Immunology of Asthma

Color index
Red: Important
Grey: Extra information
Green: Notes
Pink: Girls slides
Orange: Boys slides

IMMUNOLOGY
TEAM 439

Objectives

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

Immunology of Asthma

Asthma: a chronic inflammatory disorder of the airways that causes recurrent episodes of wheezing, breathlessness, chest tightness and cough. (pathology)

Asthma is a clinical syndrome characterized by:

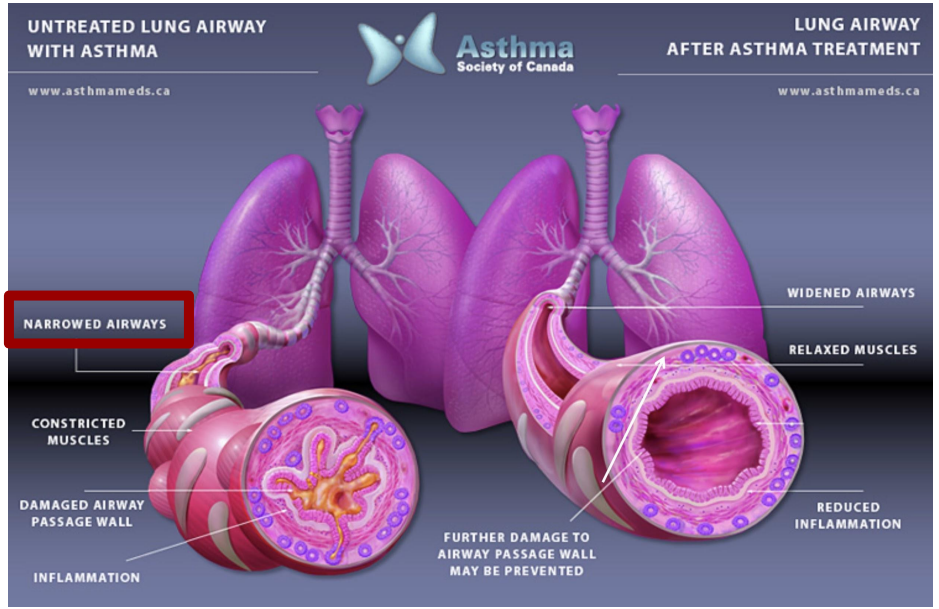
1. **Reversible** airway obstruction
2. Increased bronchial reactivity

Low threshold of sensitivity عنده يصير الشخص

3. Airway Inflammation

Symptoms of Asthma:

1. Breathlessness (difficulty in breathing)
2. Wheezing
3. Persistent cough
4. Chest tightness



Wheeze: is a high-pitched, musical, adventitious lung sound produced by airflow through an abnormally narrowed or compressed airway(s)

Classification of Asthma

Atopy: genetic tendency to develop allergy

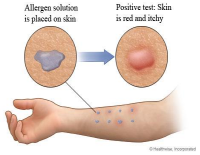
Non-atopic asthma Intrinsic

Not allergic asthma
Does not affect the immune system

Atopic asthma Extrinsic

Allergic asthma
Affects the immune system

Classification	Non-atopic asthma	Atopic asthma
Severity	More severe	Less severe
Prevalence	Older patients (10-33% of asthmatics), less common	60-90% children 50% adults
History of allergy	Not needed	Needed
Serum IgE	Normal	High
Skin test (skin prick test)	Negative	Positive (in 70-85%)
Family history	Non	May have



Role of Allergens in Asthma

Allergens sensitization is linked to the risk of developing asthma.

Allergen: an antigen that triggers an allergic reaction that are mostly proteins**.** It's the main cause **of hypersensitivity type 1.**

Types of allergens

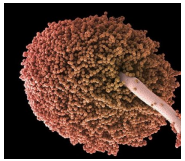
Indoor allergens

House dust mites

Domestics pets (car fur and dander)

Cockroaches (insects)

Molds (fungal spores)



Outdoor allergens

Grass pollens

Tree pollens

Weed pollens

Fungal spores (e.g. Alternaria)

Fungal spores can be considered as indoor and outdoor allergens

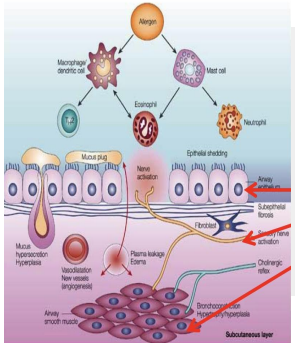
APCs & Allergic response

There are 2 subsets of DC (APC's) in the lungs:

01 **Myeloid DC** → Help in the development of asthma symptoms

02 **Plasmacytoid DC** → Aid in the respiratory tolerance to allergens

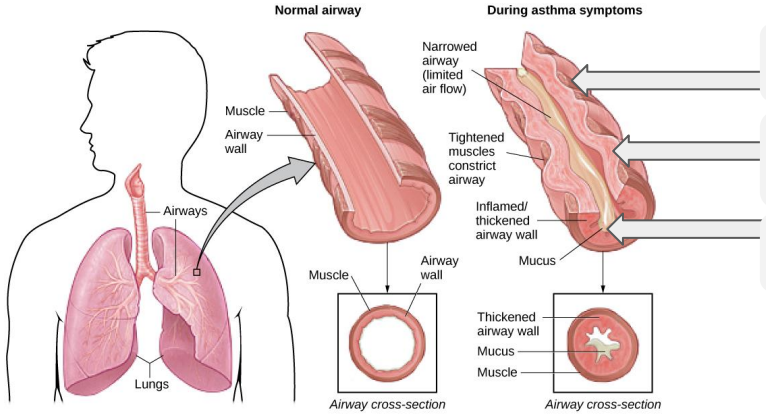
APC= Antigen Presenting cell
DC= dendritic cell



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

1.Airway epithelium (inflamed)
2.Nervous system (inflamed)
3.Bronchial smooth muscles (constriction)

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



Smooth muscles of bronchioles (constructed muscles)

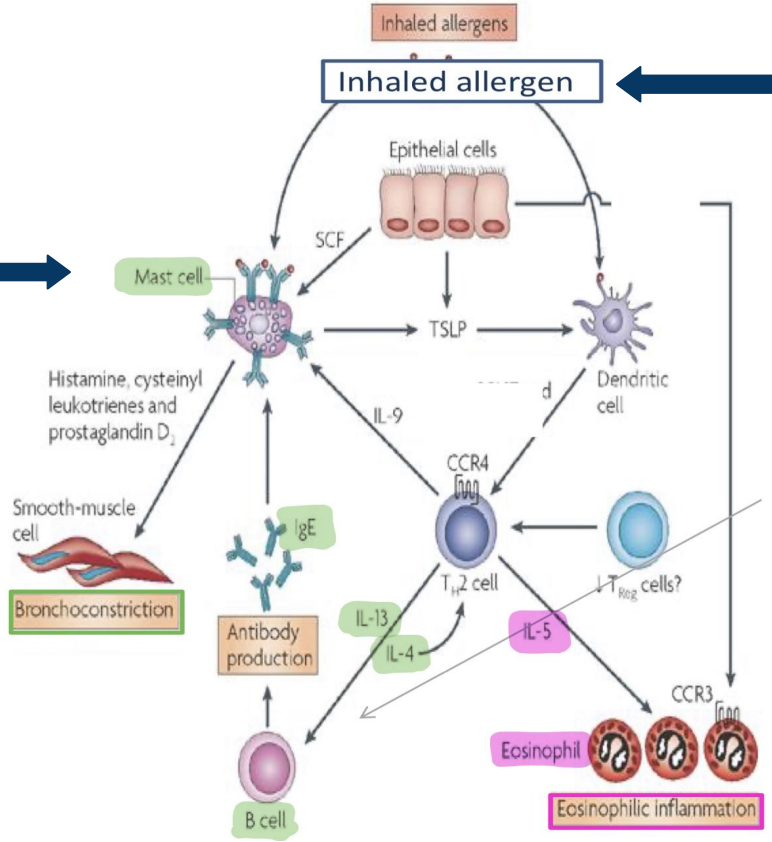
Epithelial wall (inflamed wall= thickened\narrowed)

Mucus glands (hypersecretion of mucus = obstruction)

Allergic response

In susceptible individuals (vulnerable to allergen), *first* encounter with allergens **activate B-cells to produce IgE.**

Subsequently, Inhaled allergens activate **submucosal mast cells** in the lower airways resulting in release of mediators within seconds causing:
1. Bronchoconstriction
2. Influx of eosinophils & other inflammatory cells



Explanation:
Allergen→antigen presenting cell → transform T cell to TH2 → TH2 will release :

1) IL-4, IL-13 → interact with B cell → release IgE → mast cell → release histamine → CONTRACTION OF BRONCHI

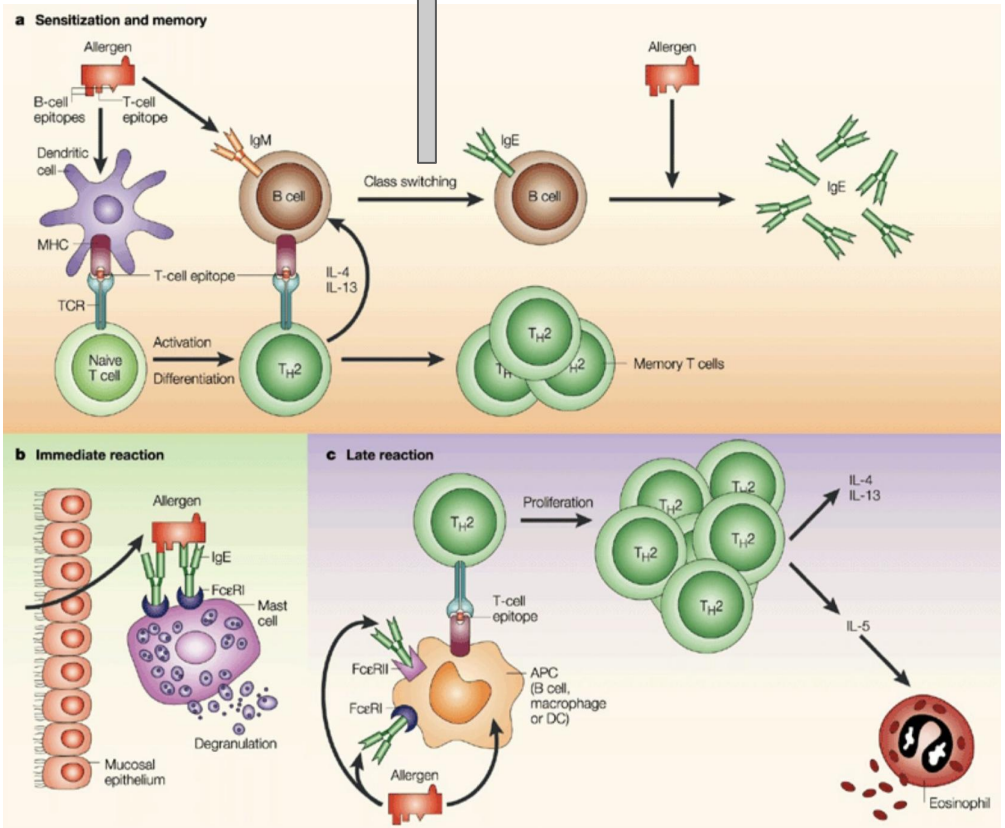
2) IL-5 → production of eosinophils → granules damage the airway epithelium → produce histamine → CONTRACTION OF BRONCHI

Be careful, the main cytokines responsible for the constriction are IL-4 and 13. IL-5 has an indirect effect. It's main function is explained later.

Asthma Pathophysiology **It's very helpful**

Allergic response

Class switching is when the IgM on the B cells switch to IgE



Extra info, focus on highlighted

a | Sensitization and memory. Initial contact with an allergen of the respiratory tract, might favour allergen uptake by potent antigen-presenting cells (for example, dendritic cells) and/or immunoglobulin-mediated capture by specific B cells. If T helper 2 is acquired, cytokines such as interleukin-4 (IL-4) and IL-13 will be produced that will cause immunoglobulin-class switching of specific B cells to immunoglobulin E (that is sensitization). Sensitization leads to the establishment of IgE+ memory and allergen-specific memory T cells. Subsequent repeated allergen contact will boost IgE+ memory that receive T-cell help to produce increased levels of allergen-specific IgE antibodies.

b | Immediate reaction. The crosslinking of effector-cell-bound IgE by allergens leads to the release of biologically active mediators (histamine, leukotrienes) by means of degranulation and, so, to the immediate symptoms of allergy. → This leads to: vasodilation bronchospasm

c | Late reaction. This is caused by the presentation of allergens to T cells, which become activated, proliferate and release proinflammatory cytokines (for example, IL-4, IL-5 and IL-13). This process might be enhanced by the IgE-mediated presentation of allergens to T cells. TH2 cytokines (for example, IL-5) induce tissue eosinophilia and the release of inflammatory mediators from eosinophils. APC, antigen-presenting cell; DC, dendritic cell; TCR, T-cell receptor.

Allergic Response

Sensitization (first exposure)

- The allergen binds to the dendritic cells, driving it to activate Th2 lymphocytes.
- Th2 cells release multiple cytokines (IL-4-5-9-13).
- IL-4 activates B cells, causing a class switch and the release of IgE, which will bind to mast cells.

None of the symptoms will manifest in this phase because the mast cell **will not** release any mediators.

Response (Second exposure)

***Early response* (within minutes):**

- Allergen will bind with mast cells, releasing mediators such as histamine and prostaglandins.
- It's a ***reversible stage*** and responds to **bronchodilators**
- Manifests clinically as:
  - Bronchial constriction
  - Airway edema
  - Mucus plugging

***Late response* (4-10 hours after early response):**

- Activated Th2 release IL-5 that stimulate the production and release of eosinophils
- Th2 will release leukotrienes that cause smooth muscle contraction and attracts more immune cells (neutrophils, eosinophils, mast cells) to the area
- Results from inflammatory cells and activation of lymphocytes and eosinophils
- Responds to **steroids** (Anti-inflammatory drugs)

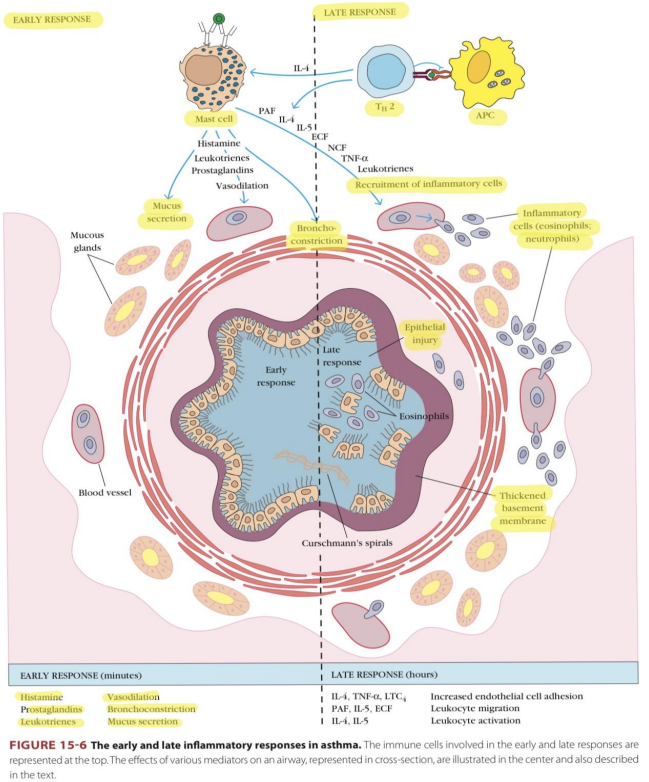


FIGURE 15-6 The early and late inflammatory responses in asthma. The immune cells involved in the early and late responses are represented at the top. The effects of various mediators on an airway, represented in cross-section, are illustrated in the center and also described in the text.

Compares early and late response

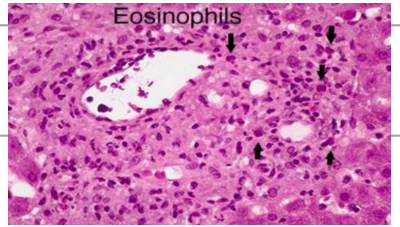
IMPORTANT SLIDE

TH2 cells & role of cytokines in allergic asthma

Allergens drive T-cells towards TH2 type → **TH2 secrete the cytokines IL(4,5,9,13)** → **Cytokines IL(4,5,9,13) promote the following:**

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

	Role in allergic asthma
IL4 (during the initial priming of TH2)	1-Regulates isotype switching in B cells from IgM to IgE. 2- Induces MHC II on APCs. 3-Induces adhesion molecules expression. 4- Activate mast cells & eosinophils.
IL5	1-induces an increase in eosinophil production in the bone marrow **(IL5 for production while IL4 for activation of eosinophils)** 2- release of eosinophils from the bone marrow into circulation.
IL13	1- induces inflammation. 2- stimulates mucus hypersecretion. 3- induces subepithelial fibrosis.
Eosinophils	1-Initiate asthmatic symptoms by causing tissue damage in the airways of the lungs. 2- production of eosinophils is inhibited by IL10 (Anti-inflammatory cytokine)
Regulatory T cells (T-Reg)	1- suppress the effector mechanisms that induce asthmatic symptoms. 2- asthmatics may lack functional regulatory T cells that can inhibit an asthmatic response.



Airway Inflammation

Activation of inflammatory cells (mast cells and eosinophils) is a major inducer of **airway inflammation** which is a hallmark in asthmatic lung.

Airway Inflammation

Airway Remodelling

Change of the histology of the mucosa

تصير متقدمة مع الزمن وراح تزيد
اعراض الasthma

Bronchial hyperreactivity

Easily triggered bronchospasm

حساسية ال bronchus تصير عاليه ويسبب Asthma attack

Airway remodeling:

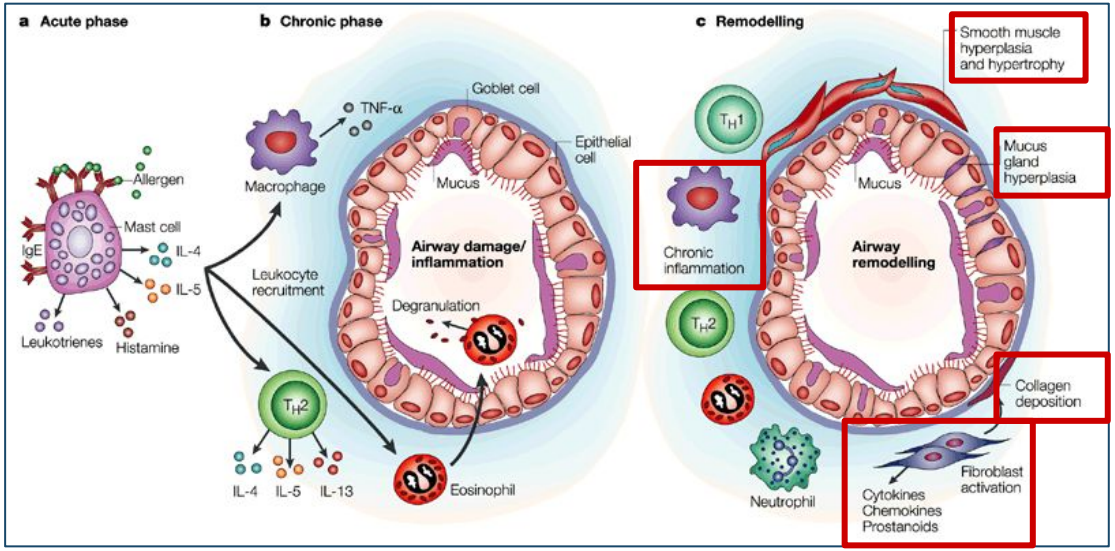


Diagram is explained in the next slide...

Airway remodeling (Healing)

Products of the inflammatory cells (cytokines) cause:

1- Airway smooth muscle cells ->
hyperplasia and hypertrophy due to repeated exposure of constriction that increases demand on cells

2- Lung fibroblasts -> hyperplasia (leads to fibrosis)

3- Mucous glands ->hyperplasia, activation of glands, and collagen deposition due to mucus hypersecretion

4- Fibroblast activation
5- Chronic Inflammation

في حالة ال Repeated exposure راح يصير فيه
chronic asthma with air remodeling
بسبب ال chronic Inflammatory process

Leads to fibrosis and <u>irreversible</u> airway obstruction

Bronchial hyperreactivity

Due to patients having increased airway reactivity, they're more likely to develop an asthma attack on exposure to **non-specific irritants:**

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

A patient with bronchial hyperreactivity should avoid exposure to nonspecific irritants to prevent developing asthma attacks.

* Allergens are specific because they will be recognized by the APCs which then will be presented to the naive T cell, etc.. (و هذي العملية تصير لكل الاشخاص)

Whereas non-specific irritants only cause asthma attacks to patients who have bronchial hyperreactivity such as asthmatics.

Take home messages

Asthma is characterized by episodic ***reversible*** airway obstruction

There are 2 types of asthma: ***extrinsic*** and intrinsic

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 reaction & airway remodelling which is ***not reversible***

Helpful videos

Asthma (Osmosis)

Asthma (Armando)

Quiz

Q1) Which of the following is a characteristic of asthma?							
A	Malaise	B	Reversible obstruction	C	Lung collapse	D	No dyspnea
Q2) Which of the following cytokines regulates isotype switching to igE?							
A	IL-4	B	IL-13	C	IL-7	D	IL-9
Q3) Which of the following cytokines is secreted by TH2 lymphocytes?							
A	IL-2	B	IL-3	C	IL-6	D	IL-9
Q4) Which of the following is a characteristic of non-atopic asthma?							
A	Majority of asthmatics	B	Positive skin test	C	Family history of asthma	D	Normal serum level of IgE
Q5) Which type of drug is appropriate to treat an asthma attack in its early response?							
A	Steroids	B	Anti-inflammatory	C	Bronchodilator	D	Aspirin

Q1) B Q2) A Q3) D Q4) D Q5) C

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