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Poster presentation

P09-04. Charge changes in the alpha2-helix in the C3 region of the HIV-1 subtype C envelope mediate neutralization escape

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Background

We have previously shown that the C3V4 region is a major target of autologous neutralizing antibodies (nAbs) in early HIV-1 subtype C infection. Here we investigated virus escape from anti-C3V4 nAbs in 3 individuals from the CAPRISA 002 cohort.

Methods

Envelope amplicons were generated from plasma at multiple time-points using single genome amplification. Amplicons selected on the basis of sequence differences were cloned, and used to generate pseudoviruses for neutralization assays. Escape mutations were identified using chimeric viruses and site-directed mutagenesis, and mapped onto helical wheel diagrams.

Results

Escape in CAP88 was mediated by 2 of 3 amino acid changes in the alpha2-helix by 6 months post-infection An I339N mutation resulted in the formation of a predicted N-linked glycan (PNG) suggesting possible glycan shielding. Sequences also contained either an E343K or an E350K substitution resulting in charge switches from negative to positive residues. Modeling of these non-contiguous changes onto helical wheel diagrams showed both residues were in close physical proximity to I339N. In CAP177, neutralization escape was not associated with changes in the number of PNGs. Three of the 5 changes observed, E337K, Q344K and E351K all lay on the same face of the alpha2-helix. However all 5 substitutions were charge changes from neutral or negatively-charged residues to positively-charged residues. In CAP206, two of the three changes observed in escaped clones (though mutagenesis data was not available) were substitutions also resulting in positive charges, G348R and N351K.

Conclusion

Neutralization escape was associated with mutations towards positively-charged residues within the alpha2-helix. Charge changes may disrupt electrostatic interactions between nAbs and their epitopes if C3 is a direct antibody target. Alternatively, since the alpha2-helix and the V4 region are spatially proximal, charge changes may affect the conformation of the V4 loop with respect to the alpha2-helix, affecting exposure of nAb targets.