Gene therapy: Targeting HSV Infection to gD Receptor-negative Cells Using a Soluble Receptor

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HSV-1 initially attaches to cells through the binding of glycoproteins C and B (gC and gB) to glycosaminoglycans (GAGs) such as heparan sulphate (HS) moieties. Subsequent entry requires interaction between gD and one of the cell surface receptors, HveA or HveC. Virus-cell fusion requires the presence of gD, gB, gH/gL in the virion, but details of the process are not fully understood. A more detailed understanding of the process involved in virus-cell fusion may assist in the generation of targeted gene delivery vectors for experimental and therapeutic applications.

The overall goal of our studies is to develop methods for target cell-specific HSV infection by directing the virus to novel receptors. One lead we have followed is the use of soluble receptor molecules. We previously reported that a soluble V-domain fragment (HveC123) of the natural HSV gD receptor HveC enabled HSV-1 entry into CHO-K1 cells lacking gD receptors and that this phenomenon was dependent on virus binding to cellular glycosaminoglycans (GAGs). We have performed optimization studies and now routinely obtain 60-80% CHO cell transduction using a replication-defective virus at an MOI of 3, comparable to the entry efficiency of this virus on CHO cells bearing authentic nectin1. We have extended these studies to test additional soluble receptor constructs. We find that a gD binding-deficient mutant version of HveC123 fails to mediate virus entry while a HveB counterpart of HveC123 stimulates CHO cell infection by HSV-1 Rd1 but not wild-type virus. Curiously, soluble HveA as well as soluble nectin1 fragments consisting of the V domain along with one or both C2-like domains have thus far failed to mediate high levels of CHO cell transduction at the same MOI. This results show that Only HveC123 is not specific for soluble
receptor-mediated entry of receptor negative cells. If we continue to modify natural viral ligand gD and soluble HveC123, we could increase possibility of making better entry activity of virus by a combination of gD and HveC123 as adaptor molecules. Also, we could use the soluble receptor to facilitate entry of virus bearing novel ligands in the HS binding molecules designed to mediate indirect virus interaction with novel receptors triggering fusion of the viral envelope with cell membranes.
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