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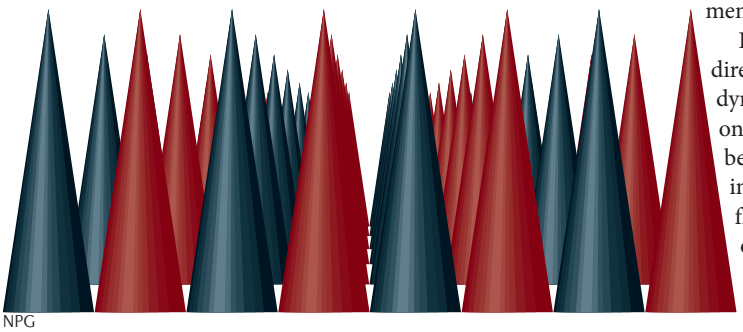
STRUCTURAL BIOLOGY

The many faces of the HIV-1 spike

> these studies ... may guide structure-based drug design efforts

The HIV-1 envelope (Env) spike facilitates viral entry into host cells by interacting with host cell receptors and mediating the fusion of viral and host membranes. Env is a trimeric glycoprotein composed of three gp120 and three gp41 subunits, which transitions from a pre-fusion closed state to a post-fusion state via intermediate open states that bind to host receptors and co-receptors. Pancera *et al.* now report the high-resolution crystal structure of the pre-fusion HIV-1 Env trimer at 3.5 Å resolution and provide insights into the structural rearrangements that facilitate viral entry; and Munro *et al.* visualized dynamic conformational changes of the Env spike on the surface of virions in real time.

Although many structural details of the Env trimer have previously been reported, the pre-fusion structure of the gp41 subunit, which drives membrane fusion, had not been solved. Pancera *et al.* crystallized a closed state of a pre-fusion HIV-1 Env trimer, which showed that four gp41 helices (α6 to α9) enclose the amino- and carboxy-termini of the gp120 subunit. This gp41 collar is clasped by the insertion of a methionine residue from helix α6 into a triple-tryptophan motif that is formed by residues in helices α8 and α9. By comparing the gp41 pre-fusion structure with previously determined post-fusion structures, the authors found that upon binding of gp120 to host receptors, the clasp is released, which weakens the interaction between gp41 and gp120 and triggers gp41 rearrangements. The formation of a long helix (termed heptad repeat 1 (HR1)) enables gp41 to penetrate the target membrane, and a second long helix, HR2, forms a six helical bundle with HR1 and brings the host and viral membranes into close proximity to promote membrane fusion.



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In a second study, Munro *et al.* directly imaged the conformational dynamics of the gp120 subunit on the surface of HIV-1 virions before and after receptor binding. The authors introduced fluorophores into variable loops of the gp120 subunit and used single-molecule fluorescence resonance energy transfer (smFRET) to detect the repositioning of these gp120 regions over time. By measuring FRET efficiencies, they demonstrated that unbound gp120 is highly dynamic and transitions between three distinct conformations, with the gp120 subunit predominately occupying a ground state, which corresponds to the closed Env configuration. Binding of gp120 to CD4 and a co-receptor surrogate led to conformational changes that stabilized the other two states. These data suggest that unbound Env proteins predominantly occupy a closed configuration but can spontaneously adopt conformations that are stabilized by binding to host receptors and co-receptors. Notably, broad-neutralizing antibodies stabilized the closed state, which suggests that stabilizing this state represents a potential strategy to impair Env interactions with host molecules.

Together, these studies clarify the mechanism of HIV-1 entry into host cells and may guide structure-based drug and vaccine design efforts.

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ORIGINAL RESEARCH PAPERS Pancera, M. *et al.* Structure and immune recognition of trimeric pre-fusion HIV-1 Env. *Nature* http://dx.doi.org/10.1038/nature13808 (2014) | Munro, J. B. *et al.* Conformational dynamics of single HIV-1 envelope trimers on the surface of native virions. *Science* http://dx.doi.org/10.1126/science.1254426 (2014)