Hot News

Interleukin 7 – A New Hope for HIV-Associated Immunodeficiency?

Treatment of HIV-infected patients with combination antiretroviral therapy results in complete suppression of HIV replication and increases in the $CD4^+$ T-cell pool in the majority of cases, in parallel with an improvement in the immune function and a reduction in the risk of opportunistic infections. However, in a certain subset of individuals, the long-term success of HAART does not always result in optimal restoration of $CD4^+$ T-cells. These so-called "immunologic non-responders" might display a low thymic activity. In this scenario, other immune therapies aimed at increasing thymic output and/or peripheral expansion of T-cells would be desirable.

In the last few years, interleukin 7 (IL-7) has been one of the cytokines evaluated as a T-cell enhancer. Interleukin 7 plays an important role in T-cell homeostasis, modulating thymic output and stimulating the expansion and survival of naive and memory T-cells as well as inhibiting T-cell apoptosis. Several preclinical and early phase clinical studies have evaluated its impact on T-cells in different conditions associated with lymphopenia. A recent study (Levy, et al. J Clin Invest. 2009;119:997-1007) has reported the results of a prospective, multicenter, open-label, phase IIa trial designed to evaluate the immunologic effects of IL-7 in HIV patients receiving long-term HAART and maintaining low CD4 counts. Although the study included only a small number of subjects (n = 14), the data are encouraging since all patients experienced significant increases in $CD4^+$ T-cells, even with the lowest dose of IL-7. The increase of $CD4^+$ T-cells was mainly due to naive and central memory subsets. There was also a modest increase, especially using the highest IL-7 dose, of cells expressing CD31, a marker associated to recent thymic emigrants. Moreover, no undesirable effects of IL-7 treatment, such as increases in T-cell activation (a main pathogenic mechanism of HIV disease), or increases in the content of proviral DNA (an indirect measurement of HIV reservoir size) were recognized. Finally, the overall tolerability was good.

Although IL-7 may prove to be a better immunotherapeutic agent than IL-2, it deserves some cautious judgment. Firstly, although the immunologic effects were sustained and $CD4^+$ counts remained elevated up to 45 weeks after discontinuation of IL-7, a detailed look at the data reveals that significant $CD4^+$ T-cell gains were only seen during treatment and shortly thereafter, especially with the lower IL-7 dose. This implies that frequent subcutaneous administration could be required, with the risk of inducing tolerance through the appearance of anti-IL-7 antibodies, as the authors acknowledge. Secondly, it is crucial to verify the real contribution of newly generated naive T-cells (coming from the thymus) to the total increase in $CD4^+$ counts, given that these are the cells bearing new T-cell receptor specificities. In this regard, the increase in cells expressing CD31 was very modest. Thirdly, although the authors stated that T-cells increased in peripheral blood had a preserved functional capacity in response to polyclonal stimulation, it is unclear to what extent their functionality was restored. In particular, virus-specific reactivities were not examined. Lastly, the level of expression of the IL-7 receptor (CD127) by T-cells should be assessed, and the proportion of T-cells expressing this marker should be analyzed. This information is relevant in light of the recent demonstration of the impact of baseline CD127 expression on T cells on the extent of $CD4^+$ reconstitution in patients starting HAART (Benito, et al. J Infect Dis. 2008;198:1466-73).

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The Role of the Host in Controlling HIV Progression

The mechanisms by which long-term nonprogressors (LTNP) are able to slow down HIV immunological damage are not well understood. Multiple factors seem to determine the lack of progression in these individuals. New chip-based technologies have opened the possibility for the simultaneous screening of a large number of variables, and to explore the impact of the complex interactions between viral and host factors that finally result in the control of HIV-induced immunodeficiency in some individuals. Interestingly, data obtained using these new tools seem to move the balance towards host genetic factors rather than viral features as key determinants of the LTNP phenotype.

One of the first reports using high-throughput experiments was conducted by GWAS (Genome Wide Association Study) on recent HIV seroconverters. Based on the search of single nucleotide polymorphisms (SNP) along the human genome, the authors tried to identify correlates with low and high viral load set points (Fellay, et al. Science. 2007;317:944-7). Three SNP at genes HCP5, HLA-C, and ZNRD1 accounted for nearly 15% of interindividual variability in viral load set points after seroconversion. Interestingly, all polymorphisms were located within the highly variable chromosome 6. Two of these SNP were associated with HLA B and C locus, supporting an involvement of the major histocompatibility complex in the control of HIV infection, most likely

through the modulation of HIV-specific cellular immune responses. Recently, another study has confirmed these findings (Limou, et al. J Infect Dis. 2009;199:419-26). Moreover, it has reported another six SNP within chromosome 6 which might be associated with LTNP. Whether these changes truly play an independent role in HIV pathogenesis or simply reflect linkage disequilibrium with the HLA locus has not been determined yet.

The array technologies have not only been used to analyze potential associations between SNP and HIV non-progression. They have also been used to identify new host genes that participate in the regulation of the viral cycle. A seminal study described more than 200 cellular factors required by the virus for an efficient replication cycle (Brass, et al. Science. 2008;319:921-6). Other similar studies, using different experimental conditions, have identified other different cellular factors (Konig, et al. Cell. 2008;135:49-60; Zhou, et al. Cell Host Microbe. 2008;4:495-504). Consequently, although many human cellular proteins interact with HIV, the extent of their involvement in controlling HIV replication remains elusive.

Gene expression studies have compared subjects with different stages of HIV infection. In one report (Hyrcza, et al. J Virol. 2007;81:3477-86), patterns of gene expression in LTNP were similar to those found in HIV-uninfected subjects. Interestingly, LTNP and uninfected persons uniformly showed a greater expression of interferon-induced genes than HIV progressors, regardless of the use of antiretroviral therapy. We recently had the opportunity to compare gene expression patterns in LTNP and progressors; interestingly, nonprogressors showed upregulation of genes associated with regulation of the actin cytoskeleton, cytokines response, and apoptosis. In contrast, progressors showed upregulated genes involved in DNA damage response and cell cycle division (Salgado, et al. XVII International AIDS Conference 2008).

In summary, new genetic tools provide the opportunity to collect huge amounts of information about the role of host genetics in HIV disease progression. Different genetic markers associated with the host immune system display an important role in the control of HIV progression. From these preliminary genetic results we now face a formidable task, which ultimately consists in unraveling the mechanisms of HIV disease progression.

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Tightening of Peer Review Standards

One of the aspects of scientific conduct that every researcher takes for granted is the assurance that the peer review system stops fraud and misappropriation of data, and maintains a certain level of originality and competition in the research field. When, in July 2008, I received an e-mail from a concerned party about a reference to an abstract from Nkengafac, et al. in a review published in The New England Journal of Medicine (Taylor, et al. N Engl J Med. 2008;358:1590-602), I wondered what all this had to do with me. It turns out that the abstract by Nkengafac (accepted in the XVI International HIV Drug Resistance Workshop, Barbados, June 2007) was a copy, word by word, of the abstract in a journal published by my group (Palma, et al. Infect Genet Evol. 2007). The only difference was the country of origin of the data; the word 'Portugal' was replaced by 'Cameroon'. Suffice to say that the transposition of the results was not so easily achieved, which called the attention of a reader, who then was kind enough to contact me and the author of the review.

I was surprised, to say the least, and immediately contacted the organizers of the Workshop for a clarification. They were as surprised as me and immediately set out to investigate the issue. However, I had noticed a second abstract by the same first author, A.D. Nkengafac, in the same workshop and ran an internet search on it. It turns out that the second abstract was also a copy of another published paper.

During the subsequent investigation a third plagiarized abstract was discovered from a second author, A. Ajua. It was also uncovered that A.D. Nkengafac had abstracts in several conferences with results that were entirely or partially copied from other papers. His affiliations varied wildly, as well as the research topics, all the co-authors were always different and none of that work ended up in a peer reviewed full paper. When contacted, Nkengafac agreed to the retraction of his abstracts. All retractions were published in Antiviral Therapy (Ajua, et al. Antivir Ther. 2008;13:849; Nkengafac, et al. Antivir Ther. 2008;13:847; Nkengafac, et al. Antivir Ther. 2008;13:845).

This case revealed that peer review can be circumvented, and that every kind of scientific communication, from an abstract to a review, independent of origin, deserves a thorough review, with an extent of cross-checking of data beyond the current review system.

Following this case, the organizers of the aforementioned workshop have instituted the policy of doing a Google search on every accepted abstract for all upcoming International HIV Drug Resistance Workshops. This policy has also been adopted by other workshops, such as CROI, and will be in full effect this year.

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