

# **T cell subsets in Asthma and Allergy**

## **-role of glucocorticoids, plasticity and microRNA-155**

### **Akademisk avhandling**

som för avläggande av medicine doktorexamen vid Sahlgrenska akademien vid Göteborgs universitet kommer att offentligen försvaras i Hörsal Lyktan, Konferenscentrum Wallenberg, Medicinargatan 20A, Göteborg

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av

**Carina Malmhäll**

Fakultetsopponent:  
Professor Lars K Poulsen,  
Allergy Clinic, Copenhagen University Hospital at Gentofte  
Hellerup, Denmark

Avhandlingen baseras på följande delarbeten:

- I. Malmhäll C, Bossios A, Pullerits T, Lötvall J.  
**Effects of pollen and nasal glucocorticoid on FOXP3<sup>+</sup>, GATA-3<sup>+</sup> and T-bet<sup>+</sup> cells in allergic rhinitis.** *Allergy*. 2007 Sep;62(9):1007-13.
- II. Malmhäll C, Bossios A, Rådinger M, Sjöstrand M, Lu Y, Lundbäck B, Lötvall J.  
**Immunophenotyping of circulating T helper cells argues for multiple functions and plasticity of T cells *in vivo* in humans - possible role in asthma.** *PLoS One*. 2012;7(6):e40012.
- III. Malmhäll C, Alawieh S, Lu Y, Sjöstrand M, Bossios A, Eldh M, Rådinger M.  
**MicroRNA-155 is essential for T<sub>H</sub>2- mediated allergen-induced eosinophilic inflammation in the lung.** *J Allergy Clin Immunol*. 2013 Dec 24. [Epub ahead of print]

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**GÖTEBORGS UNIVERSITET**

# T cell subsets in Asthma and Allergy

## -role of glucocorticoids, plasticity and microRNA-155

**Carina Malmhäll**

Department of Internal Medicine and Clinical Nutrition, Institute of Medicine  
Sahlgrenska Academy at University of Gothenburg

### ABSTRACT

The focus of this thesis is the different subsets of CD4<sup>+</sup> T cells involvement in asthma and allergy. It encloses studies of asthma and allergy in both humans and mice. The work of the three papers has been performed during a time where the field has moved from a paradigm of separate entities of the studied T cell subsets to more flexibility and plasticity in these cells due to the microenvironment. Furthermore, the field of ribonucleic acid (RNA) has grown to include new RNAs such as microRNA (miRNA), demonstrating high impact on the microenvironment.

The aims of this thesis were to determine in: Paper I. Glucocorticoid treatment during natural pollen exposure and the effects it poses on T regulatory (Treg), T helper 1 (Th) and Th2 cells in the nasal mucosa of allergic rhinitis patients. Paper II. Plasticity in circulating Treg, Th1, Th2 and Th17 cells and the relationship to eosinophilia in asthmatic individuals. Paper III. miRNA-155 affecting T cell dependent allergen induced eosinophilic airway inflammation.

The results demonstrates that glucocorticoid treatment during pollen exposure affected the number of Treg and Th2 cells as well as the balance between the subsets investigated at site of inflammation. Furthermore, T cells co-expressing several regulatory transcription factors were found in asthmatics as well as in healthy controls. Finally, miRNA-155 deficiency reduced the number of airway eosinophils, Th2, Th17 and Treg cells after allergen challenge in a mouse model of allergic airway inflammation, while the transcription factor PU.1 was upregulated. Adoptive transfer of allergen specific CD4<sup>+</sup> T cells resulted in a similar degree of airway eosinophilia in miR-155 KO and WT mice.

We conclude that nasal glucocorticoids attenuate the allergic inflammation by maintaining the local relationship between Th1 and Th2 cells as well as between Treg and Th2 cells. Furthermore, T cells ability to co-express several regulatory transcription factors in both asthmatics and healthy controls indicates plasticity *in vivo*. Finally, miRNA-155 contributes to the regulation of allergic airway inflammation by modulating Th2 responses, via the transcription factor PU.1.

Taken together these studies support that T cell shows flexibility and plasticity which can be affected by treatment, allergen exposure and miRNA expression and thus are in important regulators of asthma and allergy. Increasing the understanding of these processes may hopefully result in more specific future treatments.

**Keywords:** Asthma, Allergy, T regulatory cells, Th1, Th2, Th17, FOXP3, T-bet, GATA-3, ROR $\gamma$ t, glucocorticoids, plasticity, microRNA-155, PU.1

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