How immunology informs the design of immunotherapeutics.

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How immunology informs the design of immunotherapeutics.

- Allergen induced early and late nasal responses
- Natural seasonal allergen exposure
  - effects of corticosteroids
- Influence of treatment
  - Immunotherapy
  - anti-IgE therapy
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Mechanisms of allergic rhinitis

- **Immediate Rhinitis Symptoms**
  - Itch, sneezing
  - Watery discharge
  - Nasal congestion

- **Chronic Rhinitis Symptoms**
  - Nasal blockage
  - Nasal hyperreactivity

- Allergen
  - **Mast Cell**
    - IgE
    - Histamine
    - Tryptase
    - Leukotrienes
    - Prostaglandins
    - Bradykinin
    - PAF
  - **B Cell**
  - **T Cell (Mast Cell)**
    - IL-4, IL-13
    - IL-3, IL-5
    - VCAM-1
    - GM-CSF
  - **Eosinophil**

- **IL-4, IL-13, IL-3, IL-5**
- **GM-CSF**
- **VCAM-1**
Inflammatory mediators during allergen-induced nasal responses

Leukotrienes in allergen-induced early nasal responses:

- LTs: Slow-reacting substance of anaphylaxis
- In vitro: Released from mast cells + basophils by Ag-IgE crosslinking
- Nasal lavage, post challenge: levels correlate with symptom scores
- LTC, LTD, LTE present

Time course of tryptase in allergen-induced nasal responses: nasal fluid

Unpublished data
Allergic response

1. Allergen binds to APC and T cell (CD4+)
2. APC presents allergen to T cell, inducing Th2 cell differentiation
3. Th2 cells secrete IL-4 and IL-5
4. IL-4 activates B cells to produce IgE
5. IL-5 stimulates eosinophils
6. IgE binds to mast cells, leading to allergic response

CD80/86, CD28, HLA, CD3
Nasal biopsy
In situ hybridisation studies of nasal mucosa

Anti-sense riboprobe

Sense riboprobe (negative control)

CCR4 mRNA+ cells in nasal mucosa

Banfield G, Watanabe H, Scadding G et al Allergy epub Feb 2010
CCR4 mRNA+ cells in the nasal mucosa

Banfield G, Watanabe H, Scadding G et al Allergy epub Feb 2010
Immunofluorescence for CCR4 and CD3
8hr after allergen challenge

Banfield G, Watanabe H, Scadding G et al Allergy epub Feb 2010
IgE

IL-4

IL-5

Eosinophils

CD4

APC

Allergen

CD28

CD80/86

CD3

HLA

T cell

Th2

CCR3

CCR4

CRTH2

TSLP

B-cell

Allergic response

IgE

CD3

HLA

Th2

CCR3

CRTH2

TSLP

Allergen

CD4

APC

Eosinophils

CCR3

IL-4

IL-5
CRTH2 in allergic rhinitis

Accumulation of CRTH2-positive leukocytes in human allergic nasal mucosa
Hideaki Shirasaki, MD, PhD; Megumi Kikuchi, MD, PhD; Etsuko Kanaizumi, MD, PhD; and Tetsuo Himi, MD, PhD


DP2/GPR44/CRTh2 - chemoattractant receptor-homologous molecule expressed on Th2; PGD2-CRTh2 signalling on Th2 cells, eosinophils and basophils induces chemotaxis and up-regulates expression of IL-4, IL-13 and IL-5
CRTH2 in the nasal mucosa in allergic rhinitis

TSLP in allergic rhinitis

Acta Oto-Laryngologica, 2009; 129: 297–301

ORIGINAL ARTICLE

Overexpression of thymic stromal lymphopoietin in allergic rhinitis

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TSLP in the nasal mucosa in allergic rhinitis

Immunochemistry

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Quantitative RT-PCR

Acta Oto-Laryngologica, 2009; 129: 297–301
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Topical steroid (fluticasone propionate) in hayfever

Masuyama K et al, J Allergy Clin Immunol 1998;102:610-7
Immunohistology of nasal mucosa for T and B lymphocytes

- CD3$^+$ T cells expressing IL-4
- CD20$^+$ B cells
- CD20$^+$ B cells Expressing C$\varepsilon$
Topical steroids inhibit seasonal increases in IL-4 mRNA+ cells

Topical steroids inhibit seasonal increases in IgE mRNA+ cells

Cameron L et al., J Allergy Clin Immunol 1998;102:610-7
Immunohistology of nasal mucosa for IL-5+ T cells and eosinophils

CD3+ T cells expressing IL-5

Eosinophils expressing MBP
Topical steroids inhibit seasonal increases in IL-5 mRNA+ cells

Masuyama K et al., J Allergy Clin Immunol 1998;102:610-7
Topical steroids inhibit seasonal increases in eosinophils

Masuyama K et al., J Allergy Clin Immunol 1998;102:610-7
CD1a$^+$ Langerhans cells in nasal mucosa
Topical steroids inhibit seasonal increases in dendritic cells

Till SJ et al., Allergy 2001;56:126-131
Allergic response

Eosinophils

CD4

CD80/86

CD28

HLA

APC

Steroids

IL-4

IL-5

B-cell

IgE

Allergen

Th2

Steroids

T cell

CD3

CD28

HLA
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Immunotherapy (high dose Ag)

Natural exposure (low dose Ag) + IgE

APC

Th1

IFN-γ

IL-10

IgG

Th2

IL-4

B cell

IgE

Eosinophil

IL-5

Tr

TGF-β

IgG4

IgA

Grass pollen immunotherapy for seasonal rhinitis/asthma (Alutard SQ *Phleum pratense*)

Pollen Count/m³

Baseline

Out of season Biopsy

Second year

In season Biopsy

Grass pollen immunotherapy for seasonal rhinitis/asthma (Alutard SQ *Phleum pratense*)

Walker SM et al., J Allergy Clin immunol 2001;107:87-93
Grass pollen immunotherapy for seasonal rhinitis/asthma

Walker SM et al., J Allergy Clin immunol 2001;107:87-93
Grass Pollen Immunotherapy Induces Mucosal and Peripheral IL-10 Responses and Blocking IgG Activity


J Immunol 2004; 172: 3252-59
Grass pollen immunotherapy: IL-10 in the nasal mucosa

Allergen-specific IgG4

1. Allergen forms complexes with IgE

2. Complexes bind FcεRII on B-cell

3. Antigen Presentation and subsequent T cell activation

4. Immunotherapy induces IgG antibodies that block IgE binding
Inhibition of allergen-IgE binding to B-cells following immunotherapy

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Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomised controlled trial.


JAMA 2001;286:2956-2967

- 536 patients (959 screened)
- Aged 12-75y
- Moderate/severe symptoms
- IgE 30-700 iu/ml
Nasal Symptoms in the Ragweed Season: Effects of Omalizumab

Casale, T. B. et al. JAMA 2001;286:2956-2967.
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Eosinophils

CD80/86

APC

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B-cell

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Allergen

immunotherapy

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T cell
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