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Different receptors binding to distinct interfaces on herpes simplex virus gD can trigger events leading to cell fusion and viral entry

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Abstract

One of the herpes simplex virus envelope glycoproteins, designated gD, is the principal determinant of cell recognition for viral entry. Other viral glycoproteins, gB, gH and gL, cooperate with gD to mediate the membrane fusion that is required for viral entry and cell fusion. Membrane fusion is triggered by the binding of gD to one of its receptors. These receptors belong to three different classes of cell surface molecules. This review summarizes recent findings on the structure and function of gD. The results presented indicate that gD may assume more than one conformation, one in the absence of receptor, another when gD is bound to the herpesvirus entry mediator, a member of the TNF receptor family, and a third when gD is bound to nectin-1, a cell adhesion molecule in the immunoglobulin superfamily. Finally, information and ideas are presented about a membrane-proximal region of gD that is required for membrane fusion, but not for receptor binding, and that may have a role in activating the fusogenic activity of gB, gH and gL.

Keywords: Herpes simplex virus; HSV; Entry; Cell fusion; Receptors; HVEM; Nectin-1; gD

Contents

HSV disease and gD as a determinant of cell recognition for entry

Herpes simplex viruses types 1 and 2 (serotypes HSV-1 and HSV-2) infect a majority of persons in most human populations. Symptoms of disease are not always apparent, even during primary infection. Disease symptoms can range from mucocutaneous lesions to life-threatening encephalitis or

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systemic disease involving multiple organ systems. Transmission of infection from person to person is usually by intimate contact and sharing of body fluids containing virus. This virus can initiate infection by invading epithelial cells of the oral or genital mucosa, the cornea or skin at any location, provided the cornified layer has been disrupted. HSV replicates in the epithelium, destroying the cells and causing vesicular lesions. Virus also enters the endings of neurons that enervate the region, resulting in movement of virus to neuronal cell bodies in sensory and autonomic ganglia, where latent infections are established. Latent reservoirs of viral genomes cannot be eliminated by the immune system or current antiviral therapy, guaranteeing the infected person a life-long relationship with HSV. This relationship may be uneventful or may be characterized by sporadic or periodic reactivation of virus with recurrence of mucocutaneous lesions or, rarely, by movement of virus to the central nervous system to cause encephalitis.

Cellular targets of HSV include, but are not limited to, epithelial cells of skin and mucosa, neurons and cells of the immune system. This virus is capable of infecting other differentiated cell types, however, as is evident from disseminated disease that can occur in neonates and in immunocompromised individuals. Also, although the only natural hosts for HSV are humans, a variety of laboratory animals can be infected by this virus. Moreover, cultured cells from a variety of tissues and vertebrate species are susceptible to HSV infection. Thus, the virus has a broad host range with respect to viral entry even though not all infected cells can support a productive viral replicative cycle.

The virion component that engages in specific interactions with cell surface receptors and determines whether the cell can be infected is principally the envelope glycoprotein gD. Even though many cultured cell types express one or more of the receptors that can be recognized by gD, cells in certain organized tissues may not express such receptors or the receptors may not be accessible to HSV, accounting perhaps in part for the relatively localized nature of HSV infection and spread in normal immunocompetent adults. The purpose of this review is to summarize recent progress in defining the structure of gD; multiple conformations of gD; interfaces on gD for multiple cell surface receptors, any one of which can mediate viral entry; and the effects of mutations in gD on receptor usage, viral glycoprotein-induced cell fusion and viral entry.

Overview of HSV entry

The HSV virion is composed of a DNA genome of about 150 kbp, a capsid shell with 162 capsomers, a protein layer termed the tegument on the outside of the capsid shell and an outer limiting membrane or envelope composed of viral membrane proteins and glycoproteins embedded in a lipid bilayer. The initial interaction of HSV with the cell surface is usually binding to heparan sulfate (reviewed by Shukla and Spear, 2001), at least in the case of most cell types cultured in monolayer. This binding can be mediated by envelope glycoprotein gB or gC, serves to concentrate the virus on the cell surface and significantly enhances the efficiency of viral entry. This binding, however, is a reversible step and is not strictly required for viral entry. Entry depends on the binding of gD to one of its cell surface receptors, which include HVEM (herpesvirus entry mediator), a member of the tumor necrosis factor receptor family; nectin-1 or nectin-2, cell adhesion molecules belonging to the immunoglobulin (Ig) superfamily; and specific modifications in heparan sulfate (3-*O*-S HS) catalyzed by particular isoforms of 3-*O*-sulfotransferase (reviewed by Spear et al., 2000).

A cDNA encoding another potential HSV entry receptor was identified on the basis of ability of its expressed protein to make resistant cells more susceptible to viral entry (Perez et al., 2005). The protein, designated B5, is similar to dendritic cell protein and has motifs characteristic of proteosome subunits. Tagged versions of this unusual and highly conserved protein have been detected on the cell surface, but reagents were not available to determine whether the untagged version was expressed on the cell surface. It has not yet been shown that B5 interacts directly with HSV virions or with a virion glycoprotein. Since there is no evidence that B5 interacts with gD, it will not be considered further in this review.

Entry occurs by fusion of the HSV envelope with the cell plasma membrane or membrane of an endosome and depends on the action of three other viral envelope glycoproteins, designated gB, gH and gL, in addition to gD and a gD receptor. The current thinking is that binding of gD to one of its receptors causes conformational changes in gD that permit recruitment of gB, a homotrimer, and gH–gL, a heterodimer, and activation of their membrane-fusing activity.

The actual viral fusogen has not been identified but is thought not to be gD, for several reasons. First, although gB, gH and gL are conserved among herpesviruses and thought to constitute the basic membrane-fusing machinery, members of the gD family are encoded only by one subfamily of the herpesviruses, the alphaherpesviridae. Second, most viral fusogens are not functional unless anchored in the membrane of the virion envelope or cell surface; changes in conformation that expose another hydrophobic domain, a fusion peptide, then enable its insertion into a target membrane (reviewed by Earp et al., 2004). By contrast, truncated soluble ectodomains or glycosylphosphatidylinositol-linked forms of gD can restore entry activity to gD-negative virions (Cocchi et al., 2004) or trigger cell fusion (Jones and Geraghty, 2004), respectively. Moreover, no domain resembling a fusion peptide has been identified in gD.

The findings presented here about HSV gD may apply to other members of the alphaherpesviridae, a subfamily that includes human and animal neurotropic herpesviruses. Most members of the alphaherpesviridae (a notable exception being varicella zoster virus), but not herpesviruses belonging to the beta- or gamma-subfamilies, encode a member of the gD family. Ability of alphaherpesvirus gDs to engage members of the nectin family as entry receptors appears to be characteristic of viruses from a variety of mammalian species. The broad host ranges of many alphaherpesviruses, at least for viral entry, can be attributed to the fact that they can engage heparan sulfate, a ubiquitous cell surface component, for binding to cells, and members of the nectin family for viral entry (Mettenleiter, 2000; Spear and Longnecker, 2003). The nectin family consists