Disarming the Glycan Shield of HIV: Broadly Neutralizing Antibody PGT122 against HIV

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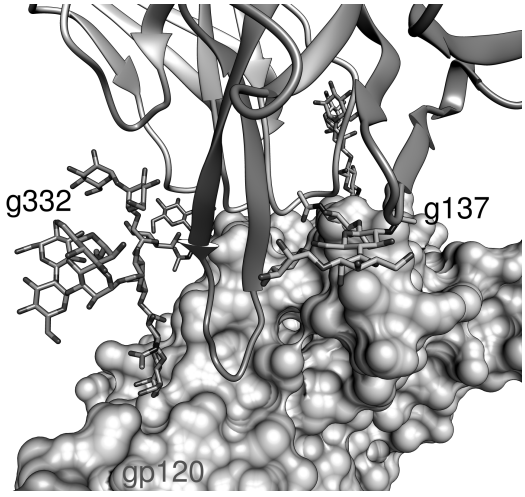
The human immunodeficiency virus (HIV) establishes a latent infection causing a slow depletion of $CD4^+$ T-cells belonging to the humoral immune system. Ultimately, this results in the stage of the acquired immunodeficiency syndrome (AIDS) in which infected individuals are highly susceptible for opportunistic diseases.

The virus itself circumvents recognition by the immune system with a high mutation rate and an envelope which contains host-cell derived features. These include the numerous glycans attached to the only viral protein on the surface of HIV, gp120. The glycans form a protective layer against immune recognition called the glycan shield.

However, some patients develop antibodies that show neutralizing properties against multiple virus strains called broadly neutralizing antibodies (bnAbs). Recently, bnAbs have been investigated for immunization via passive administration and for therapeutic use. They also serve as a template for the design of mimetic peptides. One potential candidate is PGT122, a bnAb that targets the V3 region of gp120. At its binding site PGT122 interacts with several glycans through a 26 residue long complementary determining region of the heavy chain (CDRH3).

Investigation of the interactions between the antibody and the glycans on the viral surface during affinity maturation and for peptide design, all-atom MD simulations of the investigated antibody-gp120 systems were performed on the µs timescale. These revealed distinct dynamics for each of the four simulated glycans (g137, g156, g301, g332).



Only interactions to g332 in the center of the epitope remained stable throughout the simulation time whereas the other glycans displayed a high degree of conformational freedom. Replacement of the CDRH3 loop of PGT122 with its putative precursor showed less, but stable contacts to g332. This indicates subtle optimization of the precursor Ab during affinity maturation. On the other hand, interactions with g137 were lost in some simulations which underlines this glycan's distinct role in antibody recognition. The simulations of a PGT122 derived peptide showed unphysiological structural adaptations emphasizing the importance of the V_H region for H3 structural integrity.

Thus, these simulations provide insights into the dynamics of the glycan shield and stability of CDRH3 loops for novel antiviral approaches against HIV.