Immunology of bronchial asthma

Respiratory block

First lecture

Brought to you by:

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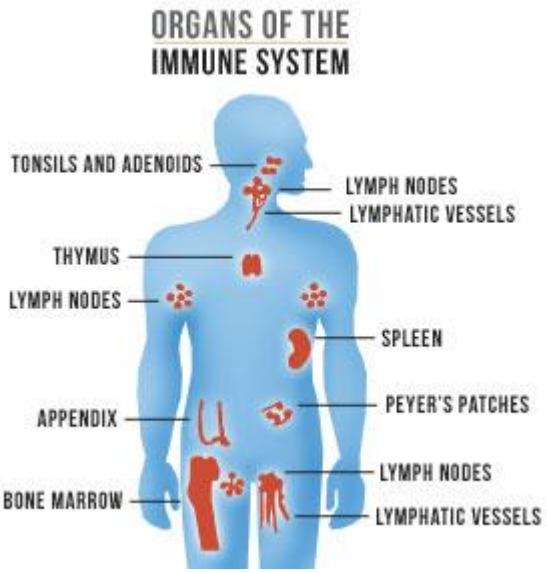


Objectives:

- 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.

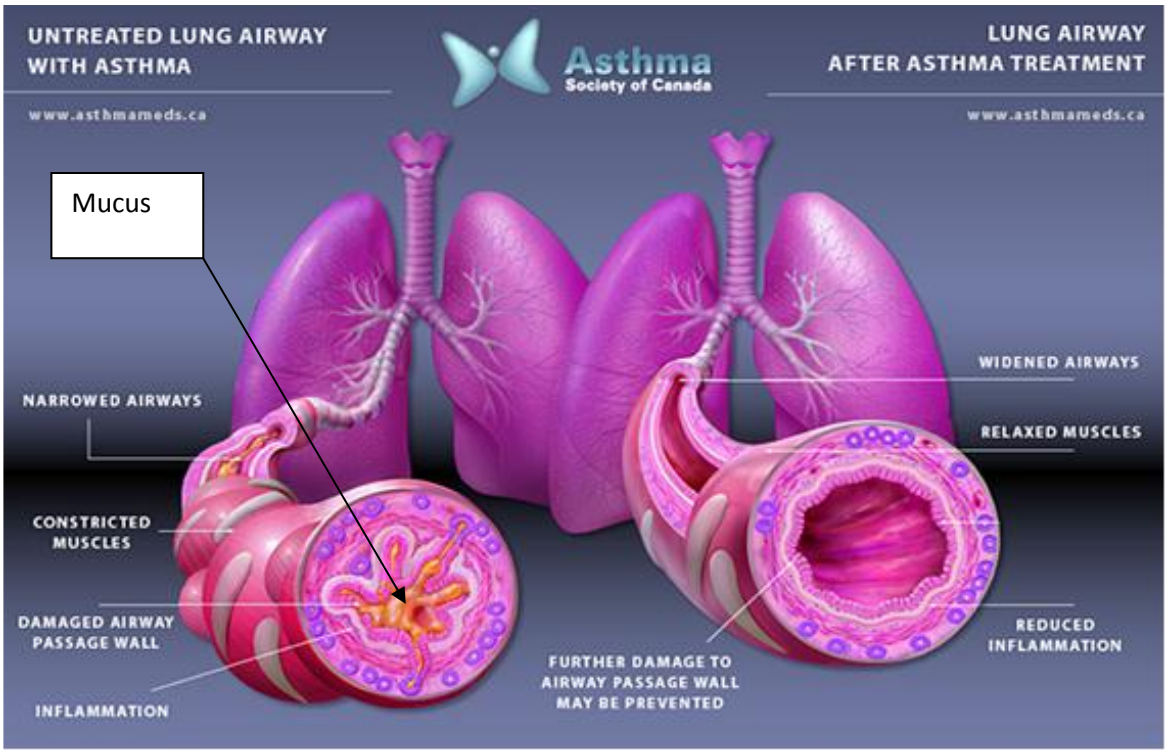
- Asthma **(both intrinsic & extrinsic)** is a clinical syndrome characterized by:

1. **Episodes of reversible airway obstruction**
2. **Increased bronchial reactivity**
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**
4. **Chest tightness**

- Airway Obstruction in Asthma



Asthma

Intrinsic (non-atopic)

Extrinsic (atopic)

(Atopy: genetic tendency to develop allergy)

No hypersensitivity type 1 which means no allergy

Hypersensitivity type 1 is found (allergy) , usually the response is producing large amounts of IgE

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

- **Negative skin tests** (used in hypersensitivity type1)
- **No clinical/family history of allergy**
- **Serum IgE levels are usually normal**
- **Older patients** (older people are less affected by allergens)
- **More severe**

Atopic (extrinsic) asthma

Allergies trigger asthma attacks in:

60-90% **Children**

50% **Adults**

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

Serum IgE is elevated

Allergens

Indoor allergens

1. House dust mites
2. Domestic pets (cat fur & dander)

If we had a patient who is allergic (hypersensitivity type 1) to cats but still lives with them we can use immunotherapy, which usually takes along time (around 2 years). In immunotherapy they basically shift the immune response from producing IgE to IgG by giving escalating doses of the allergen (no interaction with IgE on mast cells = no hypersensitivity type1), the response will differ from one patient to another.

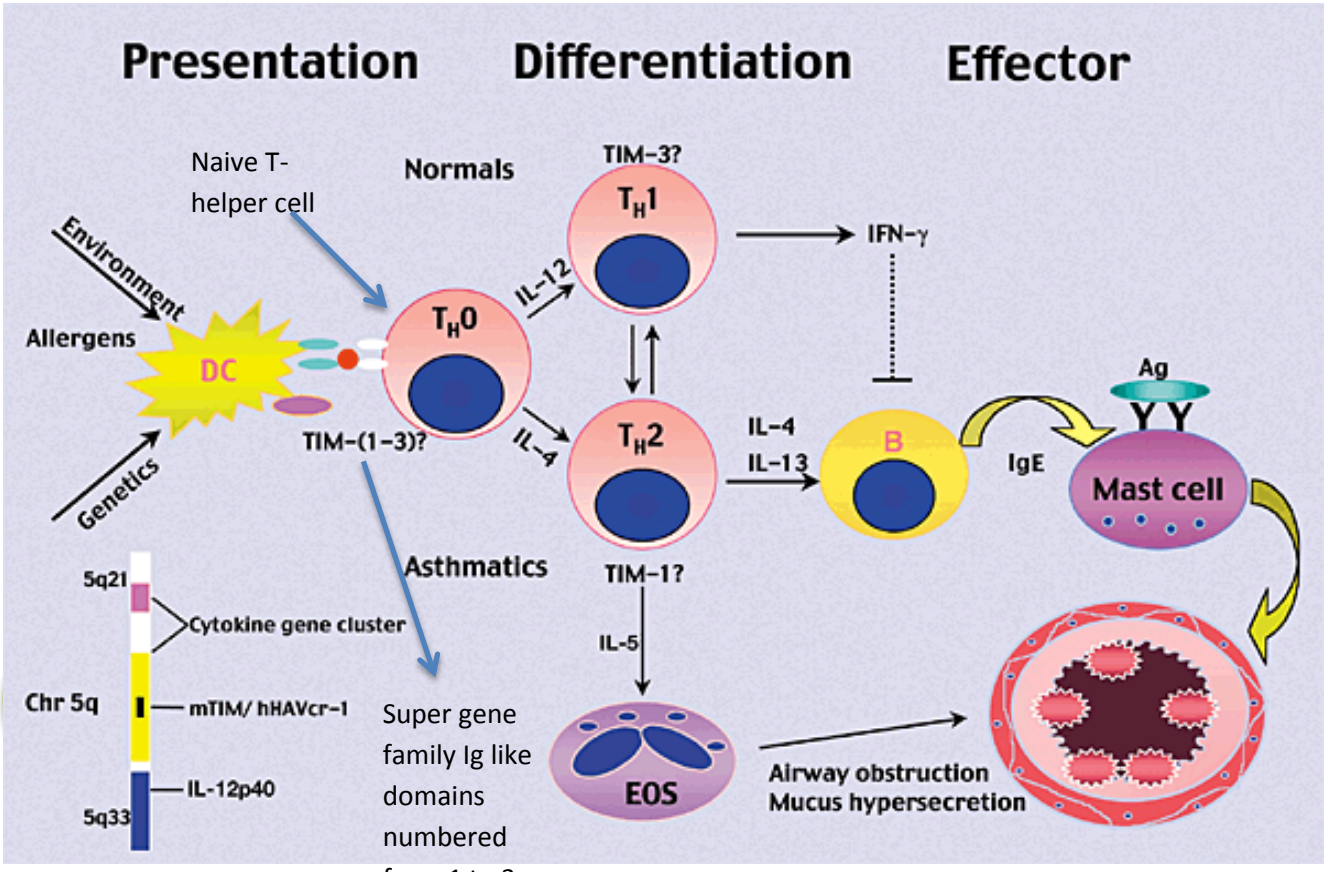
3. Cockroaches (insects)
4. Molds (fungal spores)

Outdoor allergens:

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

- **Allergen sensitization is linked to the risk of developing asthma which is related to type 1 of hypersensitivity.**
- **Induction of Allergic Inflammation**

- **In predisposed individuals:**
  First encounter with allergens stimulates production of allergen specific IgE antibodies by B cells (allergic sensitization)
- **Subsequently:**
  - **Inhaled allergens** activate sub-mucosal mast cells in the lower airways resulting in release of mediators instantly causing:
    1. Recruitment of eosinophils (Specifically for allergy and parasitic kind of infections) & pro-inflammatory cells
    2. Bronchoconstriction



Super gene family Ig like domains numbered from 1 to 3, they control certain trans membrane proteins that promote the development of immune response to asthma through TH2 pathway.

Remember antigen-presenting cells:

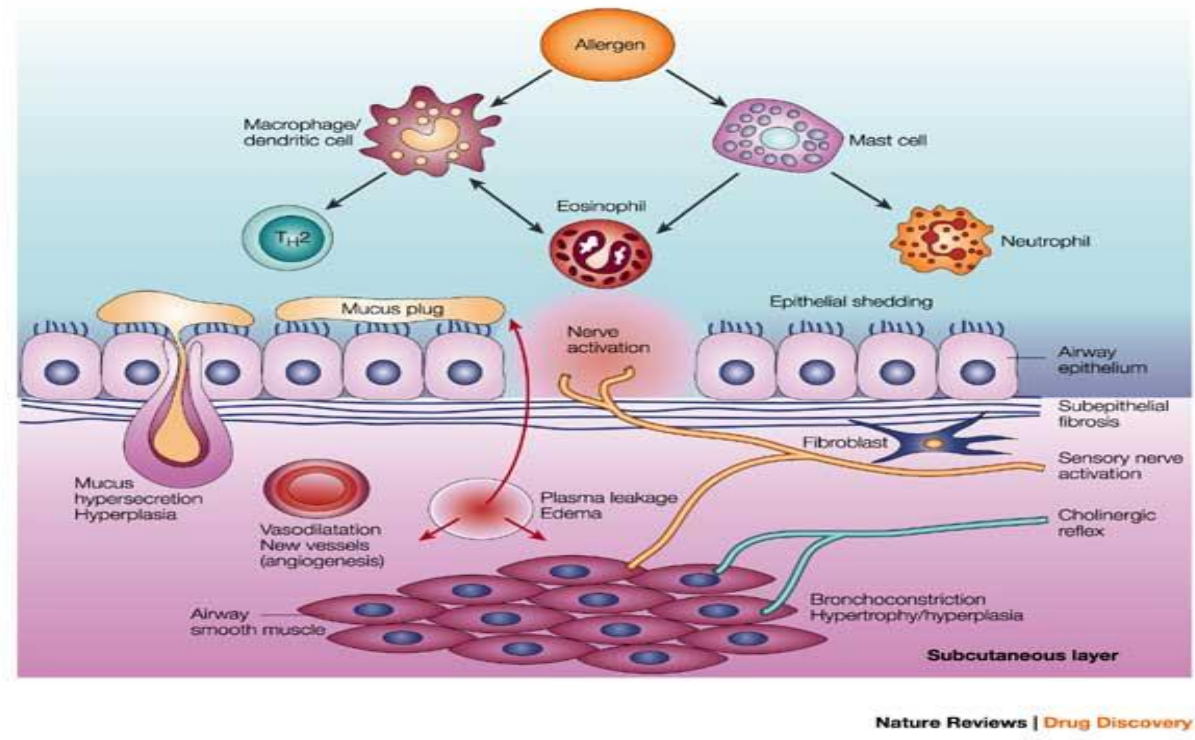
1.dendertic cells (DC).

2.macrophages.

3.B-cells.

Summary:

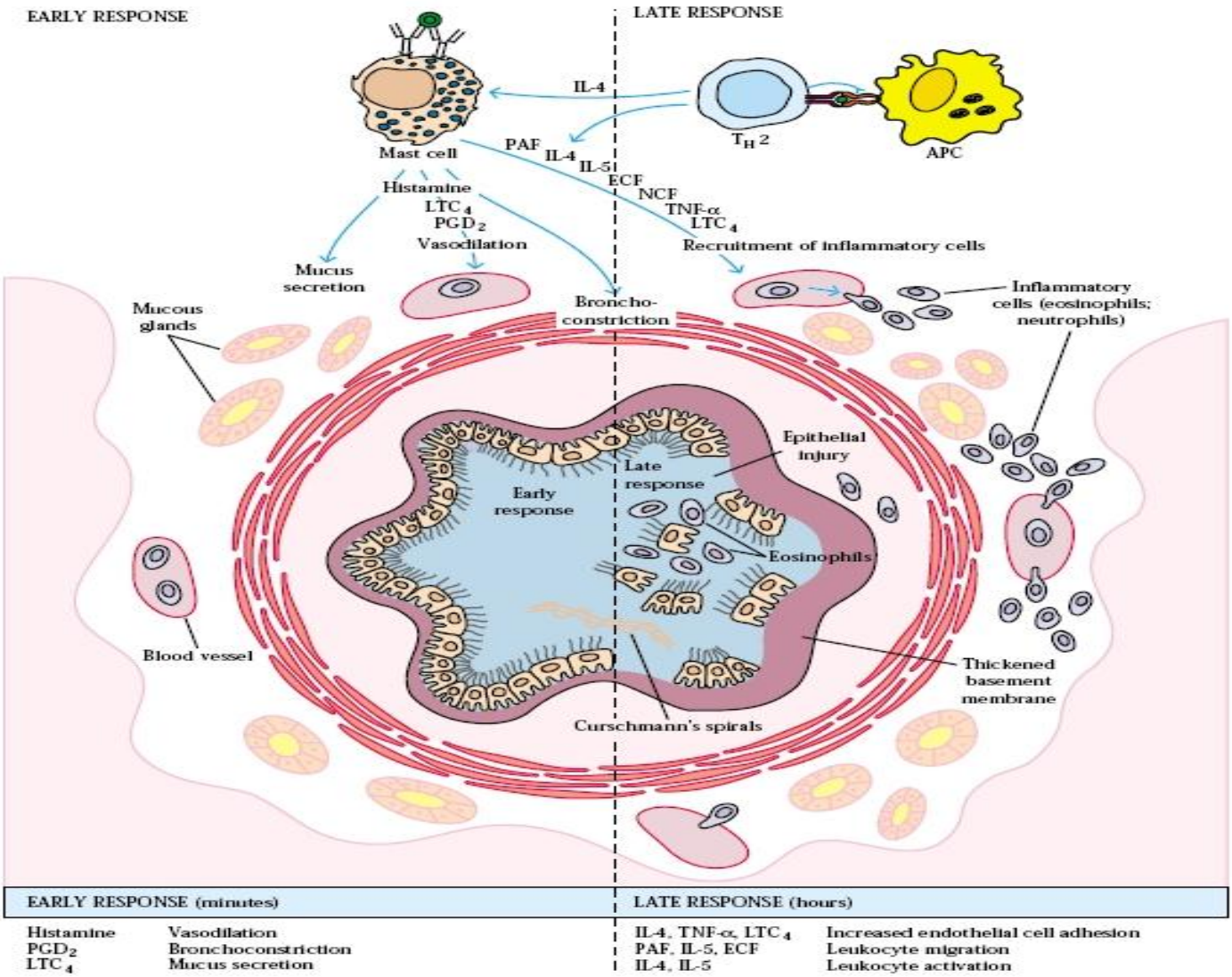
DC will present the antigens to a naïve T-helper cell (which is divided to TH1 and TH2) , the allergens will take TH2 root rather than TH1 because TH1 will produce IFN-gamma that actually inhibits the differentiation of B-cells after getting activated by TH0.When TH0 produce IL-4 TH2 will differentiate giving the specific IgE that will bind by a strong receptor to mast cells, after encountering with the allergen it produces mediators and that will lead to inflammation and mucus hyper secretion.



- **Asthma results from complex interactions among the inflammatory cells that involve:**

1. **Airway epithelium**
2. **Nervous system**
3. **Bronchial smooth muscles**

Response to allergen occur in two phases



PGD2: Prostaglandin D2 PAF: Platelet activating factor NCF: Neutrophil chemotactic factor

LTC4: Leukotriene cell 4 ECF: eosinophil chemotactic factor

Early allergic response:

1. **Occurs within minutes**
2. **Manifests clinically as:**
   - **Bronchial constriction**
   - **Airway edema**
   - **Mucus plugging**
   - **Is reversible and responds to bronchodilators**

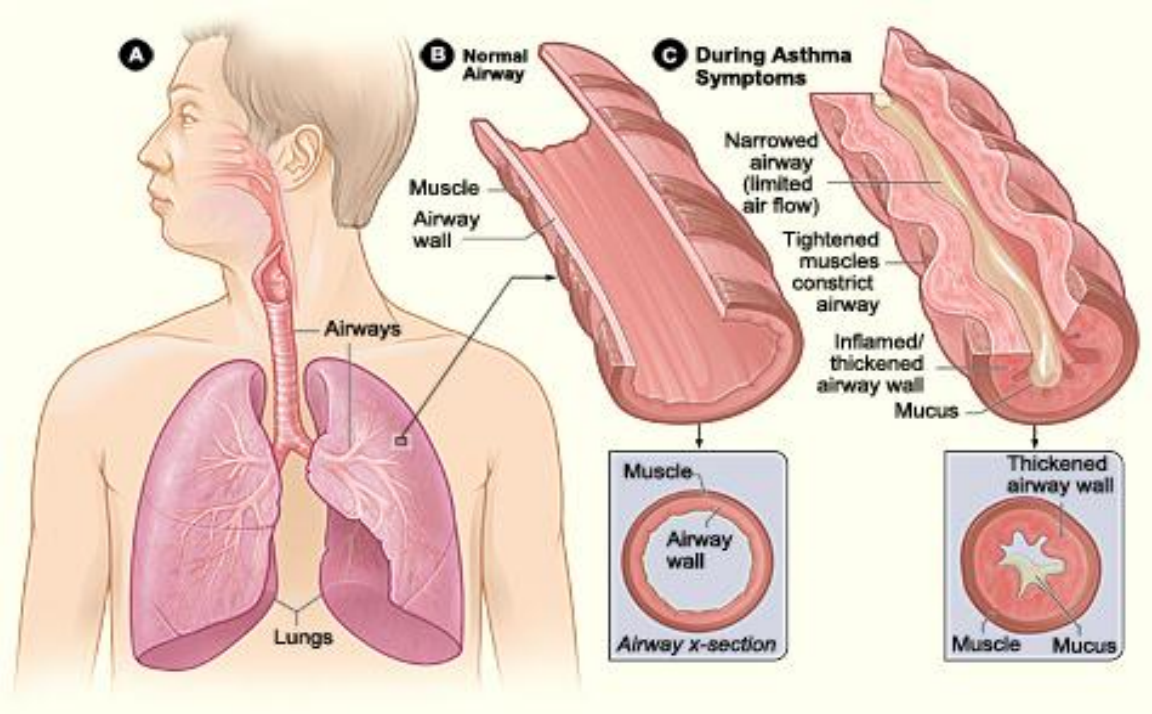
Late allergic response:

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)

Notes:

- Treating early response does not necessarily mean that late response won't occur, although it reduces the symptoms caused by mediators secreted by mast cell.
- Asthma has no cure we are only dealing with signs and symptoms and basically we are trying to reduce the severity of them (bronchodilators and steroids).
- Curschmann's spirals in late response is squamous epithelium with mucus.



- **Factors contributing in airway obstruction leading to difficulty in breathing:**

1) Smooth muscles of bronchioles (constructed muscles)
2) Epithelial wall (inflamed wall= thickened\narrowed)
3) Mucus glands (hypersecretion of mucus= obstruction)

Th2 cells and role of cytokines in allergic asthma

- Allergens drive T-cells towards Th 2 type: **(go back to diagram 2)**
- **Th2 secrete the cytokines:**
- **IL-4, IL-5, IL-9 & IL-13** **(they play an important role in hypersensitivity type 1):**

  which promote:

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

1) IL-4 (Interleukin—4) :

The main role of IL-4 is carried out during the initial priming of Th2 cells (when TH0 differentiate to give TH2) :

1. Regulates isotype switching in B cells to IgE (Premature B-cells initially form and express IgM and IgD together then isotype switching will occur depending on the allergen and immune response to (IgE,IgG..etc))
2. Induces MHC II on antigen-presenting cells
3. Induces adhesion molecule expression
4. Activate mast cells and eosinophils (major inflammatory cells in extrinsic asthma)

○ 2) IL-13 (Interleukin—13) :

1. IL-13 induces inflammation
2. Stimulates mucus hyper-secretion
3. Induces sub-epithelial fibrosis (in later stages when remodeling occurs)

○ 3) IL-9 (Interleukin—9) :

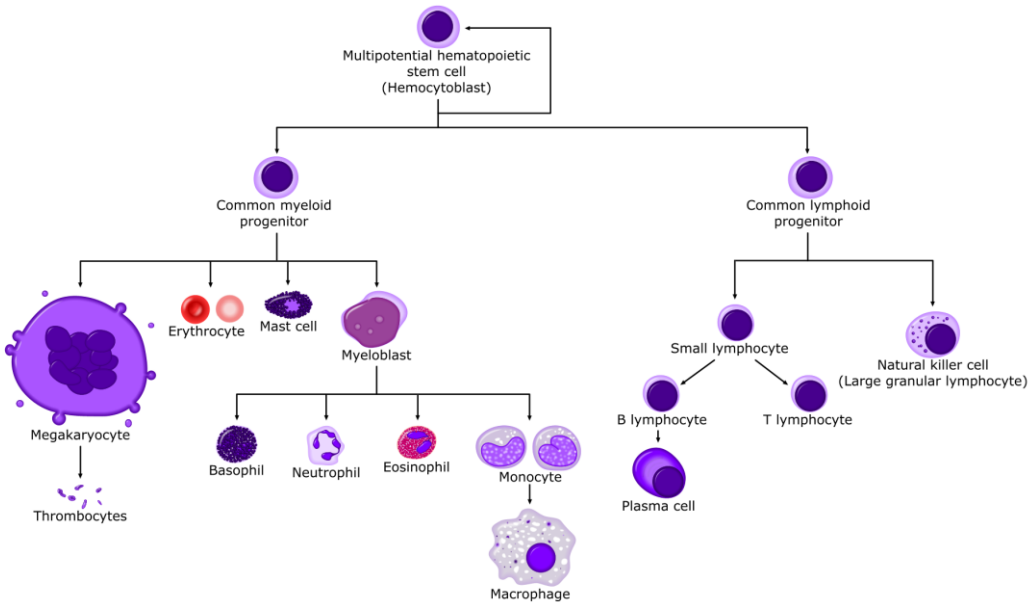
- Associated with bronchial hyper-responsiveness
- In mice it increases:
  - Lung eosinophilia
  - Serum IgE levels
- Both are clinical features of asthma

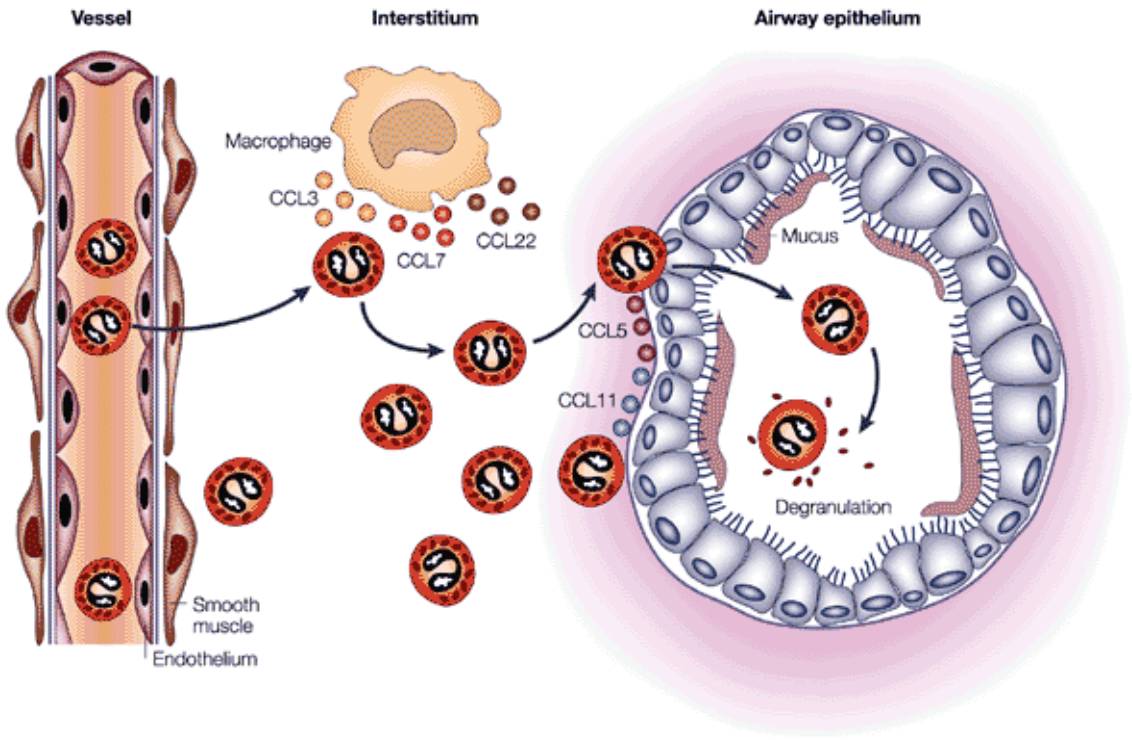
○ 4) IL-5 (Interleukin—5) :

1. IL-5 induces increased production, terminal differentiation and activation of eosinophils
2. Release of eosinophils from the bone marrow into circulation
3. B-cell growth factor and increases Ig secretion

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
- Eosinophils are produced from myeloid lineage.





-We have very important chemokines that help in the movement of the inflammatory cells from side to another.

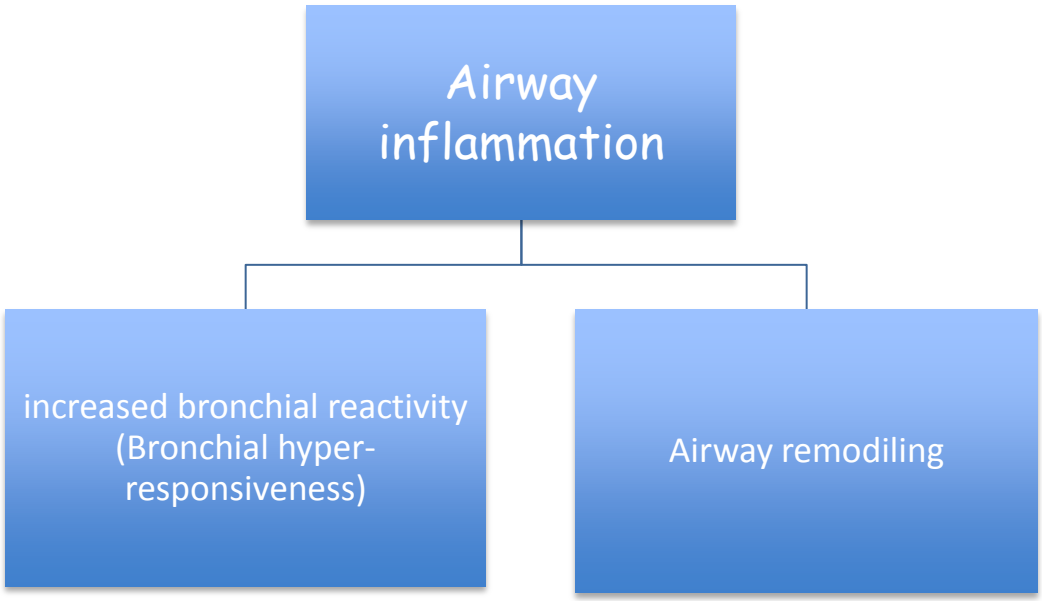
-Here we have important chemokines for eosinophils (CCL3-CCL7-CCL22-CCL5-CCL5)

-Chemokines here will bring eosinophils from blood vessels to airway epithelium where they degranulate releasing their lytic enzymes that will affect the inflammation inside the lumen.

Role of regulatory T – cells:

- **(Regulatory T cells =T-suppressor cells =Treg cells) suppress the effector mechanisms that induce asthmatic symptoms**
- **Asthmatics may lack functional regulatory T cells that can inhibit an asthmatic response**
- **Regulatory cells have special markers such as (CD44-CD4-CD25)**

Activation of inflammatory cells (mast cells, eosinophils etc,) is a major inducer of Airway inflammation (Especially in late phase of allergic asthma)



○ 1. Outcome of increased airway reactivity

○ **Predisposes patients to develop asthma attacks on exposure to <u>non-specific irritants:</u>**

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

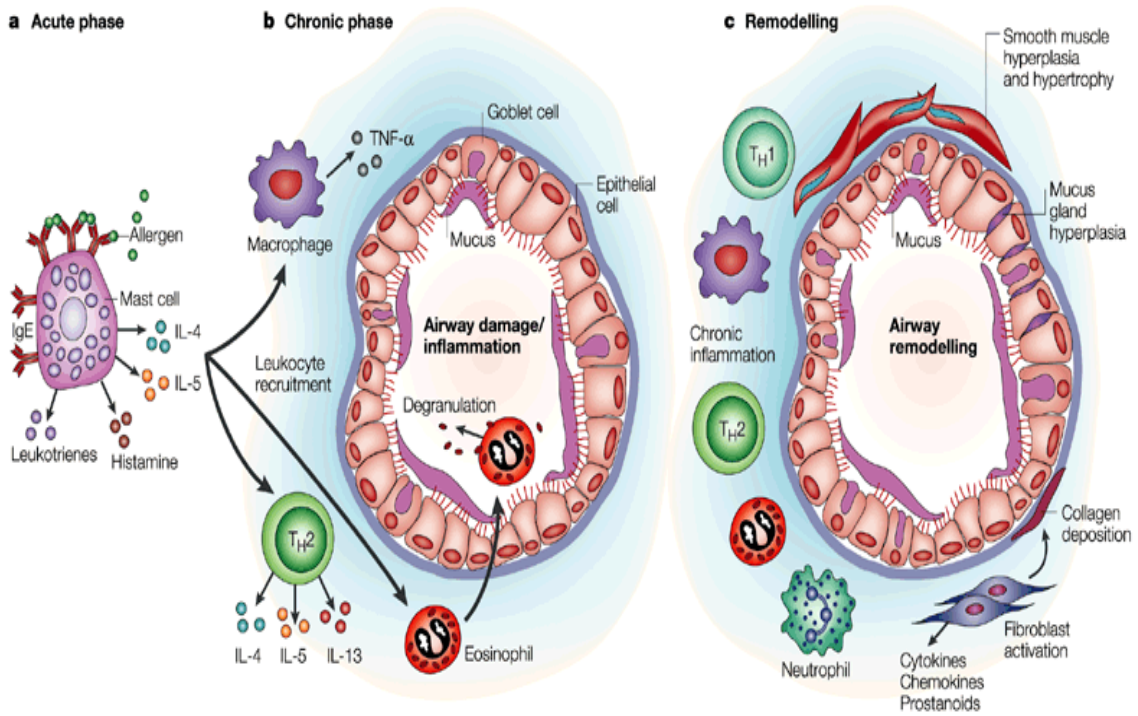
(Those are non-specific irritants which means they don't cause asthma they are NOT allergens, but they are considered as triggers of asthma attacks in people with asthma)

○ 2. Outcome of airway remodeling

Products of the inflammatory cells act on :

1. **Airway smooth muscle cells**
2. **Lung fibroblasts (lead to fibrosis)**
3. **Mucous glands**

○ **and cause : Airway Remodeling .The outcome of airway remodeling can ultimately lead to <u>fibrosis and irreversible</u> airway obstruction in some patients (cause the genetic behavior differ from patient to another even to treatments)**



A) Acute phase is reversible and we can use bronchodilators.

B) Steroids are used in case of chronic phase and also it is reversible.

C) Remodeling is irreversible so it doesn't respond to any type of treatment and chronic inflammation will be found, also cytokines ,chemokines and prostanoids will be involved and produced by lung fibroblasts.

Take home message

- **Asthma is characterized by episodic reversible airway obstruction**
- **Classified in 2 types: intrinsic & extrinsic**

  In the extrinsic type allergens drive T-cells into Th2 pattern
- **Airway inflammation is a hallmark finding in the asthmatic lung**
- **Inflammatory cells lead to increased bronchial reactions & airway remodeling which irreversible**