

Hot News

A New Era for HIV-Specific T-Cell Responses?

Long-term nonprogressors (LTNP) are defined as individuals infected with HIV for longer than 10 years and showing current CD4⁺ T-cells > 500 mm³ in the absence of antiretroviral therapy. They represent ~5% of all chronically HIV-infected patients (Cao, et al. *N Engl J Med.* 1995;332:201-8). According to levels of plasma viremia, two groups of LTNP have been defined: (i) elite controllers, who are those able to maintain undetectable levels of viral replication (HIV-RNA < 50 copies/ml); and (ii) viremic controllers, who are those with low but detectable levels of viral replication (Blankson, et al. *Immunity.* 2008;29:845-7; Saksena, et al. *AIDS Rev.* 2007;9:195-207).

Long-term nonprogressors offer a unique model for investigating potential host factors associated with HIV suppression. Control of viral replication in LTNP has been associated with lack of disease progression. Complex interactions between distinct viral and host variables exist, involving both genetic and immunologic factors (Pantaleo, et al. *N Engl J Med.* 1995;332:209-16; Buchbinder, et al. *Microbes Infect.* 1999;1:1113-20; Saksena, et al. *AIDS Rev.* 2007;9:195-207), which ultimately account for the LTNP behavior. HIV-specific T-cell responses are one of the immunologic factors that have received more attention, although a lack of consistent associations between the frequency of HIV-specific T-cells and control of viral replication suggest that not all T-cells are equivalent and that the efficacy in controlling viral replication may be largely dependent on qualitative parameters. Thus, the search for determinants of T-cell efficacy in HIV infection is a key goal.

The characterization of the differentiation phenotype of T-cells and its correlation with distinct functions has been assessed in multiple studies. However, none of them has been able to define a specific T-cell differentiation stage associated with protective antiviral function (Appay, et al. *Cytometry A.* 2008;73:975-83). Thus, the correlation between phenotype and T-cell efficacy remains at best ambiguous. In one study in which five functions of HIV-specific T-cells were examined, LTNP showed poly-functional responses with a higher quality than that seen in antiretroviral-naïve individuals with progressive HIV disease (Betts, et al. *Blood.* 2006; 107:4781-9). However, HIV-specific T-cell responses do not seem to fully explain viral suppression in these patients (López, et al. *AIDS Res Hum Retroviruses.* 2008;24:1185-95; Emu, et al. *J Virol.* 2008;82: 5398-407). Moreover, different pathways (PD-1, CTLA-4, Tim-3, AKT, etc.) are involved in the regulation of antigen-specific cellular immune responses. At this time there is scarce information about the involvement of these pathways

in the regulation of HIV-specific CD4⁺ and CD8⁺ T-cell responses in HIV-infected persons.

The failure of the Merck vaccine trial, in which an experimental vaccine designed to induce protective cellular immune responses showed no benefit, points to the need for a more detailed knowledge of the attributes of cellular immune responses that are responsible for an efficient control of viral replication. Two recent studies (Hadrup, et al. *Nat Meth.* 2009;6:520-6; Newell, et al. *Nat Meth.* 2009;6:497-9) have restored the interest for examining antigen-specific CD4⁺ and CD8⁺ T-cell responses at levels of single cells. For this purpose, the authors of those studies used a multiplex analysis based on a combination of labeled histocompatibility complex I and II multimers and polychromatic flow cytometry. In single specimens, by this approach the researchers were able to detect simultaneously T-cells with multiple specificities (from 15 to 63) against cytomegalovirus, Epstein-Barr virus, influenza, or melanoma. Moreover, when this methodology was linked to functional analysis of specific T-cells, the attributes that define the efficiency of antigen-specific T-cell immune responses can accurately be predicted. The methodology will allow screening of a broad array of antigens such as HIV, HCV, and HBV, among others. On the other hand, given the huge amount of data generated by this new methodology, an immuno-bioinformatic analysis of data arrays produced will be required. For this purpose, new software, named flow analysis with automated multivariate estimation (FLAME), has been developed (Pyne, et al. *Proc Natl Acad Sci USA.* 2009;106: 8519-24) to permit a comprehensive study of combinatorial multiplexed antigen-specific T-cell responses.

No doubt this new technology will make it easier to conduct studies addressing the attributes of HIV-specific CD4⁺ and CD8⁺ T-cell responses involved in the control of viral replication. These studies are necessary to identify the immune correlates of viral replication control. This knowledge seems to be crucial for regaining confidence in the rational design of new HIV vaccine candidates. At this time, it seems convenient to begin examining the different attributes of cellular immune responses and the different pathways involved in their regulation in patients spontaneously controlling HIV replication (elite controllers), taking as reference patients with suppressed viremia as a result of antiretroviral therapy and drug-naïve persons with typical HIV disease progression.

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Erratum *Aids Reviews* 3/2009:

In Hot News: *Interleukin 21, Essential to Control Chronic Viral Infections Norma I. Rallón.* *AIDS Rev.* 2009;11:174.

Title should be Interleukin 21, Essential to Control Chronic Viral Infections (instead of Interleukin 21, Essential to Control Chronic Ciral Infections).

In Review: *HIV-1 Resistance to First- and Second-Generation Non-nucleoside Reverse Transcriptase Inhibitors. Jade Ghosn, et al.* *AIDS Rev.* 2009;11:165-73.

Table 1 should list mutations Y181V and Y181I (instead of Y161V and Y161L).