Lessons from history: dysfunctional APCs, inherent dangers of STI and an important goal, as yet unmet

Robert K. Gieseler[1], Guido Marquitan[1], Michael J. Scolaro[1] and Michael D. Cohen[2]

[1]LTBH Medical Research Institute, Robertson Center, 200 N. Robertson Boulevard, Suite 208, Beverly Hills, CA 90211, USA
[2]David Geffen School of Medicine, UCLA, Los Angeles, CA 90095, USA

Allen *et al*. recently reviewed structured treatment interruption (STI) in HIV infection [1]. To understand the potential hazards of treatment interruptions, we must acknowledge the central role of dendritic cells (DCs) and follicular dendritic cells (FDCs) in this disease.

Although it is generally accepted that DC subsets are among the first cells infected after mucosal exposure to HIV, the continuous contribution of professional antigen-presenting cells (APCs) to the progression of HIV infection and immune dysregulation has still not been appreciated clinically. However, infection of DCs and FDCs with HIV results in impaired antigen-specific immune responses against both HIV and other challenges.

DCs had been identified as targets of HIV as early as 1986 [2]. Thereupon, Knight *et al*. clearly demonstrated that the percentage of DCs infected with HIV might exceed that of any other HIV-susceptible cell type by more than 125-fold, thus leading to DC dysfunction and depletion (reviewed in Ref. [3]). They also showed HIV budding from the plasma membrane of infected DCs, as well as the DC-mediated transfer of infective virus to T cells. All these processes precede the appearance of T-cell defects, suggesting that DCs might act as a long-term HIV reservoir (reviewed in Ref. [3]).

As to FDCs, initial studies revealed follicular atrophy in the lymph nodes of patients infected with HIV, combined with a loss of the local FDCs. Lymph node-resident FDCs were shown to both carry virus attached to their cytoplasmic protrusions [4,5], as well as to actively produce infective virions [6]. Thus, FDCs also qualify as important HIV reservoir cells [7].

Musing on these historic notes, there has long been clear evidence of a fundamental role for DCs and FDCs in the pathogenesis of HIV [2–7]. Since then, much evidence has been added. For example, it is established that DCs are being productively infected by both M-tropic and T-tropic HIV strains by exploiting a range of coreceptors [CCR3, CCR5, CXCR4 and a non-CXCR4 receptor of stromal derived factor-1 (SDF-1 or CXCL12)] broader than that engaged on T cells.

Accepting these facts has profound consequences. The lack of beneficial effects of STI in chronic HIV infection probably correlates both with an increased functional impairment of professional APCs infected with HIV and, during the initiation of immune responses, with their transfer of infective virus to HIV-specific T cells.

In the article by Allen *et al.*, one of their implications is that only few of the $CD4^+$ T helper memory (ThM) cells being specific for HIV are infected [1]. Yet, the study cited by these authors indicated that HIV-specific ThM cells contain more proviral DNA than ThM cells specific for pathogens other than HIV. Furthermore, the amount of provirus detected in HIV-specific ThM cells increased on STI [8].

We believe these and earlier findings (e.g. [3]) provide evidence for a targeted infection by professional APCs of HIV-specific T cells during their prolonged contact through the immunological synapse. Therefore, none of the suggested means of eliciting HIV-specific immunity after initial seroconversion [1,9,10] would seem to offer promise because these approaches do not replace dysfunctional, yet infective, DCs and FDCs that are part of the long-term reservoir for HIV. In this light, STI does not appear advisable.

The susceptibility of DCs and FDCs to being infected with HIV, together with their crucial immunologic function, leads to the continuous spread of HIV. Therefore, we suggest therapeutic targeting of reservoir cell populations serving as inducers of primary and secondary antigen-specific immune responses as an important goal to achieve permanent reconstitution of adaptive immunity.

References

1 Allen, T.M. *et al.* (2002) STI and beyond: the prospects of boosting anti-HIV immune responses. *Trends Immunol.* 23, 456–460
2 Müller, H. *et al.* (1986) Accessory cells as primary target of human immunodeficiency virus HIV infection. *J. Clin. Pathol.* 39, 1161
3 Knight, S.C. *et al.* (1990) HIV I infection of dendritic cells. *Int. Rev. Immunol.* 6, 163–175
4 Biberfeld, P. *et al.* (1985) Immunohistopathology of lymph nodes in HTLV-III infected homosexuals with persistent adenopathy or AIDS. *Cancer. Res.*, 4665s–4670s.Suppl. 9
5 Piris, M.A. *et al.* (1987) Persistent and generalized lymphadenopathy: a lesion of follicular dendritic cells? An immunohistologic and ultrastructural study. *Am. J. Clin. Pathol.* 87, 716–724
6 Cameron, P.U. *et al.* (1987) Western blot profiles, lymph node ultrastructure and viral expression in HIV-infected patients: a correlative study. *Clin. Exp. Immunol.* 68, 465–478
7 Tenner-Racz, K. *et al.* (1986) HTLV-III/LAV viral antigens in lymph nodes of homosexual men with persistent generalized lymphadenopathy and AIDS. *Am. J. Pathol.* 123, 9–15
8 Douek, D.C. *et al.* (2002) HIV preferentially infects HIV-specific $CD4^+$ T cells. *Nature* 417, 95–98
9 Van Baalen, C.A. *et al.* (2002) The choice of antigen for therapeutic immunization against AIDS. *Trends Immunol.* 23, 478–479
10 Imami, N. *et al.* (2002) Immune reconstitution in HIV-1-infected patients. *Curr. Opin. Investig. Drugs* 3, 1138–1145

Corresponding author: Robert K. Gieseler (rgieseler@lettherebehope.org).

http://treimm.trends.com 1471-4906/02/$ - see front matter PII: S1471-4906(02)00005-4