Functional and Phenotypic Studies of Eosinophilic Granulocytes in Patients with Eosinophilic Esophagitis

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ABSTRACT

Eosinophilic Esophagitis (EoE) is a chronic inflammatory disorder of unknown etiology, in which the esophagus is infiltrated by eosinophils and T cells. Topical corticosteroids are one of the treatment options for patients with EoE. The function of eosinophils in EoE is unknown, here we hypothesize that eosinophils serve as immunoregulatory cells. The eosinophils in the blood of untreated adult patients with EoE have a distinct phenotype. The aims of this thesis were to explore whether the eosinophilic phenotype of untreated patients with EoE can be reverted to the healthy phenotype by topical corticosteroid treatment, and to examine whether blood eosinophils from children with EoE have a distinct phenotype, different from that of healthy children. Moreover, we tested the hypothesis that eosinophils, similar to regulatory T cells, can diminish T cell proliferation and express FOXP3. The role of the eosinophilic protein galectin-10 in mediating immunosuppression was also investigated. This thesis demonstrates that the EoE phenotype of blood eosinophils is not restored by topical corticosteroid treatment, except with respect to CD18. We also show that eosinophils from patients with EoE have an immunoregulatory phenotype, i.e., increased levels of FOXP3 and galectin-10. Moreover, eosinophils from healthy subjects and patients with EoE are able to suppress T cell proliferation *in vitro*, in part *via* galectin-10. We show that eosinophils exposed to activated T cells release galectin-10 *via* DNA nets and appear to transfer this protein to T cells through synapses. Two subsets of eosinophils emerge after co-culturing. Finally, we demonstrate that the blood eosinophils of children with EoE have a distinct phenotype, different from that of healthy children and that of adults with EoE. Importantly, we reveal marked age-related differences regarding the molecular patterns displayed by the blood eosinophils of healthy donors. Our finding that eosinophils from patients with EoE have upregulated immunoregulatory molecules could indicate that the function of eosinophils in EoE is to reduce a T cell-mediated inflammation in the esophagus.

Keywords: adults, children, corticosteroids, eosinophils, eosinophilic esophagitis, FOXP3, galectin-10, inflammation, T cell suppression

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This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Topical corticosteroids do not revert the activated phenotype of eosinophils in eosinophilic esophagitis but decrease surface levels of CD18 resulting in diminished adherence to ICAM-1, ICAM-2 and endothelial cells.**
Christine Lingblom, Henrik Bergquist, Marianne Johnsson, Patrik Sundström, Marianne Quiding-Järbrink, Mogens Bove & Christine Wennerås.
Inflammation 2014; 6: 1932-1944.

II. **Eosinophils from healthy donors and eosinophilic esophagitis patients express FOXP3 and use galectin-10 to suppress T cells.**
Christine Lingblom, Madeleine Ingelsten, Jennie Andersson, Mogens Bove, Henrik Bergquist & Christine Wennerås.
Submitted

III. **Galectin-10 is secreted *via* eosinophilic extracellular traps and a subset of eosinophilic granulocytes is a strong T cell suppressor**
Christine Lingblom, Madeleine Ingelsten, Jennie Andersson, Timo Käppi, Robert Saalman, Amanda Welin & Christine Wennerås.
In manuscript

IV. **Differences in eosinophilic molecular profiles between children and adults with eosinophilic esophagitis**
Christine Lingblom, Timo Käppi, Henrik Bergquist, Mogens Bove, Richard Arkel, Robert Saalman & Christine Wennerås.
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