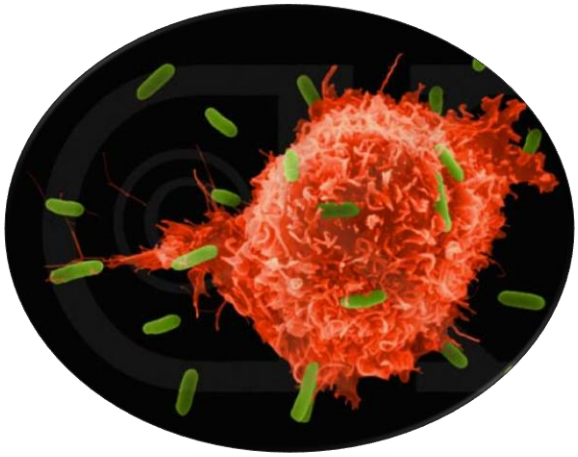
Immunology Team

Respiratory Block

431



Immunology of Asthma

- **Objectives:**
- **To the difference between extrinsic and intrinsic asthma**
- **To be familiar with types of allergens and their role in allergic sensitization**
- **To understand the inflammatory processes operating in allergic asthma**
- **To know about the airway remodeling**

Type 1 hypersensitivity

Asthma is an inflammation of the air way → treating asthma = treating inflammation

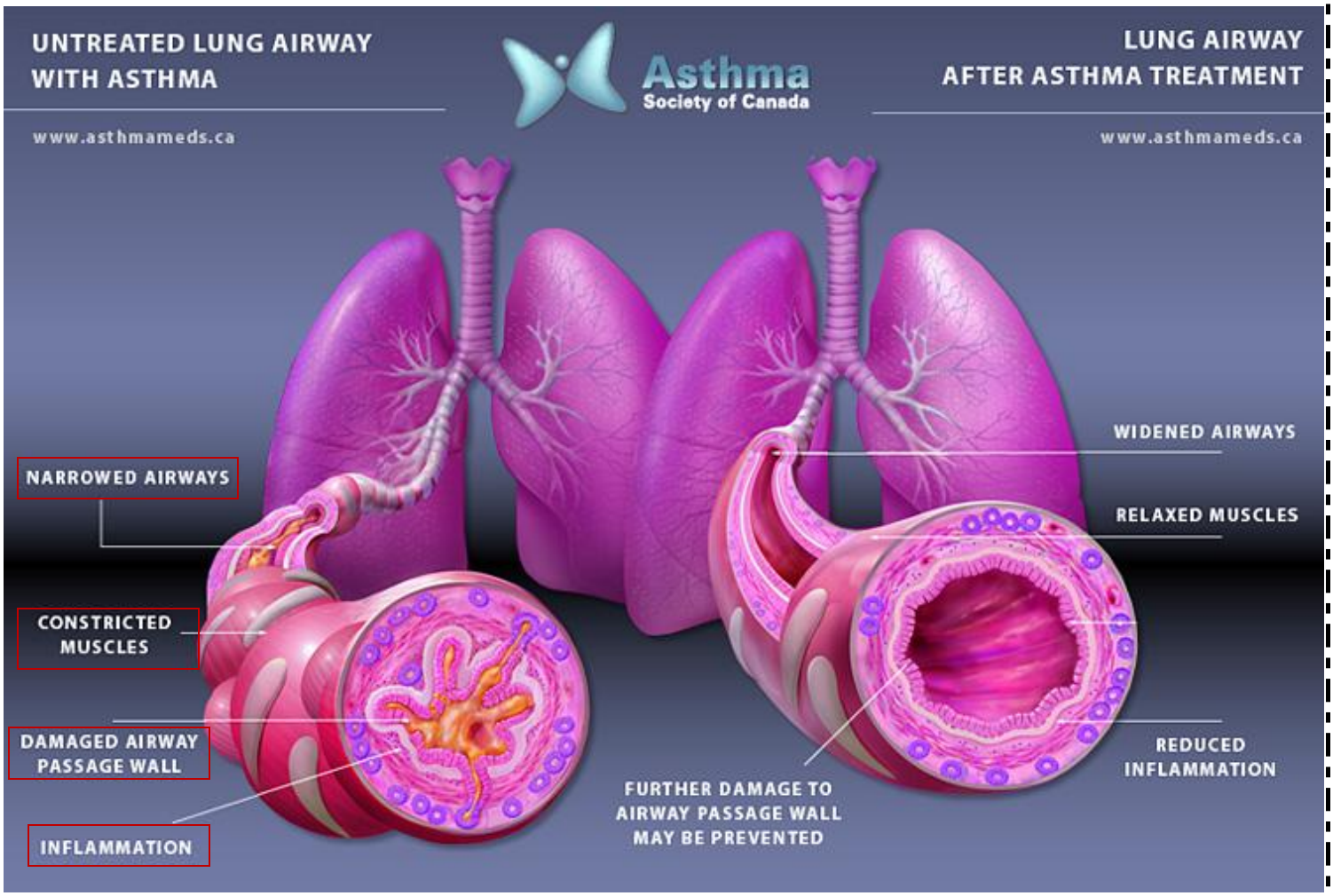
Asthma is a clinical syndrome characterized by:

1. Episodes of **reversible** airway obstruction → Can be treated by bronchodilator
2. Increased **bronchial reactivity** → Small irritant (eg. change in weather) causes cough
3. **Airway inflammation**

Patients with asthma present with one or more of the following symptoms:

1. Breathlessness (difficulty in breathing)
2. Wheezing
3. Persistent cough → Cough being worse at night
4. Chest tightness

Airway Obstruction in Asthma



Classification of Asthma

1. Intrinsic (non-atopic) → non allergic asthma , the cause not known

2. Extrinsic (atopic) →(Atopy: genetic tendency to develop allergy)

Tendency to react to allergens that other people do not react to it (have genes that make them react to allergens by secreting IgE antibodies instead of IgG class) → allergic asthma

Non-atopic (intrinsic) asthma (10-33% of asthmatics)

- **Negative skin tests**
- No clinical/family history of allergy
- Serum IgE levels are usually **normal**
- Older patients
- **More severe**

Atopic (extrinsic) asthma "Allergies trigger asthma attacks in"

Children will be suffering more than adult because they have the defected genes. After they grow up they might not have this allergy because of the hormonal changes. (Hormones have steroidal effect)

60-90% Children

50% Adults

Approximately **75-85% of patients with asthma have positive (immediate) skin test** reactions to various allergens.

Role of Allergens in Asthma

Allergen sensitization is linked to the risk of developing asthma.

Indoor allergens

- House dust mites
- Domestic pets (cat fur & dander)
- Cockroaches (insects)
- Molds (fungal spores)

Outdoor allergens

- Fungal spores (e.g. Alternaria)
- Grass, tree & weed pollens

Fungal spores

Grass pollens

Tree pollens

Antigen presenting cells (APCs) in the lung

Denderitic cells present allergens to Th2 → Th2 message the B-lymphocyte to → produce IgE antibody

Two subsets of **dendritic cells (DCs)** in the lungs:

- One subset of DCs called **respiratory tract myeloid DCs (mDCs)** help in the **development of asthma symptoms**
- Second subset known as **plasmacytoid DCs (pDCs)** aid in **respiratory tolerance to allergens**

Do not induce production of IgE so no asthma

In susceptible individuals

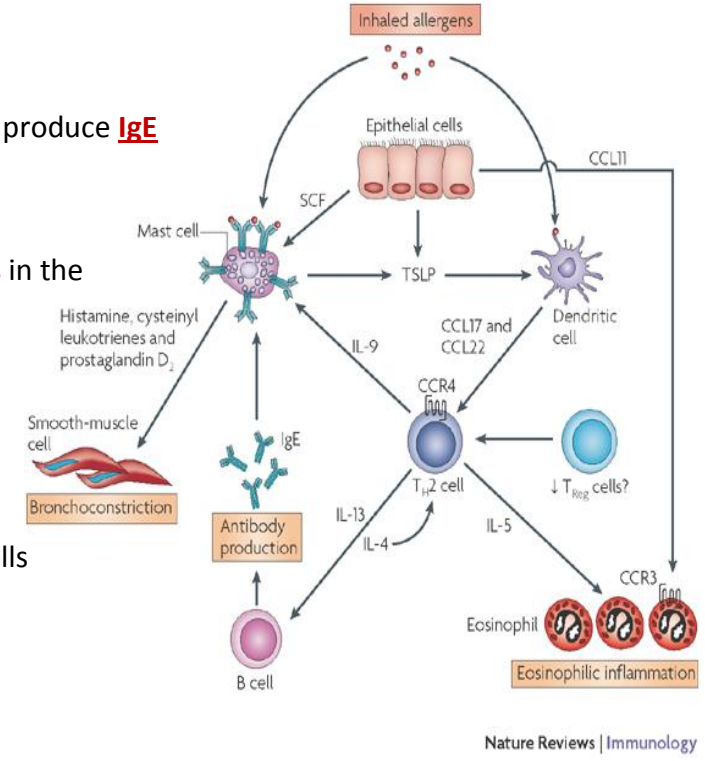
First encounter with allergens **activate B-cells** to produce **IgE**

Subsequently:

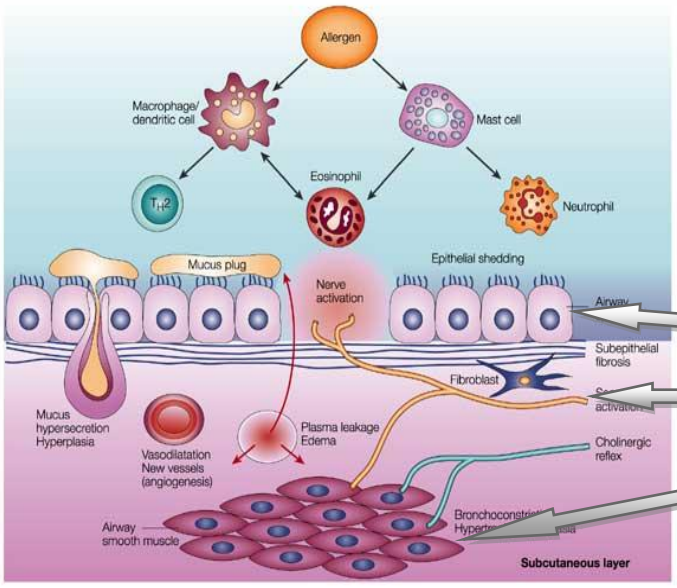
Inhaled allergens activate **submucosal mast cells** in the lower airways.

Mediators are released within seconds causing:

1. **Bronchoconstriction**
2. **Influx of eosinophils** & other inflammatory cells



Asthma results from complex interactions among the inflammatory cells that involve

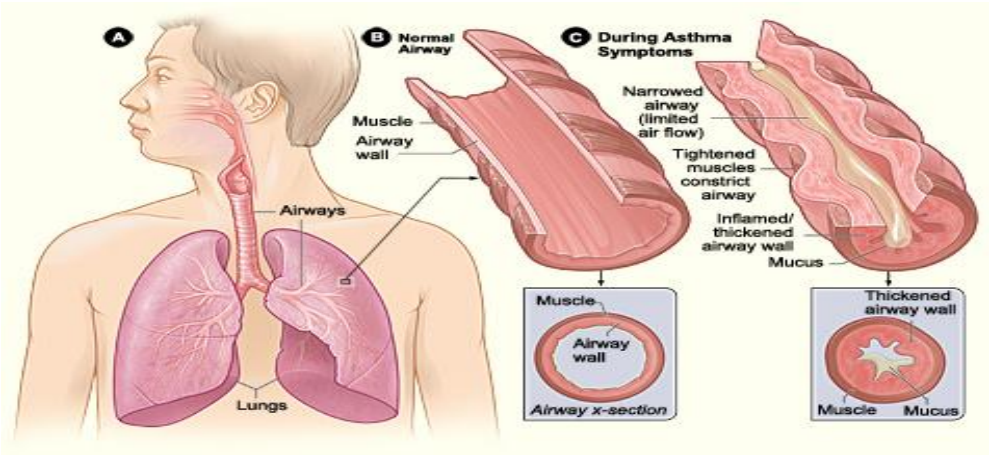


Airway epithelium

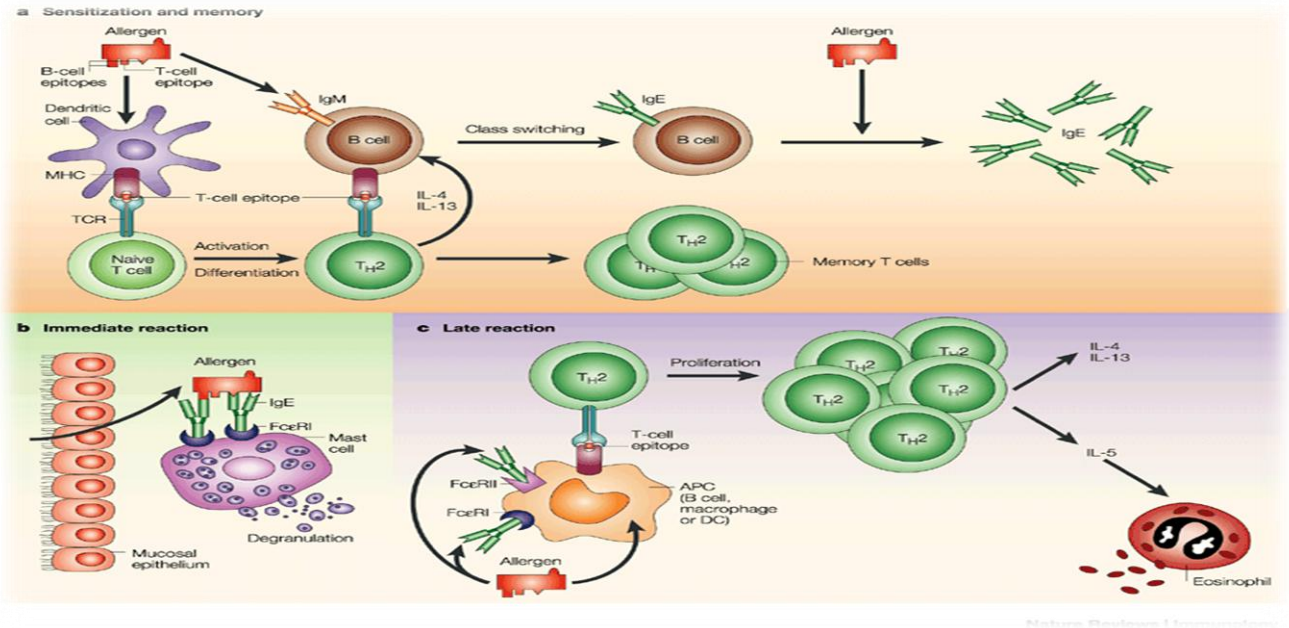
Nervous system

Bronchial smooth muscles

Factor contributing to airflow obstruction leading to difficulty in breathing include



Response to allergen occur in two phases



Early allergic response	Late allergic response
1. Occurs within minutes. 2. Manifests clinically as: - Bronchial constriction - Airway edema - Mucus plugging Is reversible and responds to bronchodilators	1. Appears 4 to 10 hours later. 2. Results from infiltration by inflammatory cells. 3. Activation of lymphocytes & eosinophils. Responds to steroids (Anti-inflammatory drugs)

Th2 cells and role of cytokines in allergic asthma

Allergens drive T-cells towards Th 2 type:

Th2 secrete the cytokines→ IL-4, IL-5, IL-9 & IL-13 which promote:

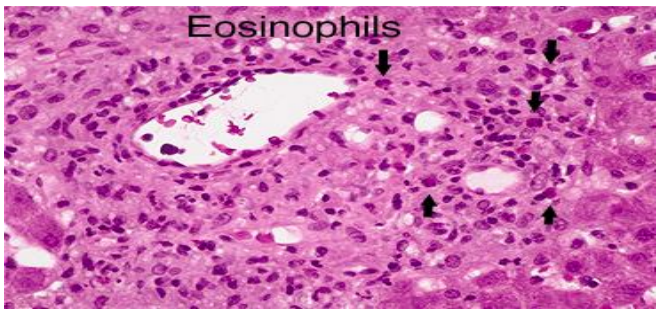
1. Production of IgE by B cells
2. Eosinophil attraction and infiltration
3. Airway inflammation
4. Increased bronchial reactivity

Role of IL-4,IL-5&IL-13 in allergic asthma		
IL-4	**IL-5**	**IL-13**
The main role of IL-4 is carried out during the initial priming of Th2 cells : **1. Regulates isotype switching in B cells to IgE.** **2. Induces MHC II on antigen-presenting cells.** **3. Induces adhesion molecule expression.** **4. Activate mast cells and eosinophils.**	**1. IL-5 induces an increase in eosinophil production in the bone marrow.** **2. Release of eosinophils from the bone marrow into circulation.**	**1. IL-13 induces inflammation.** **2. Stimulates mucus hyper-secretion.** **3. Induces sub-epithelial fibrosis.**

isotype switching is certain gene rearrangement takes place, when exposing to any allergen they switch from producing "normall" IgD and IgM to other class of antibody; IgA, IgE and IgG.

Role of eosinophils in allergic asthma

- Eosinophils **initiate** asthmatic symptoms by causing tissue damage in the airways of the lungs
- Production of eosinophils is **inhibited by IL-10**



Role of regulatory T – cells

Regulatory T cells suppress the effector mechanisms that induce asthmatic symptoms.

Asthmatics may **lack functional regulatory T cells** that can inhibit an asthmatic response.

Activation of inflammatory cells (mast cells, eosinophils etc,) is a major inducer of **airway inflammation**.

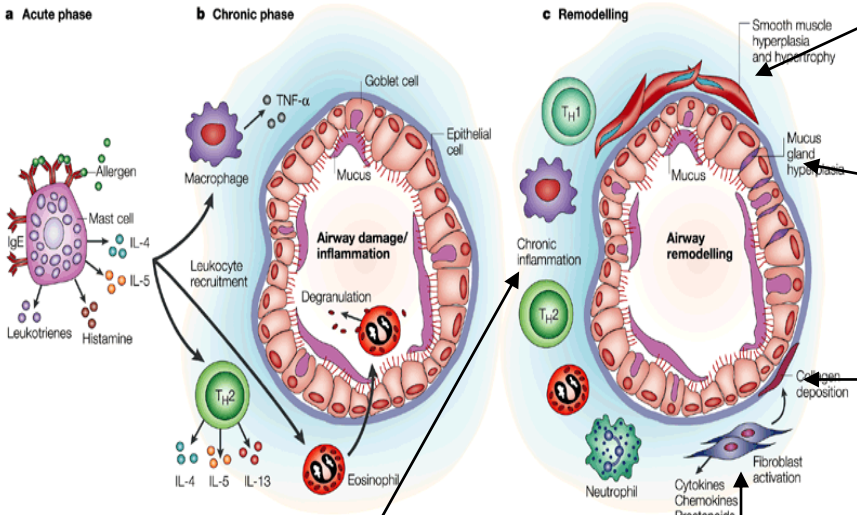
Airway inflammation is the **hallmark** in the asthmatic lung which leads to: **Increased bronchial reactivity.**

Products of the inflammatory cells act on

1. Airway smooth muscle cells
2. Lung fibroblasts
3. Mucous glands

And cause **Airway Remodeling**

Airway remodeling refers to



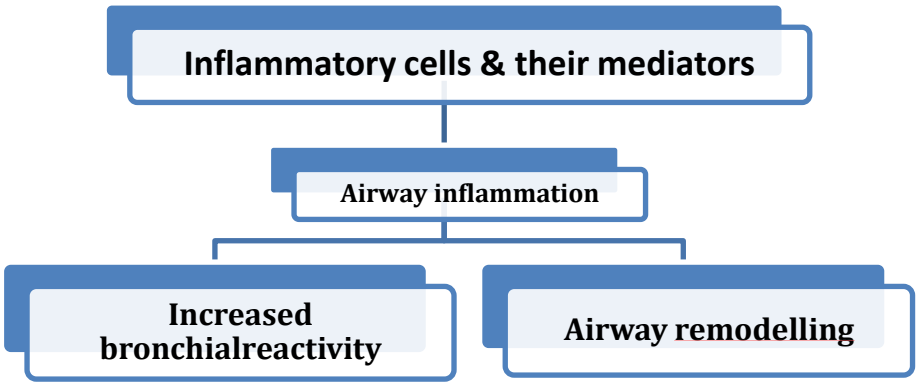
1. Smooth muscle hyperplasia & hypertrophy.

2. Mucous gland hyperplasia

3. Collagen deposition

4. Fibroblast activation

5. Chronic inflammation



Outcome of increased airway reactivity

Predisposes patients to develop asthma attacks on exposure to non-specific irritants:

1. Chemical irritants
2. Smoke & strong perfumes
3. Sulphur dioxide & air pollutants
4. Viral and bacterial respiratory infections

Outcome of airway remodeling

Can ultimately lead to fibrosis and irreversible airway obstruction in some patients

Take home message

1. Asthma is characterized by episodic reversibleairway obstruction

2. Classified in 2 types: intrinsic & extrinsic

3. In the extrinsic type allergens drive T-cellsinto Th2 pattern

4. Airway inflammation is a hallmark finding inthe asthmatic lung

5. Inflammatory cells lead to increased bronchialreactions & airway remodeling which is not revisable