Redirecting antibody specificity from the gp41 base to the V3-glycan epitope through env-based immunization

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A critical challenge for HIV-1 vaccine design is that immunization with the HIV-1 Envelope (Env) protein predominantly induces non-neutralizing antibodies (Abs) that target non-conserved epitopes of Env. These off-target Abs lack the potential to mature into broadly neutralizing Abs (bNAbs) and significantly interfere with bNAb development by outcompeting bNAb precursors in germinal centers. The gp41 base of Env is highly immunogenic and is a frequent target of non-neutralizing Abs, as base epitopes are normally occluded by the viral membrane. Thus, a variety of strategies, such as glycan masking or membrane-bound Env, are being developed to prevent base responses. Here, we report that some Abs binding the gp41 base exhibit striking amino acid identity to human V3-glycan bNAbs. Based on this observation, we hypothesized that base Abs could be redirected to target the V3-glycan epitope and matured into bNAbs through vaccine-induced somatic hypermutation. To test this hypothesis, we produced a new immunoglobulin knock-in (Ig KI) mouse expressing a macaque base Ab (Ab1718) that has remarkable amino acid identity with the human V3-glycan bNAb PGT121. Using newly engineered Env-based proteins, we show that the epitope specificity of Ab1718 can be redirected toward the V3-glycan epitope in the Ab1718 Ig KI mice. ELISA, mass spectrometry and single B-cell antibody cloning confirmed the maturation of Ab1718 away from the base and towards the V3-glycan epitope and the acquisition of V3-glycan bNAb-like mutations. In summary, our results suggest an innovative strategy to recycle non-neutralizing Abs into bNAbs through vaccination, opening new directions for HIV-1 vaccine design.