Immunology and immunotherapy in allergic disease

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Allergy

- Allergic reaction is an exaggerated or inappropriate immune reaction and causes damage to the host
- Hypersensitivity:
  - Type I: anaphylactic reaction: mediated by IgE antibodies, which trigger the mast cells and basophils to release pharmacologically active agents.
  - Type II: cytotoxic reaction: IgM or IgG antibodies bind to antigen on the surface of cells and activate complement cascade.
Hypersensitivity

- Type III: Immune complex reaction: complexes of antigen and IgM or IgG antibodies accumulate in the circulation or in tissue and activate the complement cascade. Granulocytes are attracted to the site of activation and release lytic enzymes.

- Type IV: cell-mediated immunity reaction: mediated by T cells, which release cytokines upon activation to cause accumulation and activation of macrophages.
Immunology review

- Antigen presenting cell
- T lymphocytes
- B lymphocytes
- IgE antibody
- Mast cells
- Eosinophil
Antigen presenting cells

- Function: take up antigen, process and present antigen to T cells
- Including: macrophage, dendritic cell, B lymphocyte and activated T lymphocyte
- Major histocompatibility complex (MHC)
  - class I: binds with CD8+ T cell only
  - Class II: binds with CD4+ T cell only
From: Immunology a short course, 1996 figure 10.5
From: Immunology a short course, 1996 figure 11.1
CD4+ T lymphocyte

- 2 subsets based on distinct cytokines produced
- Th1:
  - produce IL-2, IL-12, interferon (IFN)- gamma
  - activate CD8+ T cell, natural killer cells, and macrophage
  - Elimination of intracellular pathogen, facilitate delayed hypersensitivity
CD4+ T lymphocyte

- **Th2:**
  - produce IL-4, IL-5, IL-10
  - activate B cells and switch antibody synthesis to IgE
  - mediate allergic inflammation
  - preferentially activate Th2 cells leading to development of allergic disease

- Th1 and Th2 inhibit the development of each other
Cytokines

- **IL-4**: Produced by Th2 and mast cell
  - Growth factor for B cells and Th2 cells
  - Promotes IgE production
  - Inhibits Th1 cell

- **IL-5**: Produced by Th2 cell
  - Growth and differentiation factor for eosinophil

- **IL-2**: Produced exclusively by T cell: Th0 and Th1
  - T cell growth factor

- **IFN- gamma**: Produced by Th1 cell
  - Activates NK cells, macrophages, and killer cells,
  - Inhibits Th2 cell
  - Induce expression of MHC class II on many cell types
B lymphocyte and IgE antibodies

- B lymphocyte needs 2 signals to mature to IgE producing plasma cell.
  - IL-4 secreted by Th2 cells
  - Interaction of CD40 ligand on the surface of T-cell with the CD40 receptor on the B cell

- IgE antibody
  - Unbounded IgE with half life of 2-3 days
  - Bound to receptor on the surface of mast cell, basophil, dendritic cell, and eosinophil with half life of several weeks
Mast cells

- Preformed mediators:
  - Vascular permeability factor (VPF) / vascular endothelial cell growth factor – enhancing vascular permeability
  - Histamine, proteoglycan, chymase, tryptase, carboxypeptidaseA heparin
  - TNF-alpha, IL-2,3,4,13, GM-CSF, chemokine

- Newly synthesized inflammatory mediators:
  - prostaglandin D2
  - leukotriene C4, D4, B4
Eosinophil

- Developed in bone marrow under stimulation of IL3, IL5, GM-CSF
- Half life of 8-18 hours in the blood, half life of several days in the peripheral tissue
- Eosinophil migration (into peripheral tissue)
- Toxic inflammatory mediators in eosinophil:
  - major basic protein, eosinophil peroxidase, eosinophil cationic protein,
- Synthesize and release lipid mediators:
  - leukotriene C4
Immunotherapy

- Medical procedure that uses controlled exposure to known allergens to reduce the severity of allergic disease
- Disease accepted to be treated by immunotherapy:
  - Allergic rhinitis, allergic asthma, allergic conjunctivitis, insect sting hypersensitivity
- Disease not accepted to be treated by immunotherapy:
  - Food allergy, urticaria, atopic dermatitis
- Exact mechanism is not clear
- No reliable correlation between changes of the immunological parameter and clinical outcome
Immunotherapy

- Curtis (1900): immunize people with aqueous extract of whole weeds
- Dunbar (1903): immunize subjects who had grass-sensitive hay fever with animal derived (horse and goose) grass pollen antisera to subject’s nasal mucosa
- Besredka and Steinhardt (1907): anaphylactic reaction encountered during immunotherapy is due to immunizing too rapidly or with too large dose of allergen
- Noon and Cantab: introduced weight units for pollen doses and quantization of individual sensitivity by in vivo testing.
- Freeman and Koessler (1914): immunotherapy produced long lasting results
- Cooke (1915): formally introduced immunotherapy into the USA by reporting the treatment by pollen immunization of 114 patients with hay fever and asthma.
Mechanism: B cell response

- Gradual increase of allergen-specific IgG antibodies
  -- especially IgG4 subclasses (blocking antibody)
    - intercept and neutralize allergen before it bound to cell-surface IgE
    - form IgG-antigen-IgE complex and bind to the IgG receptor resulting co-aggregation with the IgE receptor and inhibition of IgE receptor triggering

- decreased allergen-specific IgE antibodies

- increase IgA and IgM antigen-specific B lymphocytes
  - May limit antigen penetration into the body from mucosa
Mechanism: T cell response

- Moving immune system from CD4+Th2 cell to Th1 cell pathway
- Alter cytokine production
  - IL-4, IL-5 as Th2 cytokines
  - IFN-gamma as Th1 cytokines
Table I. Effect of immunotherapy on cytokine synthesis

<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects</th>
<th>Site</th>
<th>IL-4</th>
<th>IL-5</th>
<th>IFN-γ</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Secrist H</td>
<td>Grass pollen and mite allergic subjects</td>
<td>Peripheral blood</td>
<td>Decreased</td>
<td>–</td>
<td>Unaltered</td>
<td>(70)</td>
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<tr>
<td>Söderlund A</td>
<td>Birch allergic subjects</td>
<td>Peripheral blood</td>
<td>Decreased</td>
<td>Unaltered</td>
<td>Unaltered</td>
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<tr>
<td>Ohashi Y</td>
<td>Patients with perennial allergic rhinitis</td>
<td>Serum</td>
<td>Decreased</td>
<td>–</td>
<td>–</td>
<td>(23)</td>
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<tr>
<td>Ohashi Y</td>
<td>Patients with seasonal allergic rhinitis</td>
<td>Serum</td>
<td>Decreased</td>
<td>–</td>
<td>Increased</td>
<td>(9)</td>
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<td>Varney VA</td>
<td>Patients with seasonal allergic rhinitis</td>
<td>Skin</td>
<td>Unaltered</td>
<td>–</td>
<td>Increased</td>
<td>(71)</td>
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<td>Durham SR</td>
<td>Patients with seasonal allergic rhinitis</td>
<td>Nasal mucosa</td>
<td>Unaltered</td>
<td>–</td>
<td>Increased</td>
<td>(74)</td>
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<td>MacDonald SM</td>
<td>Patients with seasonal allergic rhinitis</td>
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<td>Decreased</td>
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<td>O'Brien RM</td>
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<td>Tanaka A</td>
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<td>Decreased</td>
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<td>Nakai Y</td>
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<td>Peripheral blood</td>
<td>–</td>
<td>Decreased</td>
<td>Unaltered</td>
<td>(82)</td>
</tr>
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</table>
Advantage of immunotherapy

- long term clinical efficacy
  - Durhan et al.:
    - Randomized, placebo-controlled, double-blind study
    - Patients (32) with allergy to timothy grass-pollen extract received 3 years of immunotherapy treatment
    - Patients then randomized to continue with the immunotherapy or to receive placebo
    - 15 matched patients never received immunotherapy as control group
    - Presence of symptoms and need for rescue medication were measured after 3 years
Long term efficacy of immunotherapy

- No significant difference in symptom scores and use of rescue medication between two immunotherapy groups, and were lower than control group
- No difference in the late skin responses (size of swelling, number of infiltrating T cells, cells containing IL-4 mRNA) between two immunotherapy groups, and significantly lower than control group
- Immunotherapy for grass-pollen allergy for three to four years induces prolonged clinical remission accompanied by a persistent alteration in immunologic reactivity
Advantage of immunotherapy

- may prevent progression of rhinitis to asthma in children
  - Preventive Allergy Treatment Study:
    - 205 children from 6 pediatric allergy centers in northern Europe aged 6-14 years with grass or birch pollen allergy
    - randomly assigned either to receive specific immunotherapy for 3 years or to a control group
    - The children who were treated with immunotherapy had significantly fewer asthma symptoms after 3 years as evaluated by clinical diagnosis

- may prevent onset of new sensitization in allergic patients
Patient selection

- Proven allergy with skin test or RAST
- With allergic symptoms that are significant to the patient
- Attempts to avoid allergens fail or impractical
- Treatment with medicine is not fully successful or when medication is not well tolerated.
- Young patients without chronic irreversible changes in the upper airways
- Patient needs to be motivated and compliant with treatment
Immunotherapy

- Subcutaneous immunotherapy is the only approved route of administration in United States.
- Subcutaneous immunotherapy normally involves a weekly subcutaneous injection of an extract of the allergen, in solution, in increasing doses until a standard maintenance dose is reached.
- This dose is then injected subcutaneously on a regular basis (at intervals of approximately 20 days) for not less than 3 years for perennial allergens.
- Short term immunotherapy does not affect the cytokine profile and do not have long-term efficacy after discontinuation.
- Start at an earlier age, so that adverse changes to the immune system can be prevented before they become irreversible.
Sublingual immunotherapy

- widely used and investigated in Europe since late 1980’s
- keep the extract under the tongue for a couple of minutes and then swallow it
- dose of allergen is greater than subcutaneous immunotherapy (about 3-300 times higher)
Efficacy of sublingual immunotherapy

- Wilson et al.: systemic review of literature in Cochrane library
- 22 clinical studies, a total of 979 patients
- double-blinded, placebo-controlled, parallel-group studies
- highly significant reduction in symptoms as well as definite decrease in medicine intake for symptoms
- whether sublingual therapy equals the efficacy of subcutaneous immunotherapy is not clear
References