MEDICINE
KING SAUD UNIVERSITY

Revised by
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Respiratory Block

Lecture One

Immunology of Asthma

IMMUNOLOGY

436's TEAMWORK

Objectives:

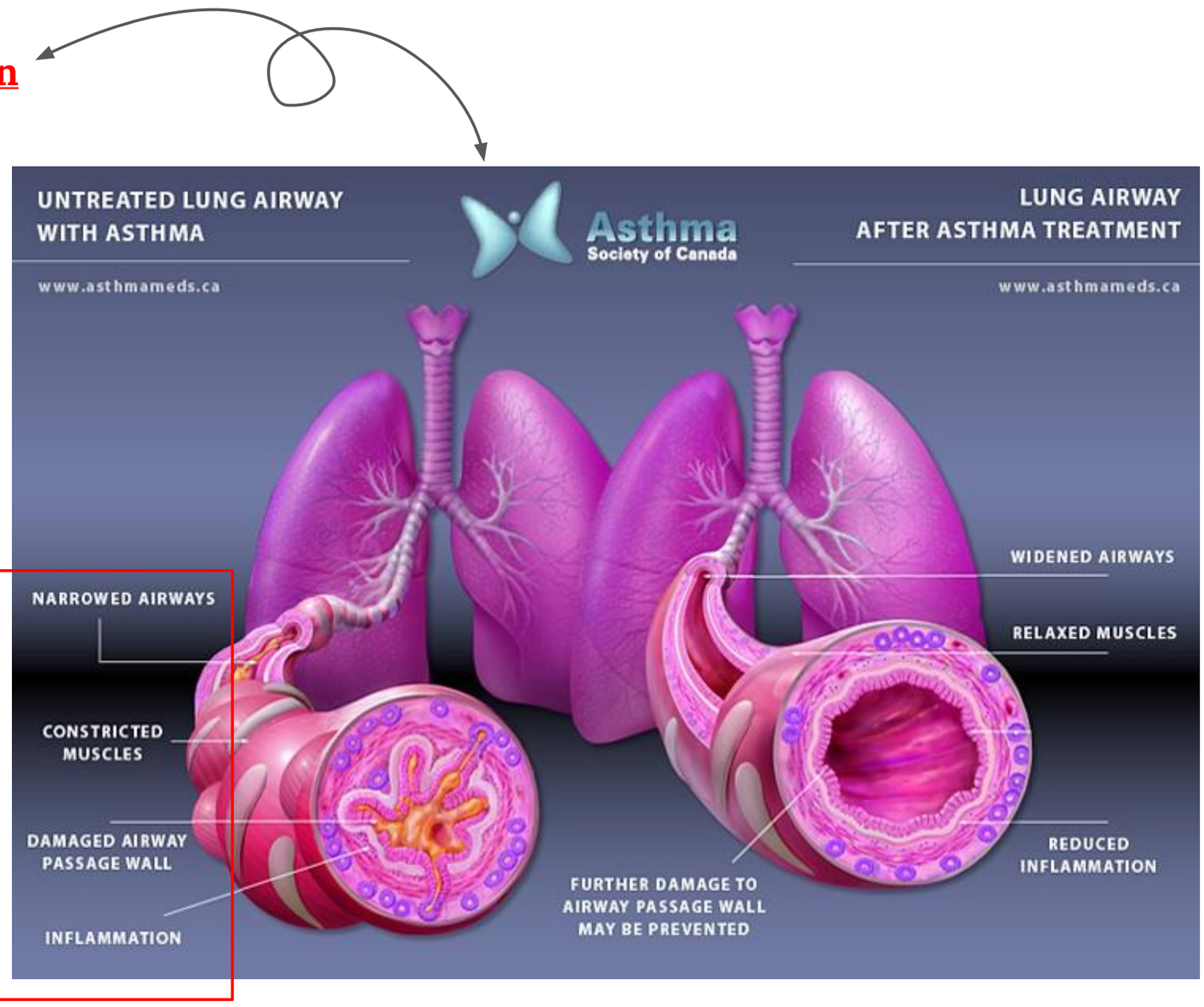
- To the difference between extrinsic and intrinsic asthma.
- To be familiar with types of allergens and their role in allergic sensitization.
- To understand the inflammatory processes operating in allergic asthma.
- To know about the airway remodeling.

- **Important.**
- **Extra notes.**
- **Doctors notes.**

Asthma

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

Classification of Asthma :

Intrinsic (non-atopic)	Extrinsic (atopic) Atopy: genetic tendency to develop allergy
(10-33% of asthmatics)	**60-90% Children** **50% Adult**
*• **Negative** skin tests (used in type I hypersensitivity) *• Serum **IgE** levels are usually **normal** • More severe • Older patients • No clinical/family history of allergy * Because it does not affect the immune system	- Approximately 75-85% of patients with asthma have **positive** (immediate) skin test reactions to various allergens - Serum IgE is elevated - As an allergic reaction - immune response.

Role of Allergens in Asthma:

Allergen Is an antigen that triggers an allergic reaction, it's the main cause of hypersensitivity type 1 (allergy).

Allergen sensitization is linked to the risk of developing asthma

Sensitization is the first response of immune system in allergy.

Indoor allergens	Outdoor allergens
- House dust mites - Domestic pets (cat fur & dander) - Cockroaches (insects) - Molds (fungal spores)	- Fungal spores (e.g. Alternaria) - Grass, tree & weed pollens

Antigen presenting cells (APCs) in the lung:

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

- **myeloid DCs (mDCs)**: help in the development of asthma symptoms
- **plasmacytoid DCs (pDCs)** :aid in respiratory **tolerance**

  to allergens

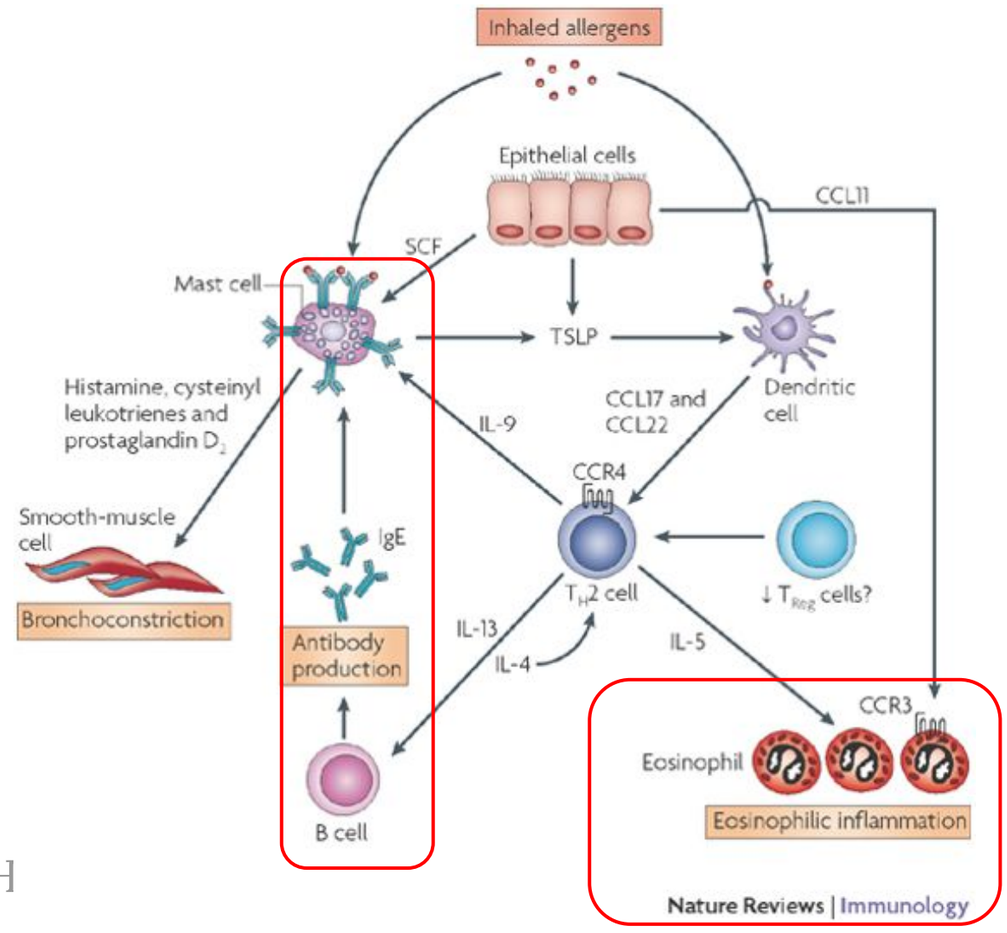
In susceptible individuals:

First encounter with allergens activate B-cells to produce IgE

<u>Subsequently:</u> 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 → TH

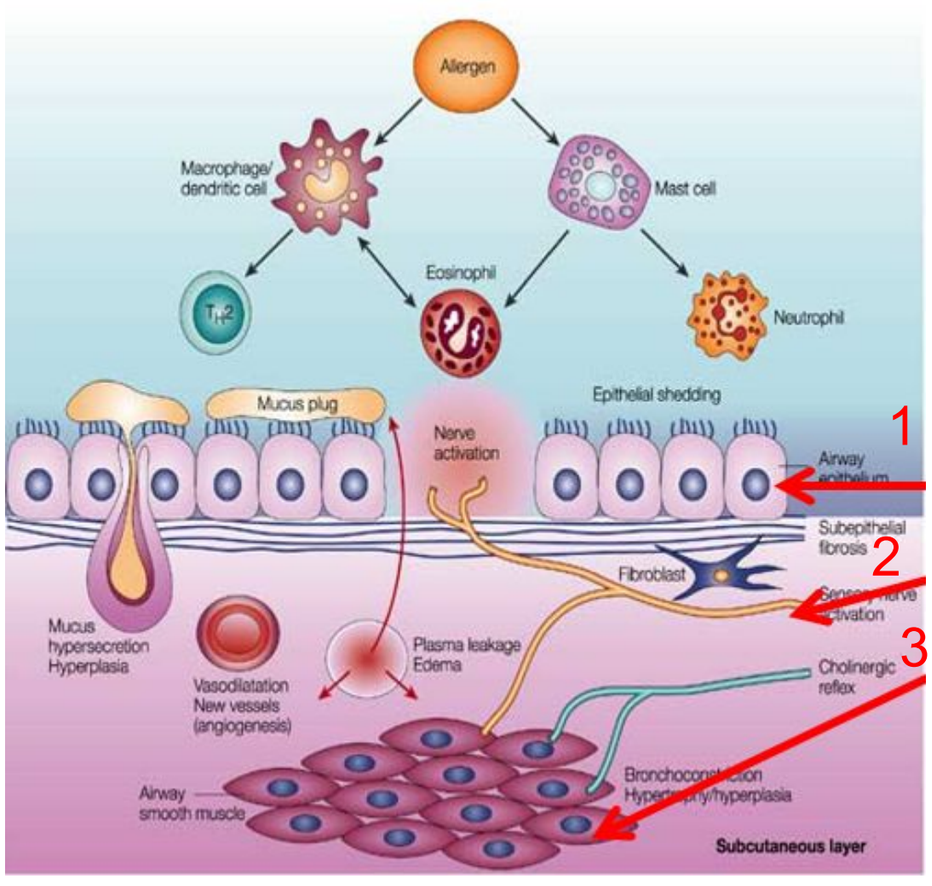
1) IL-4, IL-13 → interact with B cell → release IgE → mast cell → release histamine → <u>CONTRACTION OF BRONCHI</u>

2) IL-5 → production of eosinophils → <u>CONTRACTION OF BRONCHI</u>

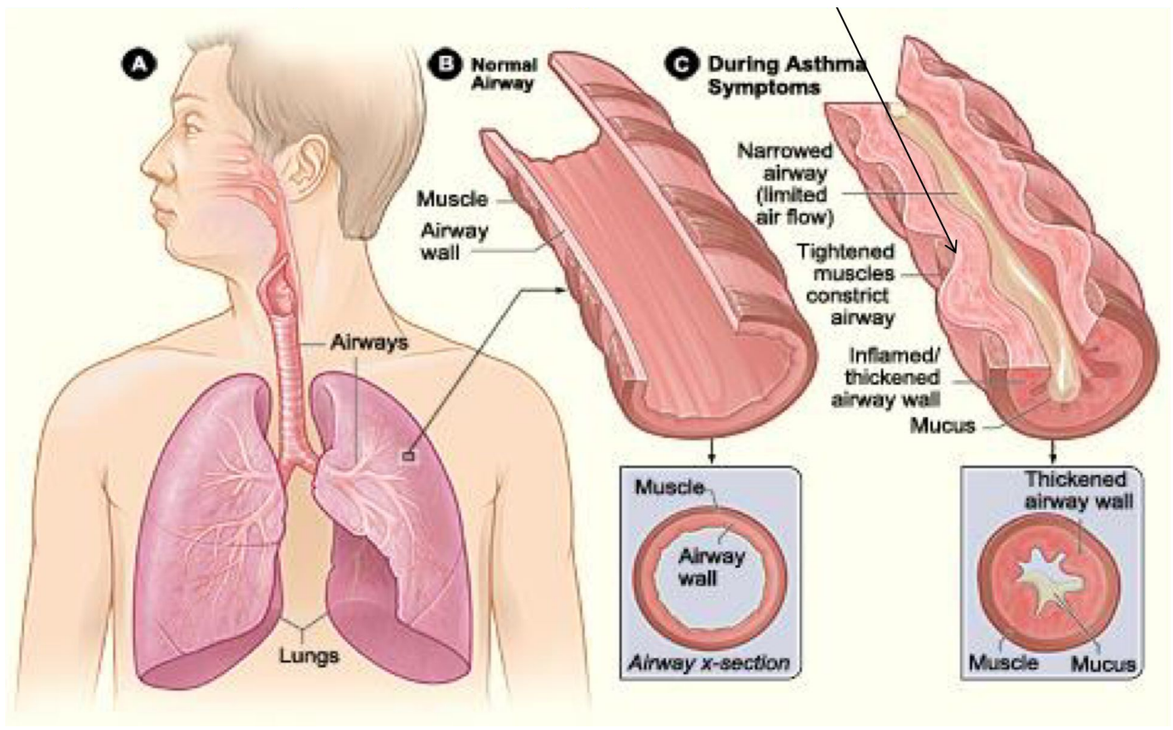
Asthma results from complex interactions among the inflammatory cells that involve:

1. Air way epithelium
2. Nervous system
3. Bronchial smooth muscles

<u>Asthma Pathophysiology</u>



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

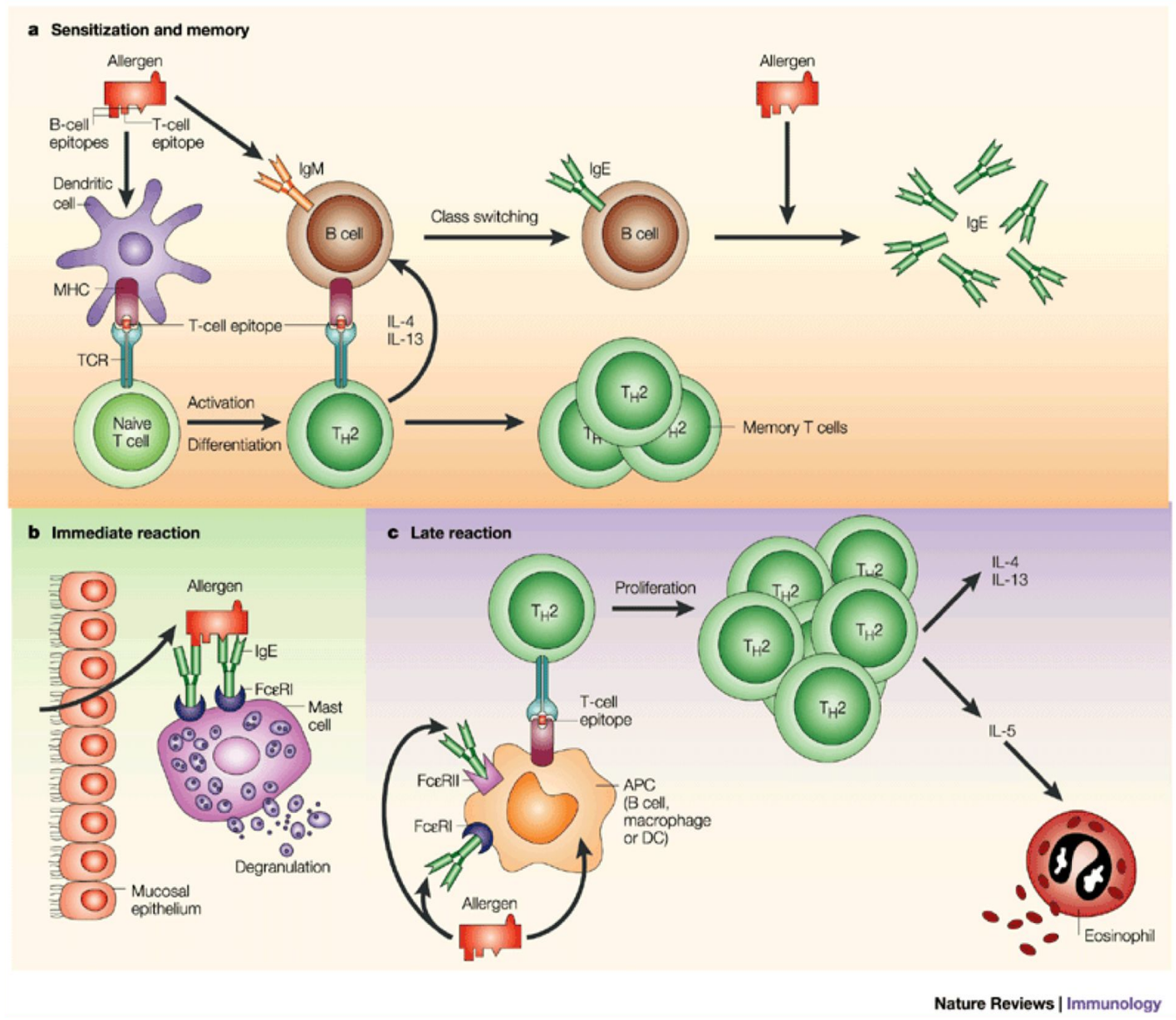


1- Smooth muscles of bronchioles (constructed muscles)

2- Epithelial wall (inflamed wall=thickened\narrowed)

3- Mucus glands (hypersecretion of mucus=obstruction)

Response to allergen occur in two phases:



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.

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.

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	1. Appears **4 to 10 hours** later 2. Results from infiltration by **inflammatory** cells. 3. Activation of lymphocytes & eosinophils
Is **reversible** and responds to **bronchodilators**	Responds to **steroids** **(Anti-inflammatory drugs)**

Normal response vs. allergic response (very helpful & short video)

Early and late allergic response

Th2 (T helper 2) 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**

Cytokines in asthma (the video is about dermatitis but the idea is almost the same)

Role of IL-4 in allergic asthma:

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**

Role of IL-13 in allergic asthma:

1. IL-13 induces **inflammation** Outcome of increased airway reactivity
2. Stimulates **mucus hyper-secretion**
3. Induces **sub-epithelial fibrosis**

Role of IL-5 in allergic asthma:

1. IL-5 induces an increase in **eosinophil production** in the bone marrow
2. **Release** of eosinophils from the bone marrow into circulation

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.**

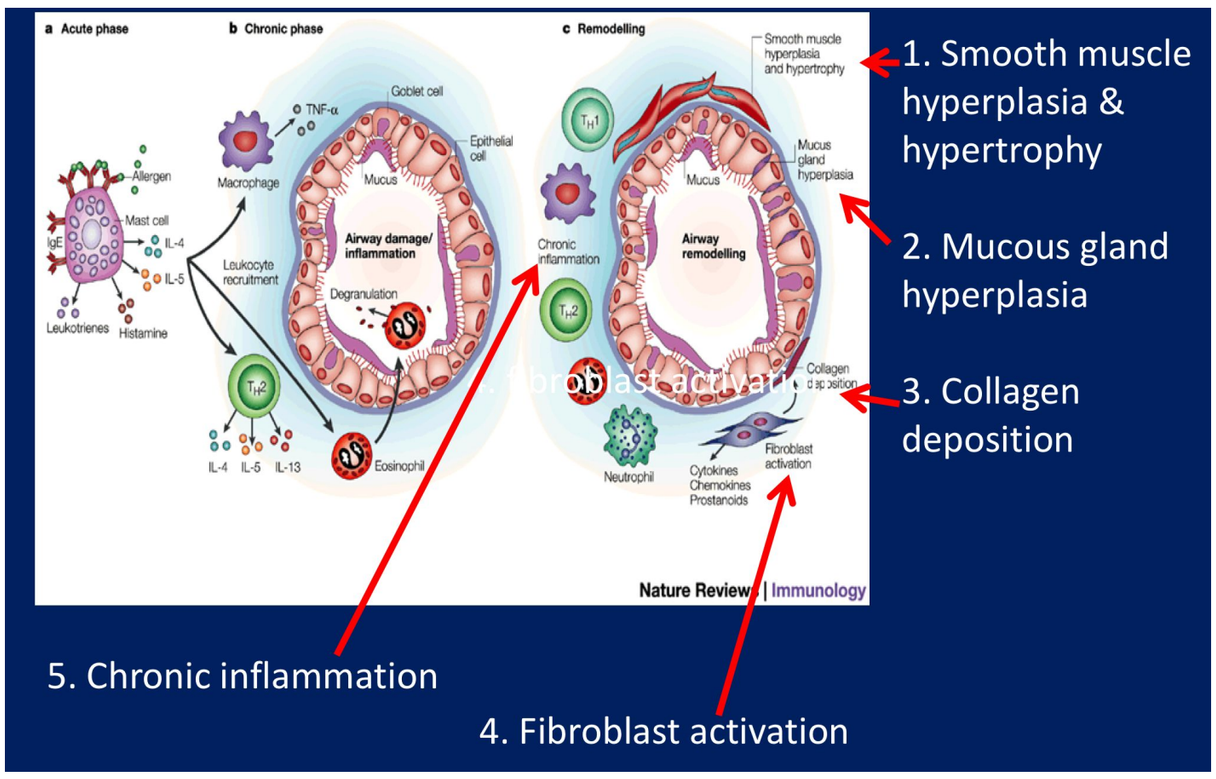
Airway inflammation is the hallmark in the asthmatic lung which leads to:
Increased **bronchial reactivity**

Products of the inflammatory cells act on:

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

and cause : **Airway Remodeling.**

Airway remodeling refer to:



Inflammatory cells & their mediators → Airway inflammation → Increased bronchial reactivity
Airway remodelling

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

(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)

Outcome of airway remodeling:

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

Take home message

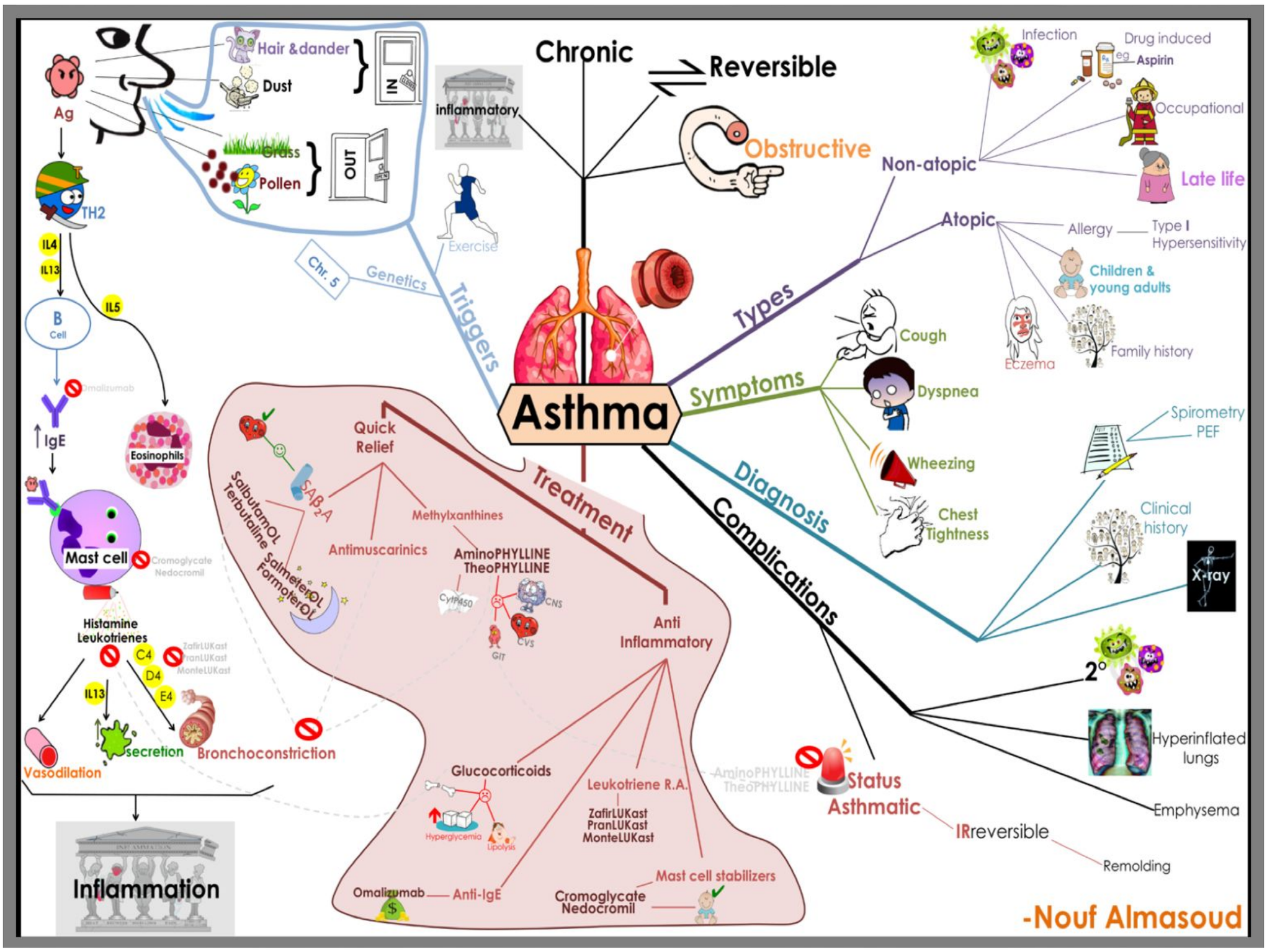
1. Asthma is characterized by episodic reversible airway obstruction.

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 is not revisable.



Useful videos

Immunology of lung

Asthma

Type 1 hypersensitivity reaction

MCQs:

1- : Which one of the following is an indoor allergen:

a) Grass
b) Cockroaches
c) Pollens
d) Alternaria

2- :Asthma is a clinical syndrome characterized by decreased bronchial reactivity:

a) F
b) T

3- :Which type of antigen presenting cells aid in respiratory tolerance to allergens:

a) myeloid dendritic cells
b) macrophages
c) B-cells
d) plasmacytoid dendritic cells

4- :Role of IL-4 in allergic asthma:

a) Induces MHC II on antigen-presenting cells
b) Induces adhesion molecule expression
c) Activate mast cells and eosinophils
d) All of the above

5- :Role of IL-13 in allergic asthma:

a) Increase in eosinophil production
b) Regulates isotype switching in B cells to IgE
c) Stimulates mucus hyper-secretion
d) Inhibition of eosinophils

6- :Asthmatics may lack functional regulatory T-cells

a)T b) F

7- :The hallmark in the asthmatic lung:

a)Increased mucus secretion
b) Decreased bronchial reactivity
c)Airway inflammation
d) Edema

8- :Airway remodeling results in reversible airway obstruction in some patients

a)T b)F

1-b
2-a
3-d
4-d
5-c
6-a
7-c
8-b

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