Structural basis for broad neutralization of HIV-1 through the molecular recognition of 10E8 helical epitope at the membrane interface

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The mechanism by which the HIV-1 MPER epitope is recognized by the potent neutralizing antibody 10E8 at membrane interfaces remains poorly understood. To solve this problem, we have optimized a 10E8 peptide epitope and analyzed the structure and binding activities of the antibody in membrane and membrane-like environments. The X-ray crystal structure of the Fab-peptide complex in detergents revealed for the first time that the epitope of 10E8 is a continuous helix spanning the gp41 MPER/transmembrane domain junction (MPER-N-TMD; Env residues 671-690). The MPER-N-TMD helix projects beyond the tip of the heavy-chain complementarity determining region 3 loop, indicating that the antibody sits parallel to the plane of the membrane in binding the native epitope. Biophysical, biochemical and mutational analyses demonstrated that strengthening the affinity of 10E8 for the TMD helix in a membrane environment, correlated with its neutralizing potency. Our research clarifies the molecular mechanisms underlying broad neutralization of HIV-1 by 10E8, and the structure of its natural epitope. The conclusions of our research will guide future vaccine-design strategies targeting MPER.