Hypersensitivity

Overview on Hypersensitivity

The adaptive immunity, having a diversity of responses involved for its function, may be involved in quite a lot of problems when it comes to tissue injury and diseases. As much as it can protect the body from harmful pathogens, it can also be implicated in situations where there is an exaggerated response leading to tissue damage. These conditions are collectively called as **hypersensitivity reactions**.

Hypersensitivity reactions can be caused by a variety of reasons. For one, our **own immune system could react with the functioning cells** within our body. Under normal circumstances, the immune system employs a screening process wherein self-detecting immune cells are eliminated from the circulation. However, in some people, this mechanism can be absent. Hypersensitivity can also be **activated in the actual presence of a microbe**. In this situation, there is an exaggeration in the efforts to neutralize the microorganism. This can lead to the destruction of the cells, tissues, and structures adjacent to the area of invasion. This mechanism is most pronounced when the microorganism is very persistent.

Environmental antigens may also play a part in tissue destruction caused by the immune reaction. In select people, a certain antibody (**immunoglobulin E or IgE**) is produced in the presence of an allergen coming from the environment, leading to the development of an allergic reaction. Hypersensitivity reactions are an overreaction of the immune system to an **antigen** which would not normally trigger an immune

response. The antigen may be something which would in most people be ignored – peanuts, for example, or it may originate from the body. In either case, the damage and clinical symptoms result from the body's response to the substance rather than damage caused by the substance itself. The vulnerability of an individual to these reactions can have a genetic link. Overreaction to innocuous antigens are linked to changes in the CD regions of **T-helper cell** membranes, explaining why reactions like peanut allergies can commonly run in families. Overreaction to self-antigens is normally due to a failure in central tolerance, and this failure can also have genetically-inheritable features.

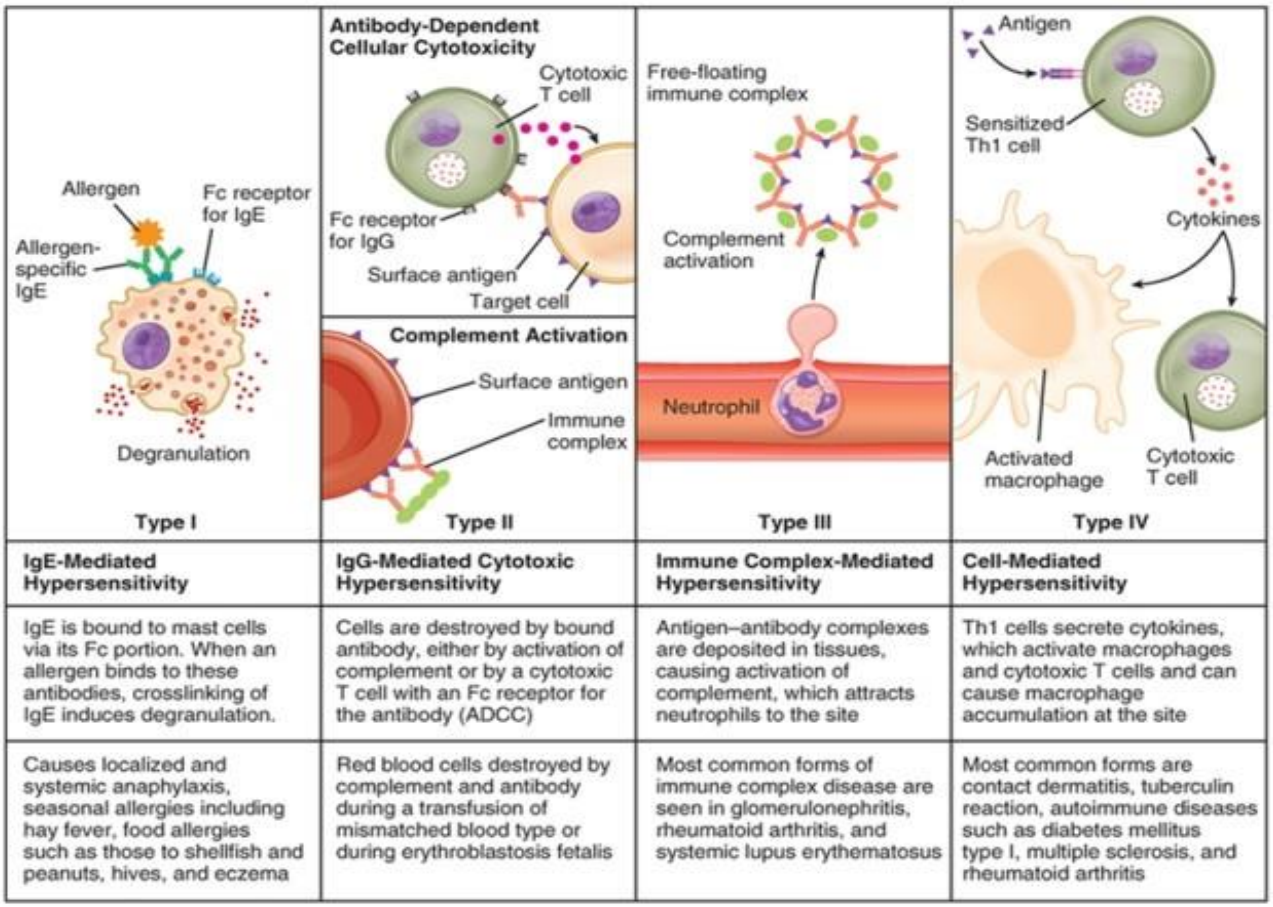
As is the case for many immune reactions, hypersensitivity reactions require two separate interactions of the immune system with the antigen. The first time an antigen enters the body, it is picked up by antigen-presenting cells (such as macrophages or dendritic cells) and taken to the nearest lymph node, where it is presented to **naïve T-cells.** Cross-linking of the antigen with T-cells, as well as co-stimulatory molecules, can lead to activation of that T-cell and subsequent differentiation into "primed" Th1, Th2, or Th17 cells, which are specific to that antigen and can stimulate further immune responses if they meet the antigen again. It is this second meeting that could result in a hypersensitivity reaction.

Types of Hypersensitivity –

In 1963, two British immunologists, Robert Coombs and Philip Gell, published in a book a new scheme for classifying different types of hypersensitivity reactions. Although knowledge on the underlying immunological processes has greatly expanded over the past 50 years, this simple classification is still used nowadays.
Coombs and Gell's classification divides allergies into four pathophysiological types, namely the immediate (type I), cytotoxic (type II), immune complex-mediated (type III), and delayed hypersensitivity

(type IV) reactions. The different pathophysiological mechanisms lead to varying latency periods for the four classes: type I allergic symptoms already appear after a few seconds to minutes; symptoms of type II reactions appear after minutes to hours; signs of type III allergic reactions set in after several hours; and finally, for type IV reactions, a long latency of hours to days is expected. Types I to III are also termed ‘humoral’ reactions, because these are mediated by soluble factors (ie antibodies), whereas in type IV, primarily cells (ie T cells) are involved. While the three humoral types have remained basically the same over the past 50 years, for the cell-mediated type IV reaction, further subclassifications have been proposed.

Although, the immune system is primarily used to protect against microbes such as bacteria, viruses, and fungi, unexpected excesses of the immune response may lead to disease states. The excessive immune responses are usually referred to as hypersensitivity reactions. The original Gell and Coomb’s classification categorizes hypersensitivity reactions into four subtypes according to the type of immune response and the effector mechanism responsible for cell and tissue injury: type I, immediate or IgE mediated; type II, cytotoxic or IgG/IgM mediated; type III, IgG/IgM immune complex mediated; and type IV, delayed-type hypersensitivity or T-cell mediated.1 In clinical practice, however, patients often display a constellation of symptoms that usually overlap several of these mechanisms. For example, individuals who are allergic to penicillin may exhibit symptoms that suggest a type I or IgE-mediated reaction such as anaphylaxis; they may also exhibit a serum sickness such as a disease that suggests a type III or an IgG/IgM immune complex– mediated reaction.



IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
IgE is bound to mast cells via its Fc portion. When an allergen binds to these antibodies, crosslinking of IgE induces degranulation.	Cells are destroyed by bound antibody, either by activation of complement or by a cytotoxic T cell with an Fc receptor for the antibody (ADCC)	Antigen–antibody complexes are deposited in tissues, causing activation of complement, which attracts neutrophils to the site	Th1 cells secrete cytokines, which activate macrophages and cytotoxic T cells and can cause macrophage accumulation at the site
Causes localized and systemic anaphylaxis, seasonal allergies including hay fever, food allergies such as those to shellfish and peanuts, hives, and eczema	Red blood cells destroyed by complement and antibody during a transfusion of mismatched blood type or during erythroblastosis fetalis	Most common forms of immune complex disease are seen in glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus	Most common forms are contact dermatitis, tuberculin reaction, autoimmune diseases such as diabetes mellitus type I, multiple sclerosis, and rheumatoid arthritis

TYPE I—IMMEDIATE OR IgE-MEDIATED REACTIONS :

This subclass is characterized by the reaction between IgE bound to mast cells and allergens, otherwise known as an **allergy**. This is mediated by a specific type of T lymphocytes called **T_H2** that is essential in the production of IgE, eventually leading to inflammation. The activation of T_H2 leads to the production of certain cytokines that are potent in mediating an additional response from other immune components. To name a few including interleukins.

IL-4: aside from the formation and activation of additional T_H2 cells, IL-14 is also responsible for the antibodies produced by B cells to switch into becoming IgE.

IL-5: this is the interleukin behind the activation of **eosinophils**, a granulocyte that is a potent effector cell for type I reactions.

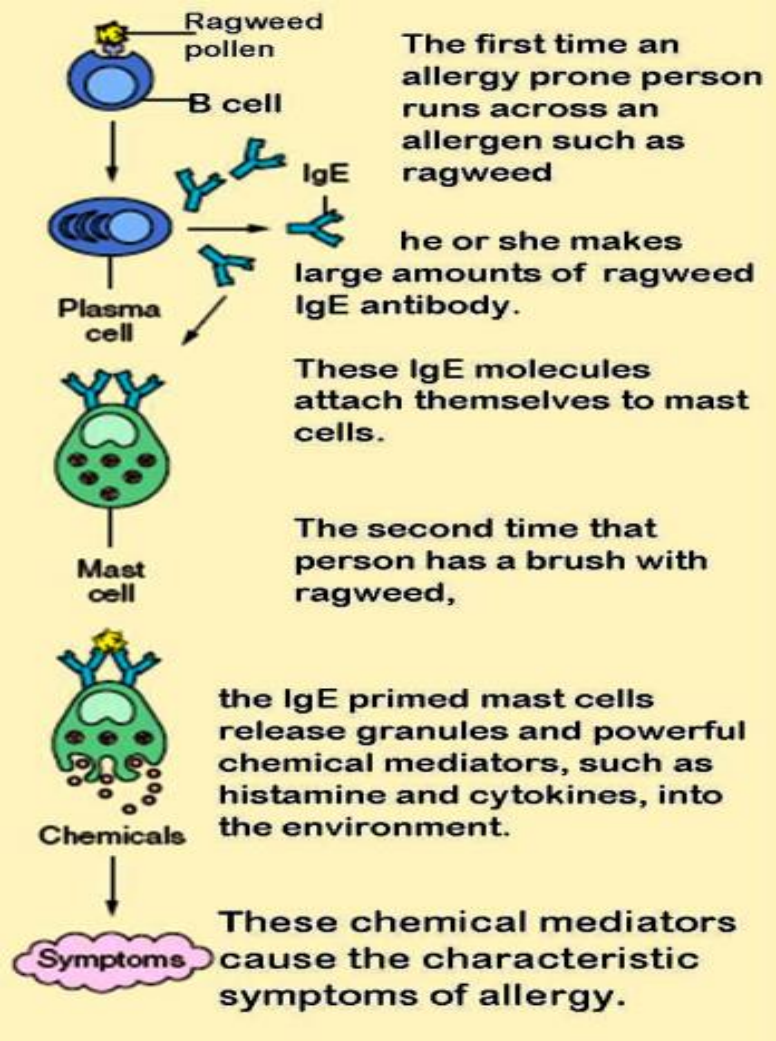
IL-13: IL-13 promotes the production of more IgE and could also act on some epithelial cells causing them to secrete mucus.

Once the reactions are in motion, effector cells involved in the immediate hypersensitivity reaction such as mast cells and eosinophils become activated, causing the classic signs and symptoms associated with allergies. Some common examples of the **early-phase** of immediate hypersensitivity are:

- Rashes or blisters in the skin
- Presence of discharges from the eyes and nose
- Hay fever
- Bronchial asthma
- Gastrointestinal abnormalities (e.g. diarrhea, vomiting)

When activated circulating effector cells, such as mast cells, come into contact with the same allergen. This can cause them to go haywire by releasing a lot of mediators that can cause inflammation and tissue damage. These include **preformed mediators** (vasoactive amines, enzymes, and proteoglycans)**, lipid-derived mediators** (leukotrienes, prostaglandin D_2 and platelet-activating factor) and other cytokines. During the **late-phase** of an immediate hypersensitivity response, the reactions that led to the activation of effector cells and the production of potent mediators are sustained. This is made possible as additional cells of the immune system are recruited despite the already eliminated allergen. Eosinophils are usually the ones present in these cases.

IgE antibodies are produced in response to parasitic infections and, along with eosinophil activation, primarily serve protective functions and help eradicate the parasites. Atopic individuals may form allergenspecific IgE antibodies in response to allergens, such as present in the environment, in foods, and in drugs. The IgE antibodies thus formed attach to high-affinity IgE receptors (FcRI), which are present on mast cell and basophil surfaces. On reexposure, the allergen is recognized by IgE antibodies bound to mast cells and basophils and leads to triggering of these cells resulting in an immediate hypersensitivity reaction. The immediate hypersensitivity reaction usually consists of two phases; an immediate response that occurs within minutes and is caused by histamine, prostaglandin D2, leukotriene D4, and kinins (and tryptase) and a delayed reaction that occurs after 4 – 8 hours and is effected by cytokines such as IL-1, tumor necrosis factor, IL-4, IL-5, IL-13, and various colony-stimulating factors such as granulocyte monocyte colony-stimulating factor. In addition to mast cells and basophils, eosinophils and neutrophils may also be involved in producing the complete spectrum of the immediate hypersensitivity reaction. Examples of immediate hypersensitivity reactions are anaphylaxis, which is characterized by dilatation of the blood vessels and constriction of the airways and may occur in response to allergens present in foods— nuts and milk; bronchial asthma, which may be caused by repeated immediate hypersensitivity and late-phase reactions in the lung tissue; and skin manifestations such as urticaria, which is a wheal and flare (erythema) reaction.



TYPE II—CYTOTOXIC OR IgG/IgM-MEDIATED REACTIONS :

In some cases, what causes inflammation and cellular destruction are antibodies. This reaction can be brought about by antibodies that bind to self-antigens (**autoantibodies**) or from **exogenous antigens** that have the tendency for exaggerated reactions.

Antibodies, particularly **immunoglobulin G and M (IgG and IgM)**, are present on the surface of some cells and in the extracellular matrix. These proteins also contain receptors that bind to specific antigens. Once

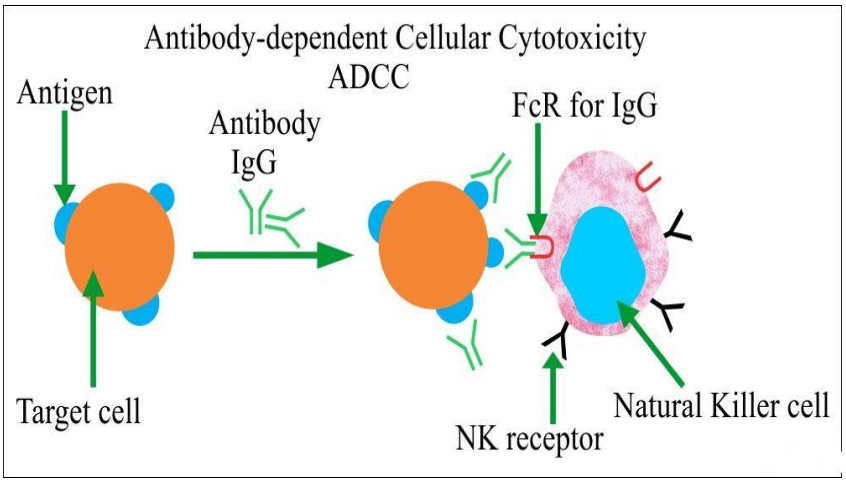
bound, a number of chain reactions ensue, ultimately leading to cell death and inflammation. In a process called **opsonization**, the bound antibodies, now called an **antigen-antibody complex**, make the microbe more visible for phagocytosis by macrophages and neutrophils. This is made possible as the complexes release cytokines leading to the activation of the **complement system**, a series of reactions that produce complement substances. These substances act as a potent mediator for further immune reactions to continue. Additionally, these act as a cytotoxic agent.

These complexes could deposit in various tissues and extracellular matrices in the body. This becomes a problem as the complement substances produced by these complexes could attract cells and mediators involved in the inflammatory process. This phenomenon is quite evident in the following cases:

- Transfusion reactions
- Hemolytic disease of the newborn
- Autoimmune hemolytic anemia, agranulocytosis, and thrombocytopenia
- Specific drug reactions
- Glomerulonephritis
- Myasthenia gravis, Graves disease, and other autoimmune disorders

Immune responses that usually afford protection against infections and eradication of malignant cells may sometimes cause damage to tissues. The immune responses commonly involve IgG and IgM and, to a lesser extent, IgA antibodies. The antibodies usually are directed against cell surface antigens such as those present on red blood cells, neutrophils, and platelets; those present on epithelial cells of glandular and mucosal

surfaces; or against those present on tissues such as basement membranes. Three underlying mechanisms commonly account for the tissue damage. First, antibodies may directly coat or opsonize cells or they may activate the complement system, which leads to the production of activated complement components that may then coat or opsonize the cells. These opsonized cells are phagocytosed and are destroyed by phagocytes that express receptors for antibodies and complement proteins. The underlying mechanism in autoimmune hemolytic anemia and autoimmune thrombocytopenic purpura is an example. Second, antibodies deposited in tissues subsequently recruit neutrophils and macrophages, which leads to tissue injury and inflammation. This is the mechanism of injury in antibody-mediated glomerulonephritis. The third mechanism of immune response is antibody-dependent cell mediated cytotoxicity, which occurs when eosinophils bind to IgE-bound helminths and release their granule components. Type II reactions can also be divided into two different subtypes. Type IIa reactions are characterized by cytolytic reactions produced by antibodies causing autoimmune hemolytic anemia, whereas type IIb reactions are characterized by cell-stimulating antibodies in patients with Graves disease (a long-acting thyroid stimulator, thyroid-stimulating hormone receptor antibodies) or antibodies to the high-affinity mast cell receptor (Fc RI) or IgE in chronic idiopathic urticaria.



TYPE III— IMMUNE COMPLEX MEDIATED :

Type III hypersensitivity reactions are primarily characterized as **reactions involving the deposition of immune complexes in various locations in the body**. These depositions are most prominent in areas that require high blood flow for the formation of other body fluids such as urine and synovial fluid. Examples of locations prone for deposition are:

- Kidneys
- Joints
- Endothelium of blood vessels

Just like the 2nd type of hypersensitivity, type III hypersensitivity starts off as exogenous (foreign antigens) or endogenous (autoantigens) antigens activate antibodies secreted by B lymphocytes. Antibodies, particularly IgG and IgM bind to the offending agent in the circulation. However, in the aforementioned locations where relatively higher blood flow is needed for the production of other fluids, these complexes tend to plant themselves and wreak havoc on those areas. Once deposited, the

complement cascade will be triggered and will then produce substances that are both locally and systemically active.

Acute serum sickness

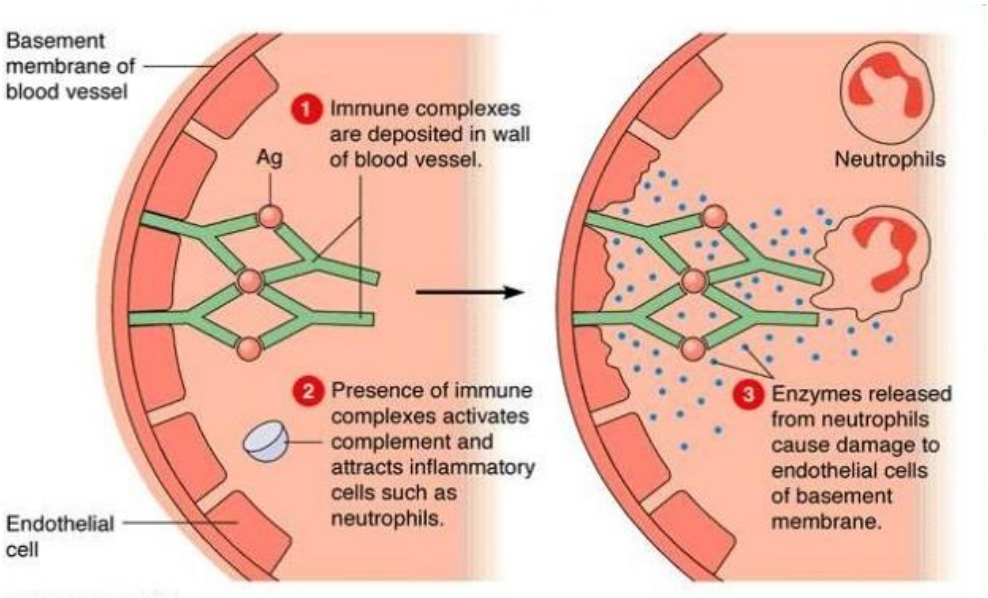
Immune complex-mediated hypersensitivity reaction is very evident in cases where sera coming from different organisms or species (e.g. anti-tetanus immunoglobulin from horse serum) is injected into human beings (e.g. when a child punctured by a nail). This is commonly called **acute serum sickness.** Although very rare, this case serves as a model in explaining what goes on during a type III reaction.

Arthus reaction

Another case that exemplifies this type of reaction is the **Arthus phenomenon**. This occurs when a locally injected antigen causes a localized reaction that is seen as necrosis of the overlying tissues. This is due to the deposition of complexes on the vascular structures found in that area.

In type II immune response, the mechanism of tissue injury involves the formation of IgG or IgM antibodies to self or foreign antigens and then the formation of complexes. The complexes deposit and activate the complement pathway, with concomitant fall in serum complement levels. The activated complement components recruit and activate neutrophils, which results in inflammation and tissue injury. The constellation of symptoms is determined by the site of immune complex deposition and not by the source of the antigen. The antigen–antibody complexes are usually deposited in small arteries, renal glomeruli, and synovial of joints and the symptoms usually are vasculitis, nephritis, and arthritis, respectively.10 One example is serum sickness-like disease, which may be acute or may have a prolonged or chronic course. This

prototypical immunecomplex–mediated disease, however, was first observed in individuals with diphtheria infections. These individuals were being treated with sera containing antibodies to diphtheria antitoxin (passive immunization) from horses that had been immunized with the diphtheria toxin. A number of autoimmune diseases may also be caused by tissue deposition of antigen–antibody complexes. Systemic lupus erythematosus is an autoimmune disease in which a large number of antibodies to DNA and nucleoproteins are produced, which complex with antigens and then deposit in the tissues and lead to an inflammatory response.



TYPE IV—DELAYED-TYPE HYPERSENSITIVITY OR T-CELL MEDIATED :

As the name implies, type IV hypersensitivity reactions are characterized by a rather delayed response mediated by either helper or cytotoxic T cells. In most cases, it is usually the helper T cells that are implicated in most cases of hypersensitivity.

Helper T lymphocytes

This specific subclass of T lymphocytes does not directly attack pathogens. Instead, it **produces interleukins and other cytokines that promote the proliferation of other immunologically active cells**. In type IV hypersensitivity, the particular type of helper T cells implicated are T_H1 and T_H17.

Helper T cells are activated when cells that present antigens such as dendritic cells and macrophages produce certain cytokines. These cytokines induce the proliferation of either T_H1 or T_H17. Once produced, these effector cells enter the circulation where they serve as guards that work long term in fending off potential pathogens.

The effects of this type of mechanism are delayed because it usually takes hours to days for the damaged interleukins to accumulate in the circulation. The interleukins produced attract cells such as neutrophils and macrophages that can phagocytose or damage the area where there are pathogens. Examples of cases where Helper T cell-mediated hypersensitivity is apparent include the following:

- Tuberculin reaction
- Contact dermatitis
- Some drug reactions
- Rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and other inflammatory diseases

Cytotoxic T lymphocytes

Unlike helper T cells, cytotoxic T cells directly kill the cells that carry the triggering antigen. For this reason, this particular subtype is highly

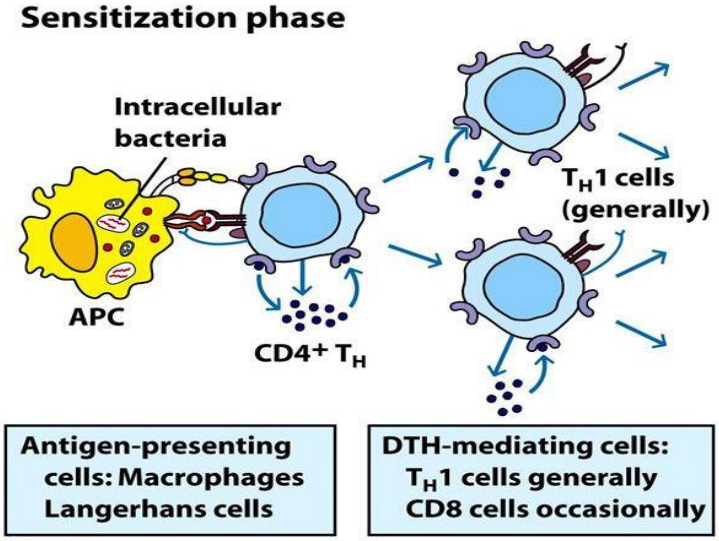
effective against viral and parasitic infections in which the offending agent is found intracellularly.

These cells do damage by releasing molecules and complexes that damage the microbe. Unfortunately, these substances are not selective only to offending agents and can be detrimental to surrounding healthy tissues. Cases where there is a cytotoxic T lymphocyte-mediated hypersensitivity are the following:

- Liver damage during viral hepatitis
- Organ graft rejection

Type IV reactions involve sensitized T cells. The type IV reaction that Gell and Coombs described, also called delayed-type hypersensitivity, is mediated by CD4 T helper cells and is a Th1 type of response.2 This response is currently called type IVa. The tissue injury is primarily caused by lysosomal enzymes, reactive oxygen intermediates, nitric oxide, and proinflammatory cytokines that are secreted by activated macrophages. The secretion of cytokines and growth factors often lead to tissue fibrosis. A delayed hypersensitivity response may be involved in the pathogenesis of a number of diseases. Examples include, type I diabetes, in which destruction of insulin-producing islet cells may be affected by lymphocytes and macrophages; multiple sclerosis, an autoimmune disorder affecting the central nervous system, in which T cells react against myelin antigens; and rheumatoid arthritis, in which a T-cell– mediated inflammation is suspected. Enumeration of the T-cell subsets has allowed further categorization of the type IV immune responses. This categorization into four subtypes—type IVa, IVb, IVc, and IVd—is based on the distinct cytokine profile, types of cells involved, and pathogenesis.11 An example of type IVa response is

contact dermatitis due to poison ivy Rhus antigen. This reaction involves Th1 type T cells that activate macrophages by secreting large amounts of cytokines such as interferon- and tumor necrosis factor-. Type IVb reactions follow a Th2 type immune response. CD4 Th2 cells produce IL-4, IL-5, and IL-13, which promote IgE production from B cells, deactivation of macrophage, and mast cell and eosinophil responses. Type IVb reactions may be involved in the late-phase allergic inflammations of the bronchi or nasal mucosa (i.e., asthma and allergic rhinitis). Type IVc reactions are mainly mediated by cytotoxic CD8 T cells. Type IVc reactions seem to be the major mechanism of bullous skin reactions such as StevensJohnson's syndrome and toxic epidermal necrolysis, where activated CD8 T cells induce apoptosis or necrosis of keratinocytes. Type IVd reactions are neutrophilic inflammation via T lymphocytes. Sterile neutrophilic inflammation of the skin in acute generalized exanthematous pustulosis is a typical example. Acute generalized exanthematous pustulosis is characterized by appearance of superficial pustules after drug ingestion or infection. In this disease, T-cell–derived CXCL-8 recruits neutrophils to the lesion and granulocyte monocyte colony-stimulating factor from T cells prevents apoptosis of the recruited neutrophils. In addition, IL-17 and IL-22 stimulate production of IL-8, which supports the accumulation of neutrophils in lesions. Behcet disease and pustular psoriasis are other examples of type IVd reactions.


Sensitization phase
Intracellular bacteria
APC
CD4+ TH
TH1 cells (generally)
Antigen-presenting cells: Macrophages Langerhans cells
DTH-mediating cells: TH1 cells generally CD8 cells occasionally