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(CAPSTONE-2): A randomised, placebo-controlled, phase 3 trial. Lancet Infect Dis 20:1204, 2020. Saullo JL, Miller RA: Cytomegalovirus therapy: Role of letermovir in prophylaxis and treatment in transplant recipients. Annu Rev Med 74:89, 2023. Tang LE et al: Chronic hepatitis B infection: A review. JAMA 319:1802, 2018. Uyeki T et al: Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemopro phylaxis, and institutional outbreak management of seasonal influenza. Clin Infect Dis 68:e1, 2019. Venkatesan S et al: Neuraminidase inhibitors and hospital length of stay: A meta-analysis of individual participant data to determine treatment effectiveness among patients hospitalized with nonfatal 2009 pandemic influenza A (H1N1) virus infection. J Infect Dis 221:356, 2020. Vyas A et al: Real-world outcomes associated with letermovir use for cytomegalovirus primary prophylaxis in allogeneic hematopoietic cell transplant recipients: A systematic review and meta-analysis of observational studies. Open Forum Infect Dis 10:ofac687, 2022. Yardeni D et al: Current best practice in hepatitis B management and understanding long-term prospects for cure. Gastroenterology 164:42, 2023. Section 12 Infections Due to DNA Viruses Lawrence Corey

Herpes Simplex

Virus Infections ■ ■DEFINITION Herpes simplex viruses (HSV-1, HSV-2; Herpesvirus hominis) produce a variety of infections involving mucocutaneous surfaces, the periph eral nervous system (PNS), the central nervous system (CNS), and—on occasion—visceral organs. Prompt recognition and treatment reduce the morbidity and mortality rates associated with HSV infections. ■ ■ETIOLOGIC AGENT The genome of HSV is a 152-kb linear, double-stranded DNA molecule (molecular weight, ~100 × 106) that encodes >90 tran scription units with 84 identified proteins. The genomic structures of the two HSV subtypes are similar. The overall genomic sequence homology between HSV-1 and HSV-2 is ~50%, whereas the proteome homology is >80%. The homologous sequences are distributed over the entire genome map, and most of the polypeptides specified by one viral type are antigenically related to polypeptides of the other viral type. Many type-specific regions unique to HSV-1 and HSV-2 proteins do exist, and a number of them appear to be important in host immunity. These type-specific regions have been used to develop serologic

assays that distinguish between the two viral subtypes. The most commonly used protein is glycoprotein G (US-4), which differs markedly in size and antigenic sites between HSV-1 and HSV-2. Either restriction endo nuclease analysis or sequencing of viral DNA can be used to distinguish between the two subtypes and among strains of each subtype. Recombi nant viruses (HSV-1/HSV-2) do circulate in nature. The variability of nucleotide sequences from clinical strains of HSV-1 and HSV-2 is such that HSV isolates obtained from two individuals can be differentiated by restriction enzyme patterns or genomic sequences. Epidemiologically related sources, such as sexual partners, mother–infant pairs, or persons involved in a common-source outbreak, can be inferred from such

patterns. Deep sequencing of sequential isolates suggests that more than one variant of HSV-1 or HSV-2 can be found in a single individual and minor mutational changes do occur within anatomic sites and over time.

The viral genome is packaged in a regular icosahedral protein shell (capsid) composed of 162 capsomeres (Chap. 195). The outer covering of the virus is a lipid-containing membrane (envelope) acquired as the DNA-containing capsid buds through the inner nuclear membrane of the host cell. Between the capsid and lipid bilayer of the envelope is the tegument. Viral replication has both nuclear and cytoplasmic phases. Only four of the 12 glycosylated envelope proteins appear to be essential for cell entry: glycoprotein D (gD), gH, gL, and gB. gD binds to cellular co-receptors that belong to the heparin sulfate or tumor necrosis factor receptor family of proteins, the immunoglobulin superfamily (nectin family), triggering a conformational change that alters activation of the gH-gL heterodimer complex that then activates gB and the fusogen glycoprotein gC. The ubiquity of these receptors contributes to the wide host range of herpesviruses. HSV replication is highly regulated. After fusion and entry, the nucleocapsid enters the cytoplasm and several viral proteins are released from the virion. Some of these viral proteins shut off host protein synthesis (by increasing cellular RNA degradation), whereas others “turn on” the transcrip tion of immediate early genes of HSV replication. These immediate early gene products, designated α genes, are required for synthesis of the subsequent polypeptide group: the β polypeptides, many of which are regulatory proteins and enzymes required for DNA replication. Most current antiviral drugs interfere with β proteins, such as viral thymidine kinase (TK) and DNA polymerase. The third (γ) class of HSV genes encodes viral structural and tegument proteins and mostly requires viral DNA replication for expression. New antiviral drugs directed at viral assembly and release are under development. CHAPTER 197 After viral genome replication and structural protein synthesis, nucleocapsids are assembled in the cell’s nucleus. Specific viral pro teases clip the end of the DNA into procapsid. In the nucleus, the nucleocapsid binds through the inner nuclear membrane to genetic vessels that fuse with the outer membrane and moves the capsid into the cytoplasm. In some cells, viral replication in the nucleus forms two types of inclusion bodies: type A basophilic Feulgen-positive bodies that contain viral DNA and eosinophilic inclusion bodies that are devoid of viral nucleic acid or protein and represent a “scar” of viral infection. The cytoplasmic capsids move along microtubules to the Golgi network where a second round of envelopment occurs. The capsids acquire their lipid envelope and most of the tegument. Cellular machinery transports the infectious virus out of the cell. Herpes Simplex Virus Infections Viral genomes are maintained by some neuronal cells in a repressed state called latency. Latency, which is associated with transcription of only a limited number of virus-encoded RNAs, accounts for the pres ence of viral DNA and RNA in neural tissue at times when infectious virus cannot be isolated. Maintenance and growth of neural cells from latently infected ganglia in tissue culture result in production of infec tious virions

(explantation) and in subsequent permissive infection of susceptible cells (co-cultivation). Activation of the viral genome may then occur, resulting in reactivation—the normal pattern of regulated viral gene expression and replication and HSV release. The release of virions from the neuron follows a complex process of anterograde transport down the length of neuronal axons. In experimental animals, ultraviolet light, systemic and local immunosuppression, and trauma to the skin or ganglia are associated with reactivation. A noncoding region of the viral genome initially felt to be three noncoding regions and now felt to be a more diverse set of noncod ing RNAs and micro-RNAs (miRNAs) collectively referred to as the latency-associated transcripts (LATs) are found in the nuclei of latently infected neurons, and deletion mutants of the LAT region exhibit reduced efficiency in their later reactivation. HSV DNA copy number is highly variable between neurons, with no direct correlation between HSV DNA copy numbers and LAT positivity. About 10% of ganglionic neurons contain viral DNA and only about 1% of these neurons express LATs. Substitution of HSV-1 LATs for HSV-2 LATs induces an HSV-1 reactivation pattern, suggesting this region of the genome apparently

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Revision #1
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Updated 2026-01-06 16:33:26 UTC by Omar Ayman