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Uncovering the Achilles' heel of the HIV-1 envelope

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New structural details illustrate how a promising class of antibodies may block human immunodeficiency virus (HIV)-1 infection and reveal valuable clues for design of an effective HIV-1 vaccine.

The findings, published by Cell Press in the January issue of *Immunity*, are particularly significant as antibody induction appears to be a key and necessary component of an effective HIV vaccine, evidenced by the recent failure of vaccines that stimulated only the T cell arm of the immune system to protect humans from contracting HIV-1.

Profound challenges have interfered with creation of a preventative vaccination to halt the global spread of HIV-1. For example, the HIV-1 envelope protein, the only target for neutralizing antibodies, is highly variable among isolates and masked by sugar molecules, allowing the virus to escape antibody attack. “Not surprisingly, only a handful of broadly neutralizing antibodies (BNAbs) have been identified and they are rarely elicited during natural human infection,” explains research leader Dr. Ellis L. Reinherz from the Dana-Farber Cancer Institute and Harvard Medical School in Boston, Massachusetts.

The BNAbs that have been identified are directed against a portion of HIV-1 called the membrane proximal ectodomain region (MPER). This region lies at the base of the viral envelope protein comprised of the gp120 protein plus the membrane anchoring gp41 subunits adjacent to the viral membrane. A major conundrum has been the basis for the lack of human antibody response against the MPER segment since it is

accessible to antibody and is highly conserved, even among different HIV-1 viral isolates around the world.

The present study reveals that much of the MPER is actually embedded in the viral membrane. As such, this stealthy segment appears to divert the immune attack elsewhere, namely to the exposed variable elements of the viral envelope and immunodominant regions which do not confer useful neutralization. The researchers also discovered a hinge in the middle of the MPER permitting segmental flexibility, an important feature in facilitating fusion of the virus with the human host immune cells.

BNAbs such as the monoclonal 4E10 antibody target this hinge area and cause the MPER to undergo dynamic changes that reveal key pieces of itself critical for viral fusion that were buried deep in the membrane. As a result, the antibody is then able to achieve a tighter hold on the virus, restrict hinge mobility and impede the ability of the virus to fuse to the membrane of the host cell.

Importantly, the published structure of the lipid-embedded MPER also identifies those few residues poking out from the viral membrane. These may be ideal targets for vaccine design if properly configured in a synthetic lipid coat that conserves the native shape of the MPER and focuses production of antibodies against this Achilles' heel of the viral envelope.

While this research is still at an early experimental stage, it provides a plausible explanation as to why previous attempts, which neglected to preserve the native conformation of the MPER necessary for eliciting a broadly neutralizing antibody with 4E10-like specificity, were unsuccessful and offers a new approach to the design of antibody-eliciting vaccines to prevent HIV-1.

Source: Cell Press