and contiguous neural tissue. Virus then spreads to other mucocutaneous surfaces through centrifugal migration of infectious virions via peripheral sensory nerves. This mode of spread helps explain the large surface area involved, the high frequency of new lesions distant from the initial crop of vesicles that is characteristic in patients with primary genital or oral-labial HSV infection, and the ability to recover virus from neural tissue distant from neurons innervating the inoculation site. Contiguous spread of locally inoculated virus also may take place and allow further mucosal extension of disease. Recent studies have demonstrated HSV viremia—another mechanism for extension of infection throughout the body—in ~30–40% of persons with primary HSV-2 infection. Latent infection with both viral subtypes in both sensory and autonomic ganglia has been demonstrated. For HSV-1 infection, trigeminal ganglia are most commonly infected, although extension to the inferior and superior cervical ganglia also occurs. With genital infection, sacral nerve root ganglia (S2–S5) are most commonly affected.

After resolution of primary disease, infectious HSV can no longer be cultured from the ganglia; however, latent infection, as defined by the presence of viral DNA, persists in 2–11% of ganglionic cells in the anatomic region of the initial infection. The mechanism of reactivation from latency is unknown. Increasingly, studies indicate that host T cell responses at the ganglionic and peripheral mucosal levels influence the frequency and severity of HSV reactivation. HSV-specific T cells have been recovered from peripheral-nerve root ganglia. Many of these resident CD8+ T cells are juxtaposed with latently HSV-1-infected neurons in the trigeminal ganglia and can block reactivation with both interferon (IFN) γ release and granzyme B degradation of the immediate-early protein ICP4. In addition, there appears to be a latent viral load in the ganglia that correlates positively with the number of neurons infected and the rate of reactivation but inversely with the number of CD8+ cells present. It is not known whether reactivating stimuli transiently suppress these immune cells, independently upregulate transcription of lytic genes, or both. Moreover, host containment in the mucosa has been demonstrated. Once virus reaches the dermal-epidermal junction, there are three possible outcomes: rapid host containment of infection near the site of reactivation; spread of virus into the epidermis, with a micro-ulceration associated with low-titer subclinical shedding; and subsequent rapid (within hours) containment of virus with widespread replication and necrosis of epithelial cells and subsequent clinical recurrence (the latter defined clinically by a skin blister and ulceration). Histologically, herpetic lesions involve a thin-walled vesicle or ulceration in the basal region, multinucleated cells that may include intranuclear inclusions, necrosis, and an acute inflammatory infection. Re-epithelialization occurs once viral replication is restricted, almost always in the absence of a scar.

Analysis of the DNA from sequential isolates of HSV or from isolates from multiple infected ganglia in any one individual has revealed similar, if not identical, restriction endonuclease or DNA sequence patterns in most persons. As more sensitive genomic technologies are developed, evidence of multiple strains of the same subtype is increasingly being reported. For example, infection of individual neurons with multiple strains of drug-susceptible and drug-resistant virus in severely immunosuppressed patients indicates that ganglia can be reseeded during chronic infection. Because exposure to mucosal shedding is relatively common during a person's lifetime, current data suggest that exogenous infection with different strains of the same subtype, while possible, is uncommon.

IMMUNITY

Host responses influence the acquisition of HSV disease, the severity of infection, resistance to the development of latency, the maintenance of latency, and the frequency of recurrences. Both antibody-mediated and cell-mediated reactions are clinically important. Immunocompromised patients with defects in cell-mediated immunity experience more severe and more extensive HSV infections than those with deficits in humoral immunity, such as agammaglobulinemia. Experimental ablation of lymphocytes indicates that T cells play a major role in preventing lethal disseminated disease, although antibodies help reduce titers of virus in neural tissue. Some clinical manifestations of HSV appear to be related to the host immune response (e.g., stromal opacities associated with recurrent herpetic keratitis). The surface viral glycoproteins have been shown to be targets of antibodies that mediate neutralization and immune-mediated cytolysis (antibody-dependent cell-mediated cytotoxicity). Monoclonal antibodies specific for each of the known viral glycoproteins have, in experimental infections, conferred protection against subsequent neurologic disease or ganglionic latency. In humans, however, subunit glycoprotein vaccines have been largely ineffective in reducing acquisition of infection. Multiple cell populations, including natural killer cells, macrophages, and a variety of T lymphocytes, play a role in host defenses against HSV infections, as do lymphokines generated by T lymphocytes. In animals, passive transfer of primed lymphocytes confers protection from subsequent HSV challenge. Maximal protection usually requires the activation of multiple T cell subpopulations, including cytotoxic T cells and T cells responsible for delayed hypersensitivity. The latter may confer protection by the antigen-stimulated release of lymphokines (e.g., IFNs), which in turn have a direct antiviral effect and both activate and enhance a variety of specific and nonspecific effector cells. The HSV virion contains a variety of genes that are directed at the inhibition of host responses. These include gene no. 12 (*US-12*), which can bind to the cellular transporter-activating protein TAP-1 and reduce the ability of this protein to bind HSV peptides to human leukocyte antigen (HLA) class I, thereby reducing recognition of viral proteins by cytotoxic T cells of the host. This effect can be overcome by the addition of IFN-γ, but this reversal requires 24–48 h; thus, the virus has time to replicate and invade other host cells. Entry of infectious HSV-1 and HSV-2 inhibits several signaling pathways of both CD4+ and CD8+ T cells, leading to their functional impairment in killing and influencing the spectrum of their cytokine secretion.

Increasing evidence suggests that HSV-specific CD8+ T cell responses are critical for clearance of virus from lesions. Immunosuppressed patients with frequent and prolonged HSV lesions have fewer functional CD8+ T cells directed at HSV. HSV-specific CD8+ T cells have been shown to persist in the genital skin at the dermal–epidermal junction contiguous to neuronal endings. Even during clinical quiescence, these CD8+ T cells make both antiviral and cytotoxic proteins indicative of immune surveillance. These resident memory CD8+ T cells appear to be "first responders" capable of controlling viral reactivation at the site of viral release into the dermis. This rapid "on and off" interplay between the virus and host helps explain the variability in clinical disease severity between episodes in any single individual. Differences of 30–60 min in host responses can result in 100- to 1000-fold differences in viral levels and can determine whether an episode of disease is subclinical or clinical.

There is a strong association between the magnitude of the CD8+ T lymphocyte response and the clearance of virus from genital lesions. The location, effectiveness, and longevity of the T lymphocytes (and perhaps of other immune effector cells) may be important in the expression of disease and the likelihood of transmission over time.

EPIDEMIOLOGY

Seroepidemiologic studies have documented HSV infections worldwide. The past 15 years have shown that the prevalence of HSV-2 is even higher in the developing than in the developed world. In sub-Saharan Africa, HSV-2 seroprevalence among pregnant women may approach 60%, and annual acquisition rates among teenage girls may verge on 20%. The global incidence has been estimated at ~23.6 million infections per year. As in the developed world, the rate of HSV-2 coital acquisition as well as the serologic prevalence is higher among women than among men. Most of this HSV-2 acquisition is preceded by acquisition of HSV-1; the frequency of genital HSV-1 in the developing world is low at present.

Infection with HSV-1 is acquired more frequently and earlier than infection with HSV-2. More than 90% of adults have antibodies to HSV-1 by the fifth decade of life. In populations of low socioeconomic status, most persons acquire HSV-1 infection before the third decade of life. Antibodies to HSV-2 are not detected routinely until puberty.