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Covalent binding of human two-domain CD4 to an HIV-1 subtype C SOSIP.664 trimer modulates its structural dynamics

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Abstract:
The human immunodeficiency virus type 1 (HIV-1) envelope glycoprotein (Env) mediates host cell infection by binding to the cellular receptor CD4. Recombinant Env bound to CD4 has been explored for its potential as an HIV vaccine immunogen as receptor binding exposes otherwise shielded, conserved functional sites. Previous preclinical studies showed an interchain disulphide linkage facilitated between Env and 2dCD4S60C generates an immunogenic complex that elicits potent, broadly neutralizing antibodies (bNAbs) against clinically relevant HIV-1. This study investigated conformational dynamics of 2dCD4WT and 2dCD4S60C bound to an HIV-1C SOSIP.664 Env trimer using hydrogen-deuterium exchange mass spectrometry. The Env:2dCD4S60C complex maintains key contact residues required for MHCII and Env/gp120 binding and the residues encompassing Ibalizumab's epitope. Important residues remaining anchored, with an increased flexibility in surrounding regions, evidenced by the higher exchange seen in flanking residues compared to Env:2dCD4WT. While changes in Env:2dCD4S60C dynamics in domain 1 were moderate, domain 2 exhibited greater variation. Lack of stability-inducing H-bonds in these allosteric sites suggest the improved immunogenicity of Env:2dCD4S60C result from exposed CD4 residues providing diverse/novel antigenic targets for the development of potent, broadly neutralizing Ibalizumab-like antibodies.