Virus Receptors and Entry

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Sequence requirements for membrane fusion mediated by Herpesvirus glycoproteins gD, gB, gH and gL

C. Schröter[1], S. Kargoll[1], B. G. Klupp[1], T. C. Mettenleiter[1]

[1]Friedrich-Loeffler-Institut, Institute of Molecular Biology, Greifswald- Insel Riems, Germany

Herpesviruses enter cells either by direct fusion with the plasma membrane or, after endocytic uptake, with the vesicle membrane. For fusion, four viral glycoproteins (g)D, gB and the gH/gL complex are required. gD is the receptor binding protein triggering fusion mediated by gB and gH/gL. Although gB shows signatures of class III fusion proteins, it is unable to mediate fusion in the absence of gH/gL. However, the role of gH/gL remains obscure. In porcine Pseudorabies Virus (PrV), gB and gH are also essential for direct viral cell-to-cell spread, while mutants lacking either gD or gL show some spread in tissue culture. We used this limited spread for reversion analysis. After several passages viral rescuants able to infect cells in the absence of either gD (PrV-gD$^-$Pass) or gL (PrV-DgLPass) could be isolated. Analysis of these mutants revealed mutations either in gB and gH (PrV-gD$^-$Pass) or in gD, gH and gB (PrV-DgLPass) indicating that lack of one fusion complex component can be compensated by changes in the remaining partners.
To test the influence of these mutations on fusion we established a transient transfection-fusion assay. Rabbit kidney cells were transfected with different combinations of plasmids expressing either wild-type glycoproteins or mutant forms and screened for syncytium formation. Results identified specific amino acids in gH and gB which either enhance or reduce the fusogenic potential. In combination with the recently published crystal structure for PrV gH and in comparison with structures for HSV-gB, these data shed more light on the molecular mechanism of the herpesviral fusion process.

Corresponding author:
Christina Schröter
christina.schroeter@fli.bund.de