PEPTIDE INHIBITION OF CYTOMEGALOVIRUS INFECTION.

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Human cytomegalovirus (HCMV) is an opportunistic pathogen in immunocompromised individuals, including HIV-infected patients with AIDS, and solid organ and allogeneic stem cell transplantation recipients. HCMV is also the leading cause of congenital viral infection in the United States and Europe. Current treatments for HCMV diseases can fail because of the emergence of drug-resistant variants or induction of adverse effects. The aim of this study is to develop peptides targeting glycoprotein B (gB), a major glycoprotein of HCMV that is highly conserved across the Herpesviridae, that specifically inhibit the fusion of HCMV with the host cell membrane. Using the Wimley and White Interfacial Hydrophobicity Scale (WWIHS), several regions within gB were identified that display a high potential to interact with the lipid surface of cell membranes or hydrophobic surfaces within proteins. Inhibitory effects of peptides analogous to WWIHS positive sequences of HCMV gB were evaluated. Human foreskin fibroblasts (HFF) were infected with the Towne GFP strain of HCMV (0.5 MOI) preincubated with peptides at a range of concentrations (78 nm to 100 µM), and GFP positive cells were visualized 48 hours post infection by fluorescence microscopy and analyzed quantitatively by flow cytometry. Peptides that inhibited HCMV infection displayed different inhibitory concentration curves indicating that each possesses distinct biophysical properties. Peptide 174-200 showed 80% inhibition of viral infection at the concentration of 100uM, and 51% and 62% inhibition at the concentrations of 5uM and 2.5uM respectively. Peptide 233-263 displayed 97% and 92% inhibitory effect at the concentrations 100uM and 50uM respectively and 60% inhibition at the concentration of 2.5uM. While peptides 264-291 and 297-315 separately did not inhibit virus infection, working together they showed 67% inhibition of HCMV infection at the concentration of 0.125µM each. This data demonstrates that peptides that target domain II of gB that contains fusion loops inhibited HCMV infection. Furthermore, the same HCMV peptides as well as the peptide that targets a trimerization domain of gB inhibited infection of HSV-1 as demonstrated by our plaque reduction assays. The hypotheses of this study is that newly developed synthetic HCMV gB peptides target the fusogenic loops of gB and these interactions result in inhibition of virus : cell membrane fusion; and further, because of the conserved nature of gB that is being targeted by our synthetic peptides, we predict that HCMV gB peptides will be effective at inhibiting infection by other herpesviruses. Peptides designed to target potential fusogenic domains of gB provide a basis for the development of novel therapeutics that interfere with HCMV infection and potentially infection with other herpesviruses.