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LOOP DELETIONS IN gp120 EXPOSE THE CD4 BINDING SITE FOR IMPROVED BINDING OF 1b12 AND F105 ANTIBODIES

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BACKGROUND: HIV-infected humans make broadly crossreactive neutralizing antibodies specific for the CD4 binding site on gp120. Vaccines based on native gp120 fail to elicit similar antibodies. Native gp120 may cover up this site to prevent antibody induction.

METHODS: Based on the 3D structure of gp120, we have identified four conserved loops that project into the CD4 binding site and may partially block antibody binding or may interfere with induction of antibodies to this site. Each loop was deleted by quick change PCR, expressed as virus-like particles in a baculovirus system, and partially purified by sedimentation through sucrose. The amount of antigen was normalized by 2G12 binding, and exposure of the CD4 binding site was determined with a panel of monoclonals and CD4-Ig.

RESULTS: Three phenotypes were observed: one mutant abrogated binding of both 1b12 and CD4-Ig, one removed 1b12 completely but had no effect on CD4-Ig, and one enhanced 1b12 binding, with minimal effect on CD4-Ig. F105 binding was enhanced even more.

CONCLUSIONS: These results suggest that naturally occurring features of the gp120 structure may inhibit antibody binding and reduce the induction of antibodies to the CD4 binding site. These structures can be removed without upsetting the overall conformation. Exposure of the CD4 binding site could occur by reducing steric hindrance or through an allosteric effect on the excursion between open and closed forms of the protein, as occurs during CD4 binding. Open forms of gp120 bearing an exposed CD4 binding site may favor the induction of broadly cross-reactive neutralizing antibodies.

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