RETROVIROLOGY

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Residue 315 regulates V3 exposure and V3 antibody recognition on HIV subtype B and C viruses

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Background

V3 mAbs often neutralize HIV subtype B viruses but exhibit poor neutralizing activity against subtype C viruses. This limited activity is typically attributed to masking of the V3 region on subtype C viruses. However, while relatively much effort has been devoted to exploring accessibility of the V3 region on subtype B viruses, V3 exposure and the mechanism(s) that might restrict V3 exposure on subtype C viruses has yet to be understood. Here we have focused on exploring the significance of the conserved V3 tip motifs GPGR and GPGQ of subtype B and C viruses for antibody recognition.

Methods

Position 315 in representative subtype B (SS1196) and subtype C viruses (ZM249M, CAP45) was switched to Gln and Arg, respectively, to assess the effect of the conserved Arg/Gln at position 315 on V3-specific neutralization. Neutralization sensitivities of the parental and mutant viruses were assessed in a single-round pseudovirus neutralization assay using a panel of neutralizing V3-specific mAbs with varying fine specificities for the V3 tip.

Results

Subtype B virus SS1196 was neutralized by all V3-specific mAbs tested here (B4e8, 2219, 268-D, 2557, 3074 and HGN194). In contrast, though as expected, mutant SS1196_R315Q was resistant to neutralization by mAbs B4e8 and 268-D, both of which require the Arg at position 315 for binding. Unexpectedly, the remaining V3 mAbs were also unable to neutralize SS1196_R315Q, despite not requiring an Arg residue at position 315 for binding. For the subtype C viruses the exact opposite was observed; both ZM249M and CAP45 were generally insensitive to antibody neutralization yet the Q315R mutants were strikingly sensitive.

Conclusion

The results suggest that V3 may be more accessible to antibody than previously appreciated in at least some subtype C viruses. However, the data also suggest that a Gln at position 315 modulates exposure of V3. Further elucidation of this mechanism is underway.

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