EMBO Molecular Medicine

Perpetuation of vaccine memory T cell responses against SIV/HIV

Yves Lévy[1,2,3]

Keywords: eradication; human immunodeficiency virus; protection; recombinant cytomegalovirus vector
See related article in Nature http://dx.doi.org/10.1038/nature10003

Results of the RV144 study of a prime-boost regimen combining a canarypox vector-based candidate ALVAC-HIV (vCP1521) and AIDSVAX B/E gp120 human immunodeficiency virus (HIV) envelope showed a modest but statistically significant 31% reduction in the rate of HIV infection in healthy volunteers (Rerks-Ngarm et al, 2009). These promising results need to be confirmed in further clinical trials and researchers are hoping to gain more information about the correlates of protection against HIV and the mechanisms of action of these vaccines. In addition, from a clinical standpoint, the RV144 study provides two interesting pieces of information. First, at the end of the first year of the study the rate of protection was up to 60% in vaccinees compared to placebo recipients. Second, no differences in terms of peak of viral load were seen between vaccinated and placebo recipients who became infected. This suggests that the protective efficacy wanes overtime and that vaccines were unable to control viral replication once a systemic infection is established.

The immune system controls pathogens through the generation of memory T cells, which can be divided in, at least, two populations of central and effector memory T cells (Tcm and Tem) ensuring protection for years after the first encounter of the pathogen. Following antigen exposure, Tcm undergone expansion, differentiation towards effector cells, which patrol mucosal tissues, the site of entry of HIV and kill infected cells. Clearly, the initial hours following exposure of HIV to mucosal tissues represents a window of opportunity for the immune system to control and/or to eliminate smaller and localized foci of HIV-infected cells. Therefore, an effective vaccine must confer to the host the capability to win the race between the differentiation capacity of Tcm and the extraordinary burst of HIV replication, which occurs within hours before the establishment of an irreversible disseminated infection.

In other words, pre-existing, vaccine-elicited Tem against HIV in mucosal sites would confer a serious advantage against virus acquisition. Taking into account that the maintenance of the Tem pool and Tem function requires the persistence of the antigen and a continuous differentiation of Tcm, how to translate this in terms of vaccine design? Most conventional HIV vaccine regimens under development are non-persistent vectors leading to the generation of Tcm, which hopefully are capable to differentiate after antigenic stimulation and, therefore, too late to control pathogen.

Hansen et al hypothesized that a vaccine able to 'pre-position' differentiated effector cells at mucosal sites would improve efficacy (Hansen et al, 2011, 2009). For this, they have developed a simian immunodeficiency (SIV) vaccine based on a recombinant herpesvirus Cytomegalovirus (RhCMV), a persistent virus capable to elicit a high frequency of Tem, a hallmark of persistent agents. The group has already reported that the RhCMV/SIV vector, expressing diverse proteins from SIV, can establish a persistent infection inducing a high frequency of long lasting SIV-specific Tem-biased $CD4^+$ and $CD8^+$ T cell responses at the periphery but also in diverse sites in Rhesus Macaques (Hansen et al, 2009). In a new and elegant paper (Hansen et al, 2011), the group has extended their initial work by comparing in a larger group of animals different vaccine regimens: in a first group, macaques received the rhCMV/SIV vector alone. In a second group, RhCMCV/SIV was followed by a boost of replication-defective Adenovirus 5 (Ad5) vaccine. These RhCMV/SIV groups were compared to a standard DNA prime/Ad5 vector regimen and to an unvaccinated control group. Interestingly, and as expected, the magnitude of $CD4^+$ and $CD8^+$ T cell response at the end of the vaccination was similar in all vaccinated animals. However, RhCMV/SIV elicited a different repertoire of SIV-specific $CD8^+$ T cells than the DNA-and/or Ad5 regimen and maintained a Tem-biased response in contrast to a more Tcm phenotype in the DNA/Ad5 vaccinated macaques.

Next, animals from all groups were challenged with the highly pathogenic SIV_{MAC239}. The number of challenges

(1) INSERM, Unite U955, Creteil, France
(2) Faculte de Medecine, Universite Paris-Est, UMR-S955, Creteil, France
(3) AP-HP, Groupe Henri-Mondor Albert-Chenevier, Immunologie Clinique, Creteil, France
Corresponding author: Tel: +33 1 4981 4442; Fax: +33 1 4981 2469;
E-mail: yves.levy@hmn.aphp.fr
DOI 10.1002/emmm.201100163

 © 2011 EMBO Molecular Medicine

needed to establish a detectable infection was similar across the groups but the subsequent course of infection differed significantly between RhCMV/SIV vaccinees and others. Almost all animals from the DNA/Ad5 groups manifested progressive infection, albeit with a lower peak of viremia than controls, while 13 of 24 animals that received the RhCMV/SIV vaccine showed a transient increase of viremia followed by a rapid decline in viral load, succeeded by periodic blips (transient detectable virus replication) over weeks and infrequently observed after 1 year. Notably, in these animals no SIV-related pathogenesis (depletion of $CD4^+$ T cells in the blood or gut) or detectable cell-associated SIV RNA or DNA was found even after cell stimulation *in vitro* and careful examination at different sites. These results clearly show an extraordinary level of SIV control or even progressive clearance of infected cells over time.

The analyses of the kinetics and the phenotype of T cell responses during the acute phase of the vaccination and following SIV challenges provide important clues for the identification of correlates/mechanisms of protection and/or control of infection.

First, the magnitude of elicited $CD8^+$ T cell responses during the vaccine phase in RhCMV/SIV-vaccinated animals correlated with the protection. This suggests that the capacity of this vaccine to seed mucosal sites in virus-specific effector cells may improve control of infection. Notably, no SIV Env-specific antibodies were elicited by the RhCMV/SIV vaccine as compared to the DNA/Ad5 regimen suggesting that measured B cell responses are unlikely to contribute to the protection in these animals.

Second, results showed that RhCMV/SIV-vaccinated animals controlled SIV infection without expansion of anamnestic responses following SIV challenges in contrast to Ad5-boosted macaques. Moreover, only around half of RhCMV/SIV-vaccinated macaques controlled infection while once infected, these animals did not control viral replication better than unvaccinated animals. This result suggests that if induction of Tem is a significant weapon against SIV something else is needed for the control of progressive infection. This makes sense considering what we know from the natural history of infection in the so-called 'elite controllers' group of patients who are capable to control chronic HIV infection for years without drugs. Although the mechanisms by which these patients do control infection and exhibit a low viral reservoir are not fully elucidated, a significant proportion of them displays expansion of polyfunctional HIV-specific $CD4^+$ and $CD8^+$ Tcm cells (Sáez-Cirión et al, 2007).

One important and original result reported by Hansel et al is the demonstration that the vaccine strategy based on the RhCMV vector led to the containment and then the sterilization of infected cells despite the establishment of SIV infection following challenges. They show that RhCMV/SIV vaccinated animals developed $CD8^+$ T cell responses against Vif, a protein not contained in the vaccine, confirming the occurrence of SIV infection following challenge in these macaques. These responses, such as residual SIV replication, waned over time suggesting a clearance of infected cells. Interestingly enough, depletion of $CD8^+$ T cells resulted in a significant increase in plasma viral load and Vif-specific T cells responses in DNA/Ad5 and control animals but not in RhCMV/SIV-vaccinated controllers. Although authors could not exclude an incomplete depletion of $CD8^+$ T cells in mucosal sites, these results suggest that the level of residual infected cells in long-term rhCMV/SIV-vaccinated controllers might have been significantly reduced to levels avoiding viral rebound and the replenishment of the reservoir.

Although these results provide arguments for the development of CMV vectors in combination with 'classic' strategies for HIV vaccine development, the clinical development of this vaccine might encounter some difficulties in healthy individuals or in immunocompromised patients. Several clinical studies have been performed evaluating attenuated CMV strains or CMV-based recombinant vaccines in human. An important consideration in evaluating live attenuated vaccines is their potential to be transmitted by vaccinated individuals to susceptible individuals with whom they have contact. Of note, administration of RhCMV-SIV vectors to either RhCMV-naive or $RhCMV^+$ rhesus macaques resulted in clinically benign primary infection and superinfection, respectively, with the shedding of RhCMV-SIV vectors in urine and saliva (Hansen et al, 2009). Further clinical trials are needed to ensure that live attenuated CMV vaccines are non-pathogenic and do not engender various long-term health risks. Regarding the development of conventional vectors, several strategies are under way to develop attenuated but replicating and immunogenic replicating recombinant vaccines (Quakkelaar et al, 2011).

> *» Besides its crucial importance for prophylactic vaccinology, these results provide also clues for the development of therapeutic vaccination and the perspective of 'functional cure' and more optimistically 'eradication' of HIV. «*

Finally, one clinical consequence of this work is that the immune system might not only control virus replication but also clear residual infected cells. To this end, Hansel et al showed that the persistence of the vaccine vector is key for long-term control and maintenance of virus-specific effector T cells ensuring an immune surveillance even when infected cells are rarely detected. Besides its crucial importance for prophylactic vaccinology, these results provide also clues for the development of therapeutic vaccination and the perspective of 'functional cure' and more optimistically 'eradication' of HIV. This new frontier of HIV research is based on the assumption that new strategies would be able to impact the reservoir by maintaining an immune surveillance by functional effector cells independently of the level of viral replication, thus preventing relapse of virus multiplication and hopefully ultimately clearing residual infected cells. An objective that seems difficult to

 © 2011 EMBO Molecular Medicine

achieve with antiviral drug intensification alone.

The author declares that he has no conflict of interest.

References

Hansen SG, Vieville C, Whizin N, Coyne-Johnson L, Siess DC, Drummond DD, Legasse AW, Axthelm MK, Oswald K, Trubey CM, *et al* (2009) Effector memory T cell responses are associated with protection of rhesus monkeys from mucosal simian immunodeficiency virus challenge. Nat Med 15: 293-299

Hansen SG, Ford JC, Lewis MS, Ventura AB, Hughes CM, Coyne-Johnson L, Whizin N, Oswald K, Shoemaker R, Swanson T, *et al* (2011) Profound early control of highly pathogenic SIV by an effector memory T-cell vaccine. Nature 473: 523-527

Quakkelaar ED, Redeker A, Haddad EK, Harari A, McCaughey SM, Duhen T, Filali-Mouhim A, Goulet JP, Loof NM, Ossendorp F, *et al* (2011) Improved innate and adaptive immunostimulation by genetically modified HIV-1 protein expressing NYVAC vectors. PLoS One 6: e16819

Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, Premsri N, Namwat C, de Souza M, Adams E, *et al* (2009) Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med 361: 2209-2220

Sáez-Cirión A, Lacabaratz C, Lambotte O, Versmisse P, Urrutia A, Boufassa F, Barré-Sinoussi F, Delfraissy JF, Sinet M, Pancino G, *et al* (2007) HIV controllers exhibit potent $CD8^+$ T cell capacity to suppress HIV infection *ex vivo* and peculiar cytotoxic T lymphocyte activation phenotype. Proc Natl Acad Sci USA 104: 6776-6781

 © 2011 EMBO Molecular Medicine