Investigating the Effect of Q27 Mutation on Receptor-binding Properties of Glycoprotein D in Herpes Simplex Virus-1

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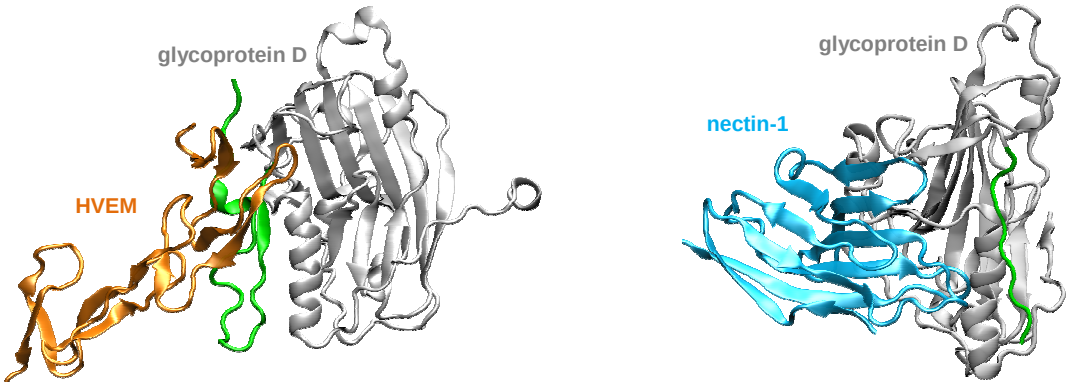
Many studies have identified herpes simplex virus-1 (HSV-1) as a possible candidate for anti-cancer therapy. The goal is to reprogram the virus in such a way that it specifically infects cancer cells and lyzes them. However, to accomplish this task, it is necessary to fully understand the fusion of the virus with its target cell, which is fundamental for infection. To infect the cell, HSV-1 makes use of an entry-fusion system consisting of four glycoproteins: gD, gB, gH and gL. gD plays a pivotal role initiating the fusion mechanism by binding to membrane proteins of the target cell (HVEM and nectin-1). Experiments have shown that Q27A mutation in gD leads to an inability to bind HVEM, therefore abolishing HVEM mediated cell entry. On the other hand, the mutation increases binding affinity of gD to nectin-1, facilitating the viral cell entry [1]. Our goal was to investigate the important role of Q27 in different steps of the binding mechanism and understand the ambivalent effect of mutation.



In our study all molecular dynamics simulations were performed with AMBER/parm99SB force field in explicit solvent. For energetic analyses and in silico alanine scan MM_GBSA (IGB Model 2) implemented in AMBER 11 was used. We simulated gD in four different states: bound to HVEM [3] and nectin-1 [4], unbound with the resolved C-terminal region [2], and unbound with the N-terminal hairpin-like loop. Both unbound states were simulated as wild-type (WT) and Q27A mutant.

Our results show that Q27A mutation affects each investigated step of the binding mechanism differently. Therefore, we provide a first comprehensive insight into the ambivalent effect of Q27A mutation and point out the important role of this amino acid for multiple steps of the binding mechanism.

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