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Can an immune-regulatory vaccine prevent HIV infection?

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Abstract

Developing vaccines to prevent the establishment of HIV infection has been fraught with difficulties. It might therefore be important to consider other new strategies. Since several studies suggest that anti-inflammatory stimuli can protect from HIV infection and because HIV replicates preferably in activated T cells, we suggest here that the reduction of immune activation through a HIV-specific regulatory T-cell vaccine might thwart early viral replication. Thus, because immune activation is a good predictor of disease progression and the immune activation set point has been shown to be an early event during HIV infection, vaccinating to achieve control of early virus-specific immune activation might be advantageous.

Keywords

HIV; immune regulation; T cells; vaccine

The groundwork of vaccine discovery is to study nature's examples as there are usually individuals that spontaneously eliminate a given pathogen. Unraveling the phenotype of such an effective immune response has, historically, been the key to a successful vaccine [101]. Unfortunately, in HIV, nature does not provide such proof of principle: we have no reliable proof of spontaneous immune-mediated clearance of HIV, neither in an animal model or in humans. Elite controllers, who mount a broad and multispecific immune response and control HIV well, still cannot eliminate the virus. In addition, it has not been so far possible to elicit an elite-control type of immunity in nonelite controller individuals, to substantially improve viral control. Consequently, we do not have a robust example of what an effective, preventive immune response to HIV could look like. Yet, current approaches to develop vaccines to prevent HIV or lower the viral set point through the generation of effector T cells [1,2] and ideally antibodies [3,4] are somewhat unidirectional. While these approaches, especially antibody-based immunizations, are powerful vaccines for the majority of infectious diseases, their usefulness remains to be proven in the HIV arena. Recent evidence from vaccine trials, where in some cases even increased acquisition of infection was noted [5,6] and in others only little success was seen [7], supports the notion

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that a conventional approach to this problem is at the very least very difficult. While the reasons for these vaccine trial failures could be manifold, the notions that immune activation correlates well with disease progression and that HIV replicates well in activated T cells, especially HIV-specific T cells [8], might be key challenges in designing a successful vaccine. Thus, the dilemma in HIV infection is that, while antiviral immunity by CD4 T cells could help to eradicate the virus [9], such T cells may also be supporters of viral replication (Figure 1).

Indeed, a multitude of reports have highlighted the detrimental role of immune cell activation in HIV-infection [10–13]. At the same time, there is increasing evidence that anti-inflammatory stimuli can protect from productive infection but also slow down disease progression in infected individuals [14,15]. In this article, we will outline some of these findings and discuss why we believe that curbing the immune response might be a promising alternative in HIV vaccine discovery – an alternative that, in our opinion, has not been considered sufficiently in current efforts to design HIV vaccines.

HIV prevention & intervention trials

Active and passive immunization protocols have been tested in nonhuman primate models of HIV infection in proof-of-concept studies. Vaccination regimens with recombinant viral vectors that induced T-cell-mediated immunity were shown to reduce replication or even decrease the incidence of acquisition of SIV in nonhuman primates [16,17]. Administration of human neutralizing monoclonal antibodies protected macaques from Simian-HIV infection [18], but so far it has been impossible to make an immunogen that elicits such antibodies. Of the 150 vaccine regimens entering clinical trials over the past two decades, only four have undergone evaluation in larger-scale, test-of-concept (Phase IIb) or efficacy (Phase III) trials. We will briefly comment on the two most recent trials, from which the most immunological data has been collected.

While the lack of protection from HIV of the Adenovirus 5 HIV-1 gag/pol/nef trivalent vaccine, tested in the recent STEP trial [5] may have been related to the narrowness of the induced T-cell response (on average, only one epitope was recognized per HIV-1 gene product in each vaccinee [19]), this notion would certainly not explain why the incidence in the vaccinated group (at least in some countries) was actually higher than in the control group. By contrast, in the recent RV144 Thailand trial, the vaccine contained ALVAC vCP1531 (recombinant canarypox vector encoding Gag, Pro and gp120, four doses) in combination with AIDSVAX B/E (Recombinant gp120) and showed low-level efficacy in reducing HIV-1 acquisition [7]. While the most frequent vaccine-induced immune responses were CD4⁺ T-cell proliferation, antibodies against HIV-1 gp120, ADCC and low-titer neutralizing antibody activities, vaccine-induced CD8 T-cell responses have not been detected.

Thus, for preventive vaccines, the initial belief in the benefits of inducing a stronger immune response is fading. While several vaccines have demonstrated immunogenicity, efficacy was a much harder target to achieve. Taken together, preventive vaccine concepts that were designed to boost HIV-specific immune responses, could not live up to expectations. Consequently, one has to consider alternative approaches to tackle HIV.

The role of immune activation to propagate HIV

It is widely accepted that chronic immune activation in HIV infected patients is associated with faster disease progression [10–13,20]. Indeed, it has been shown that progressive HIV infection and pathogenic SIV infection in nonhuman primates are associated with increased levels of lipopolysaccharide, due to a leaky gut and microbial translocation [21], which

trigger immune activation that is linked to HIV mortality [20]. Strikingly, patients with elevated signs of immune activation even before sero-conversion have reduced AIDS-free survival rates compared with those patients with reduced signs of immune activation [10,12,20] and the degree of immune activation that determines the rate of disease progression is an early event in HIV infection [11]. However, rather than preventing immune activation, the current strategy to develop vaccines to prevent HIV is to optimize the generation of effector T cells [1,2] using better vectors for immunization. Thus, this strategy has the flip-side that HIV will be propagated more readily once it infects the increased number of activated CD4 T cells elicited by the vaccine. Yet, the rationale for these efforts has been based on solid grounds: in a small subset of patients, termed 'elite controllers', control of viral replication was indeed associated with a strong and multispecific antiviral T-cell response [22]. However, it is not clear, whether such a broad response can be extended via vaccination to other infected individuals, for whom the alternate approach of an immune regulatory vaccine proposed here might be potentially of more benefit.

Indeed, nature provides other examples of how productive HIV-infection can be prevented: HIV-exposed individuals that remained HIV-negative. While the strongest association with HIV-protection in those individuals has been shown to be the genetic variation of the HIV coreceptor CCR5 that prevents viral entry into the cells, several studies strongly suggest that low levels of immune activation and the presence of anti-inflammatory stimuli might contribute to protection in these individuals [23–27]. Individuals that produce higher levels of the anti-inflammatory cytokine IL-10 due to a polymorphism in the IL-10 promoter region are less susceptible for HIV infection [14,15] and interestingly, treatment with recombinant IL-10 has been shown to prevent HIV infection in a humanized mouse model [28]. However, once infected, these high IL-10 producing individuals display higher viral loads in the acute phase of infection [14], display reduced CD8 T-cell-responses and loose CD4 T cells more rapidly than lower IL-10 producing individuals [29]. On the other hand, high IL-10 producers ultimately have decreased viral titers in the chronic phase of infection, progress significantly slower to AIDS [15] and survival rates are doubled in these patients [30]. In addition, elevated IL-10 mRNA levels are associated with a slower progression to AIDS in HIV-infected children [31]. Similarly, prevention of mucosal SIV-infection could be achieved in a nonhuman primate model by local administration of an anti-inflammatory compound that prevented immune activation [32]. These observations are also in agreement with the notion that an anti-inflammatory cytokine milieu and the absence of chronic immune activation have been repeatedly found in nonpathogenic SIV infections in natural host primates. In these animals, SIV replicates well and establishes persistence without causing clinical disease [33–35]. This outcome is associated with rapid termination of the initial type 1 interferon response in the presence of anti-inflammatory cytokines, whereas disease-prone macaques display a sustained type 1 interferon response in the presence of proinflammatory cytokines and activated effector T cells [36,37]. Collectively, these findings suggest a nonredundant role for anti-inflammatory stimuli in preventing an establishment of productive infection but also harnessing the pathogenicity of HIV.

The role of Tregs

Tregs comprise a subset of T cells with suppressor activity capable of blocking the activation (proliferation and cytokine production) of effector T cells [38]. Thus, the question whether Tregs are capable of reducing immune activation during HIV infection has attracted much attention. However, despite several years of intense research and a multitude of publications on this topic, we are still lacking a clear concept on how Treg cells influence HIV infection. On the one hand, Tregs have been associated with protection from productive infection and pathogenic disease in humans and nonhuman primates [25,36,39,40]; but, on

the other hand, Treg cells have been shown to be important for the establishment of HIV infection in humanized mice [41] and were associated with increased immune activation in humans (Box 2) [42,43].

Box 2

Protective and detrimental findings associated with Tregs

Protective

- Tregs decrease HIV replication in activated CD4 T cells [56].
- Higher numbers of Tregs are associated with decreased signs of immune activation (CD69) in uninfected high-risk sex workers [25].
- Treg numbers appear to decline at slower rates when compared with other CD4 T cells [43].
- Preserved high numbers of circulating Tregs are associated with decreased immune activation in elite controllers [40].
- High numbers of Tregs are associated with decreased signs of immune activation and reduced risk for vertical transmission in newborns [39].

Detrimental

- The increase of Tregs over time due to the disruption of the mucosal Th17/Treg balance is a characteristic of pathogenic SIV and possibly progressive HIV infection [57,58].
- FoxP3⁺ Treg accumulation in lymphoid tissues from humans and nonhuman primates is associated with disease progression, independent [42] or dependent [43] from immune activation status.
- FoxP3⁺ CD4⁺ Tregs are susceptible to HIV infection [41].
- Tregs inhibit HIV-specific CD4 and CD8 T-cell responses *in vitro* [59,60].

The major caveat in studying Treg cell function and a possible explanation for such diverging results is arguably the heterogeneity of this population, not exclusive to HIV-infection [44]. The majority of reports characterize Treg cells based on their expression pattern of defined surface markers (CD4⁺CD25⁺CD127⁻) and the transcription factor FoxP3. However, in HIV a purely phenotypic characterization is particularly problematic, as different CD4 subsets become infected with different kinetics [45,46]. To what extent this affects the expression of surface markers, CD4 T cell plasticity and FoxP3 stability has not been addressed sufficiently.

In summary, these considerations argue for a more functional definition of regulatory T cells than a merely phenotypic characterization. Recent findings that IL-10 producing, FoxP3-negative cells, so called type 1 regulatory T cells, can effectively suppress effector T-cell functions support this notion [47].

Therapeutic translation

A major setback in studying the protective role of anti-inflammatory agents was the failed clinical trial with recombinant IL-10 nearly 10 years ago [48]. In a clinical pilot study where chronically infected patients received one dose of IL-10, a transient decline of HIV-RNA was observed [49]. However, these results could not be confirmed in a randomized Phase II trial [48]. IL-10 treatment of chronically infected patients did not affect the clinical end

points of this trial including HIV-RNA levels and CD4 T-cell counts. The reason for this failure could be manifold and include the small study size ($n = 10$ per study group) and the short treatment period (4 weeks). More importantly, however, in our opinion, a promising concept was buried altogether after only one trial. Considering the enormous effort that has been put into designing protective vaccines that aim to establish an elite controller-like immune phenotype in vaccinees [50]. This appears to be premature and we believe that it is time to revisit approaches that induce regulatory immunity rather than effector T cells to tackle HIV infection. Several observations discussed above would argue that it might indeed be possible to slow down disease progression in established infection with a regulatory vaccine; however, public health considerations would argue against such an approach, which might even promote viral replication. Indeed, dampening the antiviral immunity during established infection might result in uncontrolled viral replication with an increased risk of HIV-transmission. Therefore, an immune-regulatory vaccine would best be deployed to prevent establishment of productive infection. The proof-of-principle in this case would be the observation that high levels of IL-10 have been shown to prevent HIV-infection in humans and mice. While systemically elevated levels of IL-10 in order to prevent immune activation would be a rather blunt tool on a population level, we would argue that an HIV-specific vaccine approach could be a promising alternative to current vaccination strategies.

The lack of in-depth studies focusing on therapeutic implications of the protective properties of such regulatory stimuli in HIV is obviously the major caveat in designing such approaches for HIV infection. However, in a first step, observations from other disease models could be used to define strategies with the goal to induce a distinct HIV-specific cell type with regulatory properties, which in this case needs to be defined by its ability to produce anti-inflammatory cytokines, most importantly IL-10, and the capability to migrate and accumulate at sites of viral infection. It has been shown that dendritic cells with regulatory properties are able to suppress effector T cells in various disease models through direct IL-10 secretion or the induction of other regulatory cell types [51,52]. Importantly, such regulatory dendritic cells induce not only CD4 regulatory cells but also CD8 Treg cells, which could be particularly useful in HIV as these cells would not become infected. Secondly, the induction of type 1 regulatory T cells, which are strong IL-10 producers [53] could be a promising approach. These cells develop extrathymically and can be efficiently expanded *in vitro* for proof-of-concept studies. Thirdly, a DNA vaccine that induces a regulatory T-cell response with a distinct cytokine profile, in this case IL-4 and IL-10 production, has been shown to reduce the incidence of diabetes through bystander suppression of autoreactive T cells and has shown initial promise in clinical trials of autoimmune diabetes (Figure 2) [54]. While none of these approaches describe a comprehensively developed concept, they might constitute first steps to elaborate on. Such approaches may have the potential to prevent immune activation in response to HIV infection and could thus prevent the establishment of a fertile field where HIV can easily replicate. This could result in the prevention of productive infection, as is suggested by lower infection rates in high IL-10 producers [14,15] and the preventive effect of IL-10 pretreatment in humanized mice [28].

Expert commentary & five-year view

It has become apparent that it is difficult to develop a preventive vaccine for HIV. The reasons for this are manifold and, among others, include the ability of the virus to mutate and evade antibody and/or T-cell recognition but also the intrinsic property of HIV requiring activated CD4 T cells to replicate efficiently. This unique aspect creates a dilemma, because we must weigh the benefits of inducing a strong antiviral response with the risk of helping the virus at the same time to find an even more fertile ground for replication and possibly gaining an initial foothold prior to sequestering into reservoirs from which it is difficult to

eradicate. We therefore discussed evidence indicating that dampening the antiviral immune response prior to HIV mucosal exposure could be beneficial in preventing productive infections. Less antiviral immunity might in some cases be better, a concept that deserves more exploration in our opinion.

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#.TymdgflEFD8

Box 1**Selected evidence for protective properties of anti-inflammatory stimuli in HIV (excluding Treg-associated findings)****Humans**

- Individuals with an IL-10 promoter polymorphism that results in higher levels of IL-10 are less likely to become infected and progress significantly slower to AIDS [14,15].
- Elevated IL-10 mRNA levels are associated with a slower progression to AIDS in HIV-infected children [31].
- Antiretroviral treatment of HIV-infected pregnant women increases production of IL-10 in plasma and *in vitro*, which negatively correlates with viral loads [55].

Nonhuman primates

- Anti-inflammatory cytokine profiles and reduced immune activation is associated with nonpathogenic SIV infection in African green monkeys compared with pathogenic infection in Rhesus macaques that develop AIDS [36].
- Early disruption of the innate immune response is associated with nonpathogenic infection in African green monkeys [34].

Mouse

- IL-10 pretreatment prevents HIV infection in humanized mice [28].

Key issues

- Current approaches to develop vaccines to prevent HIV that aim at the generation of effector T cells have largely been unsuccessful.
- HIV replicates preferably in activated T cells and immune activation increases the risk of HIV acquisition. Thus we face the dilemma that antiviral immunity by CD4 T cells could help to eradicate the virus but such T cells may also be supporters of viral replication.
- There is an increasing body of evidence suggesting that anti-inflammatory stimuli can prevent HIV acquisition.
- We discuss the possibility of an immune-regulatory vaccine to prevent productive HIV infection.

Figure 1. The two faces of CD4 T-cell activation in HIV infection

While antiviral immunity by CD4 T cells could help to eradicate the virus by providing T-cell help and through direct effects (**A**), the activated CD4 T cells are more susceptible to becoming infected and thus, providing an optimal environment for HIV replication (**B**).

TCR: T-cell receptor.

Figure 2. Possible way to induce a tolerogenic or regulatory antiviral response

The goal would be to induce a distinct HIV-specific cell type with regulatory properties. DNA vaccination and peptide vaccination that induce a regulatory response but also cell-transfer studies with regulatory DCs and type 1 regulatory T-helper cells have been proven successful in animal models for autoimmune diseases or graft-versus-host diseases. Naive DCs are thought to develop into rDCs upon contact with the regulatory vaccine. In the lymphatic tissue, these rDCs present the antigen in a tolerogenic fashion to CD4 and CD8 T cells. Those T cells then acquire a regulatory phenotype. In HIV infection, such cells might be able to prevent activation of HIV target cells, for example, in an IL-10-dependent fashion, which could prevent the establishment of productive infection. DC: Dendritic cell; IDO: Indoleamine 2,3-dioxygenase; PEG: Polyethylene glycol; rDC: Regulatory dendritic cell.

Data from [51–54,61].