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HIV vaccines

Can CD4+ T cells be of help?

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Defining immune correlates of protection against the human immunodeficiency virus (HIV) remains a major challenge. While the role of neutralizing antibodies and CD8+ T cell responses has been widely acknowledged and applied in vaccine development, little vaccine candidates have focused on CD4+ T cells. As the main target of HIV, CD4+ T cells play a pivotal role in HIV infection. An HIV vaccine that elicits strong, multi-specific, polyfunctional and persisting CD4+ T cell responses would therefore have the potential of lowering viral set point when HIV infection occurs or reducing viral load in already infected patients. In a combined approach with neutralizing antibodies and CD8+ T cells, CD4+ T cells cannot only enhance the magnitude, quality and durability of the desired antibody response, but will also provide the help needed to induce and maintain effective antiviral CD8+ T cell responses. In addition, the disease-modifying potential of the CD4+ T cell response, by lowering viral set point and/or viral load and thus probability of transmission, may be beneficial both at the individual and public health level.

Keywords: HIV, HIV vaccine, CD4 T-cells, T helper cells, experimental vaccines

Abbreviations: Ad5, adenovirus type 5; AIDS, acquired immune deficiency syndrome; CDC, Centers for Disease Control; HIV, human immunodeficiency virus; IFN-γ, interferon-gamma; IL-2, interleukin 2; LTNP, long-term non-progressors; SIV, simian immunodeficiency virus; TNF-α, tumor necrosis factor alpha; VC, viral controllers

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Background

In 1981 the CDC published the first clinical reports of what would become known as the acquired immune deficiency syndrome (AIDS) and in 1983 the human immune deficiency virus (HIV) was discovered as the causative agent of this disease.[1,2] In the past 30 y infections with HIV have taken more than 25 million lives and in 2011 approximately 34.2 million people were living with HIV.[3] Soon it was realized that only a vaccine would be able to stop the pandemic spread of HIV and since the mid-eighties the quest for an HIV vaccine has been a global health priority. In the past decades numerous vaccine candidates have been designed and clinically evaluated of which only three have reached phase III testing. The first vaccine candidate that was evaluated in placebo-controlled phase III studies was a recombinant monomeric gp120 protein adsorbed onto alum. This product known as AIDSVAX (VaxGen) showed no protective efficacy against HIV infection.[4,5] The failure of gp120-based vaccines and the improved understanding of the role of CD8+ cytotoxic T cells in the control of HIV replication and containment of viremia has fuelled interest in novel vaccine technologies. Plasmid DNA vaccines and recombinant vectors are particularly able to generate strong cellular immune responses. For this reason Merck's rAd5 HIV-1 vaccine (recombinant adenoviral vector expressing HIV Clade B Gag/Pol/Nef) raised great expectations until the STEP and Phambili trials were prematurely halted because the primary endpoint was not reached and an increased HIV infection rate was noted in men that were seropositive for adenovirus serotype 5 (Ad5).[6,7] The only vaccination regimen that has shown modest efficacy consisted of four priming doses with a canarypox vector ALVAC-HIV [vCP1521]* followed by two booster doses of a recombinant gp120 protein (AIDSVAX). In the RV144 clinical trial in Thailand a

protection of 30% was demonstrated 3 y after the last vaccine dose.[8]

Immune Response to HIV and Vaccine Development

The natural immune response to HIV is unable to clear the infection. Therefore immune correlates of protection are still basically unknown. However recent studies of the immune response during HIV infections, especially during the acute phase (reviewed by McMichael et al.[9]) and lessons learnt from vaccine trials are providing clues for further vaccine development.

The initial antibody responses to HIV envelope proteins are non-neutralizing.[10] Antibodies neutralizing autologous virus develop more slowly and arise 12 weeks or longer after HIV transmission whereas antibodies capable to neutralize heterologous virus arise after years of infection and only in a fraction of HIV-infected individuals.[11,12] Pinpointing the rare conditions that yield strong broadly neutralizing responses and understanding the molecular mechanisms underlying the special quality of these antibodies may facilitate the design of the antigen(s) and the definition of the condition(s) required to elicit sterilizing immunity. In addition results of vaccine studies, even the ones that failed, may provide further guidance toward success. Although antibodies induced by AIDSVAX where unable to neutralize primary isolates of HIV, non-neutralizing antibodies specific to the V2 region induced by gp120 (expressed by canarypox vector priming or recombinant protein boosting) were recently linked to the lowest infection rates among the RV144 vaccinees.[13-15] Further research is necessary to support this encouraging observation and follow-up is required to estimate the durability of this response.

The temporal association between $CD8^+$ cytotoxic T cell response and the decline of viremia in the early phase of HIV infection and the role of these cells in the control of HIV, reviewed by McDermott and Koup,[16] have led to the development of vaccines aiming at the induction of strong and persisting $CD8^+$ T cell responses. The failure of the Ad5-gag/pol/nef vaccine (STEP Trial) meant a substantial drawback for the $CD8^+$ T cell approach, especially for the use of live viral vectors. The increased susceptibility for HIV infections of adenoviral-based HIV vaccine recipients with pre-existing immunity against Ad5 was hypothetically explained by the preferential expansion of adenovirus-specific activated $CD4^+$ T cells. The mucosal accumulation of these $CD4^+$ T cells increased the susceptibility to HIV acquisition.[17] It was also established that the $CD8^+$ T cell responses elicited by the STEP vaccine resembled better those of HIV-infected subjects who evolved toward disease than of those who control infection. Still, a vaccine that induces a different quality of $CD8^+$ T cell response has shown beneficial effects in the SIV macaque model.[18]

Rationale for a $CD4^+$ T Cell-Inducing Vaccine

Based on their pivotal role in HIV infection and in view of the shortcomings of B cell and $CD8^+$ T cell approaches briefly commented above, some research teams have chosen to evaluate the potential benefit of a vaccine that aims at eliciting strong, multi-specific, polyfunctional and persisting $CD4^+$ T cell responses. Antibodies exert their effects optimally when supported by simultaneous $CD4^+$ T cell responses, and both $CD4^+$ and $CD8^+$ responses are probably needed to tackle HIV replication at the initial site of infection through innate and adaptive mechanisms.[19] A protective $CD4^+$ T cell response seems indispensable to establish a stable and long-lived vaccine-induced immunity to HIV, since naturally occurring HIV-specific $CD4^+$ T cells in individuals with persistent HIV infection seem to be functionally deficient.[19,20] This is supported by clinical data demonstrating that the loss of HIV-specific $CD8^+$ T cell function in chronic infection can be restored by vaccine-induced augmentation of HIV-specific T helper cell function.[21]

Lessons Learnt From Nature

Not all exposures to HIV lead to infection and not all HIV infections evolve toward AIDS.[22] Natural resistance to HIV is likely multi-factorial and the result of a combination of host genetics and innate and adaptive immune responses. An immunologically interesting group includes serodiscordant couples and commercial sex workers who do not become infected with HIV despite extensive exposure.[23] These highly-exposed seronegative individuals appear to be in a state of HIV-specific immune activation, and several authors have described HIV-specific $CD4^+$ T lymphocytes as potential immunological correlates of protection from persistent infection.[24-26] These phenomena indicate that HIV-specific $CD4^+$ T cell responses can be induced or augmented by exposure to HIV without infection.

During the past decade, extensive research has been done on immunological characteristics of the long-term non-progressors (LTNP), HIV-infected patients who remain asymptomatic and maintain high $CD4^+$ cell counts in the absence of antiretroviral therapy, and viral controllers (VC), patients who spontaneously control the viral load. The presence of highly functional HIV-specific $CD4^+$ T cells secreting gamma interferon (IFN-γ), interleukin-2 (IL-2) and/or tumor necrosis factor α (TNF-α) and mainly directed toward Gag proteins, have been associated with suppression of viremia in LTNP and VC.[27-29] Assuming that these $CD4^+$ T cell responses directly contribute to the more benign course of the infection in VC, the challenge lies in designing a vaccine that induces these beneficial cellular immune responses. Clinical progressors lack functional HIV-specific $CD4^+$ T cells with proliferative and cytokine-producing capacity, while $CD4^+$ T cells of non-progressors were found to respond to a wide range of HIV-antigens from different clades with the production of both type 1 and type 2 cytokines.[30] Strong p24-specific $CD4^+$ T cell responses have also been linked to efficient viral control in primary HIV infection.[31]

A Plea for $CD4^+$ T Cell Inducing Vaccines

The expected benefit of a vaccine that elicits $CD4^+$ T cell-mediated immunity lies in lowering the viral set point when HIV infection occurs or in reducing viral load in already infected patients. Modeling studies have shown that viral levels at set point

are inversely correlated with HIV disease progression.[32] Individuals who receive T cell vaccines before infection may remain asymptomatic for a prolonged period, and initiation of antiretroviral therapy may be delayed. In addition, by blunting the initial viremia and limiting dissemination in primary infection, a T cell based vaccine may also minimize the establishment of viral reservoirs when memory CD4+ T cells in gut-associated lymphoid tissue are preserved.[33]

Potential Drawbacks of CD4-Inducing HIV Vaccines

Since CD4+ T cells are the main targets of HIV their position and usefulness in HIV vaccine development remains controversial. The loss of HIV-specific CD4+ T cell responses, and consequently the loss of control of HIV replication, is potentially caused by the viruses' preference to infect HIV-specific CD4 cells.[34,35] One of the most critical questions in HIV vaccine development is therefore whether a CD4+ T cell-inducing vaccine could possibly increase the susceptibility for infection by creating a larger pool of potential target cells. In their latest review, Virgin and Walker listed up the available evidence suggesting that HIV-specific CD4+ cells are beneficial rather than detrimental, and that associations between CD4+ T cell activation and increased viremia are only correlative.[19] For instance, virus-specific CD4+ T cells are able to provide significant direct protection against acute retroviral infection,[36] and the initial burst of viral replication does not occur in HIV- or SIV-specific CD4+ T cells, but in resting CD4+ T cells at mucosal sites.[37] In addition, a strong effector-memory CD4+ T cell response is associated with diminished SIV replication after intrarectal challenge in rhesus monkeys.[38] Vaccines capable of generating and maintaining HIV-specific effector-memory T cells might therefore decrease the incidence of HIV acquisition after sexual exposure.

Experience with a CD4+ T Cell-Inducing Vaccine

Vaccine strategies aiming to induce HIV-specific CD4+ T cells mainly include protein-based and DNA vaccines.[22] Adjuvants are usually added to enhance and selectively modulate the immunogenicity of highly purified or recombinant antigens. Vaccine candidates comprised of adjuvanted polyproteins such as gp120/NefTat and p24-RT-Nef-p17 have already been shown to induce vigorous and persistent CD4+ T cell responses in healthy volunteers.[39,40] Recently we compared the magnitude and quality of CD4+ T cell responses induced by HIV-1 infection in individuals with different patterns of disease progression with the CD4+ T cell responses induced by the [p24-RT-Nef-p17] polyprotein vaccine candidate in healthy volunteers. Vaccination of healthy HIV-uninfected volunteers with an adjuvanted polyprotein vaccine induced polyfunctional CD4+ T cell responses of the same magnitude and quality as those observed in VC (manuscript in preparation). Although one should be careful not to confuse coincidence with causality, it is tempting to speculate that vaccination with an adjuvanted multi-antigenic vaccine may induce an immune status that will direct the disease course toward the VC status in case of subsequent HIV infection.

Conclusion

The ideal HIV vaccine should induce antibodies that prevent the virus from entering the body and initiating its fatal cycle of events. Increasing insights in the interaction between broadly neutralizing antibodies and viral envelope proteins and a better understanding of the factors that determine the maturation of the antibody response to HIV may assist us in designing the immunogen(s) that elicit this response. Considering that this goal may not be reached soon (or at all) fallback mechanisms need to be incorporated in future vaccine designs. A strong and polyfunctional HIV-specific CD4+ T cell component deserves to be included in this scenario, not only because CD4+ T cells will enhance the magnitude, quality and durability of the desired antibody response, but also because they will provide the "help" needed to induce and maintain effective antiviral CD8+ T cell responses. In addition, the CD4+ T cell response in itself has disease-modifying potential, by controlling viral replication, delaying CD4+ T cell decline and preventing the occurrence of opportunistic infections. By reducing the probability of virus transmission to seronegative partners, the advantages would extend from the individual to the public health level.

Author Footnote

ALVAC-HIV (vCP1521) is a recombinant canarypox vector genetically engineered to express CRF01_AE gp120 (from strain 92TH023, GenBank number EF553537) linked to the transmembrane (TM) anchoring portion of gp41 from the HIV subtype B strain LAI and HIV-1 Gag and Protease (subtype B LAI, GenBank number EF553538).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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