Immune Hypersensitivities

The immune system is a complex system of cells and molecules that allows us to detect and respond to foreign, dangerous invaders. However, the immune response is also capable of causing tissue injury and disease, resulting in hypersensitivity reactions. Hypersensitivity diseases are immune based situations where the immune system responds to foreign, innocuous invaders *(allergies)*, or to "self" tissues as though they were foreign *(autoimmune diseases)*. An immune response to an antigen may result in sensitivity to challenge with that antigen, thus, hypersensitivity is a reflection of excessive immune responses. As hypersensitivity is a pathway that leads to damage of tissue, therefore, they are mechanisms of action rather than an end outcome.

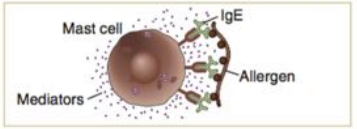
There are four types of hypersensitivities, their classification based on the immunological mechanism that causes tissue injury and disease.

- Immediate hypersensitivity (Type 1)
- Antibody-mediated (Type 2)
- Immune complex-mediated (Type 3)
- T cell-mediated (Type 4)

Immunotherapy is a treatment for hypersensitivity by altering the immune system or response in some way to enhance of suppress elements of the immune system. In regards to allergies, *desensitization* aims to reduce the allergic response by shifting from a T_H2 (IgE) to a T_h1 response and/or the production of regulatory T-cells. Autoimmunity is a combination of *environmental factors* in a *genetically* predisposed individual. MHC can sometimes act against self, making self more susceptible to autoimmune diseases.

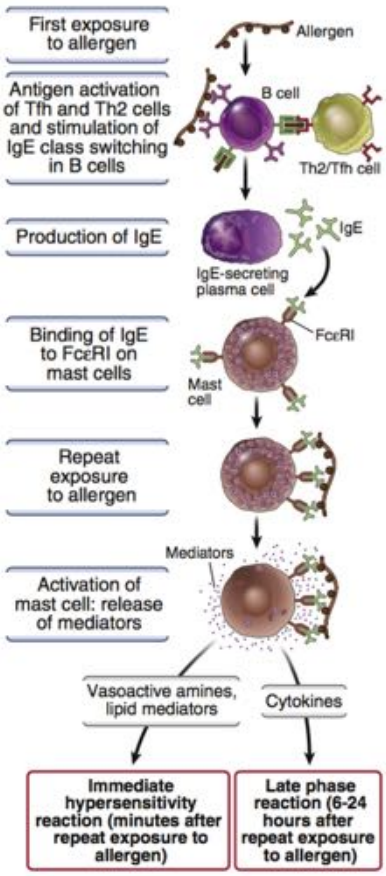
Disease	Disease mechanism	Consequence	Prevalence
Psoriasis	Autoreactive T-cells against skin-associated antigens	Inflammation of skin with formation of scaly patches or plaques	1 in 50
Rheumatoid arthritis	Autoreactive T-cells against antigens of joint synovium	Joint inflammation and destruction causing arthritis	1 in 100
Graves' disease	Autoantibodies against the thyroid-stimulating-hormone receptor	Joint inflammation and destruction causing arthritis	1 in 100
Hashimoto's thyroiditis	Autoantibodies and autoreactive T-cells against thyroid antigens	Destruction of thyroid tissue leading to hypothyroidism: underproduction of thyroid hormones	1 in 200
Systemic lupus erythematosus	Autoantibodies and autoreactive T-cells against DNA, chromatin proteins and ubiquitous ribonucleoprotein antigens	Glomerulonephritis, vasculitis, rash	1 in 200
Sjogren's syndrome	Autoantibodies and autoreactive T-cells against ribonucleoprotein antigens	Lymphocyte infiltration of exocrine glands, leading to dry eyes and/or dry outh; other organs may be involved, leading to systemic disease	1 in 300
Crohn's disease	Autoreactive T-cells against intestinal flora antigens	Intestinal inflammation and scarring	1 in 500
Multiple sclerosis	Autoreactive T-cells against brain antigens	Formation of sclerotic plaques in brain with destruction of myelin sheaths surrounding nerve cell axons, leading to muscle weakness, ataxia and other symptoms	1 in 700
Type 1 diabetes	Autoreactive T-cells against pancreatic islet cell antigens	Destruction of pancreatic islet ß-cells leading to nonproduction of insulin	1 in 800

Immediate Hypersensitivity

Immediate hypersensitivity (Type I)	Th2 cells, IgE antibody, mast cells, eosinophils 	Mast cell-derived mediators (vasoactive amines, lipid mediators, cytokines) Cytokine-mediated inflammation (eosinophils, neutrophils, lymphocytes)

Immediate hypersensitivity is a type of pathologic reaction that is mediated by IgE and mast cells. It is a rapid reaction, leading to vascular leakage, secretions and inflammation, which is often followed by inflammation. Disorders which are the result of this mechanisms are:

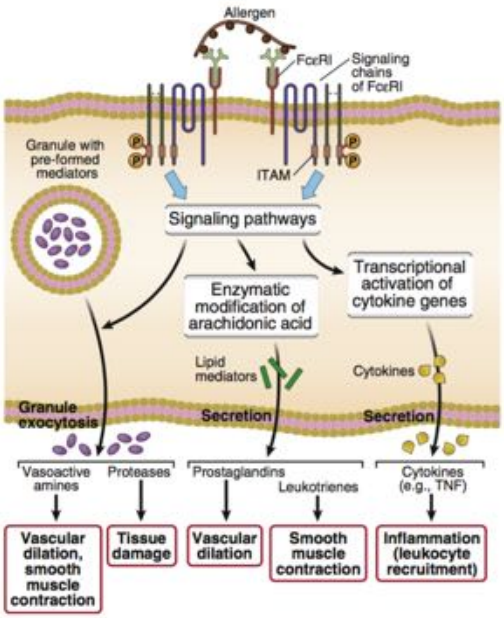
- *Allergy* – the generation of immune reaction to environmental agents
- *Atopy* – the potential to generate IgE responses to environmental antigens



The initial exposure to the allergen results in sensitization and memory, whereby the antigen activates T_H2 cells which stimulates B-cells to class switch for the production of IgE. These IgE molecules bind strongly to IgE receptors found on the surface of inflammatory cells, such as mast cells. Repeated exposure to the allergen binds to IgE on mast cells, where cross-linking results in the activation and degranulation of mast cells and the release of inflammatory mediators.

IgE antibodies produced in response to an allergen bind to high-affinity F_c receptors that are expressed on mast cells. In an atopic individual, mast cells are coated with IgE antibodies specific for the allergen. The process of coating is called *sensitisation*. Mast cells are present in all connective tissue and specific reactions are depends on the route of entry of the allergen.

Cross linking of IgE stimulates phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAMS) in the signalling chain of the IgE Fc receptor which initiates multiple signalling pathways. These pathways stimulate the release of mast cell granule contents (amines, proteases), the synthesis of metabolites and various cytokines.



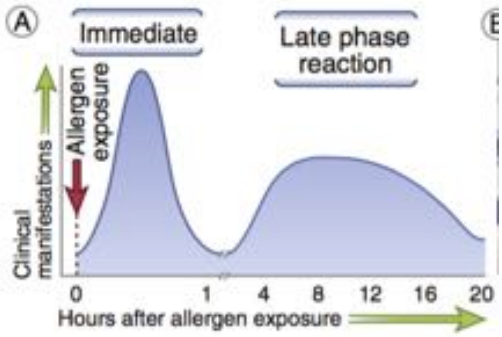
There are two types of intracellular actions:

- Activation of cytokine genes
- Mobilisation of biologically active molecules

Phases of immediate hypersensitivity

There are two phases of immediate hypersensitivity:

- *Immediate phase* consists of IgE and mast cells, which causes vascular changes. This usually occurs between 5-10 minutes.
- *Late phase reaction* may or may not be preceded by the immediate reaction. It occurs due to the infiltration of inflammatory leukocytes, such as neutrophils, eosinophils, basophils and T_H2 cells and takes 2-24 hours for the action to take place.



Clinical Syndromes

A syndrome is a group of symptoms which consistently occur together, or a condition characterised by a set of associated symptoms. As this sort of hypersensitivity is mediated by IgE, a diagnosis can be made via a skin prick test or blood test.

Allergic rhinitis, sinusitis (hay fever) are reactions to inhaled allegens, in which mast cells produce histamine whilst T_H2 cells produce IL-13, increasing mucous production and inflammation of upper airways.

Food allergies result in the release of histamine via mast cell degranulation, triggering peristalsis – vomiting and diarrhea.

Bronchial asthma is a form of chronic asthma associated with large numbers of eosinophils in bronchial mucosa, large amount of mucous secretion, smooth muscle hypertrophy and hyperactive. The inhaled allergen stimulate bronchial mast cell activation which leads to constriction and airway obstruction.

Anaphylaxis is a severe hypersensitivity response to an allergen, caused by wide-spread degranulation of mast cells, which can be life threatening. The types of allergens may include uts, shellfish, penicillin family of antibiotics and bee stings. It is characterised by:

- Edema (fluid build up) in tissue such as the larynx
- Vasodilation: drop in blood pressure
- Bronchoconstriction

Treatments

Key treatments are based on:

- Inhibiting mast cell degranulation
- Antagonising the effects of mast cell mediators
- Reducing inflammation

Syndrome	**Therapy**	**Mechanism of action**
Anaphylaxis	Epinephrine	Causes vascular smooth muscle cell contraction, increases cardiac output