HIV-1 bNAb precursors switch specificity to non-neutralizing epitopes of Env upon immunization

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A vaccine that elicits broadly neutralizing antibodies (bNAbs) against HIV-1 remains elusive. The induction of bNAbs through vaccination requires the activation of naïve B cells expressing bNAb precursor antibodies, followed by affinity maturation toward their conserved neutralizing epitopes on the HIV-1 envelope (Env). However, preclinical and clinical studies have shown that repeated immunization with soluble Env trimers elicits abundant non-neutralizing responses that frequently target immunodominant epitopes on the gp41 base. Here, we identified a subset of vaccine-induced macaque antibodies that despite having remarkably similar features to bNAbs targeting the neutralizing V3-glycan epitope of Env, target the gp41 base. Based on the high sequence similarity between these base antibodies and well-established human bNAbs, we hypothesized that base antibodies could arise from bNAb precursor lineages through somatic hypermutation. More precisely, we hypothesized that bNAb precursor lineages could be redirected to target non-neutralizing epitopes during vaccination and be diverted from the maturation trajectory required for bNAb development. Using new immunoglobulin knock-in mouse models and a novel engineered Base Protein (eBP) immunogen, we demonstrate that precursors of human V3-glycan bNAbs can switch epitope specificity toward non-neutralizing epitopes at the Env base upon immunization. We characterized the structure and mutational pattern of epitope-switched antibodies to define the mechanisms underlying the derailment of bNAb maturation. Our findings reveal a previously unrecognized aspect of antibody affinity maturation and new barriers to HIV-1 vaccine design, highlighting the importance of constraining B cell evolution during vaccine regimens that require repeated immunizations.