Asthma & Allergic Hypersensitivity

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Outline

• Hypersensitivity
• Epidemiology of asthma – overview
• Immunological mechanisms involved in hypersensitivity/asthma
• Treatment strategies: Immunological mechanisms involved
• Treatment – future directions
What is Hypersensitivity?

- Inappropriate or exaggerated immune response.
- Also called allergy (anaphylaxis)
4 types of hypersensitivity responses

- Type I – IgE (Antibody) mediated
- Type II - ADCC (IgG) mediated
- Type III - Immune complex mediated
- Type IV – Cell mediated (DTH)

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE-Mediated Hypersensitivity</td>
<td>IgG-Mediated Cytotoxic Hypersensitivity</td>
<td>Immune Complex-Mediated Hypersensitivity</td>
<td>Cell-Mediated Hypersensitivity</td>
</tr>
<tr>
<td>Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators</td>
<td>Ab directed against cell surface antigens mediates cell destruction via complement activation or ADCC</td>
<td>Ag–Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils</td>
<td>Sensitized T\textsubscript{H}1 cells release cytokines that activate macrophages or T\textsubscript{C} cells which mediate direct cellular damage</td>
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<tr>
<td>Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema</td>
<td>Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia</td>
<td>Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus</td>
<td>Typical manifestations include contact dermatitis, tubercular lesions and graft rejection</td>
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</tbody>
</table>
What happens in hypersensitivity reactions?

• **Significant tissue damage, due to:**
  – vasoactive substances
  – phagocytosis
  – complement (inflammatory & cytolytic)
  – other inflammatory mediators

• **Immune system components mediating this:**
  – antibodies - mast cells
  – T cells - basophils
Type I hypersensitivity

• Type I hypersensitivity occurs when host makes IgE response to non parasitic antigens
• Asthma - example of Type I hypersensitivity
Type I reactions can be...

• **Systemic**
  – shock like / often fatal
  – Ags - venom (bees, wasp, ants), drugs (penicillin), seafood, nuts
  – Treatment-epinephrine

• **Localised**
  – specific target tissue/organ
  – atopy: hay fever, asthma, eczema, food allergies
Genetic predisposition to allergies (atopy)

• Genetic susceptibility: Genes – *Adam33* (bronchial smooth muscle)

• Results in an atopic individual having:
  – High level of IgE
  – High number of eosinophils
Mechanism (Type I hypersensitivity)

1\textsuperscript{st} Exposure to allergen → Plasma cells produce IgE → IgE binds FcR mast cells/basophils

2\textsuperscript{nd} exposure to allergen → Allergen crosslinks sensitised mast cells/basophils → Degranulation of mast cells/basophils → Release of mediators (causing allergy symptoms)
Type I Hypersensitivity
(Allergic or Immediate)

- **Allergen**
- **Genetic Basis** (e.g. atopy)
- **Clinical effects**
  - Mucosal
  - Subcutaneous
  - Blood

<table>
<thead>
<tr>
<th>TABLE 16-1</th>
<th>Common allergens associated with type I hypersensitivity</th>
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</thead>
<tbody>
<tr>
<td><strong>Proteins</strong></td>
<td><strong>Foods</strong></td>
</tr>
<tr>
<td>Foreign serum</td>
<td>Nuts</td>
</tr>
<tr>
<td>Vaccines</td>
<td>Seafood</td>
</tr>
<tr>
<td>Plant pollens</td>
<td>Eggs</td>
</tr>
<tr>
<td>Rye grass</td>
<td>Peas, beans</td>
</tr>
<tr>
<td>Ragweed</td>
<td>Milk</td>
</tr>
<tr>
<td>Timothy grass</td>
<td>Insect products</td>
</tr>
<tr>
<td>Birch trees</td>
<td>Bee venom</td>
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<tr>
<td>Drugs</td>
<td>Wasp venom</td>
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<tr>
<td>Penicillin</td>
<td>Ant venom</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Cockroach calyx</td>
</tr>
<tr>
<td>Local anesthetics</td>
<td>Dust mites</td>
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<tr>
<td>Salicylates</td>
<td>Mold spores</td>
</tr>
<tr>
<td></td>
<td>Animal hair and dander</td>
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</tbody>
</table>

Table 16.1 Goldsby et al. 2003, 15-1 (2007)
Mechanism of Type I Hypersensitivity

Fig 16.2 Goldsby et al. 2003; 15-2(2007)
# Mediators of Type I HS

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Effects</th>
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<tbody>
<tr>
<td><strong>PRIMARY</strong></td>
<td></td>
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<tr>
<td>Histamine, heparin</td>
<td>Increased vascular permeability; smooth-muscle contraction</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Increased vascular permeability; smooth-muscle contraction</td>
</tr>
<tr>
<td>Eosinophil chemotactic factor (ECF-A)</td>
<td>Eosinophil chemotaxis</td>
</tr>
<tr>
<td>Neutrophil chemotactic factor (NCF-A)</td>
<td>Neutrophil chemotaxis</td>
</tr>
<tr>
<td>Proteases</td>
<td>Bronchial mucus secretion; degradation of blood-vessel basement membrane; generation of complement split products</td>
</tr>
<tr>
<td><strong>SECONDARY</strong></td>
<td></td>
</tr>
<tr>
<td>Platelet-activating factor</td>
<td>Platelet aggregation and degranulation; contraction of pulmonary smooth muscles</td>
</tr>
<tr>
<td>Leukotrienes (slow reactive substance of anaphylaxis, SRS-A)</td>
<td></td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Increased vascular permeability; contraction of pulmonary smooth muscles</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Vasodilation; contraction of pulmonary smooth muscles; platelet aggregation</td>
</tr>
<tr>
<td>Cytokines</td>
<td>Increased vascular permeability; smooth-muscle contraction</td>
</tr>
<tr>
<td>IL-1 and TNF-α</td>
<td>Systemic anaphylaxis; increased expression of CAMs on venular endothelial cells</td>
</tr>
<tr>
<td>IL-2, IL-3, IL-4, IL-5, IL-6, TGF-β, and GM-CSF</td>
<td>Various effects (see Table 12-1)</td>
</tr>
</tbody>
</table>

Table 16.3 Goldsby et al. 2003, 15-3 (2007)
Asthma current status

- Over 300 million patients worldwide (4.5%)
- Increase in incidence over last 50 years
- An example of new approach to treatment: Omalizumab
- Higher rates in developed countries
- Commonest chronic disease in adults and children
- Australia highest rate (21% medically diagnosed)
Innate immune system and asthma

Kim et al., 2012. The many parts to asthma. Nat Immunol.
Asthma more complex than initially thought

• More than just Th2 response
• IFN involved
Immune cells involved in asthma

- Mast cells
- Eosinophils
- NKT
- T helper
- DC
- Neutrophil

Kim et al., 2012. The many parts to asthma. Nat Immunol.
Kim et al., 2012. The many parts to asthma. Nat Immunol.
Kim et al., 2012. The many parts to asthma. Nat Immunol.
Role of cytokines

IL-13

• Regulates IgE
• Mucous secretion
• Hyper responsiveness of respiratory tract
• Important in corticosteroid resistant asthma
Treg cells

- CD4+ CD25+ T cells (Treg)
- Suppress allergic responses
- Anti inflammatory
- Suppress Th1/Th2 responses
Current therapy- Corticosteroid

- Bind to GC receptor
- Translocation to nucleus
Effect of glucocorticoids on immune response

Receptor (GR)- protein that binds DNA/affects transcription initiation

• Repression of genes in leukocytes

Decrease
  – Cytokines
  – Adhesion molecules

• Activation of some genes
  – IL-10 (anti inflammatory cytokine)

• Effect on progenitor immune cells, DCs, macrophages
  (e.g. increased phagocytosis of dead cells (anti inflammatory))
Corticosteroid therapy

- Side effects (e.g. osteoporosis)
- Some cases steroid resistant

Need for new approaches to treatment
Approach to developing new treatments

- Suppress Th2 response
- Enhance Treg cell activity
Therapies for asthma

Current approaches

• Immunomodulation/ Immunotherapy
• (Th1 vs Th2 responses)
• Blocking the effect of Th2 cytokines (e.g. monoclonal antibodies)
Parasites in therapy...

Discussed at 2012 Annual Meeting of the American Academy of Allergy, Asthma & Immunology

- E.g. Heligmosomoides polygyrus proteins dampen Th2 response
Biologic immune response modifiers

e.g. monoclonal antibodies

Example: Omalizumab (Xolair; Genentech, South San Francisco, Calif)

• 95% humanized mAb
• forms soluble immune complexes with free IgE
  – preventing cross-linking of FcεRI
  – prevents basophil and mast cell activation

Does not work in approx. 40% of patients
Allergen specific immunotherapy

• Transient increase in IgE (potentially fatal side effects in some cases)
• Aim- increase allergen specific IgG (IgG1, IgG4)
• Increase in T reg cells
• Increase in IL-12
• Treat for at least 3yrs for successful outcome
Future directions

• More research required on immune mechanisms e.g. role of Toll like receptors (TLRs)
• Investigate genes involved that may affect response to treatments
• Monoclonal antibodies that can be administered orally
References

• Goldsby et al., Kuby Immunology. 2009
• Kim HY, DeKruyff RH, Umetsu, DT. The many paths to asthma: phenotype shaped by innate and adaptive immunity. N.ature Immunology. 2010. 11(7): 577-584.

• Viswanathan Rk, Busse WW. Allergen immunotherapy in allergic respiratory diseases: from mechanisms to meta-analyses.