Pharmacology of the Respiratory Tract
Lecture 2: Allergy and IgE
Learning Objectives

- Understand that the lung is constantly exposed to pathogens and toxins

- Define the three mechanisms by which the lungs immune response removes pathogens

- Describe the role of IgE in allergic inflammation
  - IgE production, Structure, Mediator release

- Describe the mechanisms of action and therapeutic effects of anti-IgE therapy for the treatment of severe asthma
You breathe ~ 15 to 25 times per minute at rest.

You inhale and exhale 7.5 – 12.5 Litre’s of air per minute.

That totals ~ 11,000 Liters of air in a day

150,000 contaminants are breathed in everyday
Air Contaminants

Outdoor air contaminants
• Particulate Matter (PM) – pollen, dust, industrial burning
• Gases – sulphur dioxide, nitrogen oxide, ozone
• Toxic pollutants – volatile organic chemical, pesticides

Indoor air contaminants
• Home and Offices are a significant source of pollution
  • Fungus, Bacteria, smoke, odors, cleaning chemicals, paint

If we inhale ~100 bacteria every minute, why are we not always sick?
The Immune Response

The lung facing an invasion by a pathogen can call on an array of powerful acute inflammatory responses;

**Innate immune response**

**Adaptive immune response**
The lungs immune defenses I

- Since pathogens and stimuli come in many different forms – a wide variety of immune defenses are required.

1) **External Barrier**

- Size 5-7 μM
- Beat in asymmetric pattern, synchronously
- 15 cycles every second
- Propels mucus 10 mm every min

**Mucociliary clearance**: Rapidly beating cilia and mucus
2) Recognition of pathogens and foreign material

Pattern recognition receptors

Pathogen – associated molecular patterns
The lungs immune defenses III

3) Killing and removal of pathogens and foreign material

1) Opsonification
   Recognition by PARs

2) Phagocytosis
   - engulfed pathogen

3) Degradation
   - lysozymes in granules
The allergic Inflammatory Reaction

- Definition: A hypersensitive response of the immune system of an allergic individual to a substance.
  
- Red
- Swollen
- hot
- painful
- alteration of function

The “Wheal and Flare” type I hypersensitivity reaction
The Mast Cell

- Sentinel immune cell of all mucosal tissues
- Scarce in the serum
- 2 types
  - Mucosal mast cells and connective tissue mast cells
Mast Cell Degranulation

- Mast cells can be stimulated to degranulate by:
  - Direct injury (e.g. physical or chemicals (opioids))
  - Cross-linking of immunoglobulin E (IgE) receptors
  - Complement system (C3a)
# Mast Cell Mediators

<table>
<thead>
<tr>
<th>Preformed Mediators</th>
<th>Newly Formed Mediators</th>
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<tbody>
<tr>
<td>Histamine</td>
<td>Superoxide</td>
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<tr>
<td>Chemotactic factors</td>
<td>Leukotrienes C4, D4, E4</td>
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<td>Tryptase</td>
<td>Prostaglandin D2</td>
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<td></td>
<td>Prostaglandin E2</td>
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<td>Thromboxane</td>
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<td>Bradykinin</td>
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<td>Platelet activating factor</td>
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**Cytokines**

- Granulocyte–monocyte colony-stimulating factor
- Interleukin-3
- Interleukin-5

**Actions**

<table>
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<th>Edema</th>
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<td>Airway smooth muscle contraction, mucus secretion</td>
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<td>Chemotaxis of eosinophils and neutrophils</td>
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<td>Generation of bradykinin; degradation of vasoactive intestinal peptide</td>
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<th>Inflammation</th>
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<td>Cytotoxicity</td>
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<td>Airway smooth muscle contraction, mucosal edema, and mucus secretion</td>
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<th>Bronchonstriction</th>
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<tr>
<td>Airway smooth muscle contraction</td>
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<tr>
<td>Mucosal edema</td>
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<tr>
<td>Airway smooth muscle contraction</td>
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<tr>
<td>Mucosal edema, airway smooth muscle contraction</td>
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<tr>
<td>Bronchoconstriction (?)</td>
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**Cytokines**

- Stimulation, maturation, and priming of eosinophils
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Adaptive Immune Response

The initial contact of an allergen within the mucosa with APC (local event)

Allergen is phagocytosed and presented on the cell surface via the major histocompatibility complex (MHC) class II receptor

APCs present allergen within lymph glands to Th2 Cells via the T cell receptor (TCR)

Th2 cell-stimulated B cells mature into plasma cells to produce IgE

IgE is released into the circulation
Immunoglobulin E

Variable Region – allows for movement and binding of antigens, determines specificity

Constant Region -
The heavy chain is epsilon

Antigen Binding Site –
Area where antigen is bound
Mast Cell bound-IgE

- IgE is scarce in the serum

- Mast cells express high-affinity and low affinity FcεR1 receptors which binds to the constant region of IgE

- high affinity binding (Kd~10^{-10}) of IgE via is the CH3 region is essentially irreversible

- IgE molecules are specific to one particular antigen
IgE and Allergy

• IgE levels directly correlate with allergy

Therefore an attractive target to prevent allergic reactions
Uncontrolled Asthma

- Severe asthma has a major impact on health-care resource utilization
- Symptoms are not controlled by standard LABAs and steroid combination therapies

Definition: Persisting asthma symptoms despite high dose inhaled steroids (1000 µg) plus LABA and systemic steroids for over 12 months
Omalizumab (Xolair) is a humanized mAb that targets IgE.

Forms complexes with circulating IgE to form biologically inert complexes.

Humanized anti IgE was developed by grafting the variable sequence of a mouse antibody (binds human IgE) onto the constant IgG human framework (94% human, 5% murine).

This avoids clinical problems of immunoreactivity.
Administration of anti-IgE Therapy

- Dosing is based on the patients baseline IgE (IU/ml) before the start of treatment and body weight (kg).

- Administered by subcutaneous injection once or twice a month.

- Based on these measurements 75 – 375 mg of omalizumab in 1 -3 injections may be needed for each administration.

- Requires 1 hour appointment to prepare drug, administer and monitor for 30 minutes after injection
Biological Characteristics of Omalizumab

- High isotype specificity, can neutralize serum free IgE without affecting other antibody classes
- Does not bind to FcεR1 receptors therefore it does not activate mast cells
- Activity does not depend on allergen specificity all IgE is neutralized
- Does not induce extensive immune complex formation, only microcomplexes (trimeric) which are not able to induce immune-complex pathology
Treatment with anti-IgE Therapy

- Omalizumab (Xolair) dosing is effective against early and late phases of asthma
Mechanisms of Action of Anti-IgE

• Forms complexes with circulating IgE to form biologically inert complexes.

• Leads to a reduction in high-affinity FcεR1 receptors expressed on mast cell after 3 months.

• Reduces changes of IgE cross-linking therefore reduces mast cell mediator release.

• Reduces severity and symptoms of asthma attack regardless of the allergen/s.
Therapeutic effects of Anti-IgE

• Reduces severity and symptoms of asthma attack regardless of the allergen/s

• Reduces need for bronchodilators

• Have a corticoid sparing effect

• Improvement in allergic rhinitis symptoms for asthma patients that also have nasal symptoms

• Reduced hospital admissions, emergency room and doctor visits
Safety of anti-IgE Therapy

- Dosing is based on the patient’s total IgE before treatment and body weight, administered by subcutaneous injection.

- The rate of anaphylactoid type reactions is 1 per 1000 in clinical trials.

- To date, more than 35,000 patients have been treated with omalizumab since it was first approved in the USA.
Costs of anti-IgE Therapy

• Direct and indirect costs of asthma total ~ US$ 13 billion

• In Canada uncontrolled asthma costs are CAD $162 million

• Standard therapy versus with omalizumab for 5 years is CAD$50,000 (one prescription $153).