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Natural Evolution of Broadly Neutralizing Antibodies

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Abstract

Wu et al. couple next generation sequencing with structural analysis to illuminate the key processes that enable the natural evolution and selection of broadly neutralizing antibodies to HIV-1, providing a potential roadmap for the development of HIV-1 vaccine strategies to accelerate the induction of protective antibodies.

The generation of broadly reactive neutralizing antibodies is the holy grail of HIV-1 vaccine research, but no HIV-1 vaccine candidate has realized this goal to date. A substantial fraction of HIV-1-infected individuals are able to induce broadly neutralizing antibody responses over time 1 2. Interestingly, high viral loads and chronic antigen exposure typically appear to contribute to the generation of broadly neutralizing antibodies3 4, although some broadly neutralizing antibodies have also been cloned from subjects with spontaneous control of viral replication. These antibodies typically have high levels of somatic mutations5 6. While the prospect of designing a vaccine that can induce this degree of somatic hypermutation is daunting, understanding the natural evolutionary path of the development of these antibodies may provide important clues for the generation of vaccine immunogens and strategies that ultimately aim to recapitulate this pathway.

In a tour de force study, Wu et al. used next generation sequencing coupled with detailed structural determinations to reconstruct the evolutionary process that led to the development of a series of potent and broad neutralizing antibodies directed against the CD4 binding site from a single donor from 1995 to 2009. Evolutionary analyses highlight the remarkable diversity of the VRC01 lineage, with at least 6 heavy chain lineages and 5 light chain lineages. Interestingly, these clonal families fell into three major clades, with up to 25% intra-clade sequence divergence and up to 50% inter-family divergence. Each clade exhibited marked increases in somatic hypermutation over this period of time, suggestive of progressive evolution over the 15 years. Remarkably, all clonal families were represented at the earliest time points, suggesting early selection that continued to expand in parallel in a progressive manner over the study period. Strikingly, new families reflecting the selection of novel germline B cell populations by the evolving virus did not emerge. These data collectively point to the early selection and progressive development of a finite set of naïve B cell families.

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Despite dramatic sequence diversity among the clades, all representative antibodies from each family recognized an almost identical footprint on the viral envelope, sharing up to 95% conservation in the paratope surface. However, each family evolved a different structural solution to reach the unusual deeply recessed shape of this site of vulnerability on the HIV-1 envelope, illustrating that there are at least several immunologic solutions to the same structural antigenic problem. These results argue that the immune system harbors a remarkable capacity to explore a wide landscape of solutions to neutralize difficult epitopes. The early selection of several germline B cells followed by continuous evolution over a substantial period of time may therefore be critical for the generation of broadly neutralizing antibody responses.

It is well known that HIV-1 mutates at a remarkable frequency, approximately 1.5 substitutions per 100 nucleotides per year. Interestingly, this mutation rate was surpassed by the evolution of the VRC01 lineage, which incorporated approximately 2 substitutions per 100 nucleotides per year. Thus, the humoral immune response evolved more rapidly than the virus in this individual, suggesting a mechanism by which antibody lineages can achieve extraordinary diversity in the setting of chronic HIV-1 infection (Figure 1). The mutation rates in the evolution of other broadly neutralizing antibodies showed even higher mutation rates of 9 to 11 substitutions per 100 nucleotides per year for the V1V2-specific antibody CAP256 and the CD4 binding site-specific antibody CH103. Whether these accelerated rates of mutation are attributable to higher viral loads in the CAP256 and CH103 donors, easier to neutralize features of the antibody paratopes, peculiarities in the host background of the donors, or simply the fact that these antibodies evolved within the first year of infection under distinct inflammatory conditions, is unclear. Moreover, for all three antibodies, kinetic analyses of evolutionary rates suggested a trend towards more rapid evolution of the antibody response in early infection that slowed during later states of infection. These data suggest the importance of developing vaccine strategies that drive persistent B cell selection at these levels. Defining the key triggers that drive accelerated somatic hypermutation, which would allow B cells to explore immunologic solutions more quickly and rigorously, therefore may improve the ability of vaccines to elicit broadly neutralizing antibodies to HIV-1.

The concept that carefully selected Env immunogens may be able to guide B cell development down a particular pathway by sequential vaccination strategies has gained support. The evolutionary complexity highlighted in this study, however, suggests that the design or selection of discrete immunogens able to recapitulate antigen-driven B cell selection pathways will be challenging. Strategies that aim to deliver long-lasting immunogens, such as with the use of replicating vectors, are therefore being explored. Whether viral evolution is also required to drive broadly neutralizing antibody responses remains to be determined. Although a burst in viral diversity has been linked to the rapid evolution of neutralizing responses in certain cases 4, some broadly neutralizing antibodies have been isolated from subjects that exhibit spontaneous control of viral replication and therefore reduced viral diversity.

Several unanswered question remain. One key question is whether similar degrees of evolutionary complexity are required for the development of broadly neutralizing antibodies

against other key targets, such as the V2 or V3 glycan-dependent epitopes, the membrane proximal external region, and the gp120-gp41 binding interface. Another important question is whether triggers that drive accelerated somatic hypermutation can be defined and utilized to allow vaccine-elicited B cells to explore immunologic solutions more rapidly. Overall, the present studies chart the development of CD4 binding site antibodies in a remarkable level of detail, providing insights into the plasticity of the immune response and the path to the generation of broadly neutralizing antibodies.

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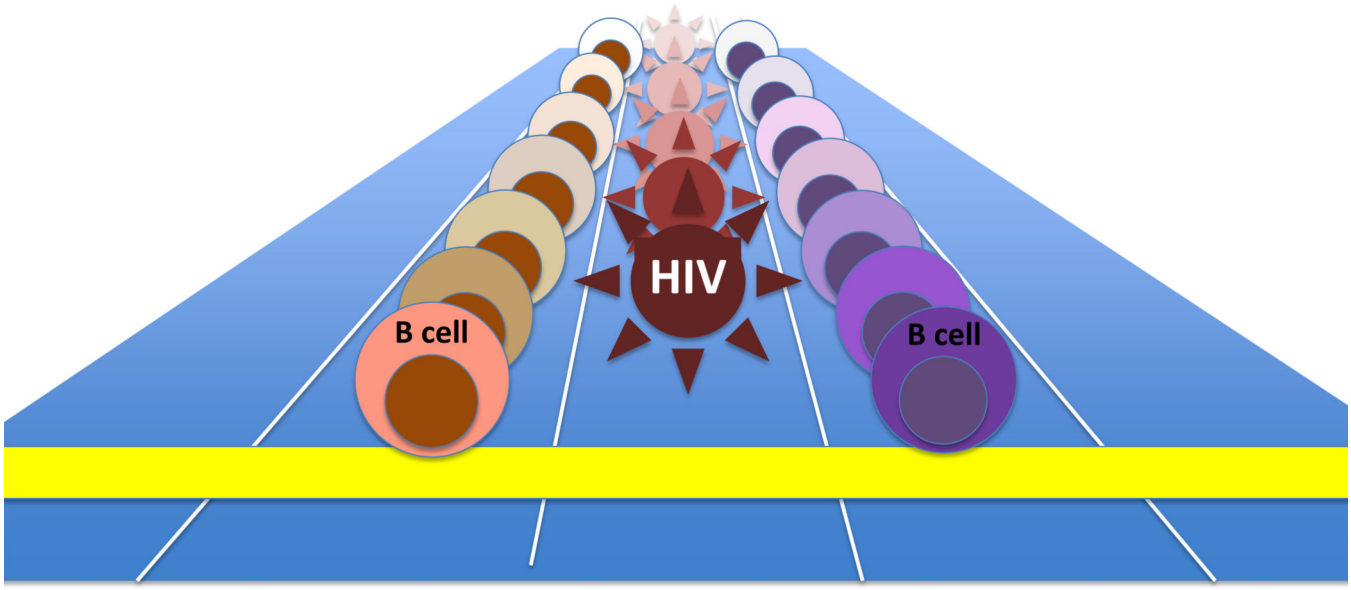

Figure 1.

Relative kinetics of the evolution of HIV-1 and the VRC01 antibody lineage. The antibody lineage evolved more rapidly than did the virus in this individual, suggesting a mechanism by which B cells can achieve extraordinary diversity in the setting of chronic HIV-1 infection.