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Review

Broadly Neutralizing Antibodies (BNAbs): templates for HIV-1 vaccine design

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For most licensed vaccines, protection efficacy is mainly conferred via the induction of neutralizing antibodies. Recently, potent and broadly neutralizing antibodies (bNAbs) have been isolated from certain HIV-1 elite controllers. The therapeutic and prophylactic efficacy of these bNAbs has been evaluated in animal models. The results were promising as bNAbs concentrations that could confer total protection were achievable by vaccination. Extensive efforts have been made to induce such bNAbs against HIV-1 infection, but none has succeeded yet. With a better understanding of the structure of bNAbs by X-ray diffraction and independent longitudinal observation of bNAbs in HIV-1 infected individuals, new ideas to guide the design of HIV-1 vaccines are expected to be proposed. Here, we reviewed strategies of viral escaping, characters and targets of HIV-1 bNAbs, and strategies of current vaccine design. Our review provides indication of potent bNAbs in role of vaccine design.

Keywords: broadly neutralizing antibodies (bNAbs), HIV-1, AIDS, vaccine design.

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HIV-1 envelope and viral escape

HIV-1 envelope glycoprotein is not only responsible for viral binding with the facilitation of receptors and co-receptors, but also serves as the main target for HIV-1 specific antibody neutralization in controlling HIV-1 viremia and disease progress via antibody's function in either impeding viral binding or blocking membrane fusion [1-9]. HIV-1 envelope is a transmembrane protein. The env gene of HIV-1 codes for the gp160 protein which forms a homotrimer. The gp160 precursor will be cleaved into gp120 and gp41 by the protease in the host cell. Thus the envelope protein is a trimer that is composed of three copies of heterodimers of gp41 and gp120. gp120 mediates viral binding with viral receptor CD4 and co-receptors CCR5/CXCR4, whereas gp41is responsible for membrane fusion [10]. HIV-1 specific antibodies induced in early stage of infection, which cannot control viral replication, are against gp41 [11,12]. After another 4 to 14 weeks, gp120-specific antibodies are induced, showing limited neutralizing ability against autologous viruses [13,14]. Meanwhile, through rapid viral replication and high error-prone reverse transcription, certain viral mutants resistant to autologous neutralizing antibodies quickly emerge and soon dominate the viral swarm [13,15]. The constant battle between neutralizing antibodies and escaped HIV-1 mutants finally leads to the appearance of bNAbs in certain long term non-progressors (LTNPs) at the cost of

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producing highly mutated HIV-1 viruses resistant to autologous bNAbs [14,16-20]. Recent progress in molecular structure has contributed greatly to the understanding of HIV-1 immune evasion which suggested an explanation that why HIV-1 envelope proteins fail to elicit effective neutralizing antibodies as other viral vaccines did [21,22]. The most common strategies recruited by HIV-1 in impeding bNAbs generation are concluded as follows:

Extensive glycosylation

Extensive glycosylation are commonly observed on envelopes of escaped viruses, which is speculated to be one of the main reasons for viral escape [13,23-29]. This "glycan shield" makes the epitopes on the envelope more inaccessible to antibodies. In addition, the glycan shield displayed on the envelope shares similarity to human glycoproteins, which has high risk to be not recognized by human B cells due to the immune tolerance to autologous antigens generated along with B cell development and maturation [30,31].

Conformational masking

Conformational masking is responsible for HIV-1 immune evasion [32]. Two functional sites on the envelope are the main beneficiaries to this strategy. One is CD4-induced binding site (CD4is), which appears on the envelope only after viral binding to CD4 receptor. The other is the membrane-proximal external region (MPER) region which is normally sealed off except when membrane fusion occurs [33]. The importance of conformational masking and heavy glycosylation in immune evasion has been well illustrated by the difference study in antibody immune responses during infection of HIV-1 and HIV-2. HIV-2 envelops are normally less conformational masked or glycosylated. Accordingly, bNAbs are commonly observed existing in HIV-2 infected individuals rather than HIV-1 infected individuals [34-38].

Paucity of HIV-1 spikes

The paucity of envelope molecules on the viral surface is another reason for envelope-induced immune evasion [39,40]. About 14 envelope spikes in average are expressed on each HIV-1viral particle, whereas the envelope spikes on other viruses are much higher [41]. Given that so few envelop spikes are displayed on the envelope protein, antibodies have difficulty in bivalent binding to two different spikes on the same viral particle. Thus, bivalent binding can hardly be achieved in HIV-1 which results the loss of efficacy.

HIV-1 epitopes targeted by bNAbs

Recently, an increasing number of bNAbs with improving breadth and potency have been identified from certain LTNPs [8,42]. In some cases, a single bNAb can recapitulate the neutralizing ability of serum [8,9,43-47]. But more often it resulted from the combined effects of multiple antibodies targeting different functional epitopes of HIV-1 envelopes [16,42,48-50]. Based on the antibody targeting activities, these functional epitopes can be classified: CD4 binding site, N-linked glycan-containing epitopes, and MPER.

CD4 binding site (CD4bs)

CD4bs, a recessed pocket in HIV-1 envelope, is highly conserved which serves as a vulnerable site for interception by antibodies [51-54]. CD4bs antibodies can bind HIV-1 envelopes by mimicking CD4 via Complementarity-determining regions (CDR) H2 and adjacent residues [55-57]. Considering the special requirement for CDR H2, the variable regions of heavy chain (VH) of these CD4-mimic antibodies identified are invariably derived from either VH1-2 [44]or VH1-46 subfamily [49]. Most CD4-mimic antibodies identified from different LTNPs are from VH1-2 [44,48,49,55,58]. Recent studies showed that only VH1-2 germline encodes Trp50, Asn58, and Arg71, which are commonly existed in CD4-mimic antibodies, suggesting their critical role in antibody structure for envelope recognition. By contrast, limitations for light chains are few. Light chains with shorter CDR L1[56,58] or CDR L3 [59] are preferred. Compared with VH1-2 derived antibodies, VH1-46 antibodies, represented by NIH45-46, are less common. Besides, special requirements for CDR L3 and residues signature are unnecessary for VH1-46 antibodies [49,60]. In some cases, antibodies recognize CD4bs by using the long CDR H3 [61]. These antibodies exhibit less breadth and potency compared with CD4-mimic antibodies, which have been isolated from different LTNPs, including b12 [62] and CH103 [61].

N-linked glycan-containing epitopes

Although HIV-1 envelopes are generally covered with heavy glycans, certain bNAbs acquired the ability to recognize these potential N-glycosylation (PNG) sites after long-term evolution [43,63-66]. Given the high homogeneity of N-linked glycans on HIV-1 envelopes with host cellular proteins, development of glycan-specific antibodies should be especially difficult as the deletion of autoreactive B cells occurs early in vivo [67]. However certain bNAbs overcome this limitation by recognizing unique structures formed by multiple glycans or by both glycans and adjacent peptides that do not exist in cellular proteins. Asn332 glycan in V3 loop, along with conformational adjacent V3 domain, is the dominate epitope among all potential N-glycosylation (PNG) sites. Large numbers of HIV-1 glycan-specific antibodies are identified, such as PGT128 [43,68], PGT135 [43] and 2G12 [69]. Notably, the targeting epitope for PGT128 contains glycans at Asn301 and partial V3 loop beside Asn332 [68]. PGT128 can recognize and penetrate the glycan shield via its long CDR H2 and H3. The target epitope of 2G12 includes N-glycans at Asn295 and Asn339 in addition to Asn332. 2G12 can recognize the epitope via combining two antigen binding fragment (Fab) to a closely dimer [70]. Generally, Asn332-V3 antibodies are equally potent as CD4bs antibodies but with a narrower breadth [43,71]. The mechanism underlying its neutralizing activity remains unclear, but interference of CD4 binding may be involved [72].

As the first bNAb isolated by single B cell cloning in 2009, PG16 can recognize conformational epitopes which included glycans at Asn160 and adjacent residues [63,73]. More antibodies targeting similar epitope were subsequently isolated, such as PGT141-PGT145 [43] and CH01-CH04 [74]. The most remarkable character for these antibodies is the extremely long CDR H3. For example, CDR H3 of PG16 consists of 28 residues which can bind glycans with Asn156, Asn160, and part of the V2 loop [64]. Another study showed that the binding site of PG16 covers two gp120 on top of the envelope trimer [75], which explains why HIV-1 envelopes are not recognized by CD4 after PG16 binding [76]. However, the breadth of PG16 is not high and fails to neutralize some sensitive HIV-1 strains, possibly caused by the loss of L-linked glycans in the V3 loop [63]. Another HIV-1 glycan-specific antibody, 8ANC195 can recognize the N-linked glycans at Asn234 and Asn276, which is very close to CD4bs in terms of conformational structure [49].

MPER

Although gp41-specific antibodies dominate the early humoral immune response, bNAbs targeting MPER are few [77-81]. As an indispensable part of membrane fusion, MPER is relatively conserved. Many factors might contribute to the low frequency of MPER-specific antibodies isolated in vivo, such as, host mimicry [82-84], steric factor [85], and hydrophobicity [82]. In addition, MPER is partially buried and only transiently exposed [33,86]. MPER-specific antibodies are usually poly-reactive. MPER-specific B cells may be selectively deleted during B cell development and maturation process [65,67,87,88]. This concept was confirmed with the identification of human proteins that can cross-react with MPER-specific antibodies [84,89]. The deletion of MPER-specific B cells has also been observed during B cell development in 2F5 knock-in mice [90].

Characters of bNAbs against HIV-1

Extensive mutations

Nearly all bNAbs identified so far are characterized with extensive somatic mutations on both VH and VL fragments [8,91-96]. The average number of mutation nucleotides for mature human antibodies are between 15 and 20 [97], whereas HIV-1-specific bNAbs carry more mutations [42]. Notably, about 40-100 mutations are observed on VH for most bNAbs [43,44,49,55,63,71,98,99]. Later studies confirmed that these mutations are indispensable to the broad and potent neutralizing activity of bNAbs, because both binding and neutralization abilities of their corresponding germline antibodies are much weakened or even abolished [49,57,61,98,100]. Somatic mutations in vivo are induced by activation-induced cytidine deaminase (AID) in germinal center B cells [101]. Hot spot sequences are mainly located within CDR fragments that explained why more mutations are scattered in CDR regions than those in framework regions (FWR). Besides, single point mutations are more often observed, whereas insertion and deletion occurred less frequently [98,101]. Generally, FWRs have a certain degree of tolerance for mutations in DNA level and replacement of mutated FWR fragments with germline counterparts does not affect binding affinity [98]. Intriguingly, when the same

replacement is examined in bNAbs, a significant reduction in neutralizing activity is observed, suggesting that the mutations in FWR fragments are critically important for neutralization [98].

Long CDR H3

CDR H3 is the most diverse sequence that is formed via VDJ recombination during the maturation of B cells [102-106] with an average length of 16 amino acids [97]. However, extremely short or long CDRs have been observed in a number of bNAbs [107]. For example, the length of CDR H3 is 30aa in PG9/PG16 [63,108-115] and 33aa in PGT145 [43]. Other bNAbs with extremely long CDR H3 include PGT121, PGT 135, 10E8, and CHO01-04 [107]. Notably, extremely long CDR H3 is not a prerequisite for all bNAbs, as its length in CD4-mimic antibodies is usually very short at around 5aa, which still shows broad and potent neutralizing activity [59].

Poly-reactivity

Poly-reactivity has been frequently observed in many bNAbs suggesting that these antibodies can recognize non-HIV-1 antigens. Given that most poly-reactive bearing B cells have been selectively deleted because of central and peripheral tolerance [67], it is interesting to explore why some HIV-1-specific antibodies can be rescued [65,82]. Some speculated that this phenomenon may be due to the paucity of envelops on HIV-1 particles which force bNAbs to seek another epitope for bivalent binding [40]. However, current evidence shows that poly-reactivity may be formed during the extremely long process of antibody maturation. Considering that most germline antibodies of bNAbs fail to bind with HIV-1 envelopes, B cells bearing these germline antibodies are possibly first activated by non-HIV-1 antigens [116,117].

Epitope	BnAb	Isotype	VH	VL	Mutation (%) of VH	HCDR3 lengths(aa)	Neutralization breadth IC50, %:	Neutralization potency (μg/ml):	Polyreactivity
CD4bs	b12	IgG1	1-3	κ3-20	13.1	20	70	2.82	yes
	VRC01	IgG1	1-2	κ3-11	32.1	14	93	0.32	no
	NIH45-46	IgG1	1-2	κ3-20	35.7	18	100	0.07	yes
V1/V2	PG9	IgG1	3-33	λ2-14	16.7	30	79	0.23	no
	PG16	IgG1	3-33	λ2-14	20.5	30	74	0.02	no
V3	2G12	IgG1	3-21	K1-5	31.7	16	41	2.38	no
	PGT128	IgG1	4-39	λ2-8	19.0	19	71	0.02	no
MPER	2F5	IgG3	2-5	κ1-13	15.2	24	67	1.44	yes
	4E10	IgG3	1-69	κ3-20	15.6	20	98	3.41	yes
	10E8	IgG1	3-15	λ 3-19	20.4	22	98	0.25	no

Figure 1 Notable characteristic of representative HIV-1 bNAbs.

Rational design of vaccines to elicit bNAbs

The importance of passive treatment with antibodies has been widely recognized. Compared with antiretroviral drugs, antibody therapy has extraordinary advantages [118-133]. First, antibody therapy provides long-term protection (two to four months) as the half-life of antibodies usually ranges from two to three weeks. Second, bNAbs with great breadth and potency are available, which can neutralize nearly 100% HIV-1strains in low concentration (0.05μg/ml). Third, given that HAART has failed to eliminate HIV-1 latency [134], the clearance of viral latent reservoirs by Fc fragment-induced immune response has been increasingly appreciated [135,136]. Antibody dependent cell mediate cytotoxicity (ADCC) helps eliminate intracellular HIV-1 virions by killing HIV-1 infected cells [137]. Fourth, certain bNAbs can inhibit cell-to-cell transmission of viral particles [138]. Finally, more effective viral control has been documented with the combined use of bNAbs and HAART according to the

stages of viral replication cycle [139-142]. HIV-1 antibody therapies have been evaluated in animal models over a decade ago with the first generation HIV-1 neutralizing antibodies, b12, 2F5, and 2G12. The results were quite discouraging as protection was not observed [143]. Moreover, antibody-resistant HIV-1 mutants emerged quickly after treatment [143-145]. With the isolation of the secondary generation of bNAbs with extreme high neutralizing breadth and potency, the therapeutic efficacy of these bNAbs were evaluated in humanized mice and rhesus macaques [138,146-148]. Results showed that treatment with single bNAb can induce a transient drop in viral load, whereas treatment with combined antibodies induces long-term control of viral loads to undetectable levels [146]. Significantly, no antibody-resistant HIV-1 variants were observed during three months of treatment. Moreover, viremia rebounds did not occur after the withdrawal of antibodies in 10%-15% of humanized mice [146-148]. In addition, a recent study showed that bNAbs can effectively reduce the size of viral reservoirs in humanized mice [148]. Moreover, bNAbs were further examined in rhesus macaques. One shot of bNAbs provided rapid control of viral loads for nearly two months at about 5μg/ml [149,150]. Interestingly, studies showed that even single bNAbs can confer long-term control of HIV-1 load in most SIV infected rhesus macaques, compared with only transient reduction in humanized mice [149,150]. The reason why bNAbs provide better control in rhesus macaques than in humanized mice remains unclear. However, the difference in immune systems may be the main reason [140]. Therefore, although the efficacy of bNAbs therapy in human needs to be further verified, the preliminary data in animal models are promising and provide hope for fighting against HIV-1/AIDS in the future.

Potent bNAbs show great prophylactic or therapeutic applications in animal models [149-152]. Vaccines that can elicit such bNAbs would be greatly valuable for the finally eradication of HIV-1/AIDS. However, previous vaccine trials tested to date failed to induce such bNAbs in both animal models and humans [153]. An increasing number of bNAbs have been identified and characterized from HIV-1-infected individuals, so how bNAbs are naturally generated within the patients deserve further investigation, which may provide valuable clues for HIV-1 vaccine design. Both host and virus factors are speculated to be responsible for the generation of bNAbs [154]. If host factors are the main reason, designing vaccines to induce bNAbs in the majority of the immunized population may be impossible. However, recent studies proved that viral factors, especially the successive emergence of HIV-1 envelopes from escaped variants, may contribute to the elicitation and maturation of bNAbs. Previous studies from rhesus macaques indicated that the envelopes of founder viruses are associated with the initiation of bNAbs because SIVs with different envelopes show distinct abilities to induce neutralizing antibodies. For example, antibodies are induced in most macaques infected with AD8 but not DH12 virus [155,156]. The importance of the initial envelope was further approved by the natural occurrence of bNAbs in an individual with HIV-1 superinfections [157]. The individual was infected with HIV-1 viruses of two different lineages. However the neutralizing antibodies were induced by the viruses in one lineage. The diversity of a viral population may be associated with the breadth of neutralizing antibodies [158,159]. Based on these findings, two vaccine strategies have been proposed: 1) HIV-1 immunogen design based on the structure of bNAbs and targeting epitopes [160,161]; 2) reproducing the natural occurrence of bNAbs in vivo by multiple successive immunizations with correlated immunogens [42,50,61,162].

Design of immunogens based on neutralizing epitopes of envelops

The HIV-1 envelope susceptible sites to bNAbs have been studied for long. Thus, modified HIV-1 envelopes and their structure mimicals have been designed and tested in animal models. Unexpectedly, bNAbs failed to be induced by this strategy [160,163]. A later study reported that the inferred germline antibodies of most known bNAbs do not bind envelopes at all, which explains why the previous HIV-1 immunogens failed to induce bNAbs [49,57,98,100]. The germline precursors of 2F5 can bind envelopes, but they cross react with autologous proteins [164]. Thus, B cells expressing 2F5 germline antibody are most likely to be removed in the process of B cell development [67,82-84].

Design of immunogens based on the inferred germline precursors of bNAbs

The recombinant envelopes and peptides that can bind

the germline antibodies by mimicking CD4bs and V1/V2 domains, respectively, have been designed for vaccination [165-167]. Theoretically, vaccination with these peptides may activate the expansion of CD4bs- or V1/V2- specific B cells. However, these trials failed because activation of B cells was insufficient. In addition, the frequency of mutations in variable regions of antibodies during B cells maturation in germinal center is high, which might be important for the neutralizing activity of bNAbs [101].

Design of immunogens based on B cell lineage maturation pathway

When mutations in mature antibodies induced by viral or bacterial infection reach to a certain level, they cannot be induced by additional stimulations [97,168-170]. Intriguingly, about 40-100 mutations accumulate in bNAbs. To explain this phenomenon, a coevolution model of viruses and antibodies has been proposed [42,49,50,61,171]. According to theory, early antibodies are elicited by the founder HIV-1 strains, which usually weakly bind envelopes of the founder viruses with low or even no neutralizing activity. After several rounds of antibody maturation in germinal center, these intermediate antibodies acquire better binding and neutralizing abilities against the early viral strains. Meanwhile, the diversity of the HIV-1 viral pool expands quickly because of the error-prone reverse transcriptase and relatively short life cycle of HIV-1. HIV-1 variants resistant to contemporaneous antibodies are selected in vivo because slight alterations in binding epitopes on envelope might exempt the virus to be neutralized by strain-specific antibodies produced in the early stages. Responding to the evolution of viruses, strain-specific antibodies also experience further mutations during affinity maturation in germinal center. Mutations at certain positions may help the antibodies to acquire additional breadth, which can neutralize both the founder and escape variants. Finally, bNAbs might appear in some HIV-1-infected individuals after the iterative repetitions of antibody mutations and HIV-1 escape. The long process of coevolution explains why bNAbs emerged after two to four years [98,171]. The elicitation and maturation of bNAbs were observed in certain HIV-1-infected individuals by two independent studies. The formation of CD4bs-specific bNAbs CH103 was first reported by Liao's group in 2013 [61], whereas a similar antibody maturation pathway was observed in V1/V2-specific bNAbs by Doria-Rose and colleagues one year later [157]. As exemplified in the maturation pathway of the CH103 family, the germline precursor of unmutated ancestor antibodies shows no detectable binding activity with HIV-1 envelopes. However, early intermediate antibodies with limited mutations that can bind HIV-1 envelopes emerged about 14 weeks after infection, which has low binding affinity at 96,500nM. Since then the coevolution of HIV-1 envelopes and antibodies is longitudinally observed. The maturation affinity of CH antibodies was noted to increase from 96,500 nM for early intermediate antibodies to 2.4 nM for mature ones. Consistent with these observations, a new strategy was proposed to elicit bNAbs in individuals by mimicking the natural occurrence and maturation of human B cells, named B cell lineage immunogen design [162]. In brief, this strategy can be divided into three steps: 1) to isolate bNAbs and corresponding intermediate precursors from LTNPs. 2) to draw the phenogenic relationship of the unmutated ancestor antibody (UA), intermediate antibodies and mature antibodies. 3) To use these antibodies as templates for designing immunogens with high binding affinity. Unlike classical immunization schemes, distinct but closely related immunogens are used for prime and boost in B cell lineage vaccination. To induce the further maturation of antibodies, multiple rounds of continuing boosts are required [74,107,172-176].

Conclusion

In summary, the most encouraging progress came from the discovery of bNAbs from HIV-1 LTNPs with single B cell cloning technique in the past few years. These antibodies can efficiently reduce viral loads and slow down the disease progress as shown in humanized mice and rhesus macaques at the concentration accessible by vaccination, thereby providing hope for the design of HIV-1 immunogens. Different strategies for immunogen designs have been proposed. However HIV-1 vaccines that can elicit such bNAbs in vivo are still presently unavailable. Our review provides indications in potent neutralizing antibodies development and vaccine design against HIV-1.

Conflict of Interest

The authors contribute equally to the manuscript and claimed no interest.

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