Immunology of Asthma

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Immunology of Asthma

- Objectives:
  - ✓ To recognize 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

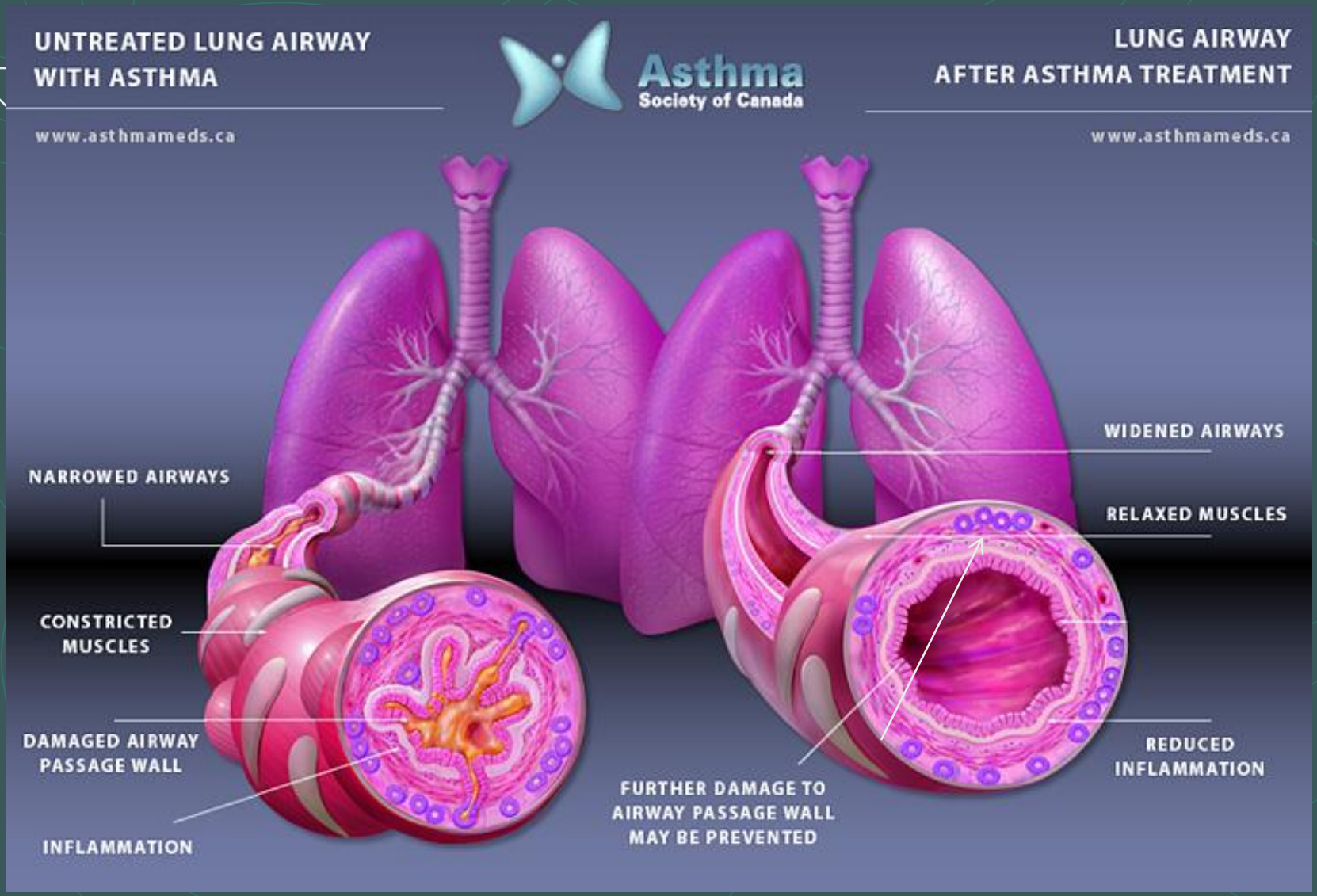
Asthma is a clinical syndrome characterized by:

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



Classification of Asthma

1. Intrinsic (non-atopic)

2. Extrinsic (atopic)

(**Atopy**: genetic tendency to develop allergy)

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:

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

Induction of Allergic Inflammation

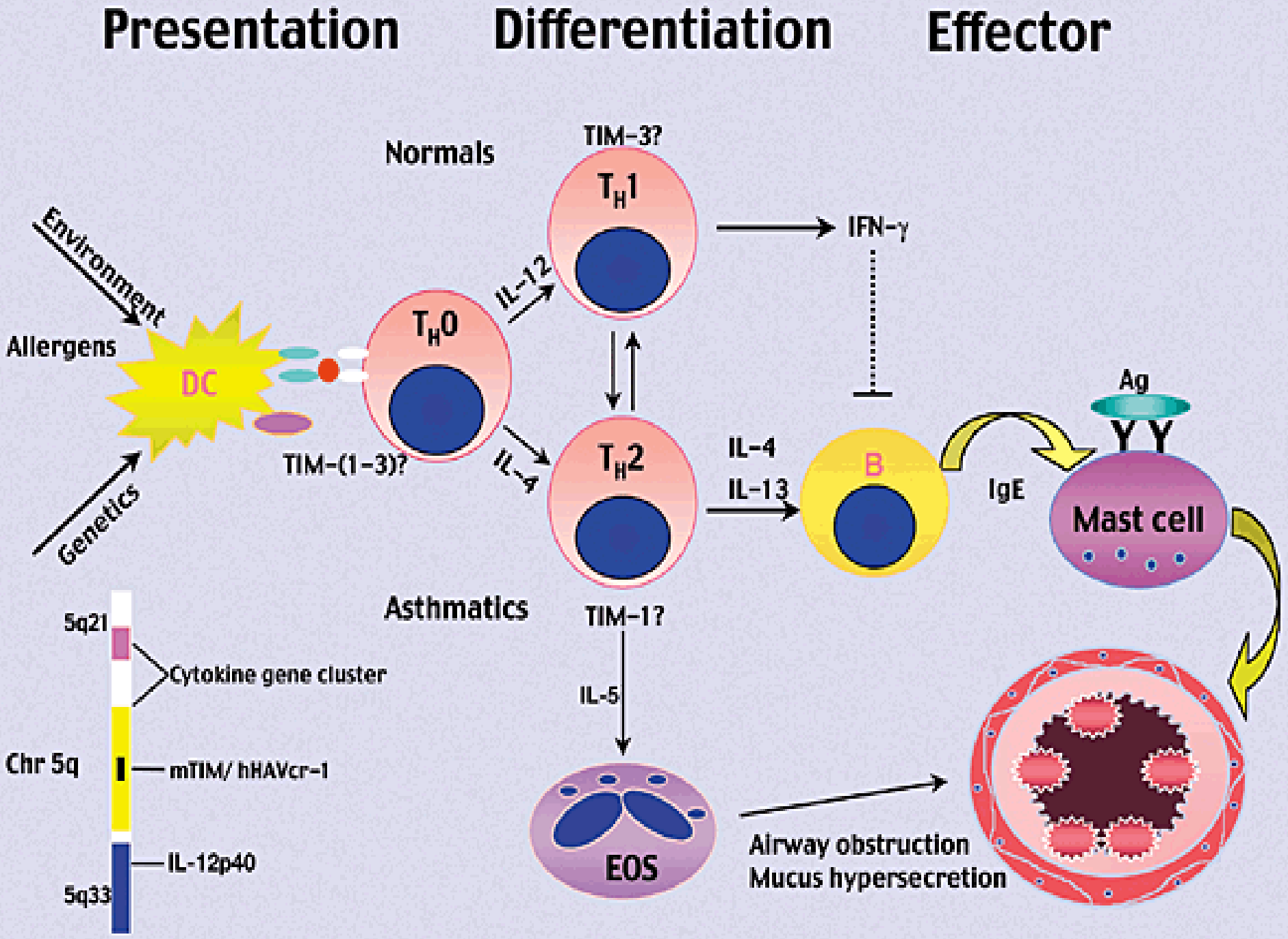
- **In predisposed individuals:**

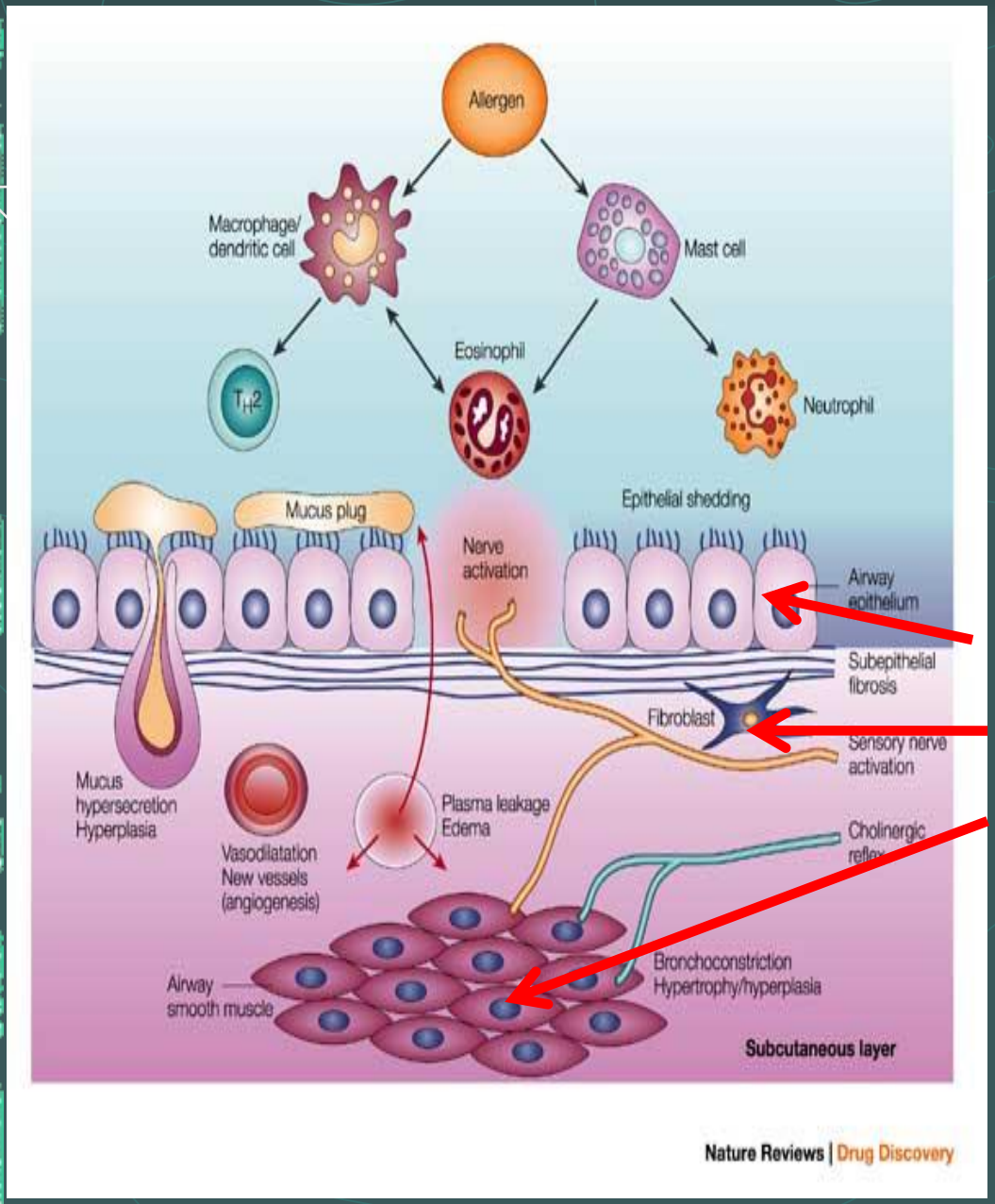
  First encounter with allergens stimulates production of allergen specific IgE antibodies by B cells (allergic sensitization)

- **Subsequently:**

  Inhaled allergens activate sub-mucosal mast cells in the lower airways resulting in release of mediators instantly causing:

  1. Recruitment of eosinophils & pro-inflammatory cells
  2. Bronchoconstriction

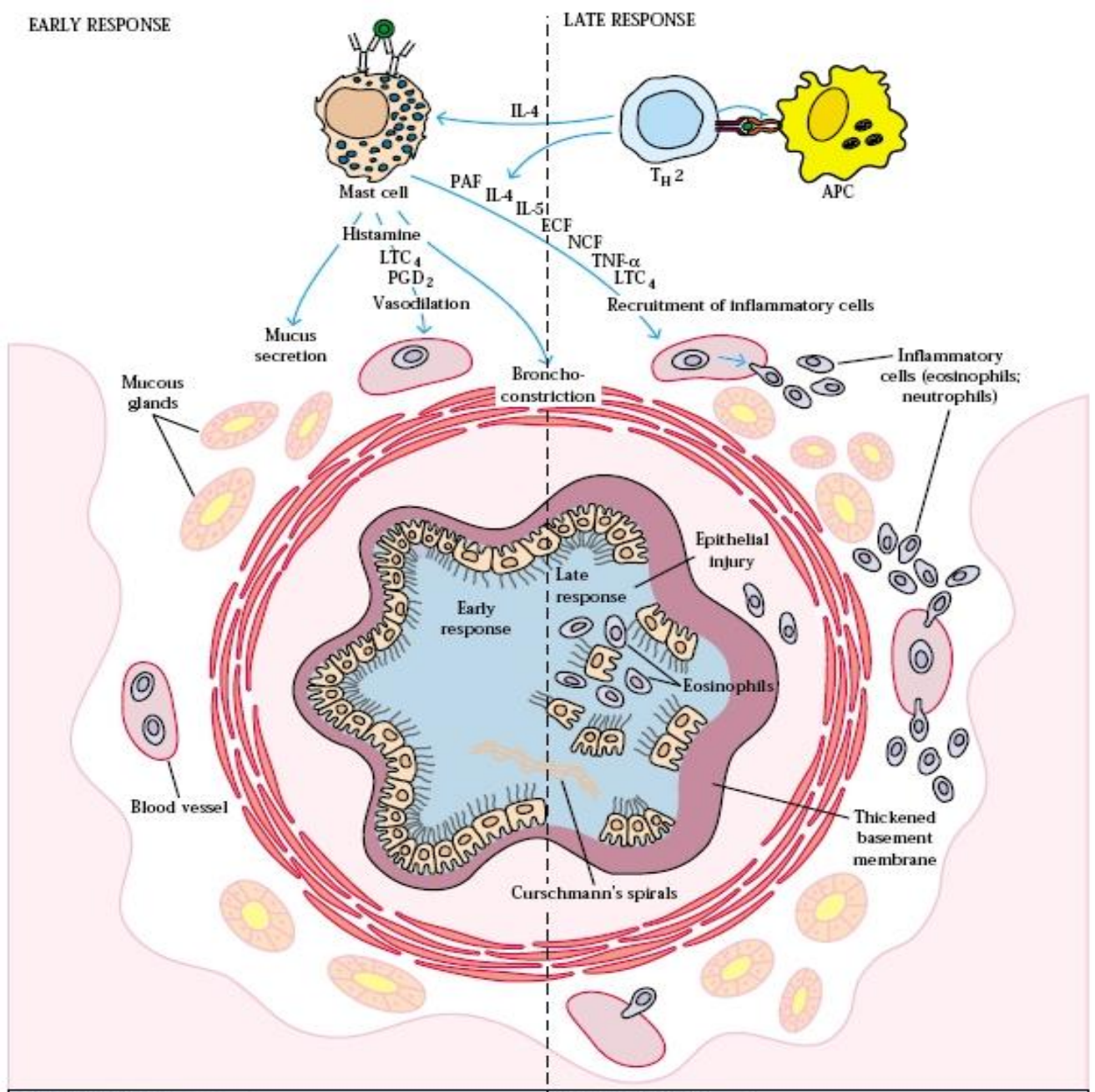

Presentation
Differentiation
Effector
Normals
TIM-3?
T_H1
IFN-γ
Environment
Allergens
DC
T_H0
IL-12
TIM-(1-3)?
IL-4
T_H2
IL-4
IL-13
B
Ag
IgE
Mast cell
Genetics
Asthmatics
TIM-1?
IL-5
EOS
Airway obstruction
Mucus hypersecretion
5q21
Cytokine gene cluster
Chr 5q
mTIM/ hHAVcr-1
IL-12p40
5q33



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



Early allergic response

1. Occurs within minutes
2. Manifests clinically as:
   - Bronchial constriction
   - Airway edema
   - Mucus plugging

Is reversible and responds to bronchodilators

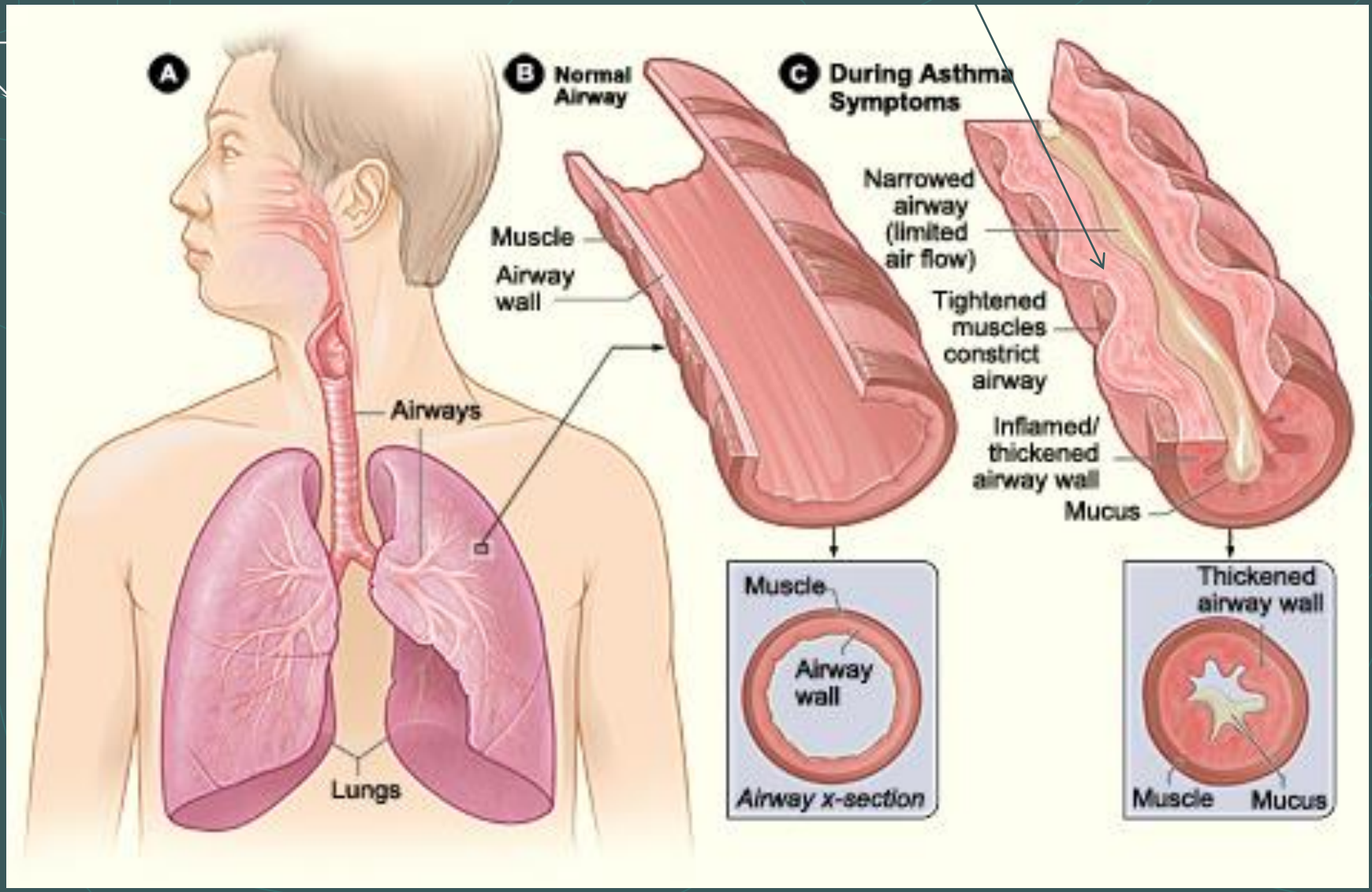
Late allergic response:

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)

Factor contributing to airflow obstruction leading to difficulty in breathing include:



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 in allergic asthma

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

Role of IL-13 in allergic asthma

1. IL-13 induces inflammation
2. Stimulates mucus hyper-secretion
3. Induces sub-epithelial fibrosis

IL-9 and asthma

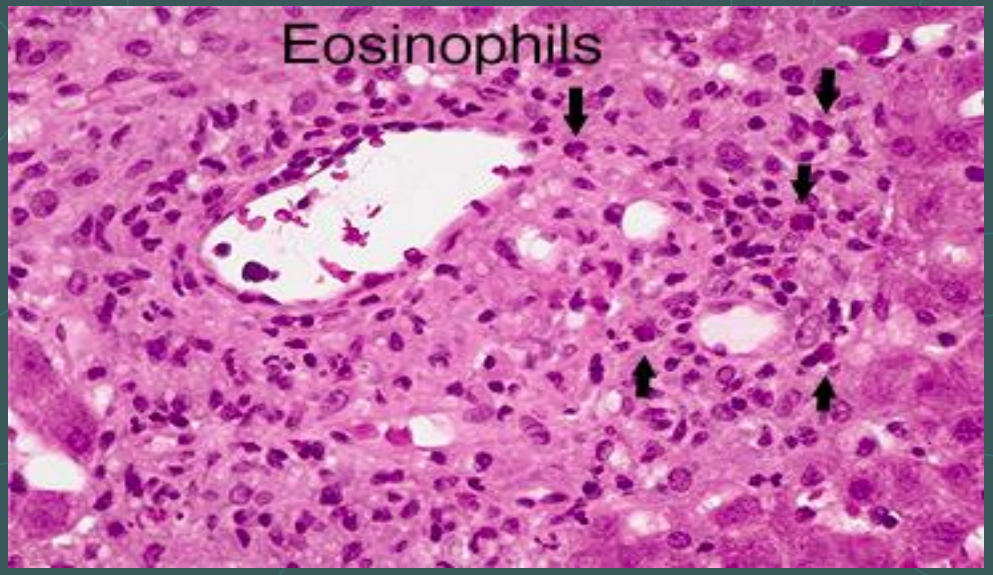
- Associated with bronchial hyper-responsiveness
- In mice it increases:
  - Lung eosinophilia
  - Serum IgE levels
- Both are clinical features of asthma

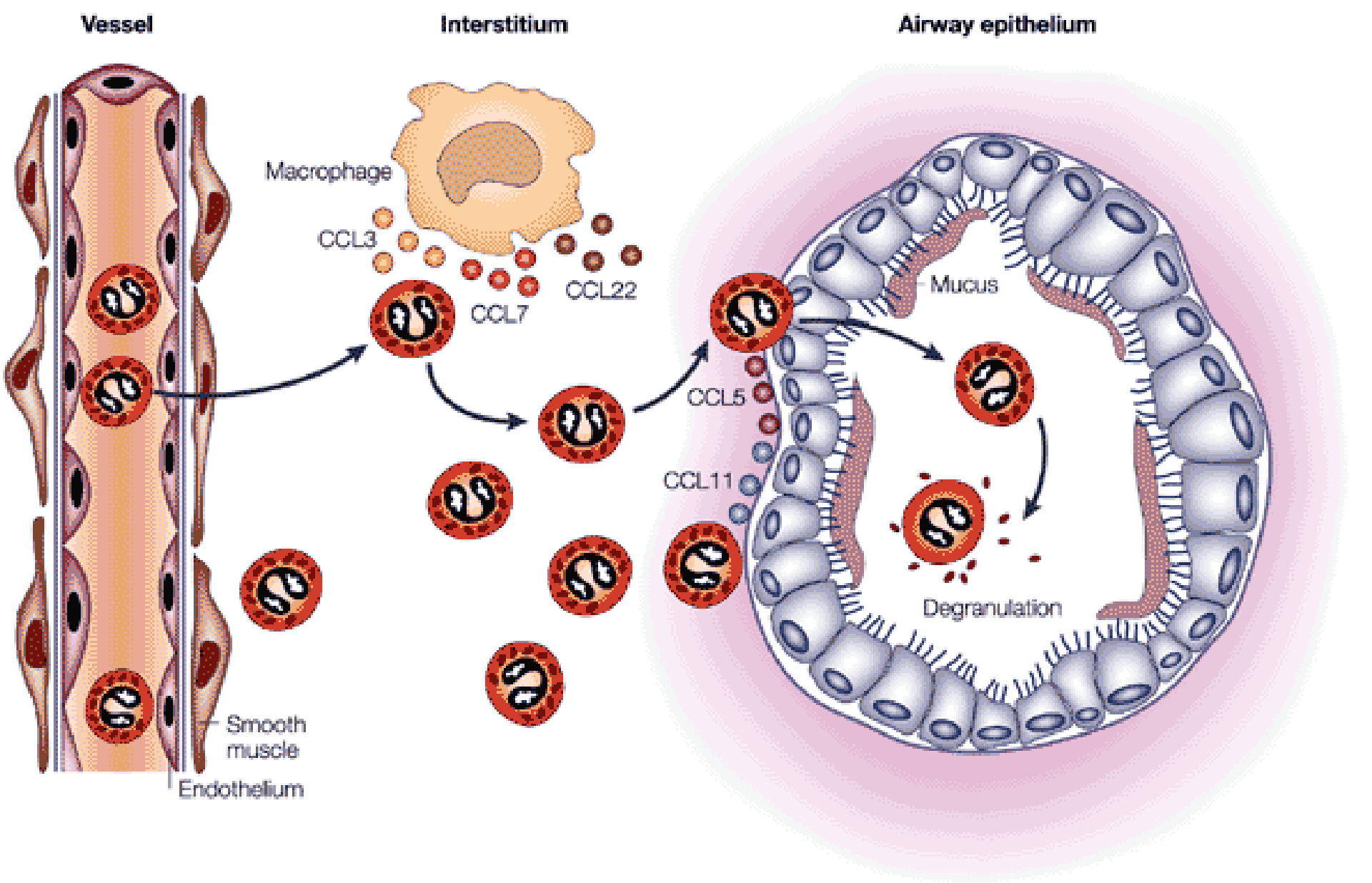
Role of IL-5 in allergic asthma

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



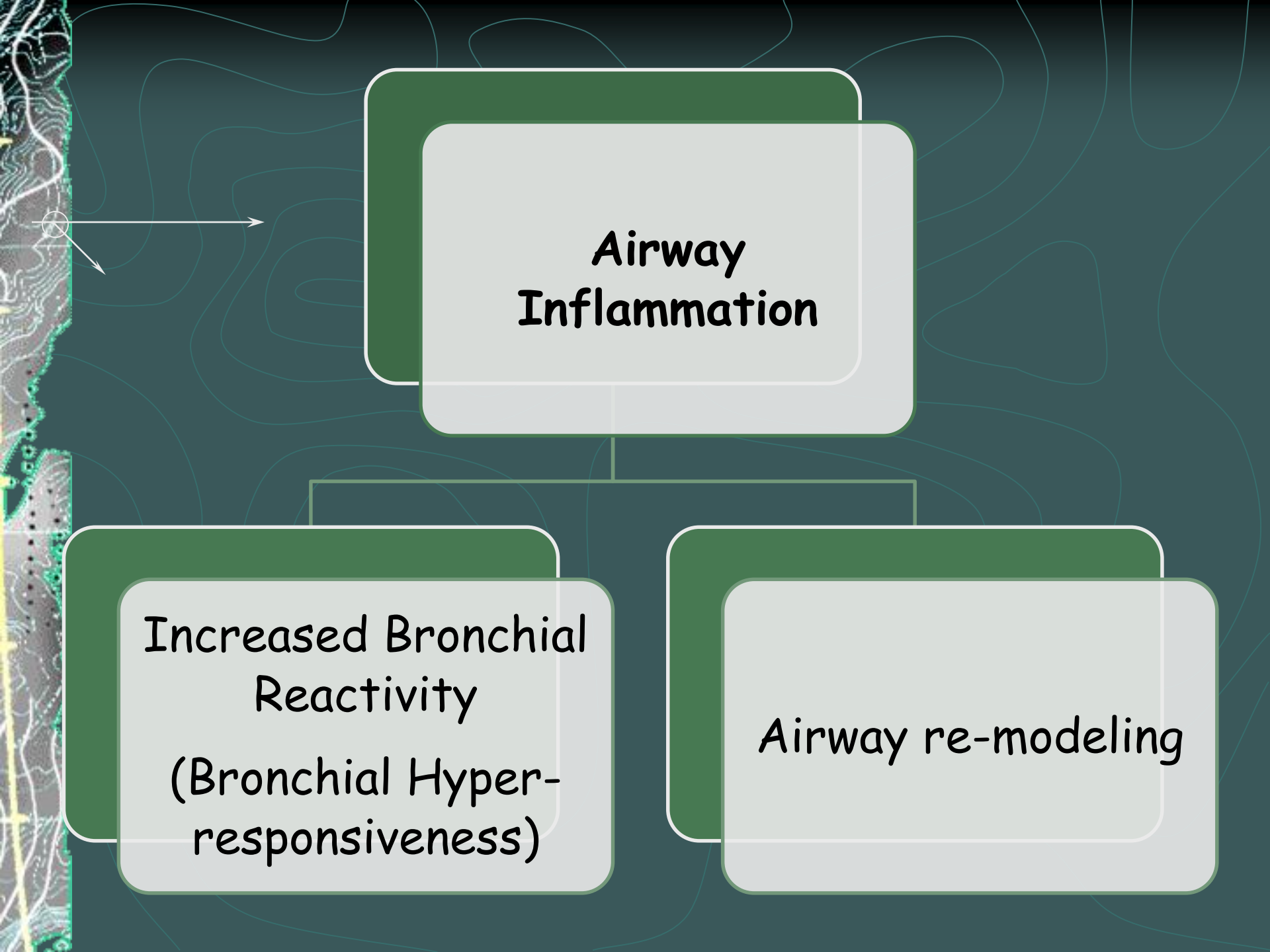

Vessel
Interstitium
Airway epithelium
Macrophage
CCL3
CCL7
CCL22
CCL5
CCL11
Mucus
Degranulation
Smooth muscle
Endothelium

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
Increased Bronchial Reactivity
(Bronchial Hyper-responsiveness)
Airway re-modeling

Outcome of increased airway reactivity

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

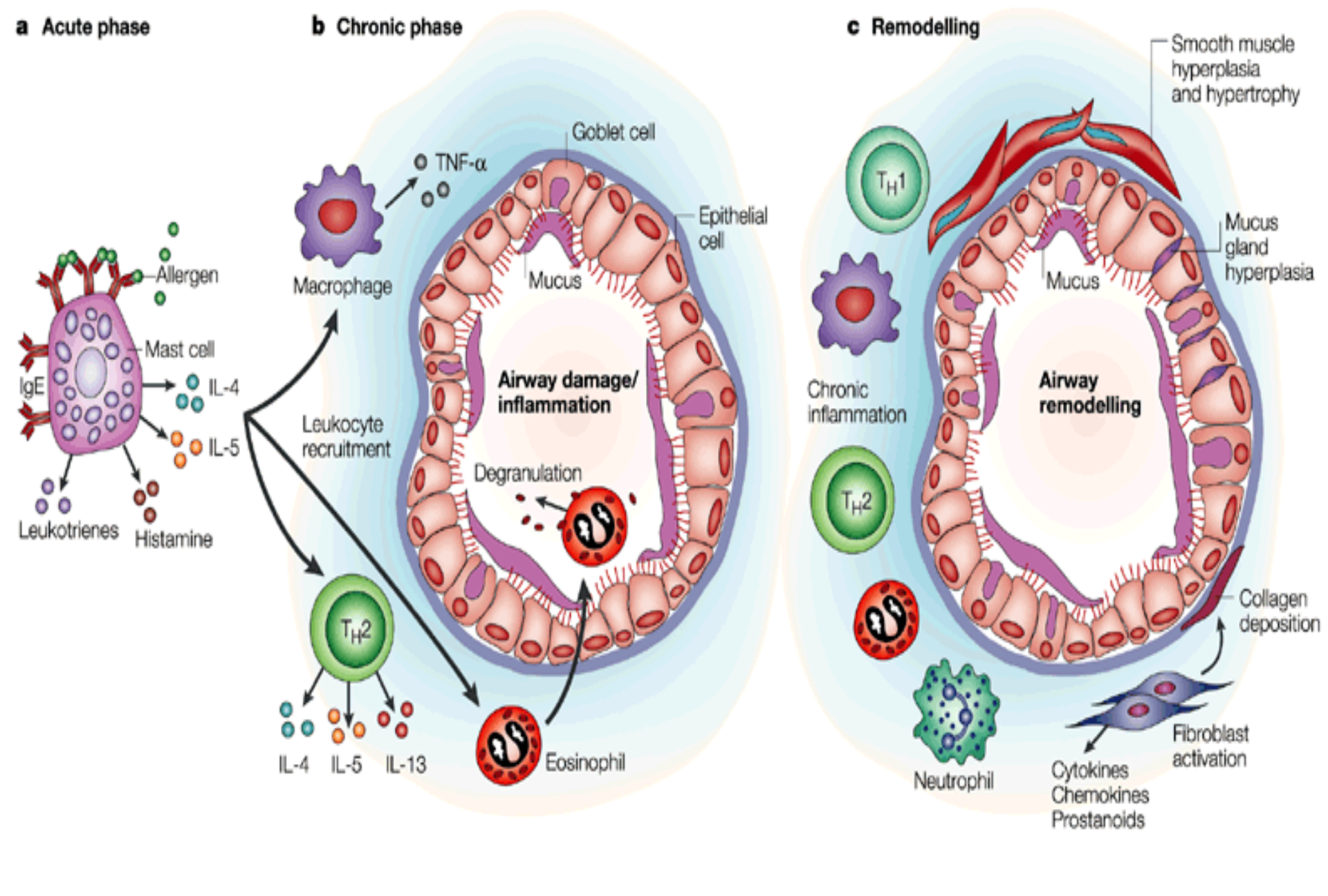
1. Chemical irritants
2. Smoke & strong perfumes
3. Sulphur dioxide & air pollutants
4. Viral and bacterial respiratory infections

Products of the inflammatory cells act on :

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

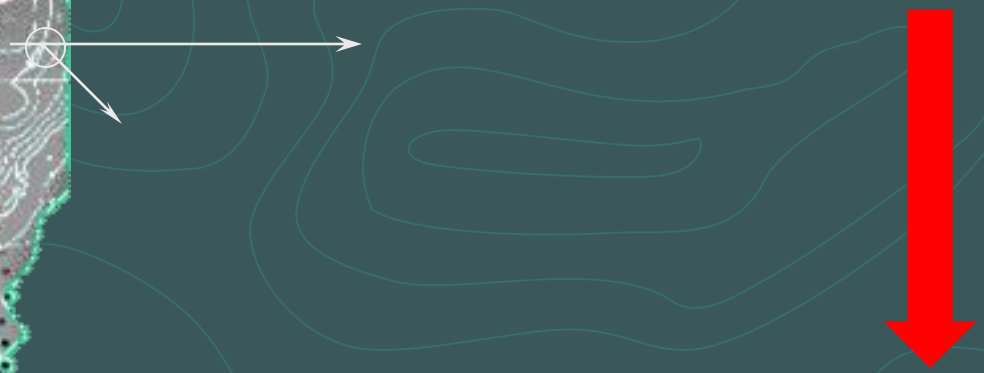
and cause :

Airway Remodeling



Airway remodeling

Outcome of airway remodeling

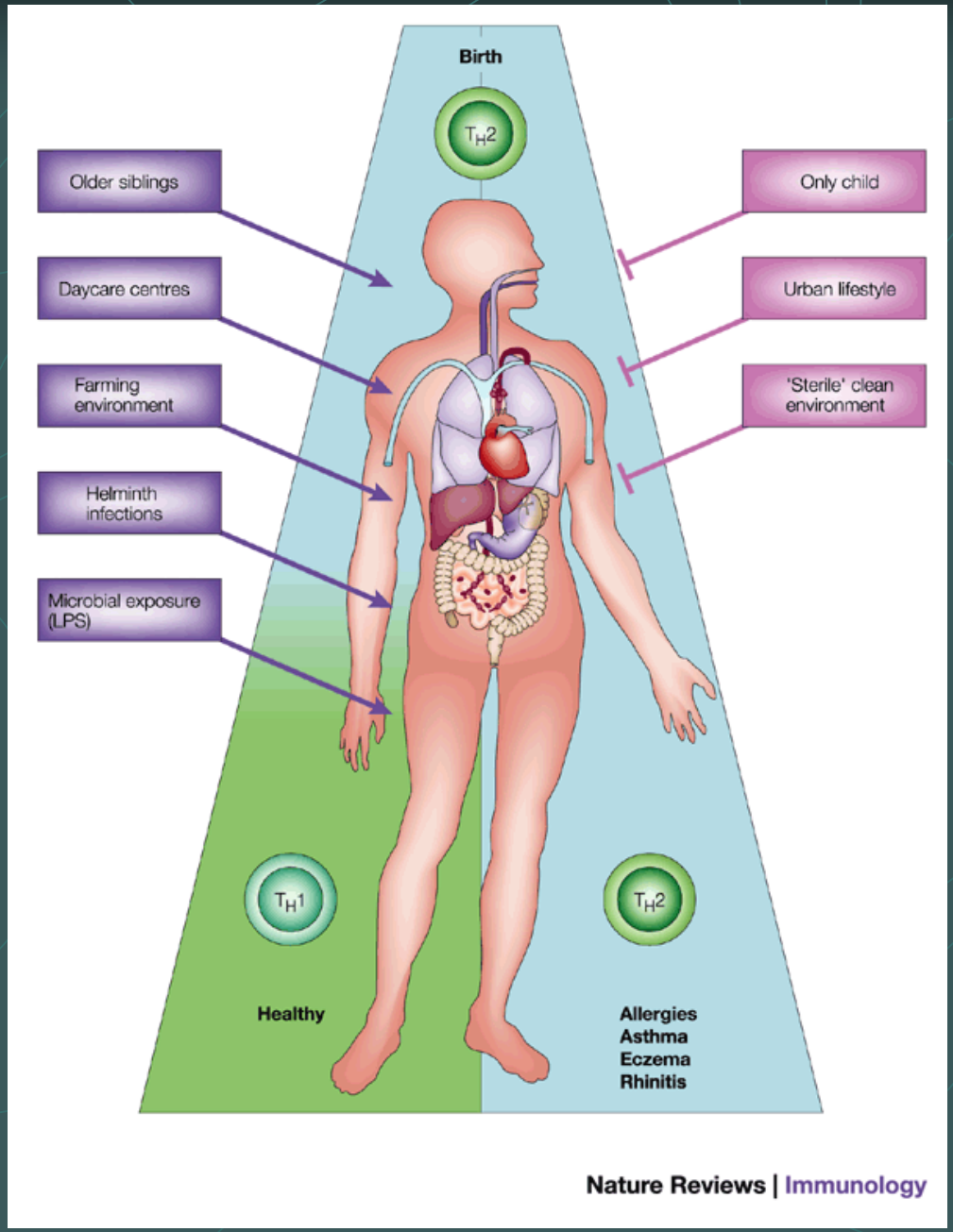


Can ultimately lead to fibrosis and irreversible airway obstruction in some patients

Take home message

1. Asthma is characterized by episodic reversible airway obstruction
2. Classified in 2 types: intrinsic & extrinsic
3. In the extrinsic type allergens drive T-cells into Th2 pattern
4. Airway inflammation is a hallmark finding in the asthmatic lung
5. Inflammatory cells lead to increased bronchial reactions & airway remodeling which irreversible

THANK YOU


Birth
T_H2
Older siblings
Daycare centres
Farming environment
Helminth infections
Microbial exposure (LPS)
Only child
Urban lifestyle
'Sterile' clean environment
T_H1
T_H2
Healthy
Allergies
Asthma
Eczema
Rhinitis
Nature Reviews | Immunology