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Oral presentation

S021-05 OA. Broadly neutralizing anti-HIV-1 antibodies disrupt a hinge-related function of gp41 at the membrane interface

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Background

A vaccine capable of stimulating protective anti-viral antibody responses is needed to curtail the global Acquired Immunodeficiency Syndrome (AIDS) epidemic caused by HIV-1. Although rarely elicited during the course of natural infection or upon conventional vaccination, the membrane proximal ectodomain region (MPER) of the HIV-1 gp41 envelope protein subunit is the target of three such human broadly neutralizing antibodies (BNAbs): 4E10, 2F5 and Z13e1. How these BNAbs bind to their lipid-embedded epitopes and mediate anti-viral activity are unclear, but such information might offer important insight into a world-wide health imperative.

Methods

Electron paramagnetic resonance (EPR) and nuclear magnetic resonance (NMR) techniques were used to define the manner in which theses BNAbs differentially recognize viral membrane-encrypted residues configured within the L-shaped helix-hinge-helix MPER segment.

Results

Two distinct modes of antibody-mediated interference of viral infection were identified. Both 4E10 and 2F5 induce large conformational changes in the MPER relative to the membrane. However, while 4E10 straddles the hinge and extracts residues W672 and F673, 2F5 lifts up residues N-terminal to the hinge region, exposing L669 and W670. In contrast, Z13e1 affects little change in membrane orientation or conformation, but rather immobilizes the MPER hinge through extensive rigidifying surface contacts.

Conclusion

We conclude that BNAbs disrupt HIV-1 MPER fusogenic functions critical for virus entry into human CD4 T cells and macrophages either by preventing hinge motion or by perturbing MPER orientation. HIV-1 MPER features important for targeted vaccine design have been revealed, the implications of which extend to BNAb targets on other viral fusion proteins.