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Titel der Dissertation: Einfluss von CD152-Signalen auf das Migrationsverhalten von TH1-Lymphozyten

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Summary

Postitioning of antigen-primed T cells in secundary lymphoid tissues and at sites of antigenic challenge is a mandatory requirement for functional adaptive immune responses. Localisation of cells is induced by chemokine-chemokinereceptor interactions.

Here, the impact of the costimulatory molecule CD152 on the migratory capacity of inflammatory Th1 cells was analysed. Primary $CD4^+$ T cells were differentiated into T_H1 cells and migration was measured *in vitro* by chemotaxis assays in transwell systems. Genetic deficiency of CD152 ($CD152^{-/-}$) reduced chemotaxis of T_H1 cells towards the homeostatic chemokines CCL19 and CXCL12 and the pro-inflammatory chemokine CCL4. $CD4^+$ T_H1 cells showed the same results after polyclonally T cell receptor (TCR) stimulation as antigenspecific activation of TCR-transgenic $CD152^{-/-}$ $CD4^+$ T_H1 cells. Serological inactivation of CD152 by specific Fab-fragments confirmed increased migration of T_H1 cells in the presence of CD152. Defined CD152-signals given by antibody-coupled microspheres and the reconstitution of CD152 in CD152-deficient cells by retroviral transduction of CD152-cDNA demonstrated, that CD152-signals can enhance chemokine-induced migration even in activated T_H1 cells. Elevation of CD152-expression on $CD4^+$ T_H1 cells induced by strong TCR-activation through high levels of antigen or by antigenpresentation through dendritic cells correlated with augmented chemotactic response of T_H1 cells.

The study illustrated that the expression of chemokine receptors does not generally display the functional migration. CD152-signals induced the surface expression of CCR7 and CCR5 but not of CXCR4. Analysis of signaltransduction pathways of CCR5 in T_H1 cells with or without CD152-signals revealed Gαi-protein dependent processes. CD152-engagement led to CCL4-induced inactivation of G-protein-coupled-kinase-2 and PI3'K-dependent Akt-activation.

Adoptive transfers of radioactively labeled T_H1-cells were used for *in vivo* studies of migration behaviour. Transferred T_H1 cells supported the relevance of CD152-signals for the localisation of T cells, because increased levels of CD152-positive cells were found in lymph nodes and in inflamed tissue after induction of an infection in the delayed type hypersensitivity model (DTH).

These data represent the plasticity of CD152-signals. CD152 does not only perform inhibitory responsibilities, moreover it directs T cells for proper localisation in draining lymphnodes and inflamed tissues. This novel function adds to the known importance of CD152-engagement in the control of peripheral immune responses. Therefore CD152 could be of therapeutic interest by regulating cellular compositions at sites of antigenic challenge.