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AIDS Rev. 2015;17:107-13

Catch Me If You Can – The Race Between HIV and Neutralizing Antibodies

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Abstract

Broadly neutralizing antibodies represent the major protective mechanism of vaccines targeting pathogenic microbes in humans and animals. For HIV, broadly neutralizing antibodies have also been shown to be protective in experimental animal models. However, despite the identification of a respectable number of broadly neutralizing antibodies from chronically infected HIV-positive persons in recent years, attempts to induce such antibodies by vaccines have generally failed over the last decades. Though unsuccessful in view of achieving a protective vaccine against HIV, many of these studies have contributed significantly to the understanding of the generation of broadly neutralizing antibodies against HIV-1 as well as to the vulnerable sites they target on the surface of the virus. Here we review the most important features of patient-derived broadly neutralizing antibodies, the long and complex B-cell maturation pathways required for their production, and the resulting consequences for vaccine development. We further address characteristics of the epitopes targeted by broadly neutralizing antibodies on the virus surface as well as mechanisms of viral escape. Taken together, the identification of vaccine candidates able to induce broadly neutralizing antibodies against HIV-1 is the major challenge in HIV vaccine development. Mutual coevolution of rationally designed HIV vaccine candidates, with affinity maturation pathways of antibodies they induce upon vaccination, may best mimic the natural situation of chronically HIV-infected patients who are able to generate broadly neutralizing antibodies.

(AIDS Rev. 2015;17:107-13)

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Key words

HIV-1. Neutralizing antibodies. Env epitopes. Antibody maturation. Single B cell sorting. Vaccine.

Virus neutralizing antibodies prevent infections with extracellular pathogens

The induction of neutralizing antibodies (nAb), which bind to the surface of pathogens and thereby block their infectivity, is the major mechanism of effective vaccine-mediated protection[1]. Immunogens eliciting such protective antibodies against viral infections comprise live-attenuated viruses (measles, yellow fever), whole inactivated viruses (polio), virus-like particles (most recently documented for papillomaviruses[2]), or subunit vaccines (hepatitis B). For a highly variable and integrating virus like HIV, these classical viral vaccine approaches are either too dangerous due to the high probability of emerging replication-competent HIV, or have failed to induce nAbs with sufficient breadth and potency to neutralize the entire spectrum of HIV types and subtypes differing in about 40-50%

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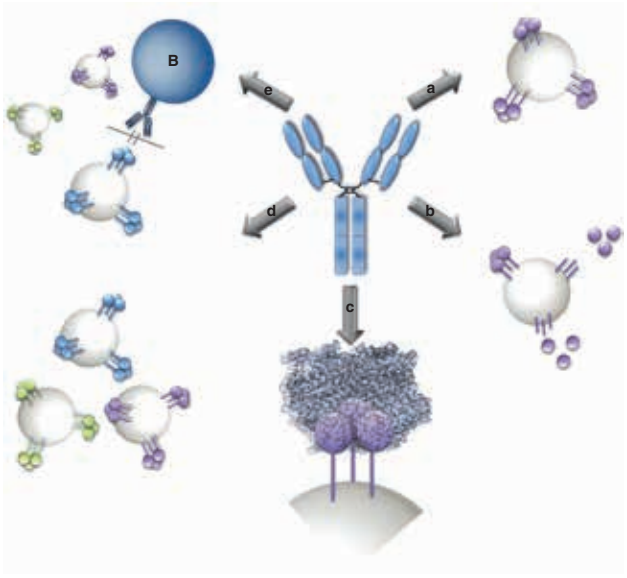

Figure 1. *Env antigenic properties and escape mechanisms from broadly neutralizing antibodies. (a) Due to a low number of Env spikes, binding of bnAbs (center, light blue) is limited and crosslinking between Env protomers (purple) is prevented. (b) Gp120 (purple balls) shedding due to non-covalent association with gp41 after cleavage fools the immune response, as novel non-functional epitopes are exposed on shedded gp120 and gp41 stumps (purple lines). (c) BnAbs access to functionally relevant entry epitopes is restricted by a glycan shield (gray), which masks the Env spike. (d) Antigenic Env variants (light blue, green) escape from neutralizing antibody response. (e) Env antigens (light blue) recognized by highly affinity matured bnAbs (light blue) are generally not able to bind and stimulate unmutated B-cell receptors (dark blue) on naive B-cells (B). bnAbs: broadly neutralizing antibodies.*

in their envelope sequences. Nevertheless, also for HIV-1, broadly neutralizing antibodies (bnAb) have been identified from chronically infected HIV-positive persons during natural infection, which were shown to protect from infection in experimental animal models[3-9], to reduce viremia in infected animals[10,11], and to delay viral rebound after treatment interruptions[12]. Thus, despite the peculiar features of HIV envelope (Env) immunogens and the multiple antibody escape mechanisms that we will address in this review, bnAbs against HIV-1 can principally be induced in a subset of patients. It still remains to be understood how to transfer the mechanisms of natural generation of these bnAbs and their complex affinity maturation pathways into efficient vaccination approaches.

HIV-1 Env antigens, a highly flexible mobile target

In contrast to other enveloped viruses, HIV-1 particles only contain a limited number of Env spikes, about 14, integrated into its lipid membrane. This number is sufficient for infection of target cells, but minimizes the exposure to and crosslinking by nAbs[13] as well as the activation of naive B-cells. Each native functional Env spike consists of three gp120 surface molecules responsible for receptor binding, which are non-covalently linked to three gp41 transmembrane proteins mediating membrane fusion during virus entry. This non-covalent linkage allows a high degree of molecular flexibility of Env during the multistep virus entry process: after binding to the primary receptor CD4, extensive conformational rearrangements have to occur in the Env trimer to expose functional coreceptor binding epitopes. The comparison of crystal structures of unliganded and CD4-bound gp120 nicely documents the conformational changes induced upon CD4 binding, which go along with changes in antigenicity[14,15]. The delayed exposure of the CD4-induced epitopes restricts nAb access to the highly conserved coreceptor binding epitopes as the virus particle is already attached closely to the cell surface at this time point[16].

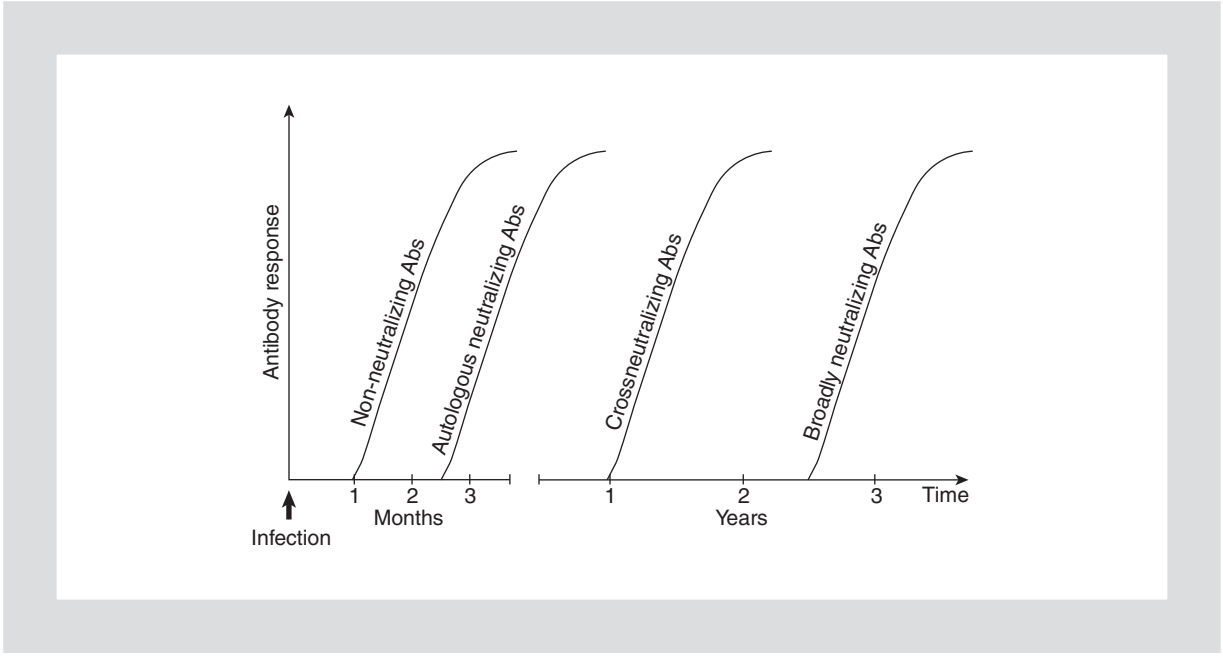

Figure 2. *Evolving broadly neutralizing antibody responses to HIV during the course of infection. Broadly neutralizing antibodies (bnAbs) need years to develop (right). The first antibody response after a few weeks is non-neutralizing, followed by antibodies neutralizing the autologous strain. After about a year first cross-neutralizing antibodies with restricted breadth appear and finally bnAbs are generated in about 20% of the patients.*

Further conformational changes occur after coreceptor binding, in particular in gp41, which folds into a six helix bundle to mediate membrane fusion between the virus and the cell[17-19].

Besides protection of epitopes relevant for HIV-1 entry through consecutive receptor-induced exposure, HIV-1 has evolved several other immune-evading mechanisms to minimize induction of as well as recognition by nAbs (Fig. 1). Non-covalent linkage of gp120 and gp41 renders the native spike unstable due to shedding of gp120 subunits into the circulation. These non-functional monomeric gp120 molecules as well as the remaining membrane-associated gp41 stumps fool the immune system by being immunodominant in terms of antibody induction. However, these antibodies are non-neutralizing.

The high variability of HIV *per se* is another factor contributing essentially to evade antibody responses mounted against the virus. Due to the high error rate of the reverse transcriptase (1-10 mutations per genome per replication cycle) as well as the recombination events, the transmitted virus evolves into a "quasispecies" shortly after infection, from which variants able to evade nAb responses can be selected. Thus, a few HIV variants able to escape the initial antibody response initiate new infection cycles despite the presence of nAbs against the infecting virus. Further, the variable loops in the gp120 molecules cover the trimeric spike to protect the more conserved functional epitopes necessary for infection from an antibody attack and therefore are particularly prone to accumulation of mutations. A peculiar feature of HIV-1 Env proteins is also their extreme degree of glycosylation, whereby N-glycans contribute about 50% of the molecular mass of Env. The composition of the Env glycans is cell-type dependent, and glycosylation affects antibody binding by masking neutralizing epitopes through steric hindrance, by conformational alterations, or by contributing itself to antibody binding[20,21]. The evolving glycan shield[21,22] is driving viral evolution as variable N-linked glycosylation sites shift in position over time, in particular in the variable regions, thus evading nAbs.

Elicitation of broadly neutralizing antibodies during natural infection

Despite the evasion mechanisms described above, in recent years very potent and broadly neutralizing Abs have been identified from a subset of patients chronically infected by HIV-1[23-27]. The best bnAbs neutralize more than 90% of the circulating HIV strains

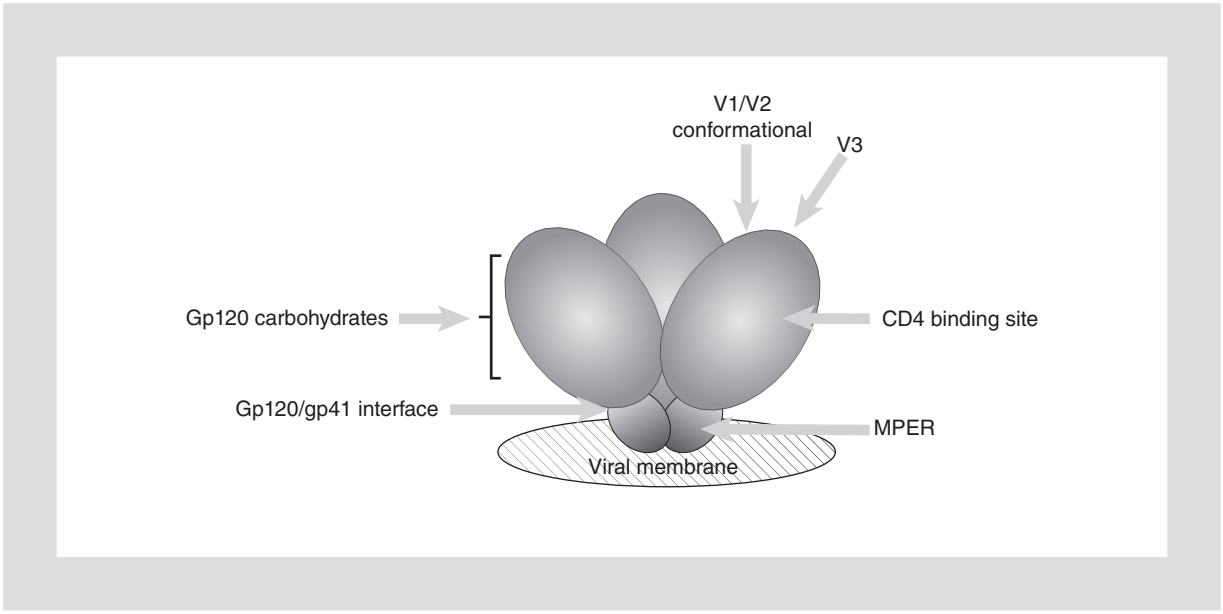

Figure 3. *Location of epitopes for broadly neutralizing antibodies on the Env spike. The trimeric Env spike is shown schematically. Gp120 is in light gray, gp41 in dark gray, and the viral membrane is striped. Broadly neutralizing antibodies can be classified according to their target region on the Env spike. MPER: membrane proximal external region.*

tested with IC_{50} (inhibitory concentration resulting in 50% neutralization) between 10 and 100 ng/ml[28]. Generally, the development of bnAbs takes time, the first ones appearing 2-4 years after infection[29] (Fig. 2). The initial antibody response against the infecting virus is generated a few weeks after infection and often targets gp41. These antibodies are followed a few weeks later by gp120-directed antibodies; however, these initial antibodies are strain-specific and non-neutralizing[30]. After only a few years, antibodies able to neutralize heterologous HIV-1 strains are detectable in about 20% of chronically infected patients. About 1% are termed "elite neutralizers" as their plasma is able to neutralize the majority of circulating HIV-1 strains[31].

The discovery of potent bnAbs in selected patient sera initiated a global effort to characterize these antibodies as well as the epitopes they target on the viral spike, with the final aim to rationally guide the design of new immunogens able to induce such antibodies upon vaccination[32-36]. Over the last years numerous studies in this field led to the recognition that only a few conserved regions on the viral spike are targeted by bnAbs[28,37]. These include in gp120 the CD4 binding site, glycan-dependent conformational epitopes in the V1/V2 loop, a glycan-dependent site at the base of the V3 loop, and in gp41 the membrane proximal external region (MPER) (Fig. 3). In fact, the first generation nAbs (b12, 2G12, 2F5 and 4E10) identified from patients based on the phage display technology or B-cell immortalization[38,39] target the CD4 binding site, a glycan, and the MPER region, respectively.

More recently, new screening technologies involving antigen-specific single B-cell sorting, followed by the cloning of the respective antibody genes[40-45], advanced the field rapidly, resulting in a plethora of new, much more potent and bnAbs (www.bnAber.org). Very potent and bnAbs identified recently in these screenings target the gp120/gp41 interface, probably interfering with the conformational rearrangements in Env required during virus entry[46,47]. Interestingly, although sugars usually are not recognized as foreign by the immune system, some antibodies are able to target HIV-1 Env glycans as these are often of the oligomannose type in contrast to complex glycans usually predominating on cellular proteins[48,49]. Among them are, besides the first-generation monoclonal antibody 2G12 recognizing a cluster of α1-2 mannose residues on gp120[50], PGT 125-128, and PGT 130-131 binding specifically to the Man8/9 glycans on gp120 and potently neutralizing across clades[51,52].

Furthermore, bnAbs share unusual properties hampering their induction. The bnAbs are often polyspecific, i.e. they cross-react with cellular proteins or phospholipids[53]. Thus, they may be subjected to tolerance mechanisms, resulting in potential elimination of the respective autoreactive B-cells. Many of the bnAbs are

characterized by long CDR3 regions in their immunoglobulin heavy chains[54-56], which can form a "hammerhead-like" structure, enabling the interaction with the HIV-1 envelope protein. Another unusual feature of HIV-1 bnAbs is the high degree of somatic hypermutations, in particular within the HCDR3 region, reaching up to 32% in some of the known bnAbs[43,57,58]. This reflects the complexity of the mutational maturation pathways required for the generation of such high-affinity bnAbs.

The dilemma: How to design Env immunogens able to induce broadly neutralizing antibodies upon vaccination?

As outlined above, bnAbs can be generated in patients chronically infected by HIV-1; however, no Env immunogen designed so far was able to induce such bnAbs upon vaccination. One reason for this may be the extensive B-cell maturation pathways required to generate these special antibodies with highly mutated and extra long HCDR3 regions, which ultimately enable high-affinity binding to the rapidly evolving Env antigens. Thus, structural analyses performed on bnAbs and their cognate epitopes do not necessarily reflect the original Env epitope, which was able to stimulate a naive B-cell having complementary B-cell receptors. Env immunogens as components of a vaccine have to recognize B-cell receptors on naive B-cells. This is the initial stimulation for B-cell differentiation and maturation pathways required for high-affinity binding antibodies finally secreted from differentiated plasma cells. Furthermore, these maturation pathways are complex as they have to lead to highly mutated and structurally peculiar antibodies by avoiding, at the same time, autoreactivity, which would lead to the elimination of the corresponding B-cells. In line with this, next-generation sequencing approaches led to the recognition that the inferred germline precursors of bnAbs often do not bind the Env antigens recognized by the mature bnAbs, further proving the discrepancy between known epitope structures for bnAbs and suited Env immunogens able to induce such antibodies[55]. Further studies on longitudinal samples from patients with bnAbs are needed to better understand the relationships between Env antigens and coevolving antibody affinity maturation. It may well be that only a mutual coevolution of Env antigens and the respective matching B-cell receptors will be able to drive antibody affinity maturation to a degree needed for broad neutralization of primary HIV-1 strains across clades.

Optimization of broadly neutralizing antibodies in view of their application as therapeutic vaccines

As long as bnAbs cannot be induced through vaccination, the large collection of bnAbs may have potential for preventive and therapeutic applications, in particular, as for some bnAbs, protection from infection has been shown in the SHIV/macaque model or in humanized mice[6,59]. However, high production costs and limited half-life restrict the applications to special cases. For instance, bnAbs may serve as postexposure prophylaxis under certain circumstances or they may prevent a rise in viremia during antiviral treatment interruptions. There is also room for further optimization of bnAbs, which may result in reduced quantities needed. Further optimization could potentially be achieved by (i) increasing antibody affinity through genetic engineering, (ii) combining various bnAbs targeting different epitopes, (iii) combining different paratopes (heteroligation) in one molecule[60], (iv) optimizing the antibody size depending on the targeted epitope, i.e. smaller antibody formats like single domain antibodies may preferentially enter the glycan shield to get access to receptor-binding pockets[61], (v) expressing and continuously secreting bnAb constructs from replicating vectors preferentially at mucosal sites[62], (vi) providing additional Fc-mediated functions like antibody dependent cell-mediated cytotoxicity (ADCC) that also target infected cells, and (vii) engineering antibodies to target cytotoxic immune cells towards HIV-infected cells[63].

Conclusions

The final goal in HIV vaccine development would still be the development of a prophylactic vaccine able to reduce the number of new HIV infections worldwide through active immunization of the healthy population. Clearly, the induction of bnAbs by this vaccine is a major aim, but this is a very ambitious aim due to the difficulties described above. On the other hand, there have been some promising results from the last large HIV vaccine efficacy trial, RV144, which was the first

to show efficacy against sexual HIV-1 acquisition, with roughly 30% efficacy at 42 months[64]. Extensive follow-up analyses showed that the major immune correlates of protection were antibodies directed against the V1V2 region of gp120; however, interestingly, these antibodies of the IgG1 and IgG3 subclass were not broadly neutralizing but preferentially mediated ADCC, an effect which was abrogated by high titers of IgA against Env[65]. Thus, besides bnAbs, additional antibody mediated mechanisms may also contribute to vaccine-induced protection. Further studies on infected and uninfected individuals have to show the contributions of the different antibody mediated protective mechanisms[66].

Acknowledgements

We thank Kathleen Mohs for her help with editing the manuscript.

Funding

The Georg-Speyer-Haus is supported by the German Federal Ministry of Health and the Hessian Ministry of Higher Education, Science and the Arts.

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