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HIV-1 Broadly Neutralizing Antibodies: Identification, Development and Vaccine Evaluation

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Abstract

Numerous human immunodeficiency virus-1 (HIV-1) broadly neutralizing antibodies (bNAbs) have been produced and details of their generation, evolution and structure provide a blueprint for effective vaccination. Recent advances in next generation sequencing (NGS) technologies have allowed high-resolution characterization of the antibody repertoire, and have enabled thorough characterization of many HIV-1 bNAbs. These bNAbs identified conserved epitopes that may be used to design new vaccines and provided new tools for prophylaxis and therapy for HIV-1 disease. In this review, we summarize the advance in HIV-1 bNAbs discovery, maturation and further describe emerging applications in vaccine design.

Keywords: Broadly neutralizing antibodies; Next generation sequencing; HIV-1; HIV immunotherapy; Vaccines

Introduction

Human immunodeficiency virus-1 (HIV-1) is a worldwide pandemic and leads to a gradual loss of immune competence in human. More than 36 million peoples were living with AIDS globally, and around 1 million individuals were died from AIDS-related illnesses according to the World Health Organization estimation in 2015 (http://www.who.int/gho/hiv/en/). However, at present, no effective HIV-1 vaccine candidates to prevent HIV-1 infection in humans have been invented.

The human adaptive immune system provides protection against HIV-1 by induces antibodies, particularly HIV-1 broadly neutralizing antibodies (bNAbs). The isolation of HIV-1 broadly neutralizing antibodies has been a long-sought goal, for only approximately 20% of HIV-1-infected individuals will develop bNAbs by several years of chronic infection. Before 2000, only a few HIV-1 antibodies with limited breadth and potency were identified, including b12, specific for the CD4 binding sites (CD4bs) [1,2]; 2G12, specific for the complex gp120-glycans [3]; and 4E10 and 2F5, specific for the gp41 membrane proximal external region (MPER) [4,5]. With the significant progress in next-generation sequencing, structural biology and other efficient methods [6-13], a variety of second-generation bNAbs that recognize the CD4bs, MPER, the V1/V2 region and the glycans-associated C3/V3 on gp120, were isolated. These second-generation bNAbs showed significant virtues than the first-generation antibodies, including greater breadth and potency, long heavy chain third complementarity determining regions (HCDR3s), polyreactivity for non-HIV-1 antigens and high levels of somatic mutations [14,15].

For infectious diseases, antibodies are valuable immunotherapeutics and the induction of high-affinity bNAbs that inactive or neutralize the pathogen is a vital component for most effective vaccines. Traditional vaccine development relied on imitating natural infection and imprinting immunological memory with killed, attenuated or subunit preparations of the pathogen, which are used worldwide for both bacterial and viral infectious diseases [16,17]. However, these approaches were not successful for HIV-1 vaccine development by the numerous mechanisms including HIV-1 evades immunity, the longer time for HIV-1 bNAbs to develop and the uncommon characterization of HIV-1 bNAbs. The development of HIV-1 bNAbs is a progressive and slow process [18] and detailed analyzing and understanding of its affinity maturation is essential for production of effective vaccination. Recent advances in next-generation sequencing of antibody gene repertoires enable the genetic record of antibody development and maturation, and permit a better understanding of the humoral responses to HIV-1 [19]. These progresses provide the development pathway of bNAb and indicate a crucial step in vaccine design which could instruct B cells to follow the inescapable maturation pathways [20-23].

We discuss here the recent progress and crucial NGS approach in HIV-1 bNAbs identification, and further prospects for vaccine design based on insights from antibody biology, structural biology and NGS technology.

First-Generation of HIV-1-Neutralizing Antibodies

According to identification time, method and neutralizing activity, HIV-1 bNAbs were classified into two groups. Four first-generation bNAbs (b12, 2G12, 4E10, and 2F5) were isolated using Epstein-Barr virus transformation and phage display methods in the early 1990s [1,24,25] (Figure 1 and Table 1). Among them, b12 was isolated from a phage-display library that recognized the CD4-binding site of gp120 [1,26] and three others (2G12, 2F5 and 4E10) were isolated via an EBV-electrofusion method that recognized gp120 glycans and gp41 MPER, respectively [24]. These four antibodies use different heavy and light chains with different HCDR3 amino acids. Also, these four antibodies exhibit limited neutralization potency and/or breadth: b12, 2G12 and 2F5 displayed less than 50% neutralization breadth and 4E10 displayed modest potency (88% neutralization breadth) with high autoreactive

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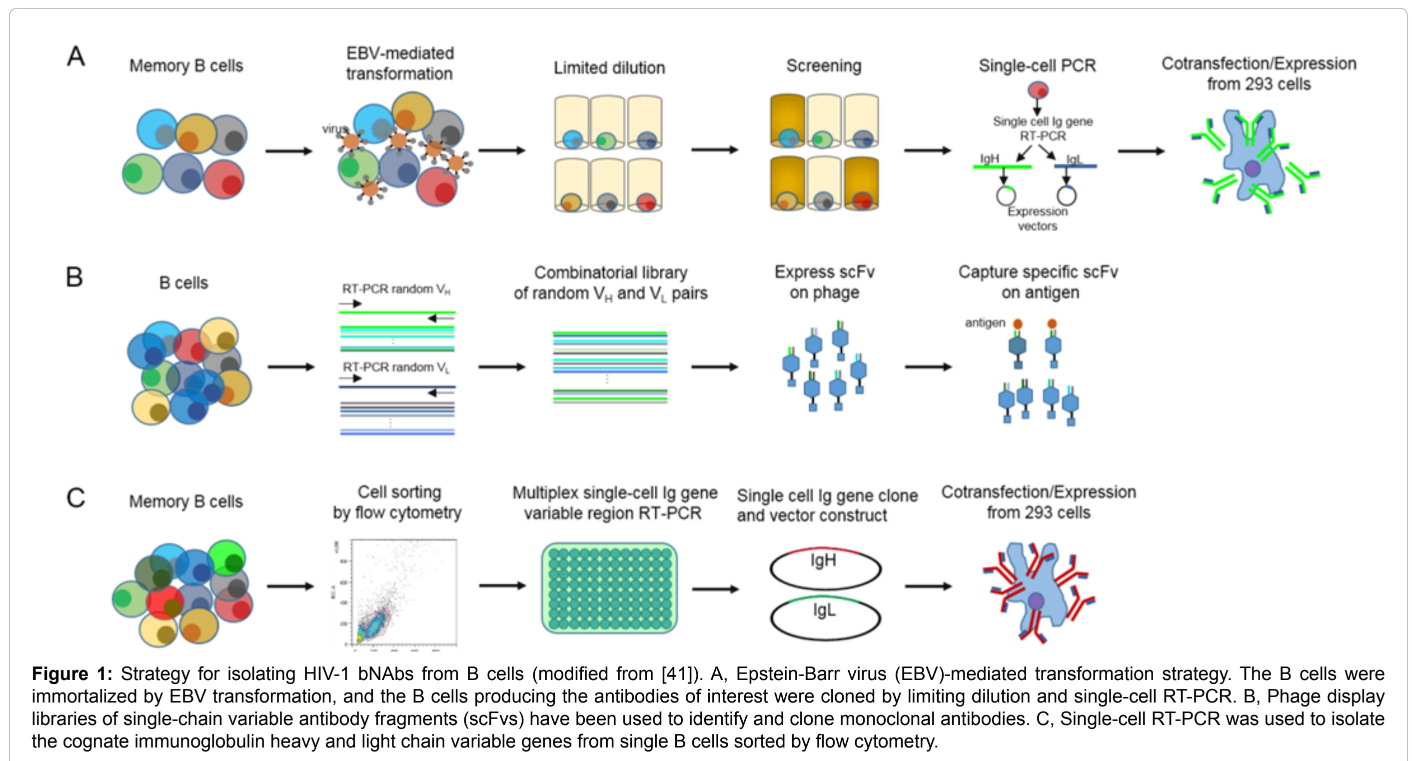

Figure 1: Strategy for isolating HIV-1 bNAbs from B cells (modified from [41]). A, Epstein-Barr virus (EBV)-mediated transformation strategy. The B cells were immortalized by EBV transformation, and the B cells producing the antibodies of interest were cloned by limiting dilution and single-cell RT-PCR. B, Phage display libraries of single-chain variable antibody fragments (scFvs) have been used to identify and clone monoclonal antibodies. C, Single-cell RT-PCR was used to isolate the cognate immunoglobulin heavy and light chain variable genes from single B cells sorted by flow cytometry.

Antibody	Specificity	Breadth[a]	Isotype	V_H	$V_κ/V_λ$	SHM[b]	HCDR3[c]	Isolation method	References
First-generation bNAbs									
b12	gp120 CD4bs	33%	IgG1	1-3	K3-20	17.3	20	Phage library	[1]
2G12	gp120 glycans	18%	IgG1	3-21	K1-5	33.6	16	EBV-electrofusion	[24]
2F5	gp41 MPER	48%	IgG3	2-5	K1-13	15.2	24	EBV-electrofusion	[24]
4E10	gp41 MPER	88%	IgG3	1-69	K3-20	15.6	20	EBV-electrofusion	[24]
Second-generation bNAbs									
PG9, PG16	gp120 conformational V1/V2 directed	70%	IgG1	3-33	λ2-14	15.4-16.8	30	Stimulated B cells	[7]
CH01-CH04	gp120 conformational V1/V2 directed	<50%	IgG1	3-20	K3-20	13.3-19.5	26	EBV-immortalization	[29]
PGT145	gp120 conformational V1/V2 directed	60%	IgG1	1-8	K2-28	22.8	33	Stimulated B cells	[9]
PGT128	gp120 carbohydrate	56%	IgG1	4-39	λ2-8	27.9	21	Stimulated B cells	[9]
PGT121	gp120 carbohydrate	53%	IgG1	4-59	λ3-21	21.2	26	Stimulated B cells	[9]
10E8	gp41 MPER	97%	IgG3	3-15	λ3-19	22.1	22	Stimulated B cells	[30]
VRC01	gp120 CD4bs	90%	IgG1	1-2	K3-11	38.8	14	Cell sorting/RT-PCR	[6]
VRC03	gp120 CD4bs	50%	IgG1	1-2	K3-20	34.9	16	Cell sorting/RT-PCR	[6]
PGV04	gp120 CD4bs	86%	IgG1	1-2	K3-20	38.2	16	Cell sorting/RT-PCR	[10]
CH30-CH34	gp120 CD4bs	80%	IgG1	1-2	K1-33	31.2-31.7	15	Cell sorting/RT-PCR	[10]
CH103	gp120 CD4bs	55%	IgG1	4-59	λ3-1	32	15	Cell sorting/RT-PCR	[31]

[a]The indicated breadth refers to the approximate percentage of viruses neutralized with IC50 values below 50 µg/ml by each monoclonal antibody
[b]Percentage of amino acidic somatic hypermutations (SHMs) calculated on the full amino acid sequence by comparing the full amino acid sequences of original (mutated) and germ lined antibodies
[c]HCDR3 amino acid length according to IMGT

Table 1: Categories and features of first- and second-generation HIV-1 bNAbs.

properties (Table 1) [4,27,28]. Although, these first-generation HIV-1 bNAbs provided a glimpses of the potential of the human immune system to effectively neutralize HIV-1, these antibodies were less than ideal to create antibody-based vaccine.

Second-Generation of Broadly HIV-1-Neutralizing Antibodies

The EBV-transformation and phage display methods are limited by the low efficiency, the inability to identify and isolate antigen specific antibody expressing B cells and the lack of high-throughput methods to screen large numbers of B cells for antibody secretion. In addition, the traditional Sanger sequencing only provide a tiny fraction of B cells, obviously missing many valuable clones and lacking comprehensive assessment of the enriched B clones during antibody maturation. Recently, significant progress has been made on the isolation of the second-generation HIV-1 bNAbs with greater breadth and potency. These new technologies based on three main methodological advances:

the selection of chronically infected 'Elite neutralizers' (representing ~1% of seropositive individuals) with high levels of cross-reactive neutralizing antibodies; the use of novel selection and screening approaches; and the development of efficient methods to isolate and analysis bNAbs.

With high-throughput microculture and single cell cloning, Walker et al. isolated two neutralizing mAbs PG9 and PG16 from an infected African donor, which bind to gp120 conformational V1/V2 epitope with an extended CDRH3 and higher neutralization breadth (Figure 2 and Table 1) [7]. Bonsignori et al. isolated four V1/V2-directed antibodies (CH01 to CH04) with a similar approach which display similar binding specificity to PG9 and PG16 but with less neutralization breadth (<50%) [29]. Further four classes of glycan-dependent antibodies (PGT121-123, PGT125-131 and PGT141-145) were identified using the same selection approach which comparable to PG9 and PG16 in terms of breadth but with higher potency [9]. Recently, Huang et al. isolated one new antibody 10E8 that binds to the gp41 MPER epitope and partially overlaps with the 4E10 epitope [30]. Compared with the first-generation MPER antibodies, 10E8 carries a higher load of somatic mutations (i.e., 22.1% in VH) and displays 5- to 10-fold more potent than 4E10 and lacks detectable polyreactivity and autoreactivity [30].

Contrary to the previous studies that selected neutralizing antibodies regardless of their epitope specificity, Wu et al. used an engineered antigenically resurfaced gp120 probe (termed resurfaced stabilized core 3: RSC3) with preserved or mutated CD4bs to fish out CD4bs-specific memory B cells [6]. Two distinct bNAbs VRC01 and VRC03 with greater breadth were identified based on this method. VRC01 is one of the most potent and broadly HIV-1 bNAb, displaying extraordinary levels of SHM (30%) and higher neutralization breadth (90%) [10]. Many additional VRC01-like CD4bs-specific bNAbs were isolated with the same approach, including PGV04, CH30-34 and CH103-106 series [10,31]. VRC01 and VRC01-like bNAbs showed an extraordinarily high levels of somatic mutations (Table 1), as well as insertions and deletions in both CDR loops and framework regions, and displayed greater potency and breadth than other epitope-specific bNAbs [6,10,31]. In addition, the V_H gene alleles of VRC01 class are found in most of the human population, suggesting that CD4bs is a preferential epitope for most bNAbs and a general induction of CD4-mimicking bNAbs is possible.

Development Pathways to HIV-1 Broadly Neutralizing Antibodies

All of the HIV-1 bNAbs characterized to data (Table 1) display one or more unusual characteristics, including polyreactivity for non-HIV-1 antigens, extensive somatic hypermutation and long CDRH3. The CD4bs-directed bNAbs displayed extraordinary maturation levels where >30% and >20% of nucleotides in heavy- and light-chain V genes differ from the germ line-encoded sequence. The V1V2-directed bNAbs showed extraordinary long HCDR3 of 24-33 residues, which was required for penetrating the glycan shield at the V1V2 site of HIV-1 vulnerability epitope. The bNAbs to V3-glycan and MPER had a moderately long HCDR3 (17-24 residues) and a relatively high load of somatic maturation (9%-24% for V_H), often involving insertion and deletions. At present, it is unclear how HIV-1 bNAbs achieve these unusually high levels of mutation and investigating the evolutionary history of B cell lineages that produce such bNAbs provides insights into strategies to elicit similar bNAbs via vaccination.

All of the second-generation HIV-1 bNAbs were isolated from HIV-specific neutralizing memory B cells which retained the genetic record of generation and maturation of bNAbs. Next-generation sequencing permit an in-depth analysis of antibody sequences and enables the construction of the exact B cell maturation pathways for most effective HIV-1 bNAbs. Three main NGS platforms with different advantages were successfully applied in antibody repertoire sequencing (Table 2). The Roche`s 454 sequencer provides a long reads (500 bp) which is suitable for full-length V region analysis [32]. However, this platform can result in high rate of insertions and deletions (indels) from homopolymers, which sets a large problem in D segment analysis. The Ion torrent sequencing platform (Life Technologies) has a fast speed and inexpensive spend [33,34],while, it also suffer from the same drawback of high homopolymer errors. The Miseq platform (Illumina) permits 300 bp paired-end sequencing with more accurate reads which is more useful in the analysis of CDR3 regions [33].

HIV-1 bNAbs usually belong to highly expanded clonal lineages (or clonotypes) and the process of B cell somatic mutation enhances antigen recognition, increasing both breadth and potency of neutralization. However, little is currently known about the exact B cell lineages pathways of most effective HIV-1 bNAbs, which hinders its use in vaccination. Recently, Wu et al. used 454-pyrosequencing and structural biology to trace the maturation pathway giving rise to VRC01-like bNAbs in several donors [10]. Among the thousands VH1 family sequences, they revealed a remarkable common pathway for development of CD4bs bNAbs starting from VH1-2, ranging from V_H sequences with a single somatic mutation to fully mature sequences. Common maturation intermediates were identified in different

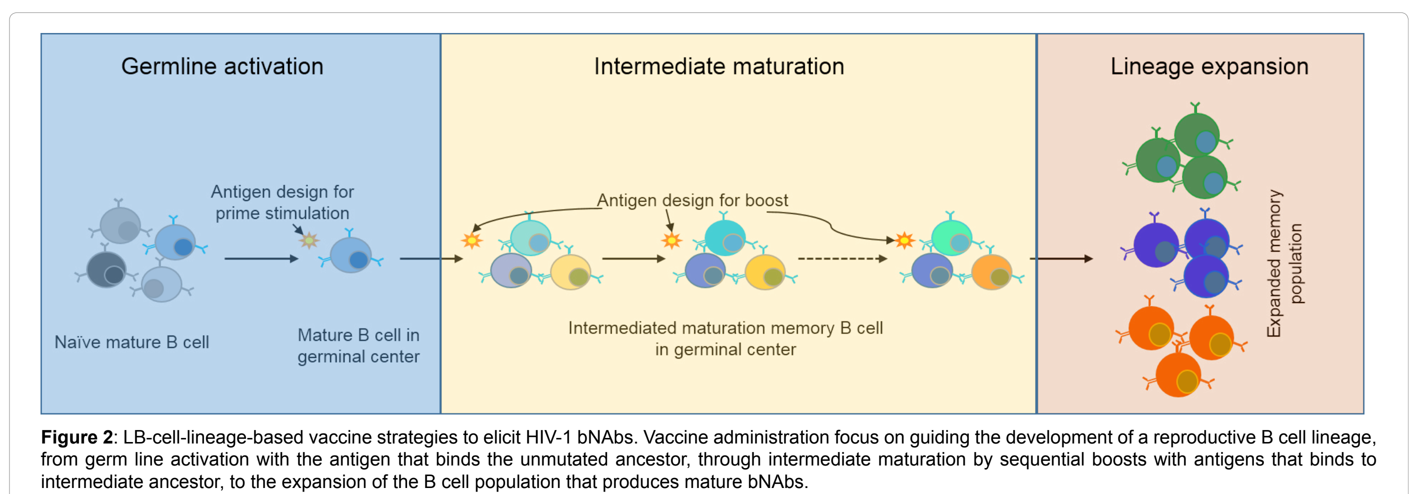

Figure 2: LB-cell-lineage-based vaccine strategies to elicit HIV-1 bNAbs. Vaccine administration focus on guiding the development of a reproductive B cell lineage, from germ line activation with the antigen that binds the unmutated ancestor, through intermediate maturation by sequential boosts with antigens that binds to intermediate ancestor, to the expansion of the B cell population that produces mature bNAbs.

Platform	Mechanism	Read length	Depth	Output	Cost/run	Advantages	Disadvantages	Error rate/type
Roche454	Pyrosequencing	500 bp	10^5-10^6 readS	0.7 G	~$ 7,000	Long reads especially useful for antibody V region sequencing	High error rate with polybase	1.4% of reads homopolymer associated indels
Illumina Miseq	Dye terminator sequencing	2X 300 bp	>10^7 reads	15 G	~$ 6,000	High throughput, High quality sequences	Short reads	3.2% of reads random substitutions
Ion Torrent	Semiconductor sequencing	400 bp	10^5-10^6 reads	10 G	~$ 1,000	Low cost, fast turn round	High error rate	1.2% of reads homopolymer associated indels

Table 2: Sequencing platforms used to analysis antibody repertoire.

individuals, which allowed a definition of the unmutated ancestor of VRC01. To further get a full characterization of VRC01-lineage maturation, Wu et al reconstructed the evolutionary process of VRC01 in longitudinal samples (15 years) of one donor [23]. Evolutionary analysis showed that VRC01-lineage evolved more rapidly than the HIV-1 virus did [23], indicating that the humoral immune responses evolved more rapidly than the virus in these chronic individuals, and providing a mechanism by which VRC01-lineages can achieve extraordinary diversity and neutralization. A similar concomitant HIV-1 evolution and antibody maturation characterization was identified in CH103 bNAb, suggesting that viral and antibody co-evolution leading to induction of VRC01-like lineage [31]. The extraordinary diversity in natural evolution and selection of VRC01-like lineage antibodies provided insights into strategies to elicit similar protective antibodies via vaccination.

HIV Vaccine Research

Understanding the production and maturation mechanisms that lead to the elicitation of bNAbs is helpful in design more effective vaccines. Induction of HIV-1 bNAbs is a key goal of HIV-1 vaccine development. Traditional immunization approaches have induced a rich catalog of successful human vaccines, however, these approaches have failed to induce broadly HIV-1 neutralizing antibodies [35,36], by the unique set of challenges posed by HIV-1 and the unusual molecular characteristics of HIV-1 bNAbs. Therefore, innovative approaches are needed to design vaccines to elicit successful protection responses.

The generation of HIV-1 bNAbs requires extensive antigen exposure and multiple rounds of hypermutation and affinity maturation, therefore, the first key step in vaccination is identifying the relevant epitopes that need to be targeted. However, the antigen that initially activates the naïve B cells may not be identical with the antigen that stimulates the affinity maturation of antibody [20,37,38]. Therefore, the B-cell-lineage vaccine design strategy may be necessary to induct a protective antibody response by using one antigen as the vaccine prime and others as boosts to drive the clonal evolution and affinity maturation (Figure 2) [14]. To move toward the successful B-cell-lineage vaccine, a numbers of ingenuity steps should be approached. First, isolation of bNAb that recognizes a sole epitope and identification of the corresponding immunoglobulin heavy and light gene pairs. Second, construct the maturation pathway of bNAb with NGS and computational methods; infer the unmutated ancestral BCR (B cell receptor) and the probable intermediate ancestor BCR. Third, design, engineer, and produce stable immunogens with enhanced affinity for unmutated and intermediate ancestor BCRs (Figure 2) [14]. For HIV-1 vaccine design, it is interesting that VRC01-like bNAbs are restricted to IGHVH1-2*02 genomic precursor which are found in different individuals, suggesting the maturation pathways may be similar among individuals and indicating that is might be possible to induce VRC01-like antibodies using the appropriate strategy [6,10]. Indeed, the convergent evolution of human antibodies in different individuals were identified in H1N1 influenza antibodies and HIN1 bNAbs have been successfully generated by priming with a DNA vaccine followed by boosting with a seasonal vaccine [39,40]. Recently, the longitudinal antibody deep sequencing of one donor from whom VRC01 has been isolated traced the VRC01 responses evolve over time which may shed light on vaccine-induced elicitation of VRC01-like antibodies [23]. Thus, by using optimizing immunogens for high-affinity binding to VRC01-like antibodies at multiple stages of clonal lineage development, one might be able to focus the B-cell response towards VRC01-like antibodies [41].

HIV Immunotherapy with bNAbs

Serum therapy was initially used in treating tetanus and diphtheria infection by von Behring and Kitasato in 1890 [42]. In the 20th century, antibody therapy was developed and many therapeutic monoclonal antibodies were successfully used in treatment of cancer, autoimmune and infectious diseases [43]. However, the clinical approved antibody-mediated immunotherapies for HIV disease was not reported yet.

The identification of HIV bNAbs allowed the design and test immunogens capable as potent therapeutics. In early studies, the cocktail of first generation bNAbs (b12, 2G12 and 2F5) were tested in humanized mice infected with HIV-1JR-CSF or HIV-1SF162 and in clinical viremic individuals [44-46]. However, this mixture failed to control viremia because of the rapid viral escape. In contrast, the immunotherapy with the second generation bNAbs led to a long-term control of viremia in humanized mice [47]. Recently, VRC01 and 3BNC117, two potent human CD4 binding site bNAb, were proved to prevent infection and suppress viremia in humanized mice and macaque [48,49]. Interestingly, 3BNC117 was successfully used in phase I and phase IIa clinical trial and was proved to be safe and effective in reducing viraemia and suppressing viral rebound during treatment interruption [50,51]. Moreover, 3BNC117 infusion improved neutralizing responses in HIV individuals indicating that 3BNC117 immunotherapy boosted host humoral immunity to HIV [52]. These researches showed that antibody-mediated immunotherapy was useful in treatment of chronically HIV-infected patients and was effectively used in clinic, which will prompt the progress of HIV prevention, therapy and cure.

Conclusion

Human adaptive immune system is essential for pathogen resistance by producing extraordinary diversity of antibody molecules, special bNAbs, via epitope recognition of foreign antigens. However, only recently a lot of HIV-1 bNAbs have been identified and analyzed with recombinant antibody technology, single-cell cloning and next-generation sequencing. Many studies have revealed the genetic diversity, structural features, antiviral properties, and maturation pathways of HIV-1 bNAbs, bringing hopes for the design of successful vaccine and immunotherapeutic strategies. In addition, the antibody-mediated immunotherapy was developed and successfully used in clinical experiment. In summary, a detailed analysis of HIV-1 bNAbs and the molecule mechanisms of neutralization and understanding the genetic and developmental pathways for antibody elicitation, is essential to ameliorate, prevent or even cure infection by HIV-1.

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