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Immunology

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Sheet ○ Slides

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As we all know that the normal function of the immune system is to differentiate between self and non-self antigens. The disorders in immune system could be ether due to hypersensitivity or deficiencies.

In a healthy immune system, harmless antigens could enter the body and either cause a small reaction or not at all. But, in case of an abnormal immune system, one of the scenarios will occur**:**

1)respond normally but doesn't turn of (chronic inflammation) which will lead to tissue damage.

2) excessive response (hypersensitivity) which will lead to collateral damage.

In this lecture we will discuss hypersensitivity;

Hypersensitivity reaction (HSR): a disorder caused by an **excessive** or **inappropriate** immune response.

Causes of HSRs:

1) Immune response directed against host tissue.

*Autoimmune diseases: inappropriate response when the immune system recognize a self-antigen as a non self antigen.

2) Inadequate control of immune response against pathogenic microbes.

*The continuous inflammation mounted against Mycobacterium tuberculosis.

3) Immune response against commensal microbes or environmental antigen.

Allergy occurs in response of a harmless antigen "allergens" which will result in a humoral response with plasma secreting IgE. Allergy is the most common disorder of the immune system (prevalence of about 20% in developed countries).

The classification of HSR is based on **type of immune response** and **the effector mechanism resulting in tissue injury**. Older classifications where of the immune reactions where dependent upon the duration by which a response is mounted:

Type	*Immune mediator of pathology*	*Mechanism of tissue injury*	*Examples*
Immediate (type I)	IgE	Mast cells and their mediators (vasoactive amines, lipid mediators and cytokines)	Allergic reactions, anaphylaxis, asthma
Antibody mediated (type II)	IgM, IgG against cell surface or extracellular matrix antigens	Phagocytosis, Ab-dependent cell mediated cytotoxicity (ADCC), receptor blocking or complement mediated lysis	Goodpasteur's syndrome, ABO incompatibility, Rh incompatibility
Immune complex mediated (type III)	Circulating immune complexes of antigens and IgM or IgG	Ag-Ab complexes activate the complement and Fc receptors resulting in activation and recruitment of leukocytes	Poststreptococcal glomerulonephritis, systemic lupus erythematosus, rheumatoid arthritis
Cell mediated (type IV)	CD4+ T cells or CD8+ cytotoxic T lymphocytes (CTLs)	Macrophage activation resulting in cytokine mediated inflammation or direct cell killing by CTLs	Contact dermatitis, tuberculosis

Notes about the table;

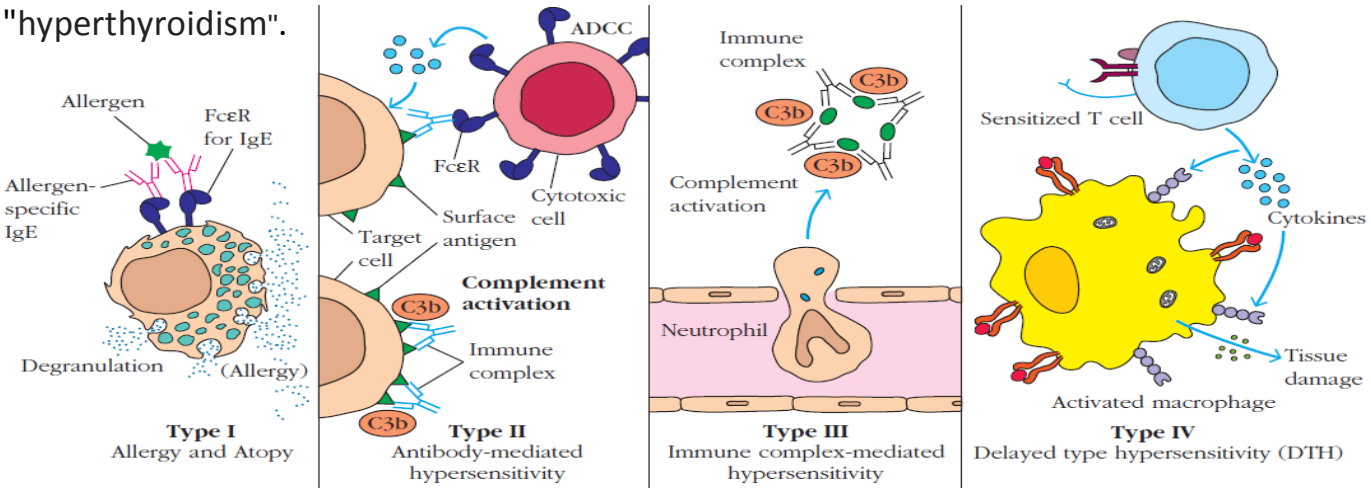
- Type one need seconds to minutes.
- Type 2 and 3: need hours, but the difference is that:

2⟶ antibodies will be produced against an autoantigen present of on cells and tissues of an individual.

3⟶ antibodies will be produced against soluble antigens, forming immune complexes, which will be trapped either in the circulation or in joints, forming inflammatory manifestations.

- Type 4 needs 48-72 hours.
- Type 5: used be part of type 2. Binding of antibodies to autoantigens(mainly receptors) on cells and tissues, leading to over stimulation of these receptor(Myasthenia Gravis).

An example is thyroid gland graves disease: in normal situations thyroid hormones (T3/T4) are secreted because of (TSH) pituitary gland hormone but in the case of graves the antibody binds against (TSH) receptor stimulating the release of (T3/T4) "hyperthyroidism".



Allergens: harmless antigen that cause allergy, have common characteristics LIKE: multivalent (containing more than one epitope per molecule) protein or glycoprotein with protease activity.

Now we will discuss type 1 exact mechanism:

The encounter of an antigen (Ag) that induces allergy (**allergen**) will result in a humoral response with **plasma cells secreting IgM that that will class switch to IgE.**

Factoros that affect the class switching from IgM to IgE include:

1- Route of administration of allergens.
2- Douse of allergens
3- TH2 cells, which are responsible of the humoral response. It's cytokines promote IgE production and it includes IL-4, IL-5, IL-10 and IL-13.

whereas a TH1 cells promote cell mediated response and inhibits the class switching process.

There is something to be understood. For s hypersensitivity reaction to occur, sensitization of the antigen must occur.

Steps for sensitization (cross priming) and Hypersensitivity: Let us connect the dots to draw the big picture:

1) When the antigen enters the body for the first time, it doesn't induce a hypersensitivity reaction, but IgM will be produced and will eventually undergo class switching to IgE. IgE has a very strong affinity to a specific receptor called FC **εR1**, which is present mainly on Basophils, Mast cells, and in small quantities on Eosinophils.

2) These receptors will uptake the IgE, ***NOT CAUSING A HYPERSENSITIVITY REACTION WHEN THE ANTIGEN IS EXPOSED TO THE BODY FOR THE FIRST TIME.*** This binding induces formation of granules, which contain inflammatory mediators. These granules don't degranulate unless a second exposure have taken place. These cells are now considered ***SENSITIZED.***

3) Whenever the body is re-exposed to this antigen, a ***hypersensitivity reaction will be induced*** when these antigens cross link of 2 membrane bound IgE on **sensitized mast cells** and basophils, causing degranulation of these cells to IgE, which as we said, are already bound to Mast cells and Basophils since the first exposure. Binding of antigens will induce intracellular signaling pathways (LYN and NAP kinases activation, leading to activation of Nuclear Factor Kappa B), which will eventually cause the release of the already formed granules, which contain Histamine, Heparin, and proteases. These are the mediators that induce the ***early phase of hypersensitivity***.

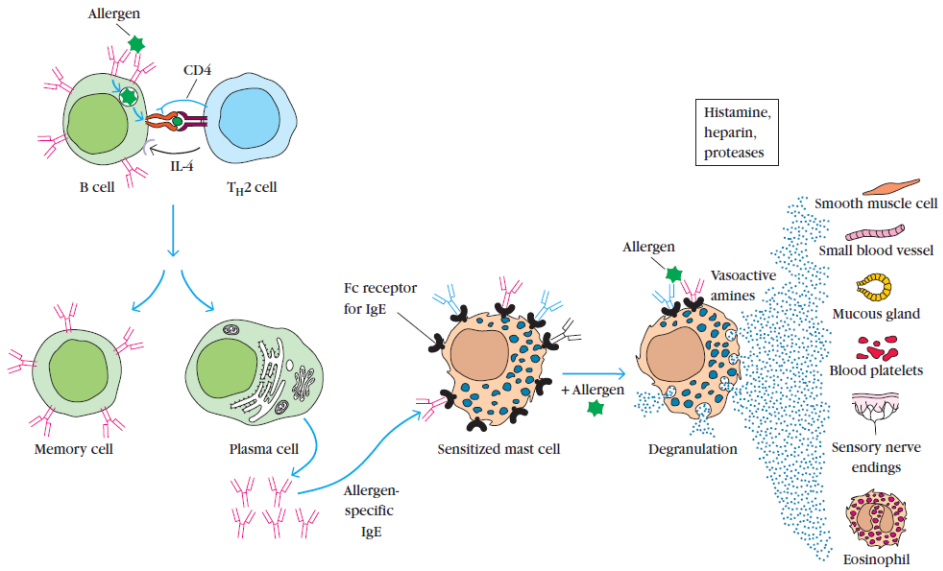
4) Late phase of Hypersensitivity is induced by the binding of IgE to FC **εR2(CD23), which are present on the surface of B cells.** FC **εR2** has low affinity to IgE. Upon binding of antigen to IgE on the FC **εR2**, production of cytokines (IL4,5,and13) will take place, producing the ***late phase of Hypersensitivity.***

What to know about IgE :

a. IgE has four constant domains
b. IgE represents the Abs with the lowest concentration in serum of a normal individual. This is likely due to:

O The $t_{1/2}$ of IgE is short compared to other Abs.
O IgE is produced only in response to a select group of Allergen or helminthiasis.
O IgE is usually sequestered into FcεRI mainly present on mast cells and basophils. FcεRII(CD23) are present on B cells.

c. IgE binds with high affinity to its receptors on **mast cell and basophil surfaces**.



- Type I hypersensitivity responses are divided into an immediate early response and one or more late phase responses.
  1- The early response occurs within minutes of allergen exposure and results from the release of histamine ,Heparin, and proteases from local mast cells.

2-The mediators released during the course of the immediate reaction induce localized inflammation. Cytokines released from mast cells(TNF-αand IL-1) , increase the expression of CAMs on endothelial cells, facilitating the influx of neutrophils, eosinophils ,and TH2 cells, which mediate the late phase of the response.

what determines specific switching to IgE?

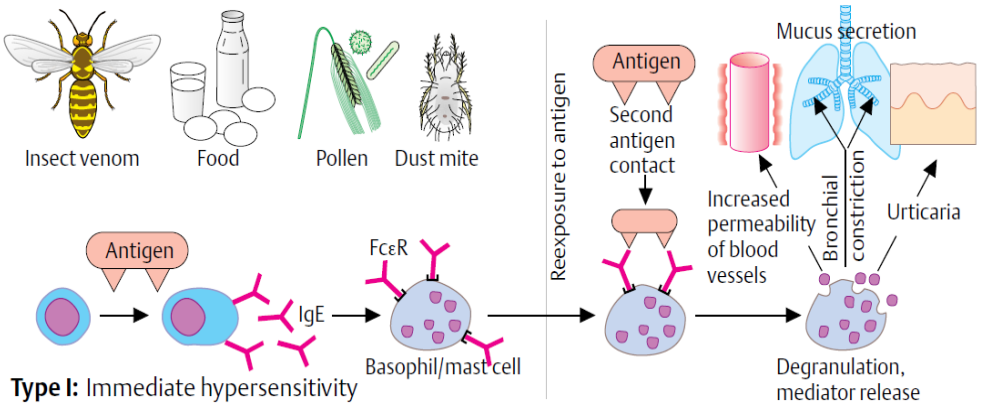
Cytokine environment, the presence of IL-4, IL-13. If we have TGF β, switching will be to IgA.

VIP notes:

1) We need IL-5 for the recruitment of eosinophils.
2) We can have degranulation of mast cells without IgE but we don't consider it allergy.

Manifestations of allergy:

1) Vasodilation.
   (may cause a shock)
2) Mucous secretion.
3) Bronchoconstriction
4) Skin rash, redness.



The clinical manifestations of allergic reactions are related to the tissue mostly affected, in addition to the biological effects of the mediators that are released during degranulation of mast cells and basophils including:

- **Histamine:** increased permeability of venules, contraction of intestinal, bronchial and arterial smooth muscles.
- **Leukotrienes and prostaglandins:** bronchoconstriction, increased vascular permeability, and mucus production.
- **Cytokines (IL-4, IL-5 and IL-13):** recruitment and activation of inflammatory cells.

Some allergic reactions continue for a long time as a result of TH2 mediated eosinophil migration and subsequent release of its mediators including peroxidase and major basic protein (late phase response).
Local manifestations mainly depend on the tissue mostly affected.
Local allergies include allergic Rhino-conjunctivitis, atopic dermatitis, food allergies and asthma.

The cause of allergy:
The cause of allergy is likely related to a complex of gene-environment interactions. In other words, atopy(the genetic tendency to develop an allergy) + the exposure to certain environment conditions= Hypersensitivity reactions. The evidence being that monozygotic twins don't always have the exact same allergy. There is an environmental factor that plays a role in inducing this reaction.

Atopy includes possible associations with HLA type, IgE production, FcεRI and II, several cytokines and chemokines with its receptors among others not associated with a certain gene.

The hygiene hypothesis, which is not proven yet, was formulated based on the observation that disorders involving the immune system are increasing in countries where the younger generation aren't getting exposed to antigens, and hygienic. In countries where diarrhea and respiratory infections among kids are relatively higher, less cases of immune diseases are being reported.

Now, let's discuss some of the localized allergies:

rhino-conjunctives: "hay fever".

- One of the most common allergic conditions. And very similar to common cold.
- Caused by airborne allergens.
- Characterized by seasonality. Mostly in spring.
- The symptoms include watery exudation of the conjunctivae, nasal mucosa, and upper respiratory tract, as well as sneezing and coughing.

Asthma (the exam has a Q on this)

- "Characterized by recurrent reversible airflow obstruction and bronchial smooth muscle cell hyper-responsiveness".
- The majority of asthmatic attacks are triggered by IgE-mediated responses to allergens such as pollens, dust, fumes or insect products; thus termed atopic asthma.
- The rest of asthmatic attacks are triggered independently of allergen stimulation and termed intrinsic asthma. The triggers include exercise, drugs or cold.(These asthma cases don't need an allergin to get induced, but are yet termed hypersensitive reactions)
- Both atopic and intrinsic asthma share the same pathophysiology, hence are considered together.
- The underlying airway edema, mucus secretion, and inflammation contribute to the bronchial constriction and to airway obstruction leading to the clinical manifestations such as shortness of breath and wheezing.
- Reversible obstruction of asthma is possible.

Atopic dermatitis (eczema)(V. Important)

- Often associated with mutations in **filaggrin** leading to defective skin barrier(in tight junctions, making them loose) and increased exposure to environmental Ags.

Food allergy

- Causes GI symptoms, however, respiratory symptoms suggest systemic Ag exposure(anaphylaxis).
- Common food items causing food allergy include eggs, shellfish and peanut.

Anaphylaxis

- systemic type 1 (IgE-mediated, immediate) HSR.
- If anaphylaxis occur, it is reversed by EpiPen, which induces vasoconstriction.
- The word anaphylaxis is recognized and feared by most health care providers because of its association with potential death from cardiovascular collapse or asphyxiation caused by laryngeal edema.
- As with other type I HSR examples, the first exposure to an allergen in genetically predisposed individuals will lead to priming (sensitization).
- Re-exposure to the same allergen systemically will cause the cross-linking of IgE that are bound to its high-affinity receptor (FC **εR1**) on mast cells and subsequent release of inflammatory mediators including histamine.

Management of allergy:

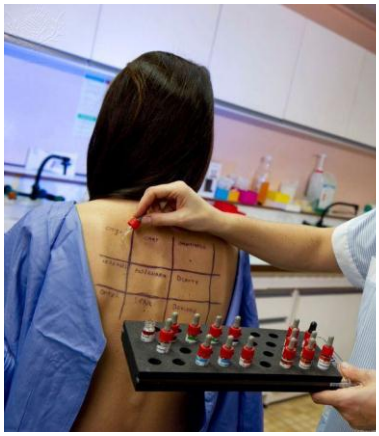
•General measures include the identification of the culprit allergen and its avoidance.

•Drug treatment aims at blocking the effect of allergy inflammatory mediators (e.g. antihistamines, β2-adrenergic agonists, epinephrine).

•Topical steroid (anti-inflammatory).

•Sodium cromoglycate(reduces mast cell degranulation).

•Desensitization (immunotherapy). It aims to improve allergy symptoms caused by a specific allergen. Allergen is injected subcutaneously in escalating doses (possible mechanisms include induction of TH1 response or induction of T_{reg} response that inhibits the polarized TH2 response



SKIN TESTING: - A panel of reduced agents, in which they are tested on the patient's skin. This testing is done to identify the allergen and advise patient to avoid it (allergen). This gives us an indication if the patient is allergic to the substance or not.
-if patient is allergic, a typical wheal(inflammation) and flare (redness) reaction will occur, indicating that the patient is allergic to this substance.

The end and good luck

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