Human eosinophils and their activation by allergens via danger signal receptors

Akademisk avhandling

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av
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Avhandlingen baseras på följande arbeten:

I. Lena Svensson, Elin Redvall, Camilla Björn, Jennie Karlsson, Ann-Marie Bergin, Marie-Josèphe Rabiet, Claes Dahlgren and Christine Wennerås. House dust mite allergen activates human eosinophils via formyl peptide receptor and formyl peptide receptor-like 1. *Eur. J. Immunol. 2007 Jul;37(7):1966-77.*

II. Lena Svensson, Elin Redvall, Marianne Johnsson, Anna-Lena Stenfeldt, Claes Dahlgren and Christine Wennerås. Interplay between signaling *via* the formyl peptide receptor (FPR) and chemokine receptor 3 (CCR3) in human eosinophils. *J Leukoc Biol. 2009 Aug;86(2):327-36.*

III. Responsiveness of eosinophils to aeroallergens may be independent of atopic status. Elin Redvall, Ulf Bengtsson and Christine Wennerås. *Scand J Immunol. 2008 Apr;67(4):377-84.*

IV. Human eosinophils are differentially activated by food extracts derived from cod fish and milk. Elin Redvall, Kerstin Andersson, Åsa Brunnström, Said Elsayed and Christine Wennerås. *In manuscript.*

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Human eosinophilic granulocytes are polymorphonuclear cells with a powerful arsenal of cytotoxic substances in their granules, which are mainly found in the gastrointestinal mucosa, and the respiratory and genitourinary tracts. Their physiological role is incompletely understood, although it is likely they protect the mucosal surfaces, perhaps by recognizing danger signals present on microorganisms or released from damaged tissue.

We have earlier shown that eosinophils can recognize and become directly activated by aeroallergens such as house dust mite (HDM) and birch pollen. Eosinophils exposed to (HDM) release both of the cytotoxic granule proteins eosinophil peroxidase (EPO) and major basic protein, whereas birch pollen extract only triggers EPO release.

Here we further investigate which receptors on eosinophils are used to signal the presence of HDM and birch pollen. Recognition was found to be mediated by the formyl peptide receptors (FPRs) FPR1 and FPR2. We also characterized the expression of this family of receptors in human eosinophils and found that they express FPR1 and FPR2, but not FPR3, similar to neutrophilic granulocytes. We also discovered that signaling through FPR1 can desensitize the eotaxin-1 receptor CCR3 rendering the cells anergic with respect to chemotaxis in response to eotaxin-1, but not regarding respiratory burst. Hence, there is cross-talk between these two receptors regarding one important effector function of eosinophils.

Eosinophilic reactivity *in vitro* to the aeroallergens HDM, birch pollen, timothy grass pollen and cat dander did not differ between individuals with allergy and healthy individuals. Hence, eosinophilic degranulation and low grade cytokine release was seen in cells derived from both allergic and non-allergic study persons. However, both allergic and healthy individuals showed decreased TNF production from eosinophils during the birch pollen season.

We have also shown, for the first time, that human eosinophils can become directly activated by the food allergens cod fish and cow's milk. Whereas cod fish evoked eosinophilic chemotaxis, milk triggered EPO degranulation. Moreover, substances resembling prostaglandin D_2 appeared to be the bioactive substances in cod recognized by eosinophils. The receptor mediating this recognition seems to be the prostaglandin D_2 receptor DP2. Our studies may increase the understanding of the complex interaction between the innate and acquired immune system in allergy.

Key words: *Human eosinophils, danger signals, allergen, formyl peptide receptors, CCR3, chemotaxis, degranulation, free oxygen radicals, receptor desensitization*