

# **Mechanisms of allergic airway inflammation. Role of bone marrow**

## **Akademisk avhandling**

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av

Svetlana Sergejeva

Fakultetsponent: Docent Jonas Erjefält  
Institutionen för fysiologiska vetenskaper,  
Lunds universitet

Avhandlingen baseras på följande arbeten:

I. S Sergejeva, A-K Johansson, C Malmhäll, J Lötval. Allergen exposure-induced differences in CD34<sup>+</sup> cell phenotype; relationship to eosinophilopoietic responses in different compartments.

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II. S Sergejeva, M Tomaki, T Pullerits, L-L Zhao, M Johnson, J Lötval. Intranasal fluticasone propionate inhibits allergen induced bone marrow eosinophilia in mice.

Pulm Pharmacol Ther. 2002; 15(2): 129-34

III. S Sergejeva, J Lötval, T Pullerits. Increased number of CD34<sup>+</sup> cells in nasal mucosa of allergic rhinitis patients: inhibition by a local corticosteroid.

Submitted for publication

IV. S Sergejeva, S Ivanov, J Lötval, A Lindén. Role of IL-17 in allergen-induced mobilisation of airway macrophages.

As manuscript

## **Mechanisms of allergic airway inflammation. Role of bone marrow**

**Svetlana Sergejeva**, *Lung Pharmacology Group, Department of Respiratory Medicine and Allergology, Institute of Internal Medicine, Göteborg University, Guldhedsgatan 10A, 41346, Göteborg, Sweden*

Allergic airway (AW) inflammation is characterized by accumulation of inflammatory cells within the AW. It is likely that the accumulation of cells within AW is a combination of increased production, migration and prolonged survival of the cells. Inflammatory cells develop from CD34<sup>+</sup>hematopoietic progenitor cells. Importantly, allergic subjects have increased numbers of CD34<sup>+</sup>progenitors in bone marrow (BM) and AW. The aims of this thesis were to determine the mechanisms underlining the allergen-induced accumulation of eosinophils and neutrophils in the AW. With reference to allergen-induced AW eosinophilia, the contribution of eosinophilopoiesis in different compartments was studied. In addition, the contribution of the pro-inflammatory cytokine IL-17 in accumulation of eosinophils and neutrophils within the AW was evaluated. The effect of local corticosteroids and systemic blockage of IL-17 cytokine, respectively, were determined. For that purpose, mice models of allergen exposure-induced allergic inflammation and nasal biopsies from allergic rhinitis patients were used.

Repeated allergen exposure of sensitized mice resulted in an increase in the number of primitive myeloid progenitors within the BM CD34<sup>+</sup>cell population. The earliest eosinophil-committed CD34<sup>+</sup>cells were restricted to the BM compartment. After the allergen exposure, a substantial part of CD34<sup>+</sup>progenitor cells was *de novo* produced. In the BM, allergen exposure increased the number of CD34<sup>+</sup>eosinophilic cells and CD34<sup>+</sup>mature eosinophils. In blood and AW, allergen exposure induced an increase in the number of CD34<sup>+</sup>eosinophilic cells, CD34<sup>+</sup>mature eosinophils and also in newly produced CD34<sup>+</sup>cells. Furthermore, allergen exposure induced a shift in differentiation of BM, blood and BALf eosinophil-committed CD34<sup>+</sup>cells towards more mature eosinophils. Importantly, AW CD34<sup>+</sup>cells from allergen-exposed mice expressed stem cell antigen (Sca-1), produced eosinophil colonies and in response to stimulation with IL-5 expressed IL-5 receptor  $\alpha$  chain (IL-5R $\alpha$ ). Moreover, AW CD34<sup>+</sup>eosinophilic cells themselves released high amounts of IL-5 after unspecific stimulation.

In the mouse model of repeated allergen exposure, administration of an intranasal corticosteroid, fluticasone propionate (FP), significantly reduced the allergen-induced elevation of BM eosinophil number, without substantial effect on the number of AW eosinophils.

In subjects with allergic rhinitis, the exposure to allergen increased the number of nasal mucosal CD34<sup>+</sup>hematopoietic cells concomitantly with up-regulation of CXCR4 expression within the CD34<sup>+</sup>cell population. Furthermore, also the number of CD34<sup>+</sup>eosinophils in nasal mucosa was increased following exposure to allergen. A local corticosteroid, FP, provided protection against this pollen-induced increase in tissue CD34<sup>+</sup>cells.

The systemic pre-treatment with an anti-IL-17 antibody in allergen-exposed mice reduced the number of AW neutrophils, but not eosinophils, without any significant changes in BM granulocyte counts. In addition, the expression of matrix metalloproteinase-9 (MMP-9) by AW neutrophils but not eosinophils was downregulated by the pre-treatment with anti-IL-17 antibody.

In conclusion, this thesis demonstrates the exclusive role of BM in the first-line commitment of hematopoietic progenitors into the eosinophilic lineage. Importantly, allergen exposure induces not only a shift in the differentiation of eosinophil-committed progenitors towards mature cells, but also increases in the number of primitive myeloid progenitors in BM. In response to allergen exposure, CD34<sup>+</sup>progenitor cells are mobilized into the airways with one mechanism being CXCR4-mediated cell recruitment. The AW CD34<sup>+</sup>cells maintain a phenotype of a true hematopoietic progenitor cells and retain the ability to multiply likely via autocrine IL-5 release and IL-5-induced up-regulation of IL-5R $\alpha$ . Local corticosteroids inhibit the allergen-induced BM and AW eosinophilopoiesis as well as allergen-induced CXCR4-mediated recruitment of CD34<sup>+</sup>cells into AW. Endogenous IL-17 increases the number of MMP-9<sup>+</sup> neutrophils in allergic AW inflammation, without substantial effect on the number of eosinophils.

**Key words:** asthma, eosinophil, CD34<sup>+</sup>cell, eosinophilopoiesis, IL-17

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