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

Huvudhandledare:
Professor Francesca Chiodi
Karolinska Institutet
Department of Microbiology, Tumor and Cell Biology

Bihandledare:
Professor Phung Dac Cam
National Institute of Hygiene and Epidemiology, Hanoi
Vietnam

Associate Professor Nguyen Tran Hien
National Institute of Hygiene and Epidemiology, Hanoi
Vietnam

Fakultetsopponent:
Professor Jorma Hinkula
University of Linköping
Department of Molecular and Clinical Medicine (IKE)
Virology

Betygsnämnd:
Associate Professor Sören Andersson,
Örebro University Hospital
Department of Laboratory Medicine

Professor Markus Maurer
Karolinska Institutet
Department of Microbiology, Tumor and Cell Biology

Associate Professor Anders Blaxhult
Venhälsan
Stockholm South General Hospital

Stockholm 2011
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-7Rα), 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-1β 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-1β 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-1β 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.

ISBN 978-91-7457-338-1