Role of IgE and IgE receptors in allergic airway inflammation and remodeling

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The Allergic Inflammatory Cascade

**First Allergen Exposure**
- **Antigen Presenting Cell**
- **B Cell**
- **Plasma Cell**
- **T Cell**

**IgE**

**Second Allergen Exposure**
- **IgE cross-linked by allergen**

**Mast Cell**
- **Depgranulation**
- **Histamine, Leukotriene, Prostaglandins, Cytokines**

**AR and Asthma Symptoms & Exacerbation**

**Cytokines**
- IL-4, IL-13

**Mast Cell Degranulation**
Mast cells can induce IgE synthesis in B cells

Pawankar R et al. J Clin Invest
Pawankar R et al, Clin Exp Allergy
Pawankar R. Curr Opin Allergy Immunol,
IgE is locally produced in the target organ

Durham et al. Eur Resp J
Twenty-five years later the receptors that mediate the binding of IgE to cells were described.

Although FcεRI is expressed on monocytes and dendritic cells (and other cell types), its expression level is 10-100 fold less than in mast cells and basophils.
Fc epsilon RI expression in NMC

High-affinity IgE receptor-bearing cells in atopic and non-atopic asthma

FcεRIα mRNA+ cells (x 10^6 cells)
- obtained from 120mL BAL

FcεRI+ cells/mm²

Rajakulasingam K. Am J Respir Crit Care Med 1998
Humbert M. Am J Respir Crit Care Med 1996
**IL-4 + IgE enhance mediator release from NMC**

- **Histamine release (%)**
  - CIR (freshly isolated)
  - CIR untreated & sensitized
  - IL-4+IgE-treated & sensitized
  - **p < 0.01**

- **IL-6**
  - pg/ml

- **IL-4**
  - pg/ml

- **IL-13**
  - pg/ml

Pawankar R Clin Exp All
Mast cell-IgE-IgE receptor axis
The prevalence of asthma is related to the level of serum IgE standardized for age and sex.

In all age groups, there was a highly significant trend for prevalence to increase with increasing Z scores ($p<0.0001$).

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**Prevalence of asthma (%)**

- Age 6 to <35 years
- Age 35 to <55 years
- Age 55+ years

$n = 2657$ of the general population with self-reported asthma or allergic rhinitis.
FcεRI-mediated Thymic Stromal Lymphopoietin Production by IL-4-primed Human Mast Cells
Function of Thymic stromal lymphopoietin (TSLP)

- Induction of $T_{H2}$-attracting chemokines CCL17, CCL22
- Priming of naïve $T_{H2}$ cells to produce $T_{H2}$ cytokines
- Promotion of development of B220+ IgM+ immature B cells from pre-B cells
- A weak comitogen for T cell proliferation
- CD4+ T cell development
TSLP as a key initiator of allergic inflammation

Humans

TSLP is expressed in epithelial cells of patients with atopic dermatitis.

The number of cells within the bronchial epithelium and submucosa expressing mRNA for TSLP are significantly increased in asthmatics as compared with controls.

Mice

Skin-specific overexpression of TSLP results in an atopic dermatitis-like phenotype.

Lung-specific overexpression of TSLP induces asthma-like airway inflammation.

TSLPR KO mice fail to develop an inflammatory lung response to inhaled antigen.
TSLP expression by human bronchial mucosal mast cells of asthmatic patients
Significant increase in number of TSLP$^+$Tryptase$^+$ cells in the airways of asthmatic patients

A. TSLP$^+$ cells/mm$^2$

B. % of TSLP$^+$ cells

C. Tryptase$^+$ cells/mm$^2$

D. TSLP$^+$ MCs/mm$^2$

E. TSLP$^+$ MCs/MCs (%)

F. TSLP$^+$ MCs/MCs (%)

G. TSLP$^+$ MCs/MCs (%)

Control Asthma

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Atopic Non-Atopic

*
TSLP production by human mast cells following aggregation of FcεRI in the presence of IL-4.

b) IgE+IL4 → wash → Anti-IgE with DMSO □

IgE+IL4 → wash → wash → with DMSO

-48h 0 16h

IgE+IL4

16 h


c) α-IgE - +

I-309 (ng/ml)

0 1 2 3 4

**

*  


d) α-IgE - +

TSLP (pg/ml)

0 5 10 15 20
Correlation of % of TSLP+ cells in mast cells with the serum IgE level, and hyperresponsibility in asthmatic patients and controls

- **IgE (U/ml) log10**
  - $r^2 = 0.131$
  - $P = 0.048$

- **Acetylcholine (μg/ml)**
  - $r^2 = 0.252$
  - $P = 0.024$
The number of AREG$^+$ tryptase$^+$ cells increases in bronchial mucosa of subjects with asthma.
Correlation between AREG\(^+\) tryptase\(^+\) cells with the extent of goblet cell hyperplasia in the airways of asthmatic subjects

- **Mucus score** = \(n_1 + 2n_2\)
- **Grade 1**
  - Goblet cell height epithelial layer < \((1/3)\)
- **Grade 2**
  - Goblet cell height epithelial layer > \(1/3\)

\(n_1\); Grade 1-cell count
\(n_2\); Grade 2 cell count

(Tokuyama K et al Am J Physiol 1990)
Rationale for anti-IgE therapy

Anti-IgE stops IgE binding to effector cells

<table>
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<tr>
<th>Mechanism</th>
<th>Treatment</th>
<th>Allergen avoidance</th>
<th>Hypo-sensitization</th>
<th>Mast-cell stabilization: cromones, isoprenaline</th>
<th>Mediator antagonists: antihistamines, antileukotrienes</th>
<th>Late-phase inhibitors: steroids</th>
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<tr>
<td>Allergen</td>
<td>IgE synthesis</td>
<td>Mast cell degranulation</td>
<td>Inflammatory mediators</td>
<td>Clinical symptoms</td>
<td></td>
<td>Adapated from Roitt J. Essential Immunology 1994</td>
</tr>
</tbody>
</table>
Immunohistochemical staining of bronchial biopsy specimens before (left) and after (right) 16 weeks of omalizumab treatment.

Representative sections show staining with antibody against:
- ECP (A and B)
- Cell-surface IgE (C and D)
- High-affinity IgE R (E and F)
- IL-4 (G and H)

Mechanisms of Action of Omalizumab

- Reduces serum levels of free IgE
- Down-regulates expression of IgE receptors (FceRI) on mast cells and basophils.
- In the airways of patients with allergic asthma, it reduces FcεRI+ and IgE+ cells and causes a profound reduction in tissue eosinophilia, together with reductions in submucosal T-cell and B-cell numbers.

The reductions in circulating levels of IgE resulting from omalizumab treatment leads to reductions in FceRI expression on mast cells, basophils and dendritic cells.

This combined effect results in attenuation of several markers of inflammation, including peripheral and bronchial tissue eosinophilia, levels of GM-CSF, IL-2, IL-4, IL-5 and IL-13.

It may also reduce allergen presentation to T-cells and the production of Th2 cytokines.

Forced expiratory volume in 1 second as a percentage of baseline in the placebo (A) and omalizumab (B) groups.

Effect of add-on therapy with omalizumab in patients with severe persistent asthma whose asthma was inadequately controlled by therapy with high-dose ICSs plus a LABA

**Conclusion**

**Benefits of Anti-IgE in atopic disease**

- Effectively reduces the incidence of allergic asthma exacerbations while decreasing the need for steroids
- Improves asthma-specific QoL and reduces the incidence of hospitalizations
- Can simplify the control of asthma with only once or twice monthly injections
- Controls the symptoms of SAR, reducing the requirement for concomitant medication
- Has a good long-term safety profile
WAO White Book on Allergy
Allergic Diseases as a Global Public Health Issue

Authored by:
- International expert allergists and clinical immunologists; has been compiled for publication under the supervision of the WAO Education Council.

Purpose:
To serve as a major resource in explaining allergic diseases, their prevalence, management, and the importance of adequate service provision for allergy patients.

Edited by Professors Ruby Pawankar, Stephen T. Holgate, G. Walter Canonica, and Richard F. Lockey
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