A V1V2 Apex bNAb precursor switches epitope specificity to the gp41 base upon immunization

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HIV-1 vaccine design aims to elicit broadly neutralizing antibodies (bNAbs) which recognize conserved neutralizing sites on the envelope (Env) glycoprotein. To achieve this, rare B cells that carry a bNAb precursor receptor must be first engaged and then matured through sequential immunization. Current immunization strategies presume that a precursor lineage, once activated, stays committed to its original epitope during affinity maturation. Here, we show that this commitment can be lost during maturation, with a bNAb-like antibody lineage shifting reactivity from the V1V2 apex toward the immunodominant, non-neutralizing base of Env. To demonstrate epitope switching, we used a monoclonal immunoglobulin knock-in (Ig KI) mouse expressing the unmutated common ancestor (UCA) of the V1V2 apex bNAb, T646. T646 UCA Ig KI mice were primed with a V1V2 germline-targeting immunogen and then boosted with engineered Base Protein (eBP), our novel reagent computationally designed to recapitulate the gp41 base of Env in the absence of gp120. After this immunization regimen, mice developed serum reactivity to eBP that was not detected prior to immunization. To determine whether this response originated from the T646 lineage, we performed single-cell sequencing of eBP-binding germinal center B cells. These B cells expressed slightly somatically hypermutated versions of the T646 UCA antibody, consistent with a change in epitope specificity without extensive divergence from the original lineage. Monoclonal antibodies generated from these cells bound eBP and competed with established base antibodies for binding to the Env base. Together, these findings show that bNAb precursor lineages can be redirected toward non-neutralizing epitopes during immunization, highlighting the need for strategies that maintain their maturation trajectory toward neutralizing sites.