Pharmacology of the Respiratory Tract: Allergy and IgE

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This lecture will provide an understanding of the role of immune system in the homeostasis of the human lung. The specific learning objectives will include:

- Define examples of biological and chemical exposures within the household
- Define the three factors important for the immune response
- Focus on the sentinel immune cell the mast cell
  - IgE production
  - IgE Structure
- Pharmacology of anti-IgE for the treatment of severe asthma
You breathe ~15 to 25 times per minute at rest.

The average adult at rest inhales and exhales 7 - 8 liters of air per minute.

That totals ~11,000 liters of air in a day of which 21% is oxygen.
Biological and Chemical Exposures within the Home

36% Pollen
31% Dust mites
33% Gas Molecules, Odors, Toxins

Germ Phase: Bacteria, Viruses, Fungi Pathogens Allergens
Gas Phase: Gas Molecules, Odors, Toxins
Solid Phase: Organic and Inorganic Particulate
Air Contaminants

• Specific Examples

• We breathe 100 bacteria every minute

• 150,000 contaminants are breathed in everyday
The lung facing an invasion by a pathogen can call on an array of powerful acute inflammatory responses;

**Innate, non-immunological response**

**Acquired, specific Immune response**
The Inflammatory Reaction

• Define: Events which occur in the tissue in response to an invading pathogen (disease-causing organism) or noxious stimuli.

• Red, swollen, hot, painful and alteration of function

• Outcome: Reactions are protective and result in healing with or without scarring, but if the pathogen/noxious agent persists chronic inflammation is deleterious.
The Inflammatory Reaction

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

• 1) **Exterior Barrier**

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

Mucociliary clearance: Rapidly beating cilia and mucus
The Inflammatory Reaction

• Since pathogens and stimuli come in many different forms – a wide variety of immune defenses are required.
  
• 2) Recognition of pathogen or foreign material

Pattern Recognition Receptors

Pathogen-associated molecular patterns
The Inflammatory Reaction

- Since pathogens and stimuli come in many different forms – a wide variety of immune defenses are required.
- 3) Mounting a inflammatory reaction to eliminate it

1) Opsonification
   - Recognition by PARs

2) Phagocytosis
   --engulfed pathogen

3) Degradation
   -lysozymes in granules
The Mast Cell

- A resident immune cell of mucosal tissues

- Contain dense granules that contain
  - **Histamine** – Binds H1 histamine receptor on smooth muscle (contraction), endothelial cells (vasodilation)
  - **Heparin** - Anticoagulant
Mast Cell Degranulation

- Mast cells play a key role in the inflammatory process

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

- Allergy is mediated by immunoglobulin E

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

APCs present allergen to Th2 Cells which release IL-4

Stimulate B cells and subsequently plasma cells to produce IgE
Mast Cell IgE

- Allergy is mediated by immunoglobulin E

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

Constant Region -
Binds to FcεR1 on mast cells

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

- Mast cells express a high-affinity receptor **FcεR1** for the constant (Fc) region of IgE
- High affinity binding ($K_d \sim 10^{-10}$) of IgE is essentially irreversible
- Mast cells are coated with IgE
- IgE molecules are specific to one particular antigen
IgE and Allergy

- IgE level directly correlates with allergy
Uncontrolled Asthma

- Severe asthma has a major impact on health-care resource utilization
- Symptoms are not controlled by standard steroids (ICS) and SABA/LABA
Treatment with anti-IgE Therapy

• 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** IgG1 human framework (94% human, 5% murine).

This avoids clinical problems of **immunoreactivity**.
Treatment with anti-IgE Therapy

- Omalizumab (Xolair) dosing is effective against early and late phases of asthma
Safety of anti-IgE Therapy

• Dosing is based on the patients total IgE before treatment and body weight, administered by subcutaneous injection.

• Asthma Quality of Life Questionnaire baseline score for omalizumab of 0.91 compared with 0.46 for placebo patients ($P < 0.001$).

• The rate of anaphylactoid type reactions is 1 per 1000 in the clinical trial programmes.

• To date, more than 35 000 patients have been treated with omalizumab as it was first approved in the USA.