Phenotype and function of CD25$^+$ regulatory T cells in infants and adults

Akademisk avhandling

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Avhandlingen baseras på följande delarbeten:

I. **Hanna Grindebacke, Kajsa Wing, Anna-Carin Andersson, Elisabeth Suri-Payer, Sabina Rak and Anna Rudin.**
Defective suppression of Th2 cytokines by CD4$^+$CD25$^+$ regulatory T cells in birch allergics during birch pollen season.
Clinical and Experimental Allergy 2004:34;1364-72.

II. **Hanna Grindebacke, Pia Larsson, Kajsa Wing, Sabina Rak and Anna Rudin**.
Specific immunotherapy to birch allergen does not enhance suppression of Th2 cells by CD4+CD25+ regulatory T cells during pollen season.
Journal of Clinical Immunology 2009:29;752-760.

III. **Hanna Grindebacke, Hanna Stenstad, Marianne Quiding-Järbrink, Jesper Waldenström, Ingegerd Adlerberth, Agnes E. Wold and Anna Rudin**.
Dynamic development of homing receptor expression and memory cell differentiation of infant CD4$^+$CD25^{high} regulatory T cells.
The Journal of Immunology 2009:183;4360-4370.

UNIVERSITY OF GOTHENBURG

Phenotype and function of CD25$^+$ regulatory T cells in infants and adults

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Active suppression by CD4$^+$CD25$^+$FOXP3$^+$ regulatory T cells (Treg) is essential for the maintenance of peripheral tolerance to both self antigens and environmental antigens. Absence of these cells in human newborns leads to autoimmune and inflammatory disorders as well as allergic disease. Thus, Treg are probably necessary for down-regulating autoimmune as well as allergic immune reactions. The aim of this thesis was to examine if Treg from birch pollen-allergic patients were able to suppress birch pollen-induced proliferation and cytokine production and if their suppressive function was affected following specific immunotherapy (SIT) against birch pollen allergy. Moreover, it aimed to describe the expression of FOXP3, homing receptors and maturation markers on Treg at various time points during the first 3 years of life compared with the expression seen in adults.

We found that pollen-allergic patients and non-allergic controls had similar proportions of Treg cells in the circulation and that Treg were equally able to potently suppress birch pollen-induced proliferation and production of IFN-γ. However, Treg cells isolated during birch pollen-season from allergic patients were not able to down-regulate birch-pollen induced production of IL-13 and IL-5, in contrast to those from non-allergic controls. Likewise, Treg from birch pollen-allergic patients who had undergone SIT for 6 months were unable to suppress IL-5 production, while their ability to suppress proliferation and IFN-γ production was retained and similar as in untreated allergic controls. Of note, we found that IL-10 was produced at higher levels in SIT patients than controls, but only when CD25^{neg} cells and Treg were cultured together and not when the CD25^{neg} or Treg cells were cultured separately. This indicates that both Treg and CD25^{neg} T cells are important and need to be present for an increased production of IL-10 to occur after SIT.

When examining the expression of FOXP3, homing receptors and maturation markers on Treg in infants we observed a rapid increase in the proportion of Treg in the circulation during the first days of life, indicating conversion to suppressive Treg from CD25^{high} Treg precursors. An appropriate localisation of these cells is essential for their ability to suppress immune responses and their migration to different tissues is determined by homing receptors. We found that that a homing receptor switch from the gut homing receptor $\alpha_4\beta_7$ to the extra-intestinal homing receptor CCR4 on Treg started as late as between 18 months and 3 years of age and was associated with maturation of the Treg. Moreover, the homing receptor expression on Treg corresponded to their actual migration properties, since Treg from cord blood migrated foremost towards the gut-associated chemokine CCL25.

In conclusion, our results indicate that Treg from allergic individuals are unable to suppress Th2 responses, but not Th1 responses, during birch-pollen season and that SIT is unable to restore the ability of Treg to suppress Th2 responses *in vitro* in spite of an increased production of IL-10. Moreover, Treg cells in infants up to 18 months of age express $\alpha_4\beta_7$ and migrate towards gut-homing chemokines, while at 3 years the cells have started to mature and to switch into extra-intestinal homing receptors.

Key words: *CD25$^+$FOXP3$^+$ regulatory T cells, human, allergy, IL-10, systemic immunotherapy, migration, homing receptors, maturation*

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