

Classification of hypersensitivity reactions

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ABSTRACT

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. The classification has been improved so that type IIa is the former type II and type IIb is antibody-mediated cell stimulating (Graves Disease and the "autoimmune" type of chronic idiopathic urticaria). Type IV has four major categories: type IVa is CD4⁺Th1 lymphocyte mediated with activation of macrophages (granuloma formation and type I diabetes mellitus); type IVb is CD4⁺Th2 lymphocyte mediated with eosinophilic involvement (persistent asthma and allergic rhinitis); type IVc is cytotoxic CD8⁺ T lymphocyte with involvement of perforin-granzyme B in apoptosis (Stevens-Johnson syndrome and toxic epidermal necrolysis); type IVd is T-lymphocyte-driven neutrophilic inflammation (pustular psoriasis and acute generalized exanthematous pustulosis). Some diseases have multiple types of immunologic hypersensitivity.

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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 (Table 1).²

TYPE I—IMMEDIATE OR IgE-MEDIATED REACTIONS

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 allergen-specific IgE antibodies in response to allergens,³ such as present in the environment, in foods,⁴ and in drugs.⁵ The IgE antibodies thus formed attach to high-affinity IgE receptors (FcεRI), 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.⁶

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,⁷ 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,⁸ which may be

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Table 1 Classification of hypersensitivity reactions

Classification	Immunoreactants	Clinical Presentation
Type I	Mast cell mediated, IgE dependent (anaphylactic, and IgE independent)	Anaphylaxis, urticaria, angioedema, asthma, and allergic rhinitis
Type IIa	Antibody-mediated cytotoxic reactions (IgG and IgM antibodies complement often involved)	Immune cytopenias
Type IIb	Antibody-mediated cell-stimulating reactions	Graves disease and chronic idiopathic urticaria
Type III	Immune complex-mediated reactions complement involved	Serum sickness and vasculitis
Type IVa	Th1 cell-mediated reactions macrophage activation	Type 1 diabetes and contact dermatitis (with IVc)
Type IVb	Th2 cell-mediated reactions eosinophilic inflammation	Persistent asthma and allergic rhinitis
Type IVc	Cytotoxic T cell-mediated (perforin/granzyme B involved)	Stevens-Johnson syndrome and TEN
Type IVd	T-cell-mediated neutrophilic inflammation	AGEP and Behcet disease

Source: Adapted from Ref. 2.

AGEP = acute generalized exanthematous pustulosis; TEN = toxic epidermal keratinocytes.

caused by repeated immediate hypersensitivity and late-phase reactions in the lung tissue; and skin manifestations such as urticaria,⁹ which is a wheal and flare (erythema) reaction.

TYPE II—CYTOTOXIC OR IgG/IgM-MEDIATED REACTIONS

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.¹⁰ 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 mecha-

nism 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 (FcεRIα) or IgE in chronic idiopathic urticaria.⁹

TYPE III—IgG/IgM IMMUNE COMPLEX MEDIATED

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 immune

complex-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

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- γ and tumor necrosis factor- α . 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 Stevens-Johnson'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.

IMMUNOLOGY

- Type I reactions are effected by mediators released from mast cells and basophils.
- Type II reactions result from formation of antibodies that are usually directed against cellular or matrix antigens and lead to localized disease.
- Type III reactions result from the deposition of antigen-antibody complexes that activate the complement pathway and then recruit and activate neutrophils and result in tissue injury.
- Type IV reactions are mediated by T lymphocytes; there are four subtypes. Some conditions involve more than one subtype.

CLINICAL PEARLS

- Penicillin can cause all types of reactions; type I, anaphylaxis and urticaria; type II, hemolytic anemia; type III, serum sickness-like reaction; and type IV, delayed type drug rash or contact dermatitis.
- An anaphylactic reaction to radiocontrast media is non-IgE-mediated hypersensitivity reaction and can be prevented by pretreatment with corticosteroid and antihistamine, whereas IgE-mediated anaphylaxis is not blocked by corticosteroid pretreatment.

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