Classification of hypersensitivity reactions

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ABSTRACT

As the primary defense against pathogens, the immune system uses numerous strategies to ensure optimal protection for the host. When immune responses go awry, however, they can cause great damage. "Hypersensitivity" is a broad term used to describe an excessive and/or pathogenic immune response to either foreign or self antigens. Gell and Coombs were the first to categorize hypersensitivity reactions into 4 types according to pathophysiology, but more recent insights into the mechanisms of these disorders have since modified the original classification system. This review describes the immune mechanisms involved in each of the modern Gell-Coombs categories.

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In 1963, Gell and Coombs[1] created the foundation for classifying hypersensitivity reactions by dividing them into four distinct groups according to mechanisms of tissue injury: type I (immediate or immunoglobulin E [IgE] mediated), type II (cytotoxic or IgG/IgM mediated), type III (immune complex mediated), and type IV (delayed type or T-cell mediated). This classification system has since then been expanded to include subtypes of types II and IV, with the intent to better reflect the immunopathology of diseases (Table 1).[2,3] In clinical practice, however, the hypersensitivity categories can overlap, and patients may display a constellation of symptoms from multiple types of hypersensitivity reactions at the same time. Syndromes that do not fit into the single Gell-Coombs classification categories are often termed mixed drug reactions, and, clinically, it may be more practical to classify these reactions by the organ systems affected. In addition, it is increasingly recognized that many medications, e.g., penicillins, are capable of inducing many types of reactions.[4]

Antigens of all types and sizes may cause hypersensitivity reactions. Large-molecular-weight protein antigens, whether self or foreign, can be processed and recognized directly by T-cell receptors or immunoglobulins. Many biologic drugs are recombinant antibodies which can form immune complexes and/or bind to Fc receptors on leukocytes.[5] In contrast, small low-molecular-weight compounds (<1000 Daltons) cannot be directly processed or presented by antigen-presenting cells, and thus they cannot elicit immune responses by themselves. However, they may stimulate immune responses in other ways. In the hapten model, small molecules (*e.g.*, penicillin, molecular weight ~300 Daltons) covalently bind to soluble serum proteins (*e.g.*, albumin) or cellular proteins to create new epitopes, which can then be antigenic. Some drugs act as prohaptens, meaning that they are inert in their native form, but their metabolites can haptenize, as is the case with sulfamethoxazole.[6] Finally, the p-i concept (pharmacologic interaction with immune receptors) proposes that some drugs that lack hapten characteristics may bind reversibly (noncovalently) to T-cell receptors or human leukocyte antigen (HLA) molecules directly, possibly in a nonspecific or cross-reactive fashion.[7] This model may help to explain why some HLA alleles render patients prone to delayed hypersensitivity reactions due to certain medications. For example, an estimated 55% of HLA-B*57:01 carriers will develop a hypersensitivity reaction from abacavir.[7] Thus, small-molecular-weight compounds can cause all types of hypersensitivity reactions.[5]

HYPERSENSITIVITY TYPES

Type I

Type I or immediate hypersensitivity is mediated by IgE specific for allergens. An overview of allergens is provided in this issue.[8] Sensitization to allergens occurs when T-helper (Th) type 2 cells and their mediators drive isotype switching in B cells to produce IgE antibodies. A large portion of IgE remains bound to the high-affinity IgE receptor FcεRI on the surface of mast cells and basophils. On re-exposure, allergen cross-links specific IgE on these cells, which causes release of mediators in two main phases. The early phase occurs within minutes and is caused by histamine, proteases (tryptase and chymase), lysosomal enzymes, and other preformed mediators released immediately on mast cell and basophil degranulation. In addition, mast cells

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produce lipid mediators, including prostaglandin D2 and leukotriene C4 from arachidonic acid and release them into circulation within 15 minutes of IgE cross-linking.

The late phase occurs 4 to 8 hours after allergen exposure and is caused by cytokines such as interleukin (IL)-1, tumor necrosis factor (TNF)-α, IL-4, IL-5, IL-13, and granulocyte monocyte colony-stimulating factor (GM-CSF) produced *de novo* by mast cells. The route and location of allergen exposure determine the ensuing symptoms. Inhaled allergens may exacerbate allergic rhinitis or asthma by causing nasal congestion, rhinorrhea, sneezing, and bronchospasm.[9–11] Topical contact with allergens can cause urticaria. Also, exposure to allergen *via* the oral or intravenous route typically produces systemic symptoms. Anaphylaxis is a potentially life-threatening type I systemic allergic response to allergens, such as foods, medications, or stinging insect venoms, and is characterized by urticaria, angioedema, bronchospasm, nausea, vomiting, diarrhea, hypotension, and, rarely, shock.[4]

It should be noted that some disorders are caused by IgE-independent, nonspecific activation of mast cells, which could be considered to be a subset of type I hypersensitivity reactions. These include systemic reactions to substances such as iodinated contrast media, biologic drugs, opiates, and others.[4] Urticaria may also be caused by mast cell activation by various stimuli[12] but may also be due to autoantibodies to the FcεRI receptor, as discussed below.

Type II

IgG and IgM antibodies are key components of host defense, which bind to microbes and aid in their direct killing *via* multiple mechanisms. Unfortunately, when these antibodies bind to self antigens, they can direct the cytotoxic response against the host itself and cause potentially extensive damage. This is the basis of type II reactions, termed cytotoxic reactions, which are characterized by IgG and/or IgM antibodies against cell-surface antigens. These antigens are typically found on circulating blood cells, such as red blood cells, platelets, neutrophils, or on epithelial cells in mucosal surfaces and basement membranes.

Type II reactions are further divided into two subtypes: type IIa and type IIb. Type IIa refers to reactions characterized by cytolytic destruction of targeted cells. IgG/IgM binding to cell-surface components causes cytotoxicity *via* three main mechanisms.[13] The first is complement-dependent cytotoxicity, which is the primary etiology in autoimmune hemolytic anemia and autoimmune thrombocytopenic purpura. Antigen-antibody complexes on the surface of cells activate the classic complement pathway, creating the membrane attack complex (C5-C9), which causes lysis of the target cell. Second, IgG antibodies can induce damage *via* antibody-dependent cell-mediated cytotoxicity. IgG on target cells binds to Fc gamma receptor IIb (FcγRIIb) on natural killer cells and macrophages, which causes them to release granules that contain perforin and granzyme to directly kill cells. Finally, both IgG and IgM can bind to Fc receptors on phagocytes to activate them and initiate phagocytosis. Type IIb reactions involve autoantibodies stimulating cells directly to create pathogenic states. For example, in Graves disease, antibodies to thyrotropin receptors stimulate the thyroid gland to produce excessive amounts of thyroid hormone. Chronic idiopathic (spontaneous) urticaria may be categorized as a type IIb disorder (at least in some patients), due to IgG antibodies directly binding to and stimulating FcεRI receptors on mast cells, which causes mast cell degranulation in the skin and, subsequently, the development of urticaria. In this subset of patients, these autoantibodies are necessary but not sufficient for mast cell activation.

Type III

In type III responses, IgG and IgM antibodies bind to antigens to form immune complexes. These complexes deposit in tissues and activate complement, which then causes organ damage. Common sites of complex deposition include small arteries, renal glomeruli, and synovial capsules of joints, thereby causing vasculitis, glomerulonephritis, and arthritis, respectively.[13] Thus, the symptoms associated with type III reactions are determined by the site of immune complex deposition and not by the source of the antigen. Antigens involved in type III responses can either be self, such as in autoimmune diseases including lupus, or foreign, as is the case in serum-sickness reactions caused by various medications, including proteins (such as thymoglobulin) or small molecules (such as penicillin or procainamide).

Type IV

Type IV hypersensitivity responses are collectively termed delayed reactions and involve T cells as the major effector cells. Sensitized T cells can cause damage directly, as in the case of cytotoxic T cells, or helper T cells may activate other leukocytes, such as macrophages, neutrophils, and eosinophils, which may impart tissue injury through the production and release of reactive oxygen species, lysosomal enzymes, and inflammatory cytokines. Relatively recent enumeration of T-cell subsets has allowed for further categorization, and type IV reactions are now divided into four subtypes according to the immune mechanisms and pathogenesis of each: types IVa, b, c, and d.[3] The classic type IV reaction as first described by Gell and Coombs[1] is now termed types IVa and is mediated by Th1 cells,

Table 1 **Modern classification of hypersensitivity reactions***

Classification Type	Immunologic Mechanisms	Clinical Examples
I	Mast cell-mediated reactions	
	IgE-dependent (anaphylactic)	Anaphylaxis, angioedema, urticaria, asthma, allergic rhinitis
	IgE-independent (nonimmunologic or anaphylactoid)	Reactions to iodinated contrast reagents and some biologics
IIa	Antibody-mediated cytotoxic reactions (IgG/IgM antibodies); complement often involved	Immune cytopenias
IIb	Antibody-mediated cell-stimulating reactions	Graves disease, chronic idiopathic (spontaneous) urticaria
III	Immune complex-mediated complement activation	Serum sickness, drug-induced lupus, vasculitis
IVa	Th1 cell–mediated macrophage activation	Type 1 diabetes, contact dermatitis (with type IVc), tuberculin test reactions
IVb	Th2 cell–mediated eosinophilic inflammation	Maculopapular exanthems, DRESS syndrome, persistent asthma, allergic rhinitis
IVc	Cytotoxic T cell–mediated reactions	SJS and/or TEN, bullous exanthems
IVd	T cell–mediated neutrophilic inflammation	AGEP, Behçet's disease

IgE = Immunoglobulin E; Th = T-helper cell; DRESS = Drug Reaction with Eosinophilia and Systemic Symptoms; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; AGEP = acute generalized exanthematous pustulosis.
**Adapted from Ref. 14.*

which activate macrophages to secrete cytokines such as interferon γ and TNF-α. A prototypical example of this type is contact dermatitis, which can occur to various substances, including poison ivy, oak, and sumac (members of the *Toxicodendron* genus). Type IVb reactions involve the production of IL-4, IL-5, and IL-13 by Th2 cells to induce eosinophilic inflammation and IgE production from B cells. For example, in patients with Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome) drug-sensitized Th2 cells promote eosinophilic survival, activation, and tissue migration to cause multiorgan injury. In addition, type IVb reactions may be involved in the late-phase inflammation of atopic disorders, such as asthma or allergic rhinitis. Type IVc is primarily mediated by cytotoxic CD8+ T cells, which directly kill targeted cells by using a number of mediators, including perforin, granulysin, and granzyme B. Type IVc reactions seem to be the underlying mechanism of tissue damage in Stevens-Johnson syndrome and toxic epidermal necrolysis, in which activated CD8+ T cells induce apoptosis and/or necrosis of keratinocytes. Type IVd responses cause tissue damage when T-cell–derived CXCL-8 (also known as IL-8) recruits neutrophils into tissues to create sterile neutrophilic inflammation, as is the case with acute generalized exanthematous pustulosis.

IMMUNOLOGY

- Type I reactions are mediated by allergen-specific IgE bound to the high-affinity FcεRI receptor on mast cells and basophils. On allergen cross-linking of these receptors, mediators (e.g. histamine) are released, which result in urticaria, angioedema, and/or anaphylaxis.
- Type II reactions are characterized by IgG/IgM binding to self antigens on the surface of cells, which can cause tissue damage by activating phagocytosis, complement-directed cytotoxicity, and/or antibody-dependent cell-mediated cytotoxicity.
- Type III reactions are mediated by immune complexes of IgG/IgM and antigens, which deposit into tissues to cause direct organ damage.
- Type IV reactions are delayed responses that are mediated by T cells and are further divided into four subtypes.

CLINICAL PEARLS

- Some medications (such as penicillins) can cause all types of hypersensitivity reactions.
- There are no known therapies that can effectively prevent IgE-mediated reactions. Medications such as H_1 antihistamines and corticosteroids only mitigate the effects of some (but not all) mediators.

- Anaphylactic reactions to some substances, such as iodinated contrast media, are not IgE mediated and can be prevented for most patients by pretreatment with corticosteroids and H_1 antihistamines.

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