A pathway to HIV-1 neutralization breadth

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Neutralization breadth is thought to be an important feature of an effective vaccine against HIV-1. A study in one individual has now identified the specific viral variant that engaged the necessary antibody precursor, as well as the viral immunotypes that drove neutralization breadth, improving understanding of how to mimic this process with a vaccine.

An obstacle to developing an effective AIDS vaccine is that the immunization strategies tested to date elicit antibodies that neutralize only a handful of HIV-1 viral variants. Yet the current pandemic is fueled by innumerable genetically distinct variants of the virus. It is thus reasonable to speculate that understanding how to induce antibodies that can block infection by many different HIV-1 variants, known as 'broadly neutralizing antibodies' (bnAbs), would be a major breakthrough toward developing a more protective HIV vaccine. In the past five years, more than 100 monoclonal bnAbs have been recovered from a small subset of individuals infected with HIV-1 (ref. 1). These antibodies target the HIV-1 envelope (Env) glycoproteins, and they can neutralize viruses that have been isolated from many different individuals. Genetic and structural characterizations have revealed that bnAbs targeting HIV-1 can arise from several immunoglobulin germline precursors, but they have atypical features, such as high levels of somatic hypermutation, long third complementarity-determining region of the heavy chain (CDRH3) domains and, in some cases, polyreactivity[1]. Moreover, most HIV-1 Env proteins do not readily bind and activate B cells expressing the unmutated common ancestors (UCAs) of immunoglobulin germ lines that have been associated with bnAb development[2].

A priority in HIV vaccine development is to understand how bnAbs are generated during natural HIV-1 infection and to translate this information into novel vaccine immunogens and approaches. However, only a fraction of individuals infected with HIV-1 produce bnAbs—and when they do, it occurs many years after infection. Most people with HIV-1 develop neutralizing antibodies (nAbs) against the autologous virus during early infection, but these antibodies have poor neutralizing activity against other, heterologous viruses[3]. How and why some nAbs follow an evolutionary path toward acquiring neutralization breadth, whereas others do not, has yet to be determined. In this issue of *Nature Medicine*, a new study by Bhiman *et al.*[4] provides mechanistic insight into how co-evolution between HIV-1 Env and a unique B cell lineage paves a path for the development of a bnAb lineage.

The authors used high-throughput B cell culture and next-generation sequencing approaches to analyze interdependent virus and antibody co-evolution during the first two years of infection in an individual infected with subtype C HIV-1, who was a participant in the Centre for the AIDS Programme of Research in South Africa (CAPRISA) cohort. It was previously shown that this individual developed a bnAb lineage that targeted the first and second hyper-variable domains (V1V2) in the Env gp120 subunit. The antibodies in this lineage contained an extended, tyrosine sulfated CDRH3 region that is characteristic of other V1V2-targeted bnAbs, and they were modestly somatically hypermutated[5].

This individual was initially infected by one HIV-1 variant, and then re-infected by a second HIV-1 variant approximately four months later—a phenomenon known as superinfection (**Fig. 1**). Bhiman *et al.*[4] demonstrate that nAb targeting of the V1V2 domain of the superinfecting viral strain by the individual's immune system led to high sequence diversity in this epitope. The nAbs that developed into bnAbs were able to neutralize the mutated V1V2 variants. Thus, the researchers extended previous findings[6–10] that the ability to tolerate autologous viral escape mutations in a single epitope is a cornerstone for increasing heterologous neutralization breadth. These findings also shift the widely held perception that bnAbs target only conserved regions of Env.

Using next-generation sequencing, Bhiman *et al.*[4] identified the UCA of the bnAb lineage and the viral Env variants circulating in this individual that were most likely to have activated the rare B cell that initially generated the bnAbs. Though the UCA was probably present during early infection, it did not interact with—and as a result could not neutralize—the primary infecting strain. However, the UCA did neutralize the super-infecting variant. This led the authors to use single-genome PCR amplification and cloning to identify minor Env variants that evolved from the super-infecting virus and were potently neutralized by the UCA, and thus seemed to have first engaged the cognate B cell. The interaction between these minor Env variants and the UCA occurred within a few months after superinfection, suggesting that early-infection cohorts such as CAPRISA are critical for defining the mechanisms by which bnAbs later develop.

However, the Env variant that initiated the bnAb lineage is not the only one of importance. Viral escape from these antibodies generated many different Env variants, or 'immunotypes', which created an evolutionary path for antibodies that could tolerate variability in the epitope. In this individual's bnAb lineage, the heavy chain sequences all arose from a single UCA, but they branched off into two distinct groups. The first group did not evolve, resulting in neutralization activity that was limited to the original form of the superinfecting virus. The second group showed evidence of continued evolution, suggesting that these antibodies were undergoing repeated rounds of selection

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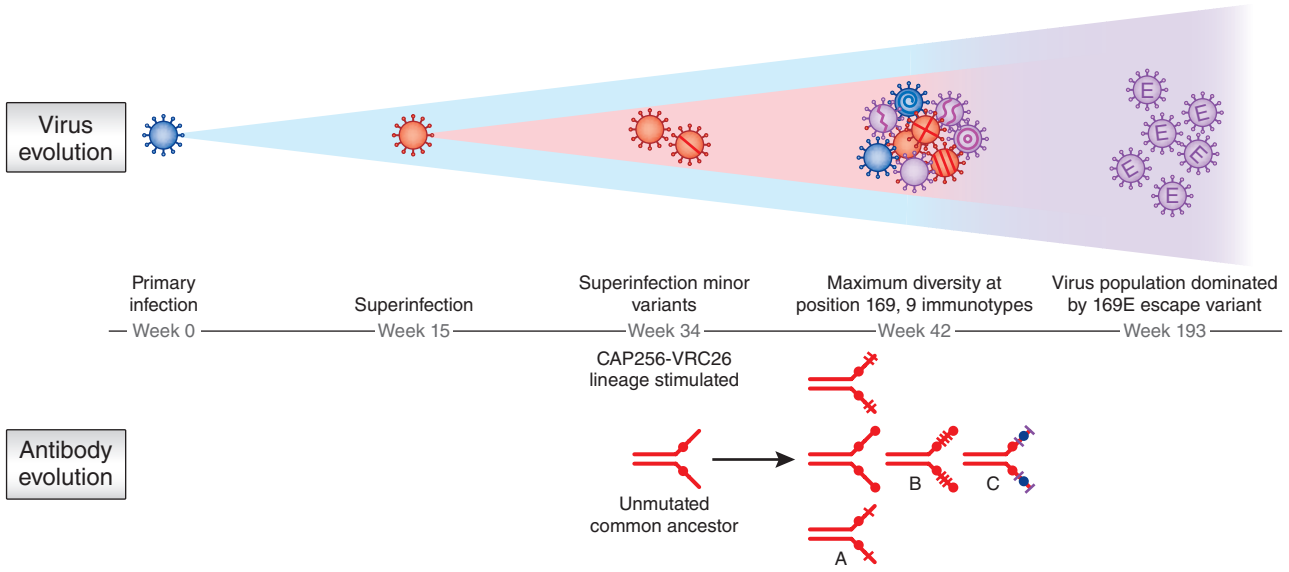

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Figure 1 Bhiman *et al.*[4] found that in an individual superinfected with HIV, bnAb arose during HIV-1 infection as a result of interdependent co-evolution between the superinfecting virus and the individual's antibody response. The primary infecting virus (blue) did not engage the unmutated common ancestor of the bnAb lineage. Instead, minor variants that evolved from the superinfecting virus (red) activated the lineage. Eventually antibody variants emerged that were resistant to the antibody lineage (purple). Some antibodies could neutralize the superinfecting virus, but they failed to mature further (A). Other antibodies showed evidence of evolution, but they could not neutralize the diverse viral variants that arose in response to this individual's immune pressure (B). The only antibodies that acquired neutralization breadth against heterologous viruses were the ones that could tolerate the epitope diversity in the autologous viral quasispecies (C).

and affinity maturation. Within the evolving antibodies, some developed heterologous neutralization breadth, while others remained strain specific (**Fig. 1**). The heterologous neutralization breadth of the VRC26 antibody lineage was strongly correlated with the ability to potently neutralize the many immunotypes found in the patient, resulting in a clear mechanistic understanding of how this bnAb developed. Ultimately, within a single bnAb lineage, there were three antibody outcomes: unmatured, strain-specific and broadly neutralizing. Thus, it will be important to gather more information about why some antibodies of this lineage remained strain-specific, whereas others developed breadth. It could be that the strain-specific nAbs in this individual are actually representative of the normal response to HIV-1, explaining why many HIV-1 infected individuals produce nAbs that potently neutralize the autologous virus yet have limited heterologous breadth.

Several factors may collectively pave the pathway to neutralization breadth in natural infection. A suitable precursor antibody germline must be present in the host B cell repertoire, and an Env variant capable of activating it must be introduced or generated. The site of recognition by the initial antibody precursor also seems to be a key player, as different pathways to breadth were previously described for V1V2- and CD4bs-targeted bnAbs[5,11]. The level of somatic hypermutation is important, but the nature of the mutations also matters. Furthermore, as shown by Bhiman *et al.*[4], temporal exposure to an array of highly related Env variants presenting different versions of the same epitope is also necessary. The authors propose that a viable vaccination strategy for mimicking these events could be to immunize with a carefully selected series of Env immunotypes from the individual studied, beginning with the bnAb-initiating Env and including the subsequent Env variants that contain the mutations most strongly correlated with heterologous breadth. It is important to investigate what type of antibody response these Env immunogens would elicit, which requires carrying out vaccination in a model relevant to the human immune system.

To date, HIV-1 immunization strategies and models have not incorporated a strategic plan for generating bnAbs, even though it is clear that very few, if any, randomly selected Env immunogens are capable of eliciting this type of antibody. In contrast, Bhiman *et al.*[4] provide a rational strategy to take forward and build upon. The bnAb lineage that they describe acquired breadth relatively rapidly (within several months after superinfection) and with moderate levels of affinity maturation, both of which are good signs for a vaccine. Thus, the findings represent an important advance in understanding how to elicit bnAb by vaccination.

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