Eosinophils, their progenitors and T helper cells in allergic airway inflammation

Akademisk avhandling

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av

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The thesis is based on the following papers:

I. You Lu, Margareta Sjöstrand, Carina Malmhäll, Madeleine Rådinger, Jeurink Prescilla, Jan Lötvall and Apostolos Bossios
New Production of Eosinophils and the Corresponding Th1/Th2 Balance in the Lungs after Allergen Exposure in BALB/c and C57BL/6 Mice.
Scand J Immunol. 2010; 71(3):176-85.

II. You Lu, Carina Malmhäll, Margareta Sjöstrand, Madeleine Rådinger, Serena E O'Neil, Jan Lötvall and Apostolos Bossios
Expansion of $CD4^+CD25^+$ and $CD25^-$ T-Bet, GATA-3, Foxp3 and RORγt Cells in Allergic Inflammation, Local Lung Distribution and Chemokine Gene Expression.
PLoS One. 2011; 6(5):e19889.

III. You Lu, Margareta Sjöstrand, Madeleine Rådinger, Carina Malmhäll, Jan Lötvall and Apostolos Bossios.
IL-33 regulates lung *in situ* eosinophilopoiesis by affecting their *in situ* proliferation, survival and migration.
In manuscript.

IV. You Lu, Carina Malmhäll, Margareta Sjöstrand, Madeleine Rådinger, Bo Lundbäck, Jan Lötvall and Apostolos Bossios.
Expression of the major trafficking related molecules in circulating eosinophil progenitors and mature eosinophils in asthma patients.
In manuscript.

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Eosinophils, their progenitors and T helper cells in allergic airway inflammation

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Abstract

Introduction: Asthma is a heterogeneous chronic lung disease associated with pronounced inflammatory changes in the airways. Eosinophilic inflammation is the trait that is best linked to symptoms and treatment responses in allergic asthma. In addition to eosinophils, T helper (Th) cells of different subsets; Th1, Th2, Th17 and T regulatory (Treg) cells, play an essential role in orchestrating allergic inflammation. Recent studies suggest that they can even affect each other´s development and function. Although the role of eosinophils and Th cells has been studied extensively, the balance of different Th cells during eosinophilic inflammation and the corresponding local lung eosinophilopoiesis has still not been elucidated.

Aim: The aim of the present thesis was to evaluate eosinophilic inflammation and the corresponding T helper cells response during allergic airway inflammation.

Methods: A classical OVA-induced allergic airway inflammation model on two commonly used mouse strains, C57BL/6 and BALB/c, was used initially to evaluate the lung eosinophilia and the corresponding Th1/Th2 balance after allergen exposure. Next, the balance of the different Th cells and the role of IL-33 in the lung during *in situ* lung eosinophilopoiesis were evaluated using the above OVA model in C57BL/6 mice. Finally, evaluation of circulating mature and progenitor eosinophils and their expression of traffick related molecules were assessed in patients with stable asthma.

Results: Allergen exposure induced a different distribution of eosinophils in the lung between the two mouse strains, with no difference in eosinophil production or Th1/Th2 balance. In C57BL/6 mice, allergen exposure led to a local expansion of all Th cells, with a dominant of Th2 cells. These Th cells showed a different local cell distribution, probably due to the different local inflammatory milieu. Allergen exposure induced lung IL-33 expression. IL-33 receptor, ST2, was expressed in all eosinophil progenitors, decreased in immature eosinophils and not expressed in mature eosinophils. ST2 was also expressed in about 60% of Th2 cells. Local blockage of IL-33 during allergen exposure impaired the number of progenitor and immature eosinophils, but not mature eosinophils or Th2 cells. Evaluation of the underlying mechanisms revealed that IL-33 enhances proliferation of lung eosinophil progenitors, protects them from induced apoptosis, and cooperates with eotaxin-1 and -2 to induce their migration. Expression of ST2 was confirmed in circulating human Th2 cells and eosinophils, both mature and progenitor, arguing for their capacity to migrate. Indeed, the last study showed that patients with stable asthma and high, but normal, blood eosinophilia had increased sputum eosinophils and increased circulating eosinophil progenitors compared to the healthy controls. Both mature and progenitor eosinophils expressed selectin PSGL-1 and integrins VLA-4 and Mac-1, although with different patterns. Mature eosinophils showed increased expression of CCR3. However, $CCR3^+$ eosinophil progenitors were more activated (increased expression of CD69 and CD25) compared to $CCR3^+$ mature eosinophils.

Conclusions: This thesis shows that allergic inflammation promotes a different local lung inflammatory milieu, resulting in both eosinophils and T helper cells distributing differently. Th2 cells dominate among other Th cells. Lung Th2 cells and lung eosinophils undergoing maturation express ST2, a receptor for a novel cytokine IL-33, released locally during airway allergic inflammation. This suggests a common link as IL-33 regulates lung *in situ* eosinophilopoiesis by affecting eosinophil progenitor proliferation, apoptosis and migration. Indeed, patients with stable asthma showed an increased number of circulating eosinophil progenitors expressing all molecules required for migration to the lung.

Keywords: eosinophils, eosinophil progenitors, T helper cells, Th2 cells, IL-33, migration, asthma

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