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New templates for HIV-1 antibody-based vaccine design

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Abstract

A current strategy for the design of neutralizing antibody-based vaccines to prevent HIV-1 transmission is that of reverse engineering, starting from a neutralizing antibody and working back to reconstruct its epitope by structure-based design technology. However, the field has been impeded by a lack of appropriate antibodies for use as templates. Recently, new antibodies have been described that may fulfil this role, invigorating the field.

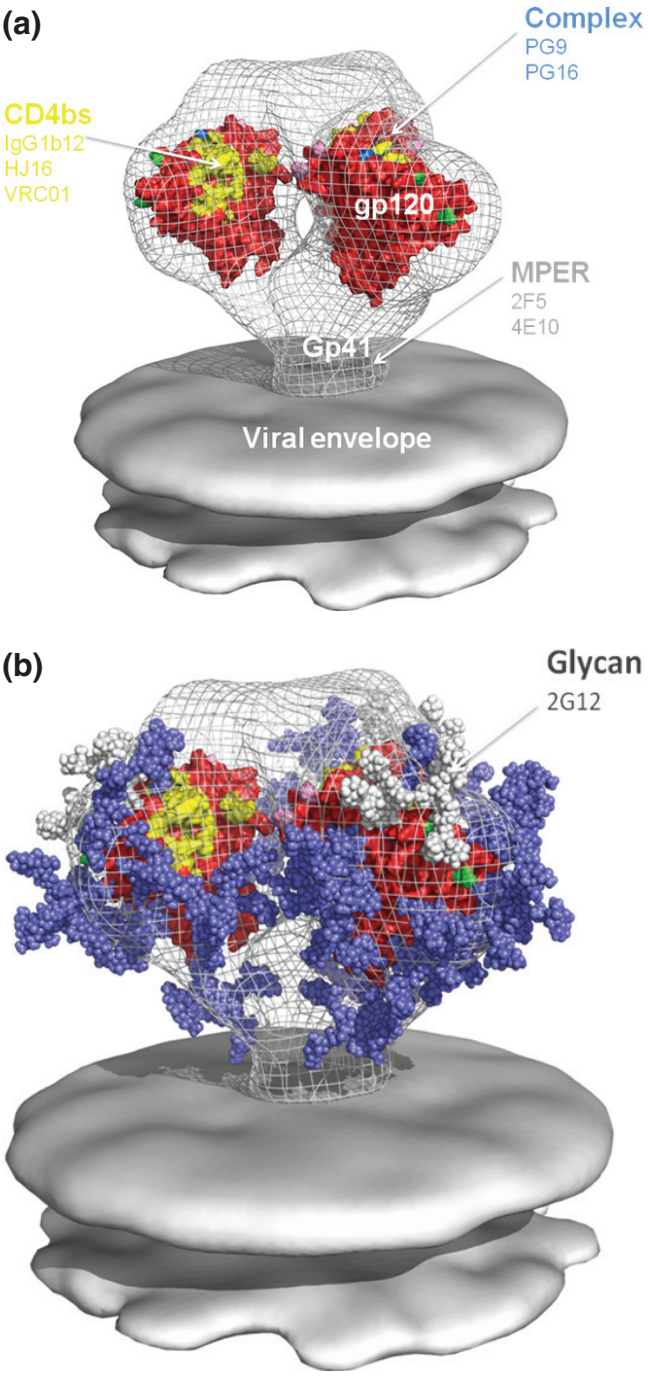
Introduction and context

The human immunodeficiency virus type-1 (HIV-1) is the cause of AIDS and responsible for a major global pandemic, with an estimated 33 million people infected. The most cost-effective mechanism of infectious disease control is vaccination, but to date we have seen only modest success at reducing HIV-1 transmission in a single vaccine efficacy trial [1].

Of the two effector arms of the adaptive immune system involved in vaccine-mediated protection against infectious disease (cytotoxic T cell and antibody), antibodies are most likely to be effective in preventing HIV-1 infection [2-4]. The only target of neutralizing antibodies (NAbs) on HIV-1 is the virally encoded Env glycoprotein. Env is a trimer of heterodimers, each of which is composed of a receptor-binding surface glycoprotein (gp120) and a fusogenic transmembrane glycoprotein (gp41), linked together by non-covalent bonds (Figure 1a) [5]. The majority of Env is cloaked in carbohydrate (Figure 1b) and is highly variable (a) in terms of amino acid sequence between individual virus strains and (b) within an individual virus in terms of Env tertiary and quaternary conformational flexibility [6,7]. These potent immune evasion strategies mean that most NAbs will bind to only a few strains of virus and frequently only with low avidity.

A recent concept is that of using NAbs as templates for recreation of their epitopes in a context different from that of the natural antigen [7-9]. For example, the sequence of a linear epitope can be used to design synthetic peptides that may induce the same specificity of antibody when used as an immunogen. Unfortunately, all linear NAb epitopes discovered to date in Env, excluding some binding within the membrane-proximal external region (MPER) of gp41 (see below), are highly variable and so induce only antibodies that neutralize a narrow range of viral strains. But neutralizing monoclonal antibodies (NMAbs) that recognize conformation-dependent epitopes and that neutralize a wide spectrum of viral strains exist, and these are under development as templates for vaccine antigen design. Until this past year, four NAbs of human origin had dominated the field: IgG1b12, a recombinant NAb derived from a phage-display library that recognizes the CD4-binding site (CD4bs) on gp120; 2G12, an NMAb binding a glycan epitope on gp120; and 2F5 and 4E10, two NMAbs binding the MPER of gp41 (Figure 1) [2,6,7]. Although the epitopes of all of these antibodies are defined and have been excellent prototypes for studying breadth of neutralization, each of these NMAbs has specific difficulties that so far have prevented its successful use as an antigen design template (for details, see [7,8]). Moreover, it is unclear whether these antibodies represent rare or even unique events in B-cell

Figure 1. Location of BNMAb epitopes on HIV-1 Env



The HIV-1 envelope glycoprotein (Env) is shown as a transparent mesh and represents three gp120 molecules non-covalently linked to three gp41 molecules on the surface of an HIV-1 virion [7]. The overall Env structure was obtained at a resolution of approximately 20 Å by cryo-electron tomography and was modified from [21]. gp120 (red) was located into the electron tomography model using the b12-bound atomic coordinates [22]. **(a)** Regions on gp120 or gp41 approximating to prototype broadly neutralizing monoclonal antibody (BNMAb) and new BNMAb epitopes are labelled with arrows. The IgG1b12-binding surface is labelled yellow, and the bases of the variable regions (missing in this structure) are labelled blue, green, and pink. **(b)** The same model with the gp120 glycans shown in blue reveals the extensive glycosylation present as an antibody evasion mechanism on Env, and glycans implicated in BNMAb 2G12 binding are highlighted in white and labelled with an arrow. HIV-1, human immunodeficiency virus type-1; MPER, membrane-proximal external region.

clonal selection or affinity maturation (or both). A related question is whether the relatively rare HIV-1-infected individuals with high-potency, broad-spectrum neutralizing antisera make individual NAbs with specificities that target highly conserved surfaces on Env or whether the neutralization breadth and potency of their sera are predominantly the sum of multiple responses each directed against a strain-specific epitope. We now have answers to these questions in the form of an analysis of the specificities of neutralization in high-titer antisera and several new NMAbs of unusual breadth and potency.

Major recent advances

The availability of high-throughput neutralization assays containing chimeric viruses expressing panels of Env cloned from diverse HIV-1 strains has allowed estimates of the proportion of HIV-1-infected individuals with substantial breadth and titer of serum neutralization [10]. This figure approaches 25% of chronically infected individuals [11-13], raising hope that such responses could be elicited by vaccination in a sizeable proportion of the general population. Strategies based mainly upon affinity trapping of distinct antibody specificities followed by functional analysis of neutralization have allowed mapping of the serum NAb response to HIV-1 with improved resolution and have revealed that the CD4bs is an important target of broadly neutralizing antibody (BNAb) [14,15]. Other regions targeted more rarely by BNAb are the gp41 MPER and the coreceptor-binding region [12]. Several of the studies found multiple NAb specificities, some of which were not accounted for by the known BNAb epitopes, implying novel conserved targets [15-17]. Representatives of such novel specificities were recently reported by Walker and colleagues [18] in the form of two related broadly neutralizing monoclonal antibodies (BNMAbs) (PG9 and PG16) that neutralized approximately 80-90% of representative HIV-1 strains with potencies approximately 10-fold greater than those of the previous BNMAbs. These BNMAbs were cloned from B cells of an HIV-1-infected individual with unusual breadth of serum neutralization activity and were found to bind complex discontinuous epitopes present only on the functional Env structure [18] (Figure 1a). Currently, it is unclear whether these BNMAbs bind epitopes that span more than one protomer within the trimer or whether they bind individual protomers that require a trimeric context to present the epitope. In either case, the quaternary structure dependency of the epitope will present particular challenges for antigen design. Another study found a new BNMAb (HJ16) reactive with an epitope within the CD4bs which is distinct from IgG1b12 but neutralizes a similar proportion (30-40%) of strains [19]. The epitope appears to be robustly expressed on monomeric gp120 under various conditions, suggesting that it may be amenable to structure-based reiteration. Finally, using a new structure-based strategy for selecting CD4bs-specific B cells, a very recent study reports on the isolation of antibodies (VRC01 and VRC02) that neutralize up to 90% of circulating strains of virus at low concentration [20]. At present, the structure of these BNMAb epitopes is unknown, but such potent and broad neutralizing activity in HIV-1-infected individuals gives hope that vaccine antigens based upon one or a few epitopes may be sufficient to protect the majority of the population from infection.

Future directions

The concept of structure-based vaccine design relies on the elucidation of the atomic structure of the target epitope, and this is under way for the recently isolated BNMAbs described above. The translation of structures into antigens for re-eliciting such NAb specificities is a major hurdle since the field has yet to demonstrate proof of principle for this concept. Antibody epitopes that are continuous or conformationally stable (or both) will be the easiest to mimic, and since epitope discovery is largely empiric, it will be important to isolate as many BNMAbs as possible to improve the chances of success in the design of antigens. Once antigens that re-elicit the desired antibody specificities are available, the next challenges to overcome will be those of B-cell immunodominance and of increasing the magnitude and persistence of the B-cell response to vaccination. Not enough is known of the mechanisms underlying these factors, but much will depend upon the adjuvants used to deliver robust T-cell help, B-cell activation, and subsequent affinity maturation and the long-term persistence of antibody-producing plasma cells at the appropriate anatomical locations. Research into all of these areas should be carried out in parallel as a high priority.

Abbreviations

BNAb, broadly neutralizing antibody; BNMAb, broadly neutralizing monoclonal antibody; Env, human immunodeficiency virus type-1 envelope glycoprotein; HIV-1, human immunodeficiency virus type-1; MPER, membrane-proximal external region; NAb, neutralizing antibody; NMAb, neutralizing monoclonal antibody.

Competing interests

The authors declare that they have no competing interests.

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