



Herpesvirus fusion machinery – a new paradigm in viral entry

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The Herpesviridae family contains eight important human pathogens including herpes simplex viruses 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and Kaposi's Sarcoma virus. Herpesviruses are enveloped, and enter cells by fusing their envelope with the cell membrane. While most other enveloped viruses use one or two surface glycoproteins for entry, herpesviruses have uniquely complex cell entry machinery. They require multiple proteins: gB, the gH/gL heterodimer, and a receptor binding protein. Receptor binding triggers fusion, which is mediated by the concerted action of gB and gH/gL. gB is the conserved fusion protein, while the role of gH/gL was unknown. I determined the crystal structure of gH/gL from herpes simplex virus 2. Counter to previous predictions, gH/gL was found to have no resemblance to any viral fusion proteins. Instead, it interacts with gB and activates it for fusion. Thus, herpesviruses use gB as the fusion protein and gH/gL as a positive regulator of fusion, a unique system that sets a new paradigm in viral entry. The critical, fusion-activating gB-gH/gL interaction presents an exciting potential anti-viral target.