical manifestations of the disease over a prolonged period.

3. Slow viral infection – characterized by an extended incubation period (months to years), followed by a gradually progressive course, leading to severe clinical symptoms and potentially death.

It should be noted that infections with short-term and long-term viral persistence are often closely interrelated, with one form potentially transitioning into another.

The replication of herpesviruses in susceptible cells is a complex process involving numerous virion-associated, cellular, virus-induced, and virus-modified enzymes. The main stages of herpes infection include: primary infection of the skin and mucous membranes, "colonization" and acute infection of ganglia, followed by the establishment of latency, during which only viral DNA present in neuronal nuclei indicates the presence of infection. Upon completion of the acute phase, free herpes simplex virus (HSV) is no longer detectable in the susceptible ganglion [17,18,19].

The mechanisms governing the transition from the acute phase, when the virus cannot be detected in ganglion homogenates, remain unclear. This transition occurs in parallel with the development of immune factors: the host immune response reduces viral replication in the skin, removes activating signals, and ganglion cells become non-permissive, establishing latent infection. Detection of herpesvirus in the ganglia of individuals who have previously experienced HSV infection indicates reactivation, which may occur either asymptomatically or with clinical manifestations on the skin and mucous membranes [14,15,16].

In an HSV-infected cell, the level of cAMP is markedly reduced. Disturbances in the balance between the host cell and HSV under the influence of triggering factors lead to increased viral replication, which clinically manifests as an exacerbation. Subsequently, a new equilibrium between the virus and the cell is established, and active HSV production ceases until a provoking factor disrupts this balance again [8,9,10,11,12,13].

Two alternative hypotheses have been proposed to explain the mechanisms of HSV persistence, allowing the development of recurrences based on either a static or dynamic viral state. According to the static hypothesis, HSV resides in paravertebral sensory ganglia in an integrated or free, non-productive state. Under the influence of a "triggering factor", the virus is activated and transported along the peripheral nerve axon to epithelial cells, where it replicates. This process is believed to be facilitated by cell susceptibility and weakened immunological control.

The dynamic hypothesis proposes continuous replication with the release of small amounts of virus from the ganglia. Upon reaching the skin via nerves, HSV creates microfoci of infection that are controlled by immune defense mechanisms, preventing or mitigating recurrences. The state of local immunity significantly affects recurrences, with immunosuppression facilitating viral replication in the skin [4,5,6,7].

Extensive experimental studies in animals have provided insights into various

aspects of herpes infection. Primary HSV infection induces latent infection in spinal and cerebral ganglia, with the virus reaching these sites via endoneral, perineural, intra-axonal routes, or through Schwann cells. In addition to the neurogenic route of HSV dissemination, the hematogenous route is significant due to the virus's pronounced erythrotropism, enabling infection of new cells [1,2,3].

HSV also interacts closely with leukocytes and even platelets, with observations of severe chromosomal damage and large accumulations of viral antigen in leukocytes. Establishment of latent infection is associated with structural changes in the viral genome, a principle demonstrated using restriction analysis and blot hybridization with 32P-labeled viral DNA compared to the virion DNA of reference HSV-1 strains [20].

Excretion of HSV via saliva, urine, and feces plays a crucial role in the pathogenesis of infection. The pathogenesis of cytomegalovirus infection (CMVI) is not fully elucidated. Humans are the sole source of CMV infection, which can occur at various stages of life. CMV infects cells of multiple organs and systems, persists in the body long-term, and is periodically shed into the external environment [21,22,23,24].

The development of CMVI depends on multiple factors, including the route of infection, individual (genetic) characteristics of the host, and the state of the immune system at the time of exposure.

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