Hot News

Dendritic Cell-Based Therapeutic Vaccination for HIV

Although combination antiretroviral therapy (cART) has changed the life expectancy and quality of life of patients with chronic HIV infection, cART is not a definitive therapy for HIV, considering that it is a life-long therapy not able to eradicate the virus. As a consequence of this limitation of cART, different immune-based strategies have been developed in order to boost the patient´s immune system, with the ultimate goal of achieving what is termed "functional cure", defined as control of HIV replication without cART. One of these strategies consists of therapeutic immunization with autologous dendritic cells that have been previously pulsed with either heterologous or autologous viral isolates.

A recent study published by García, et al. (Sci Transl Med. 2013;5:166ra2) has addressed this with promising results. The authors designed a randomized, double-blind, placebo-controlled trial that included 36 patients on cART; 24 of them were randomized to the vaccine arm and 12 to the placebo arm. The vaccine consisted of autologous myeloid-derived dendritic cells that were pulsed with heat-inactivated autologous virus isolate. After three doses of vaccine, patients interrupted cART and were followed up for 48 weeks. The primary endpoints of the study were safety and change in plasma HIV RNA load (pVL) set-point 24 weeks after cART interruption. Changes in CD4 T-cell counts and HIV-specific immune responses were included among the secondary endpoints. The vaccine was safe and able to shift the virus/host balance, with a significant drop of pVL at weeks 12 and 24 after cART interruption (0.9 and 0.8 $\log_{10}$ copies/ml, respectively) in the vaccinated group compared to placebo group. Moreover, a drop in pVL $\geq$ 1 $\log_{10}$ was achieved by half of vaccinated patients at week 12, and by 35% at week 24. Although HIV-specific T-cell responses increased in both groups after cART interruption, the increase at week 24 was significantly higher in the vaccinated group compared to the placebo group. However, the most important observation regarding immune response was that in the vaccinated group, the intensity of response was inversely associated with the level of pVL (meaning that those patients showing higher levels of T-cell response showed lower levels of pVL), whereas in the placebo group the association was direct. These results can be interpreted as a positive role of vaccine-induced T-cell responses in the partial control of pVL after cART interruption. Regarding the drawbacks of this study, three merit comment: first, although the vaccine induced a significant shift in the viral set-point, pVL rebounded in all patients; second, the vaccine did not prevent a drop in CD4 T-cell counts after cART interruption, most likely as a consequence of pVL rebound; third, the partial control of HIV replication observed in vaccinated patients waned over time.

In spite of these limitations, this study is the first double-blind, placebo-controlled trial showing that dendritic cell vaccination can elicit HIV-specific immune responses, which can significantly change the viral load set-point after cART interruption. These results are a proof-of-concept supporting further investigation in immunotherapeutic approaches, with the ultimate goal of achieving a functional cure as an alternative to life-long therapy.

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Earlier Antiretroviral Therapy in HIV – As Soon As Possible

Two recent reports in The New England Journal of Medicine have concluded that the best way to preserve the immune system, as assessed by measuring $CD4^+$ T-cells, is to begin antiretroviral therapy as soon as possible after HIV diagnosis. In the SPARTAC trial (Filder, et al. N Engl J Med. 2013;368:207-17), the authors investigated the effect of a short course of antiretroviral therapy on the subsequent $CD4^+$ T-cell decline in 366 adults with primary HIV infection. Patients were randomized to 12 or 48 weeks of therapy. In both arms, antiretrovirals were initiated within six months following HIV seroconversion. After an average follow-up of four years, only the group treated during 48 weeks experienced a significant benefit, with a reduction in the hazard ratio for the primary endpoint, which was the achievement of a CD4 count > 350 cells/µl.

In the second study, Le, et al. (N Engl J Med. 2013;368:218-30) investigated the effect of antiretroviral therapy on $CD4^+$ T-cell counts in persons with acute HIV infection, comparing those who initiated therapy within four months or thereafter. The authors demonstrated that a therapeutic intervention within the first four months following the estimated date of HIV infection increases the likelihood of reaching the primary endpoint, which was a $CD4^+$ count $\geq$ 900 cells/µl four years later. The proportion of patients was 64% in the earlier intervention arm

whereas it was 34% in those who delayed treatment initiation beyond four months.

This "restorative time window" for CD4+ T-cells suggested by both studies provides support to current recommendations in most HIV treatment guidelines (IAS-USA, DHHS, EACS) about prescription of antiretroviral therapy in recently infected individuals. The IAS-USA panel (Thompson, et al. JAMA. 2012; 308:387-402) was the first to openly favor earlier initiation of antiretroviral therapy and to treat nearly all HIV patients. In the editorial accompanying the two NEJM articles, Walker and Hirsh highlighted that the advantage of earlier antiretroviral therapy goes beyond the individual benefit, with a significant impact on public health, reducing HIV transmission. However, they did not stress how difficult is to identify persons recently infected with HIV. Moreover, they did not acknowledge the challenging situation in many developing regions, where optimal antiretroviral therapy is frequently not available even for those with moderate and/or advanced immunodeficiency.

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Siglec-1: A Novel Dendritic Cell Receptor for HIV-1 Infection

Dendritic cells (DC) are essential antigen-presenting elements that regulate both the innate and acquired immune response in HIV-1 infection. This process requires HIV-1 binding to the DC surface. Initial studies suggested that DC-SIGN (dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin) on immature dendritic cells (iDC) could interact with the HIV-1 gp120 envelope protein and this complex be internalized into iDC. During this process, the virus should remain intact, with iDC behaving as a "Trojan horse" for the spread of HIV-1 infection.

After iDC maturation, mature DC (mDC) interact with CD4+ T lymphocytes by a cell-to-cell contact zone, which facilitates an efficient transmission of HIV-1 to CD4+ T-cells without infection of mDC. This process was denominated "trans-infection" and is critical in the pathogenesis and progression of HIV-1 disease (Geijtenbeek, et al. Cell. 2000;100:587-97). However, the role of DC-SIGN as key factor involved in these processes was not supported in later studies (Sanders, et al. J Virol. 2002;76:7812-21). Thus, to date, the mechanisms of HIV-1 capture and trans-infection mediated by DC remain unclear and might be different, depending on distinct DC subsets and the specific chemokine/cytokine environment.

A recent report (Izquierdo, et al. PLoS Biol. 2012;10:e1001448) has identified Siglec-1 (sialic acid-binding Ig-like lectin 1) as the surface receptor on mDC that boosts the uptake of HIV-1 and its capacity to trans-infect CD4+ T-cells, leading in turn to HIV-1 progression. Siglec-1 is a type I transmembrane protein involved in cell-to-cell interactions recognizing sialyllactose from gangliosides present on the HIV-1 surface. Siglec-1/sialyllactose-HIV-1 complexes are internalized into mDC in a sac-like compartment where HIV-1 particles are stored. This new proposed mechanism might allow HIV-1 to avoid immune recognition while mDC are loaded with HIV-1 particles that can be transmitted to CD4+ T-cells. The authors also demonstrated that the inhibition of Siglec-1 by specific antibodies or interference RNA abolished both the capture and trans-infection of HIV-1 by mDC. Interestingly, this mechanism of viral capture and trans-infection might be used by other viruses with sialyllactose into its lipid membrane such as HTLV-1.

Altogether, these findings expand our understanding of HIV immune pathogenesis and provide new insights into the mechanisms involved in the increased risk of cardiovascular disease in HIV-infected patients. Interestingly, Siglec-1 is highly expressed on circulating monocytes/macrophages and mDC in patients with both coronary and peripheral arterial disease (Xiong, et al. Atherosclerosis. 2012;224:58-65; Dopheide, et al. Thromb Haemost. 2012;108:1198-207). Therefore, activated monocytes/macrophages and mDC expressing Siglec-1 might release proinflammatory chemokines, leading to proliferation and activation of T-cells. Moreover, lipopolysaccharide, a biological marker for microbial translocation, may induce expression of Siglec-1 on monocytes/macrophages and mDC. Thus, Siglec-1 could contribute to the increased rate of subclinical atherosclerosis typically seen in HIV-infected individuals.

The discovery of Siglec-1 as a key factor for HIV-1 spread warrants further research. It may provide important clues about novel therapeutic approaches to prevent HIV-1 dissemination, microbial translocation, and potentially, cardiovascular disease in HIV infection.

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