Anti-HIV Passive Immunization in Animal Models

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Abstract

Antibodies constitute a powerful weapon to fight viral infections. Recent advances in the identification and characterization of broadly neutralizing antibodies (bNAbs) of HIV have reinvigorated testing of passive immunization with bNAbs to prevent HIV infection. Using monkeys or humanized mice as challenge models, passive infusion of the potent and broad bNAbs has been shown to be highly protective against HIV. This review summarizes the current state of the anti-HIV passive immunization in animal models.

Keywords: HIV vaccine; Passive immunization; Animal models; Antibodies

Introduction

Developing a safe and effective HIV vaccine is a global priority, but it is also thought to be among the most daunting challenges in medicine [1,2]. So far only the RV144 vaccine efficacy trial in Thailand, testing the canarypox prime, gp120, ALVAC/gp120 B/E vaccine, has met with limited success, with an estimated vaccine efficacy of 31.2% [3]. A lot of effort has been put into the development of new tools to prevent and control HIV infections. Passive immunization with protective antibodies is one such approach, which has a long history in the fighting against infectious diseases [4]. Antibody-based approach is attractive because of the diversity of mechanisms of action. In addition to binding and directly neutralizing virus, antibodies can also control and eradicate infections through a variety of other mechanisms via the interaction with our innate and adaptive immune systems [5,6]. Therefore, passive immunization with human neutralizing antibodies has gained momentum as an alternative strategy to prevent HIV infection.

Broadly neutralizing HIV antibodies

HIV infection is usually initiated by one or a few transmitted/founder (TF) viruses, however, the virus evolves to extraordinary diversity due to the exceptional selective pressure exerted by antibody and T cell responses over the course of infection [2,7].

The antibody, in turn, responds by making somatic hyper mutations that result in a spectrum of cross-reactive neutralizing antibodies capable of recognizing the newly emerged viruses [2,7,8]. The continuous virus-antibody "arms race" has resulted in a collection of broadly neutralizing antibodies (bNAbs), which can act antivirally against a wide spectrum of HIV viral strains by targeting the relative conserved epitopes on the surface of envelope [9]. Using bNAbs to prevent and/or cure infection is currently evaluated as one of the major intervention strategies for HIV, for which the potency and breadth of the bNAbs will be a key factor.

Due to the establishment of large cohorts of HIV infected individuals and the advancement of technologies to culture and screen memory B cells for neutralization and to sort Env-specific B cells, many bNAbs with great potency and breadth have been discovered recently [9,10]. There are five main targets for bNAbs, which are the five known epitope clusters on the Env trimer [2]. The V1/V2 apex epitope is recognized by the early identified bNAbs including PG9 and PG16 [11], and also some recent additions with similar epitope specificity including PGT145 [12] and PGDM1400 [13]. The second epitope targeted by bNAbs such as VRC01 [14], VRC07 [15] and 3BNC117 [16] is the CD4 binding site. The epitope recognized by bNAbs such as PGT121, PGT128 [12] and 10-1074 [17], the V3 glycan region represents the third target. Another epitope targeted by bNAbs such as PGT151 [18] is gp120-gp41 quaternary interface. Finally, the membrane proximal external region of gp41 is also one epitope that can be recognized by bNAbs such as 10E8 [19].

Antibody protection studies in animal models

Abundant evidence has shown that administration of bNAbs by passive infusion in animal models can protect HIV infection. There are several animal models that have been used to mimic the transmission of HIV in humans. Simian immunodeficiency virus (SIV) infected non-human primates (NHPs) are the most closely related animal models to human transmission events [20], however, the Env proteins of HIV and SIV are so different that antibodies specific for HIV Env cannot cross-neutralize SIV [10]. Therefore, chimeric simian/human immunodeficiency viruses (SHIVs), which express HIV Env in the backbone of SIV, have been used to infect NHPs to study HIV bNAbs. Because of

the limited number of SHIVs available and different neutralization phenotype of commonly used SHIVs and HIV [10], humanized mouse models, which can be directly infected by HIV, are also extensively used in antibody protection studies.

In some of the early studies, mice with severe combined immunodeficiency (SCID) transplanted with normal human peripheral blood leukocytes (hu-PBL), designated hu-PBL-SCID mice were used to demonstrate the protective efficacy of some early discovered neutralizing antibodies, such as b12 [21,22] and BAT123 [23,24]. Protections against HIV infection by passive immunization with newer generation of bNAbs, for example, 2G12 [25], VRC01 [26,27], PG16 [28] and PGT126 [29], were also

demonstrated recently in immunodeficient mice transplanted with human hematopoietic stem cells (hu-HSC) or bone marrow/liver/thymus (BLT).

For antibody protection in SHIV challenge model, one of the earliest studies was using polyclonal HIV IgG derived from HIV-infected chimpanzees. Passive immunization of pig-tailed macaques with the HIV IgG protected them against intravenously challenging with a HIV strain DH12 based SHIV [30]. Some proof-of-principle studies for protection with neutralizing antibodies were performed using the first-generation bNAbs, like 2F5, 2G12, F105, 4E10 and b12 alone [31-33] or in combination [34-36].

Table 1 SHIV protection studies with next-generation bNAbs.

Citation	SHIV	bNAbs	bNAb Dosage	Virus challenge time	Virus challenge route	Note
Moldt et al., 2012	SF162P3	PGT121	0.2-5 mg/kg	1 d	Vaginal	• Sterilizing immunity was achieved in all animals administered 5 mg/kg and 1 mg/kg and three of five animals administered 0.2 mg/kg PGT121.
Shingai et al., 2014	AD8-EO DH12-V3AD8	VRC01, 45-46m2, 3BNC117, PGT121 and 10–1074	0.2-50 mg/kg	1 d	Intrarectal	• Partial protection at higher concentrations. • Neutralizing titers are predictive of protection.
Pegu et al., 2014	SF162P3 BaLP4	VRC01, PG9, and 10E8	0.3-20 mg/kg	2 d	Mucosal Vaginal Intrarectal	• Anti-CD4 antibody did not provide effective protection *in vivo*. • VRC01, 10E8, and PG9 conferred complete protection, albeit at different relative potencies.
Ko et al., 2014	BaLP4	VRC01, VRC01-LS	0.3 mg/kg	5 d	Intrarectal	• Enhanced FcRn-binding mutant bnAb, VRC01-LS, dispalyed improved protection against primate SHIV infection than wild type VRC01.
Rudicell et al., 2014	BaLP4	VRC01-LS, VRC07-523-LS	0.05-0.3 mg/kg	5 d	Intrarectal	• VRC07-523 prevented infection in NHPs at a 5-fold lower concentration than VRC01.
Saunders et al., 2015	BaLP4	Simian VRC01-LS	Four times of 5 mg/kg	52 d	Intrarectal	• Simianized antibody sustained therapeutic levels for 5 months. • Two months after the final antibody administration, animals were completely protected against viral challenge.
Moldt et al., 2016	SF162P3	PGT126	0.4-10 mg/kg	1 d	Vaginal Intrarectal	• Neutralizing antibody affords comparable protection against vaginal and rectal SHIV challenge in macaques.
Gautam et al., 2016	AD8-EO	VRC01, VRC01-LS, 3BNC117, and 10-1074	20 mg/kg	7 d	Intrarectal	• A single injection of four anti-HIV-1-neutralizing monoclonal antibodies in blocking repeated weekly low-dose virus challenges of the clade B SHIVAD8. • Median protection time from 8 to 14.5 weeks.
Julg et al., 2017	325c	PGDM1400 and CAP256-VRC26.25	0.08-2 mg/kg	1 d	Intrarectal	• PGDM1400 was fully protective at the 0.4 mg/kg dose, whereas CAP256-VRC26.25-LS was fully protective even at the 0.08 mg/kg dose.
Julg et al., 2017	SF162P3 325c	PGT121 and PGDM1400	5-10 mg/kg	1 d	Intrarectal	• SHIV-SF162P3 was sensitive *in vitro* to PGT121 but resistant to PGDM1400, whereas SHIV-325c was sensitive to PGDM1400 but resistant to PGT121. • Only the PGT121+ PGDM1400 combination protected against this mixed SHIV challenge.
Xu et al., 2017	BaLP4 325c	VRC01/ PGDM1400-10E8v4	5 mg/kg	5 d	Mucosal	• SHIV BaLP4 was sensitive to VRC01 and the trispecific antibody but was resistant to PGDM1400. • SHIV 325C virus was sensitive to PGDM1400 and the trispecific Ab but was resistant to VRC01. • The trispecific Abs conferred complete immunity against the mixture of SHIVs, but not the single Abs.

Among them, the b12 antibody targeting CD4 binding site, has been extensively investigated in SHIV challenged monkeys, and really helped us understand the mechanism and durability of antibody protection [37-39]. With the identification of newer generation bNAbs, many more protection studies were conducted by different groups **(Table 1)**. Burton and colleagues showed that one potent bNAb, PGT121, could protect monkeys from infecting by the SHIV-SF162P3 challenge virus at lower serum concentrations than observed before [40]. VRC01 [41-44], its FcRn enhancing version with LS (M428L/N434S) mutation [15,43,44], its simianized version [45] as well as its more potent clonal relative VRC07 [15], have been well studied in multiple SHIV protection experiments. Two recently identified V2-specific antibodies, PGDM1400 and CAP256-VRC26.25 with exceptionally high potency, provided full protection against a novel clade C SHIV-325c virus at very low infusion doses [46]. Some other antibodies, such as 3BNC117, 10-1074 [42,43], PGT126 [47], PG9 and 10E8 [41] have also demonstrated protection **(Table 1)**.

However, none of these bNAbs neutralizes all of viral isolates, thus single bNAbs can select resistant viruses to establish infection if the animals were challenged with a diverse swarm of viruses [48]. Therefore, combination is required for bNAb prevention strategies. Julg et al. showed that PGT121 alone and PGDM1400 alone both failed, but the combination of these two bNAbs provided 100% protection against a mixed challenge with SHIV-SF162P3 and SHIV-325c [48]. Another way to do bNAbs combination is constructing them into bispecific or trispecific antibodies. One trispecific antibody (VRC01/PGDM1400-10E8v4), combining the potency and breadth of three bNAbs into one molecule, conferred complete immunity in nonhuman primates against a mixture of SHIVs with different sensitivities to the single antibodies [49]. Ho and colleagues combined bNAbs with antibodies targeting host cellular proteins like the viral receptors CD4 or CCR5 into bispecific antibodies, and showed one of them, 10E8V2.0/iMab provided protection against HIV challenge in hu-HSC mice [50].

Conclusion

Due to the vigorous development of the antibody field, together with the growing number of broad and potent HIV monoclonal antibodies identified, it's an extraordinary opportunity to use the passive immunization approach for HIV prevention. In SHIV challenged monkeys and HIV challenged humanized mice, passive immunization studies using bNAbs, especially the potent second-generation ones, were highly successful in protecting animals against viral infection. Although the Fc-mediated effector function was showed important [37], the mechanisms of protection are not fully understood. We also don't know whether this approach is able to protect uninfected humans from acquiring HIV. On-going clinical trials called Antibody Mediated Prevention (AMP) studies are being conducted by two groups in high-risk homosexual men in the Americas and heterosexual women in Africa, testing whether VRC01 can prevent HIV infection, with results expected by 2020 [51]. However, using the currently identified single antibody, like VRC01, targeting a single neutralization-sensitive epitope is unlikely to provide enough protection. Thus, broader and more potent bNAbs with longer half-lives and lower manufacturing costs need to be tested alone or more importantly in combinations. A vaccine would induce multiple antibody specificities and mediate innate and adaptive immune responses, which are not imparted by passive immunization. But before a safe and effective HIV vaccine is developed, passive immunization could contribute to HIV prevention efforts.

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