Hypersensitivity

Hypersensitivity reactions occur when the normally protective immune system responds abnormally, potentially harming the body. Various autoimmune disorders as well as allergies fall under the umbrella of hypersensitivity reactions, the difference being that allergies are immune reactions to exogenous substances (antigens or allergens), whereas autoimmune diseases arise from an abnormal immune response to endogenous substances (autoantigens). A symptomatic reaction only occurs in sensitized individuals, i.e., they must have had at least one prior asymptomatic contact with the offending antigen. Hypersensitivity reactions are commonly classified into four types. Type I hypersensitivity reactions are immediate allergic reactions (e.g., food and pollen allergies, asthma, anaphylaxis). Type II hypersensitivity reactions are referred to as cytotoxic, as they involve antibodies that are specific to particular tissues within the body and cause destruction of cells in these tissues (e.g., autoimmune hemolytic anemia, Goodpasture syndrome). Type III hypersensitivity reactions are immune complex-mediated, with tissue damage caused by antigen-antibody complex deposition (e.g., many vasculitides and glomerulonephritides). Type IV hypersensitivity reactions (e.g., TB skin tests, contact dermatitis) are delayed and cell-mediated and are the only hypersensitivity reaction that involves sensitized T lymphocytes rather than antibodies. Unlike true hypersensitivity reactions, which occur after sensitization, nonallergic hypersensitivity reactions (e.g., pseudoallergies) cause mast cell activation and histamine release after initial exposure to a trigger substance (e.g., radiocontrast media).

Definitions

Hypersensitivity reaction: a condition in which the normally protective immune system has a harmful effect on the body

Allergy: an abnormal immunological response to an otherwise harmless environmental stimulus (e.g., food, pollen, animal dander)

Autoimmune disease: an abnormal immunological response directed against an antigen that is actually part of the body itself

Stages

Sensitization: initial asymptomatic contact with an antigen

Effect: harmful immune response following sensitization and subsequent antigen contact

Types: Hypersensitivity reactions are classified into five types (following Gell and Coombs' classification)

Type I hypersensitivity consists of the IgE-mediated immediate hypersensitivity responses found in anaphylaxis and asthma attacks and slower responses caused by inflammatory cascades triggered by mediators released in the immediate reaction and by accompanying Th2 responses.

Type II hypersensitivity is mediated by the direct effects of antibody and complement-mediated killing or opsonization.

Type III hypersensitivity is mediated by the formation of antigen–antibody complexes that either activate complement for direct toxic effects or attract inflammatory cells, especially neutrophils that bind the complexes by Fc receptors and cause tissue damage.

Type IV hypersensitivity can be subdivided depending on the type of T cell activated by the immune response.

Type I hypersensitivity: immediate (atopic or anaphylactic)

Type I hypersensitivity is an allergic reaction. Exposure to the allergen may be by ingestion, inhalation, injection or direct contact. The difference between a normal immune response and a type I hypersensitivity response is that plasma cells secrete IgE antibodies that bind to mast cells and basophils that then release histamines, a vasodilator, and heparin, a blood thinner. These cause inflammation at the site as blood flow to the affected tissues is increased. The reaction may be either local or systemic. Symptoms vary from mild irritation to sudden death from anaphylactic shock. This is why allergies are manifested as red and watery eyes,

runny nose and hives. Asthma is a form of anaphylaxis, as a combination of oedema and airway constriction prevents tissues from getting sufficient oxygen.

Examples of type I hypersensitivity include:

allergic asthma
allergic conjunctivitis
allergic rhinitis ('hay fever')
anaphylaxis
angio-oedema
atopic dermatitis (eczema)
eosinophilia
urticaria (hives).

Type II or Antibody-Mediated Hypersensitivity

Type II hypersensitivity is mediated by IgM or IgG targeting membrane-associated antigens. A sensitization phase leads to production of antibodies that recognize substances or metabolites that accumulate in cellular membrane structures. In the effector phase, target cells become coated with antibodies, a process termed opsonization, which leads to cellular destruction by three mechanisms: (1) phagocytosis, (2) complement-dependent cytotoxicity (CDC), and (3) ADCC. First, IgG or IgM antibodies coating target cells can bind to Fc receptors present on cells such as macrophages and neutrophils and mediate phagocytosis. IgG or IgM antibodies can also activate complement via the classical pathway. This leads to deposition of C3b, which can mediate phagocytosis. Complement activation also leads to production of the MAC, which forms pores in the cellular membrane resulting in cytolysis (CDC). Finally, IgG antibodies can bind FcγRIII on NK cells and macrophages, mediating release of granzymes and perforin and resulting in cell death by apoptosis (ADCC).

The most common cause of type II reactions are medications including penicillins, cephalosporins, hydrochlorothiazide, and methyldopa, which become associated with red blood cells or platelets leading to anemia and thrombocytopenia. The mechanisms involved in type II hypersensitivity also play a role in cellular destruction by autoantibodies.

Type III Hypersensitivity

Type III hypersensitivity is caused by circulating immunocomplexes and is typified by serum sickness (a drug reaction in which multimeric drug-antibody aggregates form in solution). Preformed immunocomplexes deposit in various vascular beds and cause injury at these sites. Multimeric antigen-antibody complexes are efficient activators of the complement cascade through its classical pathway. The vascular beds in which immunocomplexes are deposited are determined in part by the physical nature of the complexes (their aggregate size, charge, hydrophobicity, etc.), and the specificity of deposition at particular locations can be surprisingly precise in some diseases. Typical sites of injury are kidney, skin, and mucous membranes. Type III hypersensitivity is common in systemic lupus erythematosus (SLE) and underlies most of the pathophysiology of this chronic autoimmune disease. Some inflammatory reactions may blend features of type II and III hypersensitivity with the formation of immunocomplexes in situ.

Type IV Hypersensitivity

Type IV hypersensitivity is also called delayed-type hypersensitivity (DTH) because the tissue reaction usually occurs 24 to 48 hours after exposure to antigen. Type IV hypersensitivity is a cell-mediated immunoreaction that is dependent on the presence of a significant number of primed, antigen-specific T cells (see Fig. 2-29D). This type of reaction is typified by the response to poison ivy, which typically reaches its peak 24 to 48 hours after exposure to antigen. Plant antigens (haptens) react with and modify cellular proteins that are then targeted by the sensitized T cells. Interaction of $CD8^+$ T cells with antigen presented in the context of class I MHC results in the activation of these T cells and induces them to kill target cells displaying these antigens. APCs also display antigen in the context of class II MHC to activate $CD4^+$ T cells to secrete cytokines, including IL-2, which result in the proliferation of $CD8^+$ T cells. The result of these interactions is the amplification of antigen-specific T cells that initiate the hypersensitivity reaction over the course of a few days.

Delayed-type hypersensitivity also describes a positive response to the common test for tuberculosis (subcutaneous injection of mycobacterial purified protein derivative, or PPD). In this case, inactivated toxoid from mycobacteria recruits

pre-primed T cells and macrophages, which initiate an inflammatory response. A positive test occurs only if a significant number of antigen-specific T cells are already present as a result of prior (or ongoing) exposure to mycobacterial antigens. Paradoxically, patients with disseminated tuberculosis may not respond to PPD because of significant immunosuppression produced by severe infection. The interaction of T cells and macrophages with antigen results in the production of IFN-γ and TNF-α to orchestrate a strong inflammatory reaction that may be granulomatous in character (see below). Some types of natural killer cell inflammatory responses may be described as delayed-type hypersensitivity in that they are mediated exclusively by cellular components of the immune system but are not antigen specific.

Note -Type V hypersensitivity categorizes the damage caused by agonist effects of antibodies binding to endocrine receptors.