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Bayesian Integrative Approach Identifies Hidden Intermediates in DH270-Induced Structural Transitions of HIV-1 Envelope

CONFERENCE ABSTRACT

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Abstract

HIV-1 Envelope glycoprotein (Env) undergoes a sequence of structural transitions, from a closed conformation to an open structure, initiates host-cell infection, and alters exposure of antibody epitopes. Closed-to-open transition proceeds through both short-lived disordered and more stable open-occluded intermediates, exposing distinct antibody binding surfaces. Designing effective HIV-1 vaccines requires a deeper understanding of how Env opening changes antibody engagement. DH270 is a broadly neutralizing antibody with neutralization capacity against a range of HIV-1 strains, and stabilizes closed Env structure. Env structural changes on microsecond timescales, induced by DH270 binding, were first captured at high temporal resolution using time-resolved, temperature-jump small-angle X-ray scattering (TR, T-Jump SAXS). Interpretation of these low-resolution data are challenging due to substantial conformational heterogeneity involved in binding processes. To enable high-confidence structural interpretation of TR, T-Jump SAXS signals, a novel integrative approach combining Markov state models, homology modeling, and a Bayesian inference framework to fit theoretical structures to experimental data was developed. Structural models for each known Env conformation,

closed, disordered, open-occluded, and open, each in one of several possible DH270-bound states were generated. This yielded 9,600 unique DH270-bound Env models. Comparison of theoretical SAXS profiles from these models, along with experimental data indicates open-occluded intermediate and partially DH270-bound closed Env states contribute substantially to DH270-induced Env motions. Inclusion of these partially bound encounter complexes significantly improves model fits. Disordered intermediate and fully open Env conformations appear to play no role in DH270-induced structural response, consistent with prior evidence that DH270 stabilizes closed Env conformation. Improvements to the fit remain needed and suggests additional, as-yet-unidentified Env conformational states may be required to fully capture experimental TR, T-Jump SAXS signals. These results can be leveraged to engineer antibody affinity and neutralization potency in potential vaccine immunogen candidates. Newly characterized structural transitions provide a foundation for future structure-guided HIV-1 vaccine design.

Keywords: HIV-1, SAXS, time-resolved, structural biology, modeling, protein dynamics, immunogen design, vaccine, broadly neutralizing antibodies