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Regulation and role of IL-7 production in HIV-1 infection

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ABSTRACT

The concentration of interleukin-7 (IL-7) in human serum is elevated in various clinical conditions associated with lymphopenia, including HIV-1 infection. IL-7 is an essential factor for T cell differentiation and survival, and it was suggested that high serum IL-7 concentration may represent a homeostatic response to T cell depletion, which may promote T cell regeneration.

In order to increase our understanding on the regulation of IL-7 production, we investigated specimens from HIV-1 infected patients during chronic infection and in long term non-progressors (LTNPs). Serum IL-7 levels correlated with T-cell depletion in HIV-1 infected individuals. In some patients, we observed that serum IL-7 decreased upon progression to AIDS, suggesting a role for IL-7 in T-cell maintenance in sporadic cases. Interestingly, IL-7 levels were significantly lower in stable LTNPs than in patients who lost the LTNP status in a 3-year follow-up ($P < 0.001$), indicating that serum IL-7 concentration might be a valuable marker for maintenance of the LTNP status.

The number of CD8+CD28⁻ T cells increases significantly during aging and during HIV-1 infection. These cells have a reduced expression of the IL-7 receptor alpha (IL-7R α), as compared to CD8+CD28⁺ T cells. As CD8+CD28⁻ T cells have been associated with dendritic and T cell suppression, we analyzed whether an increase in CD8+CD28⁻ T cell numbers during HIV-1 infection could lead to impaired T cell responses. Peripheral blood CD8+CD28⁻ T cells of both HIV-infected and non-infected individuals promoted dendritic cell activation. The CD8+CD28⁻ T cell accumulation during HIV-1 infection may thus contribute to inflammatory reactions and immune activation.

Stromal cells and intestinal epithelial cells are known to produce IL-7. The mechanisms and cellular factors regulating IL-7 production are still unclear. We assessed whether IL-1 β and IFN- γ , cytokines produced during inflammatory conditions, may impact on IL-7 production. We used human intestinal epithelial cells (DLD-1 cell line) and bone marrow stromal cells (HS27 cell line) to evaluate IL-7 production at the mRNA and protein levels. To assess whether treatment of HS27 cells with IL-1 β and/or IFN- γ leads to changes in the gene expression of cytokines, Toll-like receptors (TLRs) and chemokines, we analysed gene expression profiles using the whole-genome microarray Human Gene 1.0 ST. We found that IFN- γ enhanced the expression of IL-7 protein and mRNA ($P < 0.001$) in both cell lines. IL-1 β treatment led to a significant down-regulation ($P < 0.001$) of IL-7 mRNA expression in both cell lines. The gene profiles revealed dramatic changes in expression of cytokines and their receptors, of IFN regulatory factors (IRF-1 and 2) and of important chemo-attractants for T cells. The microarray results were verified by additional methods. Our results were discussed in the setting of inflammation and T-cell survival in the gut compartment during HIV-1 infection where stromal and epithelial cells may produce factors that contribute to impaired IL-7 homeostasis and homing of T cells.

It was previously reported that IL-7 might stimulate T cell activation and CD95 mediated T cell apoptosis. HIV-1 infection leads to B cell abnormalities including increased apoptosis via the CD95 death receptor pathway and loss of memory B cells. Here we present a novel mechanism that can lead to increased B cell apoptosis in the presence of high IL-7 concentration. T cells cultured with IL-7 induced high CD95 expression on resting B cells together with an increased sensitivity to CD95 mediated apoptosis. As the mediator molecule responsible for B cell priming to CD95 mediated apoptosis we identified the cytokine IFN- γ that T cells secreted in response to IL-7. In the serum of HIV-1 infected individuals IL-7 and IFN- γ levels were in correlation and the level of both cytokines correlated with CD95 expression on circulating B lymphocytes in non-viremic individuals. These results indicate a potential link between IL-7 and the increased B cell apoptosis observed in HIV-1 infected individuals.

In conclusion the results presented in this PhD thesis highlight mechanisms of regulation of IL-7 production dependent on the number of circulating T cells and on the exposure of IL-7 producing cells to high levels of inflammatory cytokines. We also present data on the role of IL-7 in regulating CD95 expression and CD95 mediated apoptosis on B cells through IFN- γ produced by T cells; the impact of this finding on the outcome of IL-7 therapy during HIV-1 infection will be verified by ongoing clinical studies.

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