Computational analysis of the conformational stability and receptor binding properties of glycoprotein D of herpes simplex virus-1

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In most human populations herpes simplex virus-1 (HSV-1) has a high prevalence and can cause common symptoms as oral skin lesions but also bears a certain risk of more severe systemic infections.

To infect its target cell, the virus makes use of an entry-fusion system consisting of four glycoproteins: gD, gB, gH and gL. Glycoprotein D (gD) plays a pivotal role in initiating the fusion-mechanism by binding to membrane proteins of the target cell and possibly recruiting the other three glycoproteins to the formation of a fusion complex. One of three receptors known to be recognized by gD is the herpes virus entry mediator (HVEM), which belongs to the tumor necrosis factor receptor (TNFR) family. Crystallographic structures of gD before and after binding to HVEM [1,2] reveal that interaction with the receptor leads to rearrangements of the C- and N-terminus of gD and thereby transduces the signal to gB and gH/gL through a motion of the Prolin-rich pro-fusion-domain (PFD).

In the unbound state the C-terminal region (291-306) of gD occupies the same groove as its N-terminal region (1 to 16) when gD is bound to HVEM. Therefore, the C-terminus has to detach before the N-terminus can move in its position to mediate the interaction with HVEM.

To analyze the dynamic properties of gD regarding binding of the C-terminus to the protein core and enhance our understanding of subsequent HVEM binding, we performed molecular dynamics simulations of wild-type free gD and two mutants (Q27P, W294A), as well as HVEM bound gD. We used the MM_GBSA-Tool implemented in AMBER 11 to calculate binding free energies between the C-terminus (291-306) and the gD core (22 to 289) of free gD, and also between HVEM and gD.

The analysis revealed that the mutations of W294A and Q27P decrease the interaction energy between the C-terminus and the gD core compared to the wild-type simulation. This may result in a higher flexibility of the C-terminal region and thereby an easier detachment. Furthermore, we could identify residues of gD and HVEM which contribute to specific receptor recognition.

[1] Krummenacher C, Supekar VM, Whitbeck JC, Lazear E, Connolly SA, Eisenberg RJ, Cohen GH, Wiley DC, Carfi A. Structure of unliganded HSV gD reveals a mechanism for receptor-mediated activation of virus entry. *Embo J* **2005**;*24(23)*:4144-4153.

[2] Carfi A, Willis SH, Whitbeck JC, Krummenacher C, Cohen GH, Eisenberg RJ, Wiley DC. Herpes simplex virus glycoprotein D bound to the human receptor HveA. *Mol Cell* **2001***;8(1)*:169-179.