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HIV vaccination: turning the spotlight on effector memory T cells as mucosal gatekeepers

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Abstract

The accumulating failures in HIV vaccine development demonstrate that the immunization approaches used so far are insufficient to reproduce the naturally occurring immunity that controls the virus in long-term non-progressors, HIV controllers, and continuously exposed sex workers. They also underscore the desperate need for new approaches in the design of more effective vaccination protocols. Recent findings might have brought us closer to that goal by providing proof of concept for a novel preventative HIV vaccine by establishing CD8 effector memory T cells within the mucosal sites of transmission.

Introduction and context

When HIV was first discovered in 1983 [1,2], the race was on to develop an effective vaccine. Twenty-six years later, despite enormous efforts, we have still not reached the finish line. The recent failure of the STEP phase 2b clinical vaccination trial [3,4] using relatively innocuous adenovirus serotype 5 (Ad-5) vectors containing HIV T cell epitopes has caused many to question the ability of cellular immunity to contribute to an effective HIV vaccine.

Retroviruses that cause AIDS in primates, including HIV and its close relative, the simian immunodeficiency virus (SIV), belong to the family of lentiviruses (or 'slow' viruses). They are known for inducing clinical disease only after a prolonged period of relatively stable chronic infection, during which time the immune system slowly but steadily declines. However, the infection kinetics clearly consist of a two-phased process. The initial, acute phase is characterized by an exceedingly high viral replication rate accompanied by a massive loss of memory $CCR5^+CD4$ T cells, particularly those that reside within the gastrointestinal tract [5-9]. To a lesser extent, macrophages and some dendritic cells that express CD4 and CCR5 are also affected. This is followed by a chronic phase of variable but usually incomplete virus control, which eventually develops into AIDS [10].

The frequent mutations of the replicating virus which lead to incredible genomic heterogeneity impose an enormous challenge for the design of an effective vaccine. Perhaps more important in this context is the ability of the virus to specifically target immune cells, thereby increasingly breaking down the immune system itself and inevitably leading to the development of AIDS.

Major recent advances

Back to the drawing board

It is not certain why the STEP trial failed, and why it even increased the risk of HIV infection in those individuals with pre-existing Ad-5-specific immunity. One possibility is that the expansion of Ad-5-specific CD4 memory T cells could have created a permissive environment for HIV infection [11]. Nevertheless, two recent studies could not confirm a correlation between the numbers of expanded Ad-5-specific T cells and an increased risk of HIV infection in vaccinees with pre-existing Ad-5 immunity [12,13]. This suggests that other flaws undermined the success of the Ad-5/HIV vaccination strategy and that new concepts need to be considered in order to reach the finish line of successful vaccination.

Several studies have demonstrated that $CD8^+$ cytotoxic T cell (CTL) responses play a crucial role in the initial

containment and early control of HIV or SIV replication [10,14-16]. In primary infections, a potent anti-HIV or SIV specific CTL response is detected at a time when a humoral response is weak or nonexistent, suggesting that $CD8^+$ effector cells are key controllers of early viremia [15,16]. Nevertheless, SIV-macaque models demonstrated that measuring cellular immune responses to an SIV vaccine, using *in vitro* assays on blood samples, does not faithfully predict the efficacy of the vaccine. Low levels of protection against SIV were observed in the face of rather vigorous vaccine-induced immune responses [17]. Also, live, attenuated SIV infection provided potent protection against wild-type SIV, whereas only weak anti-SIV immune responses were measured *in vitro* [18,19], suggesting that vaccine-induced protection against HIV/SIV might be critically dependent on localized, likely mucosal-specific immune responses *in vivo*.

Consistent with the importance of the local response, and further underscoring the central, early contribution of CD8 T cells, are the results from nonhuman primates demonstrating that depletion of CD8 T cells *in vivo* resulted in enhanced AIDS viral replication during the acute phase, increased loss of $CCR5^+CD45RA^-CD4$ T cells in the intestine, reduced humoral responses and, ultimately, in an accelerated lethal outcome of the disease in the infected monkeys [20-26].

The efficacy of virus-specific CD8 CTLs to control viral replication and/or prevent AIDS led to the concept that an effective vaccine should lead to the induction of a strong and early viral-specific CD8 immune response that, although unable to provide sterilizing protection, ought to be able to control the viral load and delay or prevent the onset of disease, as well as reduce the potential for secondary transmission.

A major step forward: providing proof of concept

Unlike naïve T lymphocytes and central memory T cells (T_{CM}s), effector memory T cells (T_{EM}s) have the ability to reside long-term in non-lymphoid tissues, such as the gut mucosa, and to provide immediate effector function, without the pre-requisite of an initial proliferation step [27]. This suggests that the generation of vaccine-induced mucosal HIV-specific T_{EM}s might provide front-line protection to prevent the initial early phase of HIV infection.

An important recent study by Hansen *et al*. [28] provides direct support for this new paradigm. They demonstrated that Rhesus macaques inoculated with rhesus cytomegalovirus (RhCMV) vectors containing an SIV Gag, Rev-Tat-Nef fusion protein, and Env were protected from progressive wild-type SIV infection after repeated limiting-dose intrarectal challenges. Moreover, the protected animals that were repeatedly infected via the mucosal route showed no evidence of systemic infection months later, suggesting that the infection was contained locally, well before extensive viral replication or systemic spreading of the virus. Interestingly, and in contrast to the CMV vector-based protection that generated a high frequency of SIV-specific T_{EM}s, an Ad-5-boost vaccine regimen, using the same limiting-dose intrarectal challenge protocol, instead induced a strong T_{CM}-biased immune response that did not provide protection against SIV challenge.

Future directions

Turning the spotlight on T_{EM}s as the mucosal frontline defenders

Earlier SIV/macaque model studies also showed that partial successful SIV protection was reached when immunization was performed via the intranasal or oral route [29,30], further stressing the issue that the induction of mucosal immunity might be key for a successful HIV/AIDS vaccination strategy. Most HIV infections are acquired across a mucosal barrier, and the mucosal immune system forms the main HIV reservoir, the most important target for HIV replication, and it endures the major early T cell losses [5,6,8]. The depletion of mucosal T cell responses is probably the result of direct infection of T cells and immune exhaustion due not only to chronic activation by HIV, but also to activation by intestinal bacteria. The rapid and severe depletion of mucosal $CCR5^+CD4$ memory T cells [5,6,8] results in a considerable translocation of bacteria across the mucosal barrier [31]. Especially critical is the loss of Th17 CD4 memory cells, a major contributor to impaired barrier function [32]. Together these processes contribute to the induction of chronic systemic immune activation and T cell exhaustion.

In order to generate protective immunity, future HIV vaccines will probably have to include the induction of viral-specific T_{EM} populations at relevant mucosal entry surfaces as one of the absolute goals. A successful protective immune response will need to be able to sense a low dose of viral epitopes endogenously produced by naturally infected cells, and to eliminate those infected cells before extensive viral replication and the loss of mucosal CD4 memory T cells occurs. This may require specific immunization strategies other than systemic immunization, and the development of more accurate assays to distinguish mucosal HIV-specific T cell responses from those of peripheral cells. But most of all, we need to understand and identify the mechanisms and factors that can direct vaccine-induced differentiation and maintenance of highly effective and long-lived

mucosal T_{EM}s that can contribute to form the first line of defense and destroy the pathogen before it gets a chance to destroy its host.

Abbreviations

Ad-5, adenovirus serotype 5; CCR5, chemokine (C-C motif) receptor 5; CD4, cluster of differentiation 4; CMV, cytomegalovirus; CTL, cytotoxic T cell; RhCMV, rhesus cytomegalovirus; SIV, simian immunodeficiency virus; T_{CM}, central memory T cell; T_{EM}, effector memory T cell.

Competing interests

The author declares that she has no competing interests.

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