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## Host Controls of HIV Neutralizing Antibodies

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### Abstract

The unusual traits of broadly neutralizing antibodies for HIV-1 are stimulating new strategies to induce their production through vaccination.

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A key goal of developing a vaccine for human immunodeficiency virus-1 (HIV-1) is that it should stimulate the production of broadly neutralizing antibodies (bnAbs) that recognize conserved regions of the viral envelope. Unfortunately, no candidate vaccine has proved capable of eliciting such antibodies, possibly because conserved epitopes are obscured by dense glycan “shields” on the viral surface, or because of a failure to produce HIV-1 envelope immunogens that retain their native structure. After 20 years of immunization studies and three HIV-1 vaccine efficacy trials, the induction of bnAb responses by HIV vaccines remains elusive. However, progress in circumventing host factors that limit bnAb induction is now leading to new concepts in vaccinology and immunogen design that hopefully can be applied not only to HIV-1, but also to other vaccines in need of bnAb induction such as for hepatitis C and influenza viral infections.

A minority of HIV-1-infected individuals generate the amounts of bnAbs needed to neutralize a high percentage of virus, but this amount of antibody is present in the plasma only after months to years of infection. The advent of new technologies has allowed the isolation of bnAbs from such patients, the expression of bnAbs, and the reconstruction of bnAb lineages through computational methods. Consequently, much progress has been made in identifying new viral envelope epitopes that are recognized by bnAbs, elucidating the structure of these epitopes, and defining the developmental pathways of B cells that produce bnAbs. We now know that bnAbs bind to at least four regions of the HIV-1 envelope: the binding site on the viral envelope protein gp120 for T cells (CD4 co-receptor for HIV-1); the membrane-proximal region of envelope protein gp41; and two overlapping, glycan-rich regions around the first, second and third variable (V1, V2, V3) regions of gp120 (1).

HIV-1 bnAbs have one or more unusual traits: high amounts of somatic hypermutation; poly- or autoreactivity with host or environmental antigens; and a long variable heavy-chain ( $V_H$ ) complementarity-determining region 3 (HCDR3s) (2), the most diverse component of the antibody’s antigen-binding site. Unfortunately, the production of antibodies with these traits is generally disfavored by the immune system.

High-affinity antibody results from the somatic hypermutation and affinity-driven selection of B cells in germinal centers of lymphoid tissues. B cell receptors (BCRs), which recognize antigen, possess an immunoglobulin moiety that is identical to the antibodies that these lymphocytes manufacture once stimulated. Whereas pathogens such as influenza virus induce high-affinity, protective, neutralizing antibodies with ~5%  $V_H$  mutations, HIV-1 bnAbs have from ~15% to ~30%  $V_H$  mutations (2). In general, a ceiling exists for affinity maturation such that the dissociation constant ( $K_d$ ) for binding of antigen to the BCR is  $\approx 0.1$  nM (3). With the exception of HIV-1 bnAbs, far fewer than 30% mutations are needed in most antibodies to attain nanomolar affinities for antigen. Indeed, the accumulation of antibody mutations eventually decreases binding of the BCR to antigen and reduces cell survival. It is not known what drives mutation rates in the evolution of bnAbs to HIV-1 above those found in neutralizing antibodies to other pathogens. To acquire structurally disfavored antibodies necessary for broad neutralization, it may be that somatic hypermutations must recur over prolonged periods. The high frequency of mutations in bnAbs may reflect the difficulty of acquiring atypical genetic changes necessary for bnAb activity. Insight into the functional importance of bnAb somatic mutations has come from the observation that some mutations that accumulate in antibody framework regions are required for broad neutralization (4).

Polyreactivity (antibody binding to multiple, dissimilar antigens) and autoreactivity (binding to one or more self-antigens) are common traits of bnAbs (5–8). In some cases, the poly- or autoreactivity of BCRs is the result of the viral mimicry of host antigen; this reactivity is sufficient to activate central and peripheral tolerance (7–10). Hope for eliciting bnAbs that may be affected by immune tolerance comes from the observation that in mice genetically engineered to produce bnAbs, a minority of B cell clones enter the peripheral lymphoid tissue as anergic, or functionally silenced, that can be activated by appropriately designed immunogens (10).

Is bnAb poly- or autoreactivity necessary for antiviral activity? One possibility is that bnAb polyreactivity is required for binding to sparse “spikes” of gp120 on the surface of HIV-1 virions, with effective bnAb binding dependent on interaction with both gp120 and associated host membrane epitopes (6). The neutralizing activity of bnAbs that react with membrane-proximal gp41 envelope protein and lipids is abrogated by mutations that eliminate antibody binding to the viral membrane.

Many bnAbs have unusually long HCDR3 regions. HCDR3 lengths in bnAbs specific for glycan epitopes in the V1 and V2 regions of gp120 range from 24 to 37 amino acids compared to a median of ~15 in other antibodies (11). Newly generated human B cells that express BCRs with long HCDR3 regions are frequently counterselected in the bone marrow, presumably because long HCDR3 regions tend to confer self-reactivity that invokes clonal deletion or interfere with the pairing of heavy and light chains as antibody architecture is forged during B cell development (12). Thus, the pool of B cells bearing receptors with long HCDR3 is reduced before their stimulation with antigen, thereby contributing to their rarity in response to HIV-1.

Other examples of viral mimicry of host are glycans on HIV-1 virions that are host-derived and are key targets of bnAbs. The presence of self-glycans on virions also has been proposed to limit the induction of glycan-targeting bnAbs by immune tolerance mechanisms (13). Modified glycans have been synthesized to not resemble self-glycans, but as yet have not induced glycan-specific antibodies that bind virions (13).

All B cell lineages are initiated by antigen binding to unmutated BCRs on naïve B cells, and lineages that produce bnAbs to HIV-1 are initiated by autologous virus or possibly cross-reactive host antigens (2, 8, 14). A strategy being tested is to design immunogens that bind to naïve BCRs and/or to later members of bnAb clonal lineages, so as to drive selectively disfavored or subdominant lineages (2) (see the figure). One of several new crystal structures of the gp120 trimer should guide the design of native HIV-1 envelope immunogens (15). Recent success in mapping coevolution of the viral envelope and bnAbs in HIV-1–infected individuals has identified epitopes as vaccine candidates that actually induced bnAbs in the setting of infection (11, 14). However, because bnAbs are not made soon after HIV-1 infection but rather take months to years to develop, vaccination may also require repetitive immunizations over longer periods of time.

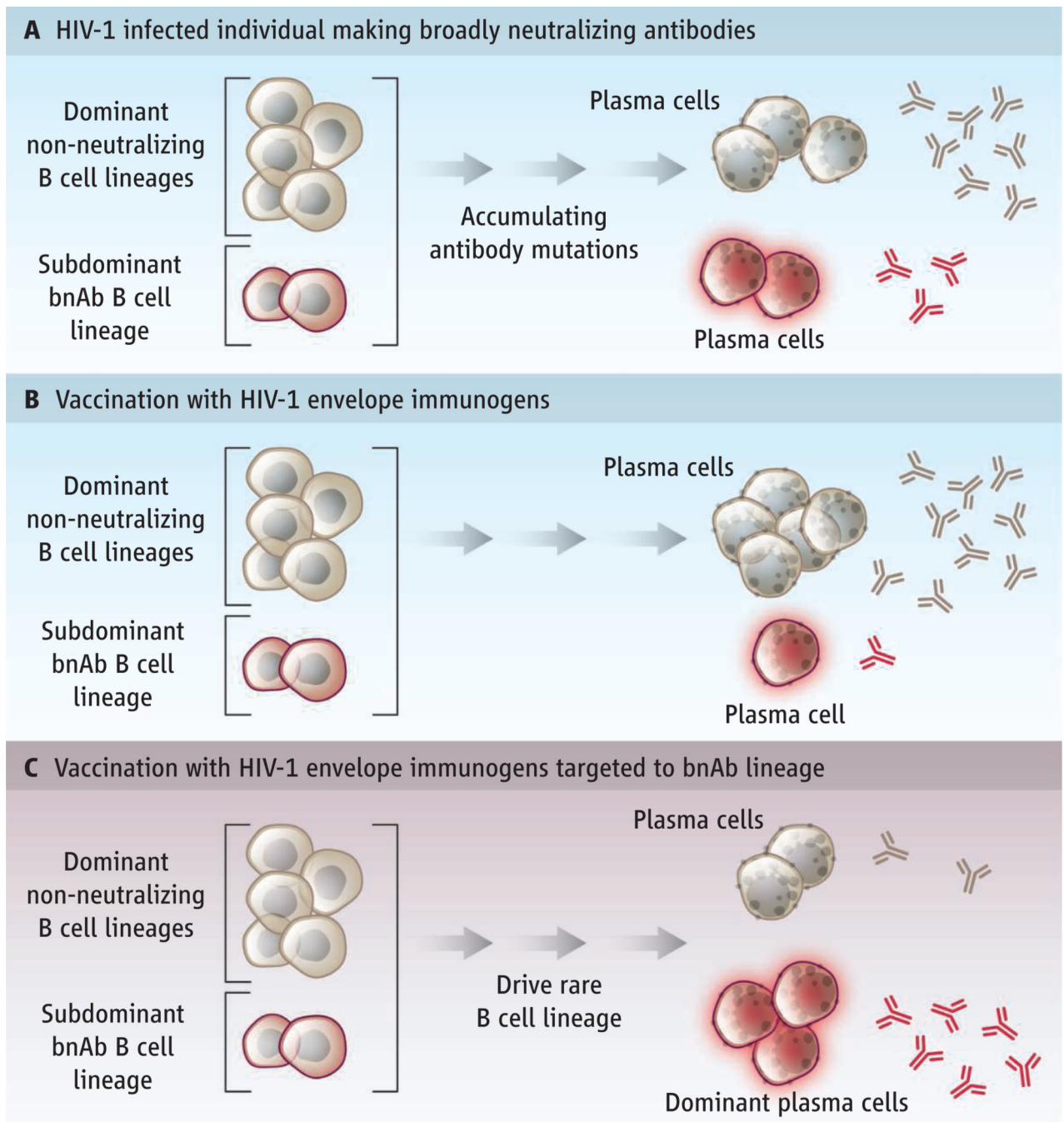
Both immunologic tolerance and difficulty in designing native viral envelope immunogens have conspired against eliciting the production of bnAbs to HIV-1 through vaccination. Now that these factors are better appreciated, we can hopefully accelerate the development of this much needed vaccine, as HIV-1 still infects more than 2 million people and kills more than 1 million people every year, worldwide.

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**Figure 1. Eliciting broadly neutralizing antibodies to HIV-1**

(A) During chronic HIV-1 infection of an individual, a rare B cell clonal lineage that produces a bnAb can emerge and survive after a long antibody maturation process in which large numbers of somatic mutations have accumulated. (B) In the setting of vaccination, B cells capable of generating bnAbs may be present at low frequency, along with higher-frequency non-bnAb B cells. Upon immunization, responding B cells differentiate into plasma cells, but non-bnAb-producing B cells are dominant. (C) The goal of successful immunization for bnAb induction is to use immunogens that specifically and selectively

target the rare bnAb-producing B cell precursors and drive those lineages to become sufficiently dominant to produce protective plasma and tissue fluid bnAbs.