Structure-based design of improved antibodies against HIV

Bjorkman, Pamela J[1]*, Galimidi, Rachel P.[1], West, Anthony, P., Jr.[1], Scharf, Louise
[1]California Institute of Technology, Biology and Biological Engineering, Mail Code 114-96, bjorkman@caltech.edu
* Corresponding Author

Keywords: *Antibodies, Avidity, HIV, Immune evasion, structure-based design.*

Abstract

The HIV-1 envelope (Env) spike, a trimer of gp120/gp41 heterodimers, utilizes antibody-evasion strategies including mutation, glycan shielding, and conformational masking. While important, these features are not unique to HIV-1: other viruses employing these strategies elicit IgG antibody responses that provide sterilizing immunity or viral clearance. A potentially unique antibody-evasion strategy for HIV-1 involves hindering IgGs from using both antigen-binding Fabs to bind bivalently. This is accomplished by the small number and low density of Env spikes, which prevent most IgGs from inter-spike cross-linking (bivalent binding between spikes), and the architecture of the Env trimer, which impedes intra-spike crosslinking (bivalent binding within a spike). We hypothesized that predominantly monovalent binding expands the range of HIV-1 mutations permitting antibody evasion, whereas designed reagents capable of bivalent binding through intra-spike cross-linking would be more broad and potent across multiple strains of HIV-1. To test this idea, we evaluated intra-spike cross-linking reagents constructed from anti-HIV-1 IgG Fabs. Separation distances between bound Env-bound Fabs were measured using a DNA-based "molecular ruler" to derive approximate distances between epitopes within virion-associated Env trimers. This allowed identification of homo- and heterotypic Fabs joined with optimal separation distances that exhibited synergy of up to >700-fold in potency as well as enhanced breadth in neutralization across HIV-1 strains. These results support the hypothesis that HIV-1 evolved a low number of Env spikes to facilitate antibody evasion and suggest a method to create highly potent anti-HIV-1 reagents with increased resistance to viral mutation.

This work was supported by the Director's Pioneer Award [1DP1OD006961-01 to P.J.B.] and National Institutes of Health HIVRAD [P01 Al100148 to P.J.B.].