Department of Microbiology, Tumor and Cell Biology

Chronic Immune Activation and Lymphocyte Apoptosis during HIV-1 Infection

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Föreläsningssalen vid Institutionen för Mikrobiologi, Tumör and Cellbiologi (MTC), Theorellsväg 1, Karolinska Institutet

Fredagen den 17 februari, 2012, kl 09.00

av
Nicolas Ruffin
MSc.

Huvudhandledare:
Prof Francesca Chiodi
Karolinska Institutet
Institutionen för Mikrobiologi, Tumör and Cellbiologi

Bihandledare:
Dr Bence Rethi
Karolinska Institutet
Institutionen för Mikrobiologi, Tumör and Cellbiologi

Prof Martin Cranage
St. George’s University of London
Division of Clinical Sciences
Centre for Infection & Immunity

Fakultetsopponent:
Prof Alan L. Landay
Rush University Medical Center
Department of Immunology/Microbiology

Betygsnämnd:
Docent Eva Sverremark-Ekström
Stockholm University
Wenner-Gren Institute
Department of Immunology

Prof Markus Maeurer
Karolinska Institutet
Institutionen för Mikrobiologi, Tumör and Cellbiologi

Prof Anders Vahlne
Karolinska Institutet
Institutionen för laboratoriemedicin
Avdelningen för klinisk mikrobiologi

Stockholm 2012
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 cells 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.

© Nicolas Ruffin, 2012