Ligand Recognition and Plasticity in HIV Envelope Glycoprotein gp120

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Crystallographic analyses of core portions of HIV gp120 glycoproteins showed how these viral envelope protein bind to CD4, the primary cellular receptor for HIV, and to a neutralizing antibody fragment, Fab 17b, which has a binding epitope overlapping with that of HIV co-receptors CCR5 and CXCR4. The structure of gp120 in this complex has a substantial cavity next to CD4 residue Phe43 in the interface between gp120 and CD4 at the focus of protein-protein interaction. Thermodynamic analyses indicated that gp120 undergoes remarkable conformational ordering when it binds CD4 or 17b. We have subsequently performed computational analyses of the intrinsic flexibility of core gp120. We have also produced the F43C mutant variant of the D1D2 portion of CD4, which was designed for addition of chemical moieties in place of the Phe43 side chain, and we analyzed structure-activity relations from the binding of a library of thiol-reactive compounds to produce D1D2-F43C-X derivatives. Some of the derivatives bind more tightly to gp120 than does wild-type CD4. Crystal structures were determined for five derivatized D1D2 proteins in complexes with core gp120 and Fab 17b. Chemical entities bind into the Phe43 cavity, and the cavity expands in response to ligands. This plasticity in gp120 is also associated with modified binding properties in cellular assays.