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The Role of CD4$^+$ T cells in the Development of an Efficacious HIV Vaccine

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Abstract

HIV infection has caused serious public health disaster during the past three decades. The rapid discovery of antiretroviral drugs and the implementation of combination antiretroviral therapy in many countries over the past two decades have led to a marked decrease in HIV-associated mortality and morbidity. However, the antiretroviral therapy alone has been unable to eradicate the virus from HIV-infected individuals. To reduce the incidence of HIV infection on a global scale, vaccine is still the most cost-effective method. Due in part to the lack of a comprehensive understanding of immune correlates of protection, an effective HIV vaccine has not yet been developed. Since CD4$^+$ T cells play a central role in orchestrating various arms of immune responses, vaccines that mobilize CD4$^+$ T cells should help to elicit desired immune responses for the prevention of HIV infection. The current knowledge on subsets of CD4$^+$ T cells and their perceived roles in mediation and formation of post-vaccination protective immunity are discussed.

Keywords: CD4$^+$ T cell; Vaccine; HIV

Introduction

Since the first case of Acquired Immunodeficiency Syndrome (AIDS) was reported in 1981, the disease has caused approximately 36 million of deaths globally. AIDS is caused by infection with Human Immunodeficiency Virus (HIV). There are currently an estimated 35 million people living with HIV/AIDS [1,2].

HIV belongs to the *Lentivirus* genus and *Retroviridae* family. Its replication is controlled by a reverse transcriptase that lacks proof-reading mechanism, rendering a high mutation rate of approximately 3×10^{-5} per nucleotide per life cycle of HIV replication [3]. In addition, recombination as well as insertion and deletion happen frequently during viral replication and thereby further increased its genetic diversity [4]. As a consequence, HIV is hard to control either by drugs or immune responses.

Although the introduction of combination antiretroviral therapy (ART) has significantly reduced HIV-associated mortality and morbidity, and improved the quality of life in most HIV-infected individuals, the therapy alone cannot cure the disease. Preventative vaccine is considered to be the most cost-effective method to reduce the incident of new HIV infection. To develop an efficacious vaccine against HIV, the crucial role of CD4$^+$ T cells must be better understood. Here, we review the new development on various subsets of CD4$^+$ T cells, and discuss how these information might be employed in the development of vaccines against HIV.

Major Clinical Trials of HIV Vaccine

HIV has a small genome of approximately 10 kb that comprises of 9 genes encoding structural proteins (Gag, Pol, Env) and regulatory proteins (Tat, Rev, Nef, Vpr, Vif, Vpu), respectively. The viral particle is encapsulated by a lipid membrane bilayer in which HIV envelop (Env) glycoprotein spikes are embedded. Through binding to cell surface receptor (CD4) and co-receptor (CCR5 or CXCR4) by the Env protein, HIV infects CD4$^+$ T cells and eventually causes AIDS. These viral structure and virological properties have been exploited to the development of antiviral drugs, and employed in the designing of vaccine targets. Despite vast knowledge has been acquired on HIV virology and immunology, it has been difficult to translate them into the development of an efficacious HIV vaccine.

Table 1 summarized several major HIV vaccine clinical trials conducted in the last two decades; despite capable of inducing measurable immune responses, none of which has yielded satisfactory clinical outcome. Early efforts had been placed on eliciting antibody responses using various forms of Env vaccine, culminating in phase III clinical trials, VAX003 and VAX004, in which recombinant gp120 proteins were tested as vaccine candidates. However, both trials failed to demonstrate protection against HIV acquisition in human volunteers [5,6]. Follow-up mechanistic studies have revealed that the ectodomain of Envprotein is comprised of highly variable, heavily glycosylated core and loop structures surrounding the HIV receptor-binding regions [10]. Since changes occur in N-linked glycosylation frequently [11], antibodies targeting carbohydrates are generally not efficient at preventing HIV infection, with a few exception [12]. Furthermore, high rate of mutation often occurs in the loop region, thus making strain-specific neutralizing antibodies unable to efficiently neutralize the viral mutants. In addition, some Env epitopes induce non-neutralizing antibodies that compromised the induction of neutralization antibodies [13]. Much effort is still being placed on the discovery of broadly neutralizing antibodies and design appropriate immunogens to induce broadly neutralizing antibody responses.

Name	Trial sites	Immunogen	Targeted immune response	Efficacy	References
VAX004	USA, Canada, Netherlands	AIDSVAX B/B gp120	CD4+ T cells, antibodies	No efficacy	[5]
VAX003	Thailand	AIDSVAX B/E gp120	CD4+ T cells, antibodies	No efficacy	[6]
STEP Study (HVTN502)	USA, Canada, Latin America	MRKAd5 HIV-1 gag/pol/nef B	CD4+ T cells, CD8+ T cells	No efficacy	[7]
Phambili trial (HVTN503)	South Africa	MRKAd5 HIV-1 gag/pol/nef B	CD4+ T cells, CD8+ T cells	No efficacy	[8]
RV144	Thailand	ALVAC-HIV vCP1521 and AIDSVAX B/E rgp120	CD4+ T cells, CD8+ T cells, antibodies	31.2% efficacy	[9]

Table 1: Major clinical trials of HIV vaccine.

With growing knowledge of the antiviral activity of cytotoxic T cell (CTL) in the 1990s, the pendulum of AIDS vaccine development has swung to using various methods to induce HIV-specific CD8+ T cells [14,15]. One of the leading candidates was an adenovirus-based Gag vaccine that induced high magnitude of CD8+ T cell response and protected against SHIV challenged in non-human primates (NHP) [16,17]. Encouraged by the optimistic results in animal models, further clinical trials were performed. Unexpectedly, two large efficacy trials of the CTL-based vaccine neither prevented the acquisition of HIV infection nor reduced viral load or preserved CD4+ T cell counts post infection [7,8], thus revealing discrepancies in the vaccine-induced responses between NHP models and real-life infection in humans. Furthermore, whether CTL-based vaccine is of any importance has been questioned.

However, a subsequent study using DNA vaccine prime and adenovirus vector boost strategy showed that protection against SIV infection in rhesus monkeys can still be achieved. Important, the protected monkeys have high-frequency of CD8+ T cell responses against 11 to 34 epitopes, which is much more than that in the STEP human clinical trial where only and average of 5 epitopes were recognized [18]. This suggests the breadth of CD8+ T cell response maybe important, in addition to the magnitude of the response. Such increased breath, should be important at coping with viral escape from CD8+ T cell control [19]. Therefore, the current consensus is that CD8+ T cell-based vaccines need to elicit responses with great magnitude, improved breadth, and poly-functionality [20-22].

Most intriguingly, in the RV144 phase III clinical trials, a vaccine regimen consists of priming with recombinant canarypox vector designed to stimulate CD8+ T cells, and boosting with recombinant glycoprotein 120 subunit designed to elicit neutralizing antibodies, resulted in a 31.2% vaccine efficacy at the prevention of acquisition of HIV infection [9], despite neither vaccine used alone accomplished any significant effects.

Since CD4+ T cells assist the induction of antibody and CD8+ T cell responses, they should be carefully considered as a component of HIV vaccine. However, CD4+ T cells are the major targets for HIV infection, vaccine-induced CD4+ T cells may acquire an activated phenotypes that make them more susceptible to HIV infection. Indeed, it has been found that vaccine-induced CD4+ T cells contribute to the enhanced SIV replication and accelerated disease progression [23]. In contrast, others have reported that CD4+ T cells are beneficial in the prevention of SIV infection in experimental models [24]. In HIV-infected humans, a strong HIV-specific CD4+ T cell response is associated with a better control of viremia [25]. Further analysis of the RV144 results revealed that HIV-specific CD4+ T cell responses are positively correlated with vaccine efficacy [26]. Other than providing help, there are a small fraction of CD4+ T cells that have cytotoxic capacity and express granzyme A. These cells are expanded during acute HIV infection in some individuals and appear to help to suppress viral replication [27].

Above evidences reinforced the idea that a successful HIV vaccine strategy should aim to induce a CD4+ T cell response, in addition to B cell and CD8+ T cell responses. To harness CD4+ T cells in the development of an efficacious HIV vaccine, we need to first re-evaluate the functional diversity of CD4+ T cell subsets.

The importance of CD4+ T cell subsets in mediation and formation of post-vaccination protective immunity

Upon encountering antigens and adequate co-stimulation signals, naive CD4+ T cells are activated, polarized, and differentiated into distinct subsets including Th1, Th2, Th9, Th17, Th22, Regulatory T cell (Treg), Type I Regulatory cell (Tr1), and Follicular Helper T cell (T_{FH}). Each subset has unique phenotype, cytokine secretion profiles, and transcriptional factors. Based on the stages of differentiation and anatomic locations, they can also be classified into central memory cell (TCM), effector memory cell (T_{EM}), and tissue-resident memory cell (T_{RM}) (Table 2). These T cell subsets either work independently or in concert to modulate other arms of immune responses. Use vaccines to stimulate specific subset of CD4+ T cells, if possible, should help the generation of higher quality antibody and CD8+ T cell responses. Following are a briefly review of the phenotypic and functional properties of each CD4+ T cell subset.

Th1: Through interacting and licensing dendritic cells, T helper 1 (Th1) cells contribute to the induction of cytotoxic T lymphocytes (CTLs) [61], and the maintenance of memory CTLs that can rapidly produce effector cells upon reinfection to eliminate pathogens [62]. In HIV infection, CTLs have been shown to suppress HIV-1 replication in cell cultures and they are associated with better control of viral loads in HIV-1 infected individuals [63-66]. The loss of Th1 cells during HIV-1 infection renders inefficient generation of new CTLs, and failure to prevent disease progression. A vaccine intended to stimulate effective antiviral CTL responses should thus contain a component for inducing sufficient Th1cells.

T cell subsets	Phenotypic markers	Cytokine secretion profile	Transcription factors	References
Naïve cells	$CD3^+$ $CD4^+CD45RA^+$ $CCR7^+$ $CD62L^+$ $IL\text{-}7R^+$	IL-2	Th-POK	[28-30]
Th1	$CD3^+$ $CD4^+CXCR3^+IL\text{-}12R^+$ $IFN\gamma R^+$	IFN-γ, IL-2, TNFα,TNFβ	T-bet, Eomes	[31-36]
Th2	$CD3^+$ $CD4^+$ $IL\text{-}4R^+CCR3^+$ $CCR4^+CCR8^+$ $CRTh2^+$	IL-4, IL-5,IL-6, IL-13	GATA3, STAT5, Gfi-1	[32,34-38]
Th9	$CD3^+$ $CD4^+$	IL-9	PU.1	[12,13]
Th17	$CD3^+$ $CD4^+$ $IL\text{-}23R^+$ $CCR4^+$ $CCR6^+$ $IL\text{-}6R^+$ $CD161^+$	IL-17, IL-17F, IL-21, IL-22, IL-26	RORγt, RORα, RORC2	[30,34,36,39-41]
Th22	$CD3^+$ $CD4^+$ $CCR4^+$ $CCR6^+$ $CCR10^+$	IL-22	AhR	[42-45]
Treg	$CD3^+CD4^+$ $CD25^+$ $CTLA4^+$ $CD127^-$	IL-10, TGF-β	Foxp3	[30,34,36,46-50]
Tr1 (type 1 regulatory)	$CD3^+$ $CD4^+$ $CD25^-CD127^-$ or $CD3^+$ $CD4^+$ $CD49b^+$ $LAG3^+$	IL-10, TGF-β	Not known	30,47,51,52
T_{FH} (follicular helper)	$CD3^+$ $CD4^+CXCR5^+$ $SLAM^+$ $OX40L^+$ $CD40L^+$	IL-21, IL-4	Bcl6,Ascl2	[53-57]
T_{CM} (central memory)	$CD3^+$ $CD4^+$ $CD45RA^-IL\text{-}7R^+$ $IL\text{-}15R^+$ $CD44^+$ $CCR7^+$ $CD62L^+$	IL-2, IL-21	Bcl6	[30,58,59]
T_{EM} (effector memory)	$CD3^+$ $CD4^+$ $CD44^+$ $IL\text{-}7R^+$ $IL\text{-}15R^+$ $CCR7^-$	IFN-γ,IL-4,IL-5,IL-17	Blimp1, T-bet	[30,58,59]
T_{RM} (tissue-resident memory)	$CD3^+$ $CD4^+$ $CD11a^+$ $CD69^+$ $CD103^+$	IFN-γ	Not Known	[59,60]

Table 2: Characteristics of T helper cell subsets.

Th2: T helper 2 (Th2) cells modulate humoral immune responses and promote host defence against extracellular pathogens such as bacteria and parasites [67-70]. By interacting with Th2 cells, B cells undergo activation, proliferation and production of antigen-specific IgG antibodies, or the secretion of IgA antibodies [71]. IgG antibodies are a common form of neutralizing antibody against HIV. Secreted IgA antibodies play a key role in defending HIV-1 infection since the initial HIV infection often occurs at the mucosal surface [72]. Thus, a vaccine geared to stimulate anti-HIV antibodies must also include antigens to activate Th2 cells.

T_{FH}: Follicular T helper cells (Tfh) help the formation and maintenance of germinal centers (GCs) [57]. In GCs, Tfh cells provide survival and proliferative signals to B cells to facilitate B cell proliferation, differentiation into plasma B cells or memory B cells, as well as antibody affinity maturation and class-switching [73]. Furthermore, Tfh cells assist B cells to produce broadly neutralizing antibodies (bNAbs) more swiftly [74]. However, a small fraction of Tfh cells are productively infected by HIV, rendering them defective [75]. Thus, use vaccine to induce Tfh response, and protect them from being destroyed by HIV infection should be beneficial for the elicitation of better quality neutralizing antibody responses against HIV. In fact, elucidating specific phenotypic and functional features of those Tfh cells that help to induce bNAbs, and harnessing these cells in HIV vaccine development had been topics of intense discussion in a recent NIH workshop [76].

Th17: T helper 17 (Th17) cells principally function in the protection against extracellular pathogens [41], through producing cytokines to maintain the integrity of the mucosal barrier and modulate the immune homeostasis at mucosal sites [77]. Mucosal tissues are the first barrier against HIV infection and a major site for HIV replication, thus a robust Th17 cell response contributing positively to the prevention of HIV infection [77]. HIV-specific Th17 cells are induced during early HIV infection [78]. In NHP models, a severe loss of Th17 cells was found in pathogenic SIV infections, whereas no obvious Th17 cell depletion has been shown in nonpathogenic SIV infections that occur in sooty mangabeys and African green monkeys [79,80]. Thus, a vaccine that induces Th17 cells should contribute to the prevention of HIV infection or the control of disease progression post infection.

Treg: Distinguished from other subsets of $CD4^+$ T cells by expressing the master transcription factor Foxp3, regulatory T cells (Treg) suppress immune responses through the secretion of inhibitory cytokines such as IL-10, TGF-β and IL-35 [81,82]. Its role in HIV infection is uncertain currently. On one hand, by suppressing immune activation, Treg helps to reduce the detrimental persistent immune activation causing by HIV infection, and thus preventing disease progression [83]. On the other hand, Treg can inhibit HIV-specific immune responses, and thereby facilitate viral replication under certain circumstances [84,85]. Whether a vaccine should elicit Treg warrants further investigation.

In addition to the above mention $CD4^+$ T cell subset, the potential roles of other subsets such as Th22, Tr1, and T_{RM} in the development of HIV vaccine are unclear. However, the contribution of these other subsets to the overall success of vaccine-induce immune response to HIV should be investigated in future studies.

The Induction of HIV-Specific $CD4^+$ T cell Responses by Vaccination

To design an effective vaccine to stimulate HIV-specific $CD4^+$ T cells, antigens with higher immunogenicity are needed. Studies have demonstrated that HIV Gag can induce strong $CD4^+$ T cell response. In fact, the majority of identified $CD4^+$ T cell epitopes resided in Gag region. In addition to Gag, Nef, Env, Pol and Vpu have also been

showed to elicit CD4+ T cell responses [27,86-90]. Furthermore, Env-specific CD4+ T cells are detected in the RV144 phase III clinical trial of HIV vaccines [9]. Thus, multiple epitopes from several HIV proteins should be considered in the design of an effective vaccine [91].

Other than specific HIV protein, the genetic diversity of HIV needs to be addressed in the design of a vaccine against HIV. To solve this problem, mosaic, conserved, central and consensus sequences have all been used in vaccine design in order to cover a wide range of HIV sequences [91-93]. Additionally, by careful selection of flanking sequences, the immunogenicity of polyepitope vaccine may be improved [94]. In future studies, head-to-head comparison among these methods should be performed to discern the pros and cons of each of the method for vaccine design.

Once the vaccine antigens are determined, the induction of specific T cell subsets that have biased cytokine secretion profiles may be dependent on the adjuvant of choice. Adjuvants are known to boost the potency, quality, and longevity of antigen specific immune responses through interacting with antigen presenting cells (APCs) [95-97]. Many forms of adjuvants have been examined in clinical and preclinical studies. The most common ones are aluminium salts (Alum), polynucleotides (polyIC, polyICLC)oligonucleotides (CpG), lipopolysaccharide (LPS), lipopeptides (Malp-2, Pam3Cys), and imidazoquinoline (R-8848) [96,98-102]. Results from previous studies have shown that polyIC and polyICLC elicited higher magnitude of CD4+ T cell responses than R-848, CpG, Malp-2, Pam3cys and LPS [103]. Among the squalene-based adjuvant, $AS01_B$ is more superior to $AS02_A$ and $AS02_V$ at eliciting CD4+ T cell responses [104]. These adjuvants should be tested in conjunction with candidate HIV vaccines.

Prospective on the Development of Vaccines Capable of Eliciting HIV-Specific CD4+ T cells

The development of vaccines that activate HIV-specific CD4+ T cell have confronted with many difficulties. First of which is the lack of knowledge on specific phenotype of CD4+ T cells that are immune correlates of protection [105]. Further comparative study between elite controllers and regular progressors should help to identify phenotypic markers of CD4+ T cells in association with the lack of HIV disease progression. Studies have shown that dysregulation of differentiation from central memory CD4+ T cells to effector memory cells is associated with immunological failure in HIV-1 infected individuals [106]. In subjects received candidate HIV-1 vaccine, CD107a+ CD4+ T cells are generated and these cells are relatively more resistant to depletion caused by HIV infection [107]. Thus, vaccines that preserve memory T cells and induce more CD107a+ cells should be beneficial.

Elicitation of specific subsets of CD4+ T cells by vaccination is going to be difficult since we still do not known how to create unique cytokine milieu *in vivo*. A novel dendritic cell (DC)-targeting strategy may help. In the DC targeting method, an antigen is conjugated with an antibody that recognize specific surface marker on DC surface, and thereby more efficiently bring the antigen to DC for processing and presentation [108], and consequently more efficient priming of T cells. Indeed, antigens target different subsets of DCs appears to elicit differential patterns of immune responses [109]. For instance, antigen targeting at Dectin-1 stimulates more cytokines secretion than targeting CD205 [110]. Further exploration of this vaccination strategy may help to discovery methods for activation specific CD4+ T cell subsets.

Conclusion

An effective HIV vaccine is urgently needed for the prevention of HIV infection and reducing AIDS associated mortality and morbidity. However, there are many obstacles in the development of HIV vaccines. First, high genetic diversity of HIV makes it a challenge to deal with all HIV strains using a single vaccine sequence. Second, even though both humoral and cellular immune responses can be elicited by candidate HIV vaccine or natural HIV infection, the viruses evade immune recognition through generating escape mutations. Third, CD4+ T cells are the major target of HIV, vaccines that activate CD4+ T cells may also generate more target cells that are susceptible to HIV-1 infection. Finally, the immune correlates of protection are not clearly understood. Though a simple principle for designing an efficacious HIV vaccine does not exist, the partial success of RV144 phase III HIV vaccine trial has showed a mixture of vectored vaccine and protein vaccine administer in a prime-and-boost regimen is promising [9]. With a better understanding of the immunology of HIV infection, and more data coming out of human clinical trial of candidate HIV vaccines, an improved version of HIV vaccine will be developed eventually. To carefully select adjuvants in the formulation of vaccines, and to manipulate the activation of different subsets of DCs may lead to directional activation of desirable T helper cell subsets, and thus achieving better vaccine immunogenicity. Whatever that version of vaccine may be, antigens that activate CD4+ T cells surely must be included as a key component.

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