CC16 in allergy and allergic inflammation

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien vid Göteborgs universitet kommer att offentligt försvaras i Föreläsningssalen, våning 3, Guldhedsgatan 10A, Göteborg

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av
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Avhandlingen baseras på följande arbeten:

I. **Sofi Johansson, Christina Keen, Arne Ståhl, Göran Wennergren and Mikael Benson.**
Low levels of CC16 in nasal fluid of children with birch pollen-induced rhinitis.
Allergy. 2005 May;60(5):638-42

II. **Sofi Johansson, Bill Hesselmar, Sigurdur Kristjánsson, Nils Åberg, Ingegerd Adlerberth, Agnes E. Wold, Göran Wennergren and Anna Rudin.**
CC16 levels in infants in relation to allergy and respiratory syncytial virus infection.
Submitted for publication

III. **Sofi Johansson, Göran Wennergren, Nils Åberg and Anna Rudin.**
Clara cell 16-kd protein downregulates T_H2 differentiation of human naive neonatal T cells.
J Allergy Clin Immunol. 2007 Aug;120(2):308-14

IV. **Sofi Johansson, Kerstin Andersson, Göran Wennergren, Christine Wennerås and Anna Rudin.**
Clara cell 16-kDa (CC16) protein inhibits the migration of human eosinophils towards fMLF but not towards PGD2.
Submitted for publication

CC16 in allergy and allergic inflammation

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Clara cell 16-kDa (CC16) is an anti-inflammatory protein mainly produced in the lung epithelium by Clara cells. Patients with asthma have lower levels of CC16 in bronchoalveolar lavage fluid and serum compared with healthy controls. In OVA-sensitised and challenged CC16-deficient mice, eosinophilia and the production of Th2 cytokines in the lung is higher compared with wild-type mice. Moreover, CC16 has been shown to inhibit cytokine production from a murine Th2 cell line and to inhibit the migration of rabbit neutrophils. CC16 also binds to the mast-cell derivative PGD_2 and inhibits the stimulation of the DP1 receptor.

For this reason, the first aim was to investigate whether CC16 levels in nasal lavage would be lower in children with allergic rhinitis compared with healthy controls. Our second aim was evaluate whether a low level of CC16 in plasma early in life is involved in the development of asthma, eczema and allergic rhinitis (ARC). Our third aim was to examine whether CC16 would inhibit Th2 differentiation and if CC16 would inhibit PGD_2 and fMLF-induced eosinophil and neutrophil migration.

CC16 was measured in nasal lavage samples from children with and without birch-pollen induced allergic rhinitis and serum samples from Icelandic children with or without RSV bronchiolitis. CC16 levels were also measured in plasma samples from a prospective birth cohort study at birth, and at four, 18 and 36 months. Clinical evaluations regarding the development of asthma, eczema and ARC were made at 36 months of age. Moreover, the effect of CC16 on Th2 differentiation was measured with an *in vitro* model for allergic T-cell sensitisation using human autologous neonatal mononuclear cells. The migration of eosinophils and neutrophils was assessed in a microplate migration system using specific ligands and receptor antagonists.

We found that the levels of CC16 were significantly lower in nasal lavage fluid in children with birch-pollen-induced rhinitis compared with healthy controls both during and after the pollen season. Plasma levels of CC16 in children peaked at four months but we found no relationship between low levels of CC16 at any of the time points and the development of asthma, eczema or ARC. However, the CC16 serum levels were higher in children with RSV compared with healthy controls and we noted that the healthy Swedish children had significantly higher levels of CC16 in plasma compared with healthy Icelandic infants. CC16 did not inhibit cytokine production of human Th2 cells. However, CC16 was able to inhibit Th2 differentiation induced by birch pollen allergen via the dendritic cell. CC16 did not inhibit PGD_2-induced eosinophil migration but CC16 inhibited the migration of both neutrophils and eosinophils towards fMLF.

To conclude, levels of CC16 in plasma during the first years of life do not appear to be related to the development of asthma, eczema or allergic rhinitis. Instead, low levels of CC16 in asthmatic and allergic patients may be due to epithelial damage and the reduced re-growth of Clara cells. Reduced CC16 production may cause an increase in the allergic inflammatory response and thus lead to more severe asthma or allergy.

Key words: CC16, CC10, uteroglobin, Clara cell, allergy, asthma, children, allergen, respiratory syncytial virus, T cell, eosinophil, neutrophil, fMLF, PGD_2

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