L1: 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

Motivation quote:

The difference between who you are *and* WHO YOU WANT TO BE *is what you do.*

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- Red = Important Notes
- Orange = Further Explanation
- gray = Additional Notes
- Green = Example
- Navy: boys notes
- Purple: girls notes

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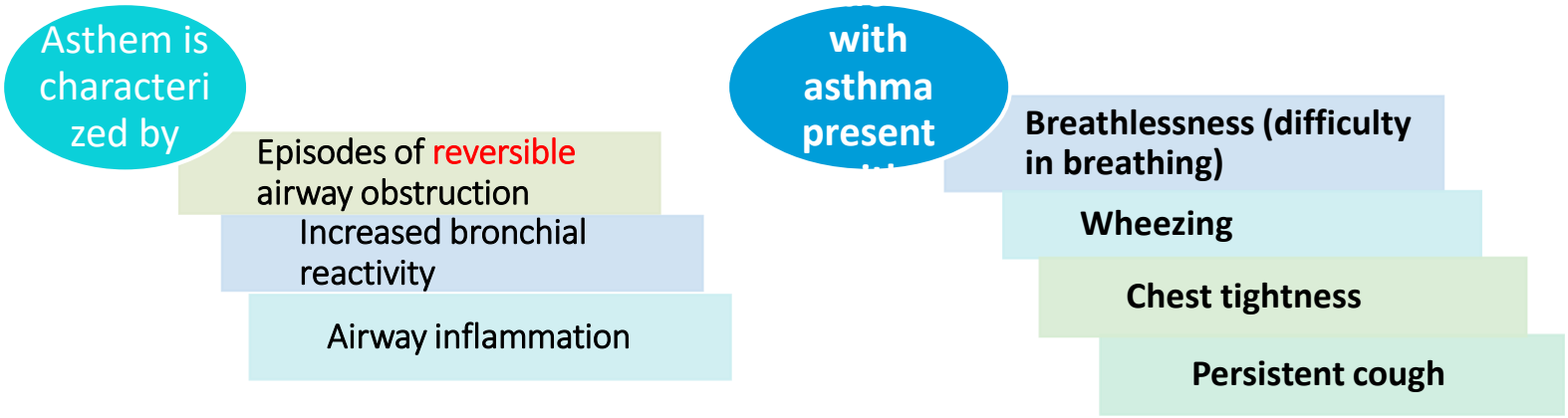
Overview of asthma



What is an allergen?

Is an antigen that triggers an allergic reaction, it's the main cause of hypersensitivity type 1 (allergy).In bronchi asthma it's a hypersensitivity type I

	Extrinsic "Atopic"	Intrinsic "Non Atopic"
Skin Test	Positive	Negative
Allergy	Associated with allergy	No history of allergy
Allergen	Outdoor allergen 1- Fungal Spores 2- Grass 3- Tree	Indoor Allergens 1- House dust mites 2- Domestic pets 3- Cockroaches
Data	* 60-90% Children *50% Adults *Approximately 75-85% of patients have positive skin test to various allergens *↑in IgE Level.	*10-33% of asthmatics *More sever *Serum IgE levels normal *More in Older patients

Induction of Allergic reactions by:

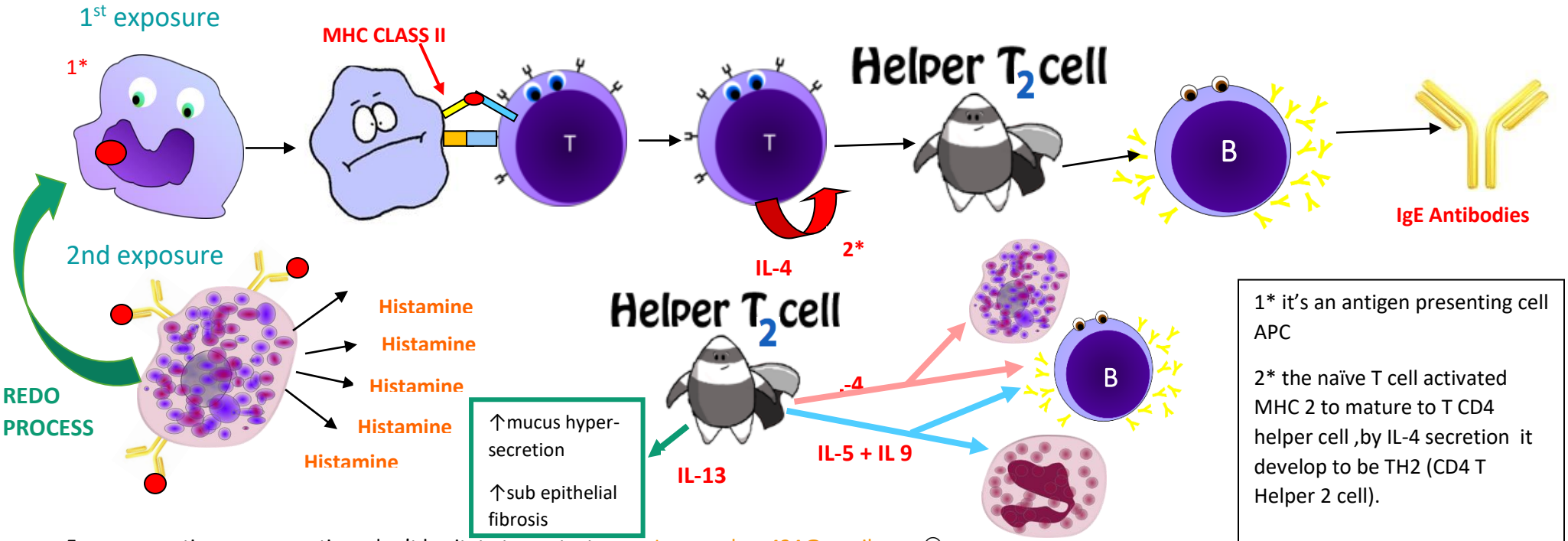
Sensitization Phase

- when the allergens get into an atopic person for the first time, it is presented by Aantigen presenting cells to the Naïve T Cell (T_{H0}), which differentiates to(T_{H2}) cells . the T helper 2 cell stimulates the B Cells to produce IgE antibodies

Challenge Phase

- second encounter with the allergen causes IgE antibodies to bind to the allergen, causing mast cells to degranulate and release mediators that lead to the known symptoms of asthma (recruitment of eosinophils and pro-inflammatory cells in addition to broncho-constriction, mucus secretion

Who does hypersensitivity 1 developed:



1* it's an antigen presenting cell APC

2* the naïve T cell activated MHC 2 to mature to T CD4 helper cell ,by IL-4 secretion it develop to be TH2 (CD4 T Helper 2 cell).

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Body Response to Allergens in 2 phases:

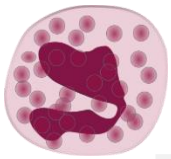
Early Allergic Response	Late Allergic Response
• Occurs within minutes. • Manifests as: Bronchial constriction, airway edema, and mucus plugging. • Includes both sensitization phase and challenge phase. • It can be reversed by using bronchodilators.	• Happens 4 to 10 hours after the early response. • Results from infiltration of inflammatory cells. • Leads to the activstion of lymphocytes and eosinophils. • Responds to anti inflammatory drugs (steroids)

Allergens drive T-cells to proliferate into Th2 type which produces cytokines

They promote *Production of IgE by B cells / Eosinophil attraction and infiltration /Airway inflammation /Increased bronchial reactivity*

IL4	*IL-13*	*IL-9*	*IL5*
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*	*induces inflammation* *Stimulates mucus hyper-secretion* *Induces sub epithelial fibrosis*	*Associated with bronchial hyper-responsiveness* *In mice it increases* *Lung eosinophilia* *Serum IgE levels*	*induces increased production, terminal differentiation and activation of eosinophils* *Release of eosinophils* *B-cell growth factor and increases IgE secretion*

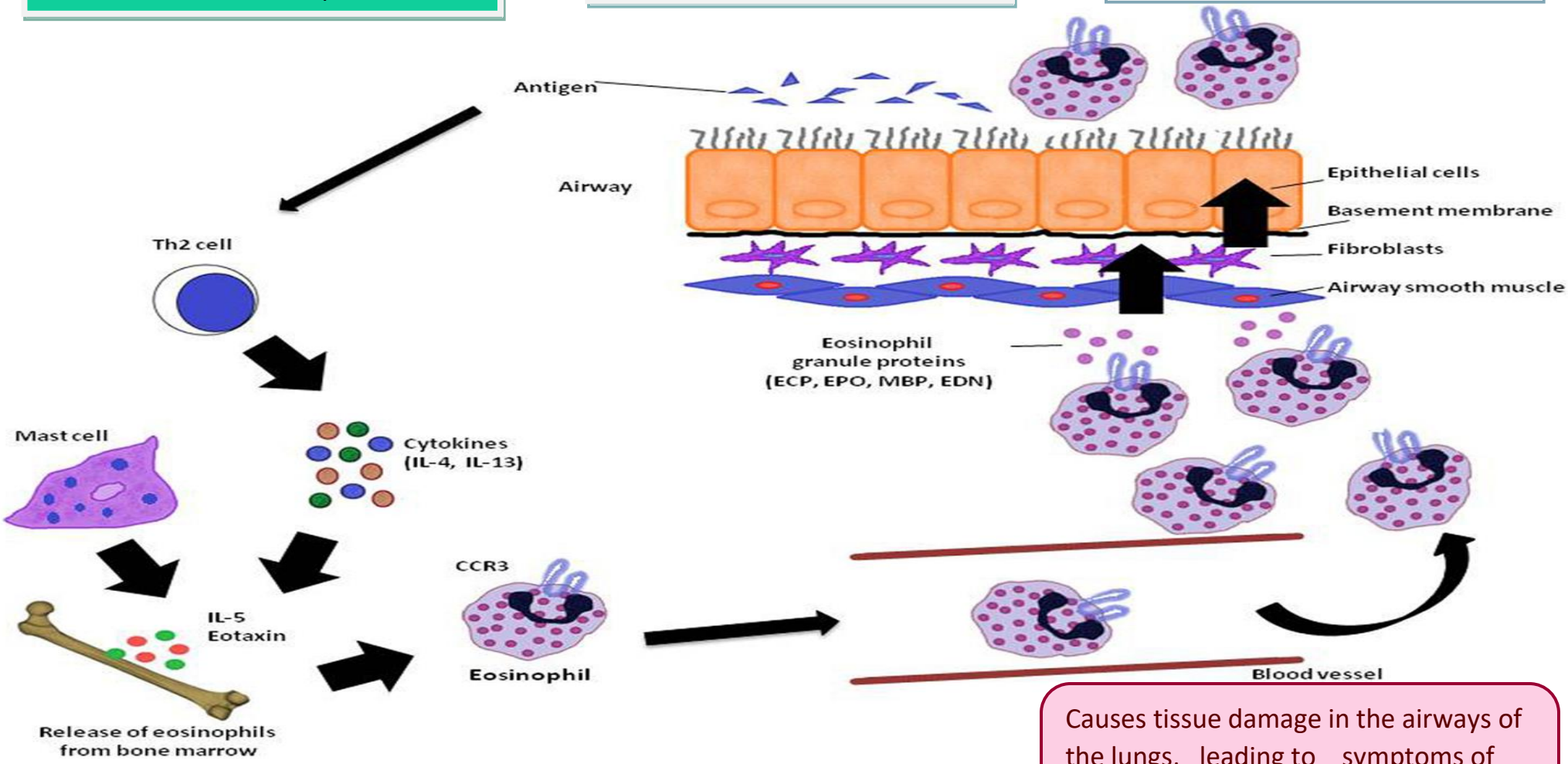
Eosinophils Role in Asthma



Eosinophils are thought to play a cytotoxic role, hence they can release certain substances such as major basic protein which can then destroy the bronchial mucosal epithelium

Eosinophils produce leukotrienes and platelet activation factor which both contribute to broncho-spasms in asthmatic patients

IL-5 is a chemokine responsible for the proliferation of the number of eosinophils in asthma, it's produced by TH-2 cells and mast cells.



Causes tissue damage in the airways of the lungs, leading to symptoms of asthma. Its production is inhibited by IL-10.

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Role of T reg (regulatory) cell in asthma

Regulatory T cells suppress the effector mechanisms that induce asthmatic symptoms

Asthmatics may lack these regulatory T Cells.

NOTE: the activation of inflammatory cells such as mast cells and eosinophil's causes the induction of Airway Inflammation, which is one of the characteristic features of Asthma.

Airway Inflammation can take two forms :

1- Increased Broncial Reactivity (Bronchial Hyper-responsiveness

Makes patients prone to develop Asthma attacks when exposed to non-specific allergens such as

- A- Chemical irritants.
- B) Smoke & strong perfumes.
- C) Sulphur dioxide (air pollutants)
- D)Viral and bacterial respiratory infections

2- Airway Remodeling:

Which is the result of products of the inflammatory cells acting on: Airway smooth muscle cells, Lung fibroblasts, & Mucous glands.

NOTE: Airway remodeling can ultimately lead to fibrosis and irreversible airway obstruction in some patients

- *The different between asthmatic and predispose patient is that in asthmatic the chronic phases is stronger .*

- *In asthmatic patients we use both bronchodilator and anti-inflammatories*

E.g. Vento line and steroids.

- Asthma: reversible + hyper-reactivity + inflammation
- Symptoms : Breathlessness + Wheezing + Persistent cough + Chest tightness.

Classification of Asthma	extrinsic (Atopic) asthma	Intrinsic (non-atopic)
Cause	Allergy	Unknown
Percentage of Asthmatics	60-90% Children 50% Adults	10-33%
Target Patients	All	Elderly
Skin Test Result	Positive (immediate)	Negative
Serum IgE Levels	High	Normal
Clinical/Family History	Yes	None
Severity	Less severe	More severe

- Allergens in Asthma :
  - 1-Indoor allergens E.g Cockroaches
  - 2-Outdoor allergens e.g. Grass
- First encounter with allergens → production of allergen specific IgE
- Second exposure to the allergens → mast cells degranulation → release of mediators → Recruitment of eosinophils & pro-inflammatory cell + Bronchoconstriction

- Response to allergen occur in two phases :

1- Early allergic response (within minutes) : Bronchial constriction + edema + Mucus plugging → reversible and responds to bronchodilators

2- Late allergic response(4 to 10 hours) : Results from infiltration by inflammatory cell + Activate of lymphocytes & eosinophils → Responds to steroid (Anti-inflammatory drugs)

- Cells & role of cytokines

•Allergens cause T-cells to transform into TH2 cells

•TH2 secrete cytokines (IL-4,5,9,13) which promote:

•Production of IgE by B cells •Eosinophil attraction and infiltration • Airway inflammation •Increased bronchial reactivity

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Roles of interleukins			
IL-4 (during the initial priming of Th2 cell)	IL-13	IL-9	IL-5
1.Regulates isotype switching in B cells to IgE 2.Induces MHC II on APC 3. Induces adhesion molecule expression 4. Activate mast cells and eosinophils	1.induces inflammation 2.Stimulates mucus hyper-secretion 3.Induces sub-epithelial fibrosis	1.Associated with bronchial hyper-responsiveness 2.In mice it increases: -Lung eosinophilia -Serum IgE levels	1. 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

1- Airway re-modeling an Outcome of airway remodeling: Can ultimately lead to fibrosis and irreversible airway obstruction in some patients
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 : smooth muscle cells + Lung fibroblasts + Mucous glands à and cause : Airway Remodeling

Role of eosinophil in allergic asthma:

1- initiate asthmatic symptoms by causing tissue damage in the airways of the lungs

2- Production of eosinophils is <u>inhibited</u> by IL-10

- Role of regulatory T – cells: suppress the effector mechanisms that induce asthmatic symptoms → So Asthmatics may <u>lack</u> 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 :

1- Bronchial Hyper-responsiveness → Outcome of increased airway reactivity : Predisposes patients to develop asthma attacks on exposure to <u>non-specific irritants</u>

MCQS

1- Asthma is a clinical syndrome characterized by irreversible airway obstruction :

A- T B-F

2 - In skin test the result of intrinsic asthma is

A-negative B- Positive

3 - Serum IgE levels are usually abnormal in

A-intrinsic asthma

B-extrinsic asthma

C-non atopic asthma

4 - which one of the following Stimulates mucus hyper-secretion:

A-IL 4 B-IL 6 C-IL 13

5 - Eosinophils initiate asthmatic symptoms by :

A-release histamine

B-tissue damage

C-bronchodilator

6 - Production of eosinophils is inhibited by:

A-IL 9 B-IL 10 C-IL 13

7 - airway remodeling is irreversible :

A-T B-F

1-B
2-A
3-B
4-C
5-B
6-B
7-A

Wish you the best of luck in you exams – Immunology team