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Chronic Immune Activation and Lymphocyte Apoptosis during HIV-1 Infection

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ABSTRACT

HIV-1 infected individuals are subject to a chronic immune activation resulting from HIV-1 replication, microbial translocation, and lymphopenia. Despite the great advance of antiretroviral treatment (ART), the immune activation remains associated with poor immune reconstitution during HIV-1 infection. The overall aim of this PhD thesis is to contribute to a better understanding of the causes and consequences of immune activation, possibly leading to the design of improved therapy for HIV-1 infected individuals.

Premature senescence of T cells, as a consequence of immune activation, is thought to be associated with the increased levels of CD28- T cells during HIV-1 infection. In ***Paper I***, the phenotype and functional properties of CD28- T cells from HIV-1 individuals naïve to treatment, under ART and uninfected controls were assessed. Despite displaying similar markers of senescence, and late differentiation, we found that whereas CD28- T cells from untreated patients are highly susceptible to both spontaneous and activation-induced apoptosis, the same T cell population from ART-treated patients showed an enhanced capacity to proliferate upon weak TCR stimulation. Importantly, apoptosis of CD28- T cells from untreated patients was correlated with HIV-1 viral load, and their decreased ability to proliferate was associated with a reduced IL-2 production. High levels of CD28- T cells during HIV-1 infection might result from the chronic immune activation, whereas their sustained levels despite ART, is likely to arise from their capacity to proliferate under weak TCR signaling. Furthermore, with a capacity to produce IFN-γ, TNF and perforin, CD28- T cells from HIV-1 infected individuals might also contribute to the immune activation.

The mechanisms underlying the loss of memory B cells and the decline of serological memory during HIV-1 infection remain elusive. As microbial translocation and the associated immune activation have been shown to correlate with T cell depletion, we evaluated, in ***Paper II***, the association between the serum levels of soluble CD14, a marker of microbial translocation, with the loss of resting memory B cells in HIV-1 infected individuals. Soluble CD14 levels were found to correlate with both the decline of resting memory B cells, and their increased expression of IL-21R. IL-21R expression on memory B cells was increased during HIV-1 infection, and also negatively correlated with the levels of circulating memory B cells. Notably, IL-21R positive memory B cells were more prone to apoptosis, measured by higher Annexin V staining and lower Bcl-2 expression, as compared to B cells lacking the receptor. Furthermore, TLR triggering by microbial products resulted in IL-21R expression on memory B cells *in vitro*. Our results identify a novel role for microbial translocation and the associated immune activation, contributing to the loss of memory B cells during HIV-1 infection.

Lymphopenic conditions are associated with increased IL-7. This cytokine involved in T cell homeostasis, is also found to be elevated in HIV-1 infected individuals concomitantly with low CD4+ T cell counts; although the regulation of IL-7 production is not fully understood in the context of HIV-1 infection. Using human intestinal epithelial (DLD-1) and bone marrow stromal (HS-27) cell lines, we investigated in ***Paper III***, the consequence of pro-inflammatory cytokines on IL-7 production, measured at the mRNA and the protein levels. Whereas IFN-γ induced high IL-7 production in both cell lines, IL-1β treatment led to the opposite effect. We also analyzed the gene expression profiles of HS-27 cells treated with IL-1β and/or IFN-γ using the whole-genome microarray Human Gene 1.0 ST. Both cytokines resulted in enhanced expression of genes implicated in T cell immunity, particularly important during HIV-1 pathogenesis. Our results show that the immune activation can lead to profound change in stromal and epithelial cells, which in turn might shape immune responses.

While IL-7 is known to participate to T cell homeostasis, it has recently been shown that this cytokine possibly contribute to B cell defects, leading through IFN-γ release by T cells, to Fas up-regulation and sensitivity to Fas-mediated apoptosis. We further evaluated IL-7 regulation of T cell survival in ***Paper IV***, and observed that B cells, co-cultured with IL-7 treated T cells, proliferated, displayed a phenotype of differentiated cells and secreted high levels of immunoglobulins (Igs). The Ig secretion was demonstrated to be a consequence of CD70 up-regulation on T cell upon IL-7 treatment. IL-7 led also to BAFF production by T cells, which enhanced B cell survival. In the context of HIV-1 infection, such mechanisms might be implicated in the B cell activation and hypergammaglobulinemia observed in patients.

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