Understanding Pathophysiology of Allergic Diseases for better Interpretation of Test Results

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We are doing many tests for the diagnosis of allergic diseases and finding the causative agents. Allergic diseases are caused by hypersensitivity by the immune system, and allergic tests have also been developed and carried out with an immunological mechanism. If we understand the immunological mechanism of allergic diseases associated with the test, we think, it may be helpful to modify the test method or to interpret the results according to the individual patient.

Allergic (including atopic) and other hypersensitivity disorders are inappropriate or exaggerated immune reactions to foreign (innocent) antigens. Inappropriate immune reactions include those that are misdirected against intrinsic body components, leading to autoimmune disorders. Hypersensitivity reactions are divided into 4 types by the Gell and Coombs classification. Hypersensitivity disorders often involve more than 1 type.

Type I reactions (immediate hypersensitivity) are IgE–mediated. Antigen binds to IgE that is bound to tissue mast cells and blood basophils, triggering release of preformed mediators (eg, histamine, proteases, chemotactic factors) and synthesis of other mediators (eg, prostaglandins, leukotrienes, platelet–activating factor, cytokines). These mediators cause vasodilation, increased capillary permeability, mucus hypersecretion, smooth muscle spasm, and tissue infiltration with eosinophils, type 2 helper T (TH2) cells, and other inflammatory cells.

Type I reactions develop <1 h after exposure to antigen.

Type I hypersensitivity reactions underlie all atopic disorders (eg, allergic asthma, rhinitis, conjunctivitis) and many allergic disorders (eg, anaphylaxis, some cases of angioedema, urticaria, latex and some food allergies). The terms atopy and allergy are often used interchangeably but are different. Atopy is an exaggerated IgE–mediated

immune response; all atopic disorders are type I hypersensitivity disorders. Allergy is any exaggerated immune response to a foreign antigen regardless of mechanism. Thus, all atopic disorders are considered allergic, but many allergic disorders (eg, hypersensitivity pneumonitis) are not atopic.

Atopic disorders most commonly affect the nose, eyes, skin, and lungs. These disorders include conjunctivitis, extrinsic atopic dermatitis, immune-mediated urticaria, immune-mediated angioedema, acute latex allergy, some allergic lung disorders (eg, allergic asthma, IgE-mediated components of allergic bronchopulmonary aspergillosis), allergic rhinitis, and allergic reactions to venomous stings.

Skin prick (intrademal) testing is a bioassay that detects the presence of allergen-specific IgE on a patient's mast cells. A positive reaction implies that mast cells within other target organs (ie, eyes, nose, lungs, and gastrointestinal tract) would also react upon exposure to that allergen. When allergen is introduced into the skin of a patient during skin testing, it comes into contact with cutaneous mast cells. Binding of the allergen occurs if the patient's mast cells are coated with IgE recognizing that specific allergen. If both IgE and allergen are present in sufficient quantities, then adjacent IgE molecules directed against the allergen may be crosslinked on the cell surface and initiate intracellular signaling. These events lead to mast cell activation, release of the contents of intracellular granules (degranulation), and the de novo generation of inflammatory mediators. Degranulation releases preformed vasoactive mediators and enzymes, such as histamine, tryptase, chymase, and carboxypeptidase. Histamine is the major mediator of the wheal and flare response, but other mediators (eg, prostaglandin D2) are also involved, as the size of the wheal does not correlate directly with the concentrations of histamine released.

The clinical result of these cellular events is a positive skin test or a transient "wheal-and-flare" reaction. This reaction consists of a localized central area of superficial skin edema (wheal) surrounded by erythema (flare). This pruritic reaction represents the immediate phase of the allergic reaction. Late-phase reactions (LPRs) may develop at skin test sites in some individuals. These consist of deep tissue swelling, warmth, pruritus, and erythema beginning one to two hours after testing and resolving in 24 to 48 hours. LPRs are mast cell mediated and IgE dependent, although they do not predict symptoms on exposure and are not used in the diagnosis of IgE-mediated allergy.

Type II reactions (antibody-dependent cytotoxic hypersensitivity) result when antibody binds to cell surface antigens or to a molecule coupled to a cell surface. The antigen-antibody complex activates cells that participate in antibody-dependent cell-mediated cytotoxicity (eg, natural killer cells, eosinophils, macrophages), complement, or both. The result is cell and tissue damage. Disorders involving type II reactions include hyperacute graft rejection of an organ transplant, Coombs-positive(drug-induced) hemolytic anemia, Hashimoto thyroiditis, and anti-glomerular basement membrane disease (eg, Goodpasture syndrome).

In some instances antibodies against cell-surface receptors have cell-stimulatory (agonist) effects without

necessarily being cytotoxic. An example is Graves' disease (hyperthyroidism, autoallergic thyroiditis) in which IgG antibodies directed against the thyroid-stimulating hormone (TSH) receptor is produced. some patients with chronic urticaria have histamine-releasing IgG autoantibodies against the ε subunit of the high-affinity IgE receptor(FcεRIα). The antibody is believed to activate normal mast cell function by receptor cross-linking and in this sense is cytostimulating rather than cytolytic. In myasthenia gravis, on the other hand, autoantibodies directed against acetylcholine receptors have been identified. These have antagonist properties leading to a failure to sustain maintained or repeated contraction of striated muscle.

Type III reactions (immune complex disease and Arthus reaction) cause inflammation in response to circulating antigen-antibody immune complexes deposited in vessels or tissue. These complexes can activate the complement system or bind to and activate certain immune cells, resulting in release of inflammatory mediators. Consequences of immune complex formation depend in part on the relative proportions of antigen and antibody in the immune complex. Early, there is excess antigen with small antigen-antibody complexes, which do not activate complement. Later, when antigen and antibody are more balanced, immune complexes are larger and tend to be deposited in various tissues (eg, glomeruli, blood vessels), causing systemic reactions. this mechanism operates, at least in part, in farmer's lung (forms of extrinsic allergic alveolitis). Other examples of type III reactions include erythema nodosum leprosum, serum sickness, SLE, RA, antigen-antibody complex glomerulonephritis, and deposition of antigen-antibody complexes at other sites such as the skin as in certain vasculitic skin rashes. Type III reactions develop 4 to 10 days after exposure to antigen and, if exposure to the antigen continues, can become chronic.

Type IV reactions (delayed hypersensitivity) are T-cell-mediated.

T cells, sensitized after contact with a specific antigen, are activated by reexposure to the antigen; these cells preferentially produce interferon (IFN)-γ and interleukin (IL)-2 and are therefore characteristic of the T helper type 1 (Th1) lymphocyte. Contact dermatitis, an important allergic disease, is another example of a type IV reaction with a prominent Th1-type cytokine response. Th2 cells on the other hand elaborate IL-4, IL-5, IL-9, and IL-13 and are involved in atopic allergic reactions as well as parasitic helminthic disease. Some T lymphocyte-mediated hypersensitivity reactions, of which early-onset (insulin-dependent) diabetes is an example, involves CD8+ cytotoxic T cells. After cell-cell contact, programmed cell death (apoptosis) of the target is initiated. Disorders involving type IV reactions include subacute and chronic hypersensitivity pneumonitis, allograft rejection, the immune response to TB, and many forms of drug hypersensitivity.

Patch testing is an essential investigation to identify specific allergens in allergic contact dermatitis (ACD) or, in some cases, to make the diagnosis of ACD. Patch testing is based upon the principle that in sensitized individuals, primed antigen-specific T lymphocytes of the Th1 phenotype circulate throughout the body and are able to recreate

a delayed-type hypersensitivity reaction when nonirritating concentrations of the antigen are applied to normal skin.

Initial reading – The patches typically are left in place for a period of two days (48 hours), which allows adequate penetration of the allergen into the skin. To reduce the number of false-positive readings, the initial evaluation is generally performed between 15 and 60 minutes after the patches are removed, when the transient erythema has resolved. Patients should avoid removing the skin marks before the second reading is performed. Strong positive allergic reactions are erythematous and infiltrated, often with minute papules or vesicles that may coalesce into bullae. The reaction may extend beyond the margins of the patch and is usually associated with pruritus. In all cases, positive reactions should be evaluated within the clinical context to establish their relevance.

Second reading – A second reading is critically important to distinguish irritant reactions (which fade) from true allergic reactions (which persist) and to identify allergic reactions that do not appear at the time of patch removal. The time of the second reading varies among different patch testing centers, but generally is on day four or five. Day four readings appear to be associated with a low number of false-negative reactions. Performing the second reading too soon may miss some delayed reactions, whereas performing the second reading too late may result in missing some positive reactions that fade rapidly, such as those due to fragrances. An additional reading at day six or seven may be useful to identify a small number of late, positive reactions, in particular to nickel, neomycin, and corticosteroids.

Some hypersensitivity reactions do not fall neatly into the type 1–IV classification. For example, activation of the plasma cascade via factor XII, prekallikrein, and high-molecular weight kininogen leads to bradykinin formation, the critical mediator of hereditary angioedema.

Pseudoallergic reactions (nonimmune-mediated hypersensitivities), which are in fact as frequent as true immune-mediated reactions, is not well understood and may rely on different mechanisms. The majority of these reactions imitate the clinical features of immediate reactions (erythema, urticaria, angioedema appearing within 1 hour after drug intake). Pseudoallergic reactions can be elicited by many drugs, they may require higher doses, and the typical initial symptoms for IgE-mediated anaphylaxis, namely palmar and/or plantar itch, are perhaps less common. High tryptase levels after some reactions underline the role of mast cell degranulation, at least in some of these reactions.

〈Classification of Hypersensitivity Reactions and related allergic disease〉

	Type I	Type II		Type III	Type IV			Nonimmunologic Nonimmunologic
		a	b		Th1	Th2	cytotoxic	
Descriptive term	Immediate-type (IgE-dependent, or anaphylactic) hypersensitivity	Cytolytic, or cytotoxic, reactions	Cell-stimulating reactions involving altered cell function (or signaling)	Antigen-antibody complex-often called 'immune complex' - hypersensitivity reaction	Classical delayed type hypersensitivity	Cell-mediated eosinophilic hypersensitivity or chronic allergic inflammation	Tissue injury by cytotoxic T lymphocytes	Pseudoallergy
Initiating event	Antigen (allergen) interacting with mast cells or basophils passively sensitized by IgE	IgG antibody interacting with cell surface antigen	IgG cell-stimulating antibody interacting with cell surface receptors involved in cell signaling	Antigen-antibody complexes, in and around the microvasculature, which activate complement	Antigen presentation to sensitized CD4+ type 1 T lymphocytes (also called T helper(Th) type 1 cells)	Antigen presentation to sensitized CD4+ type2 T-lymphocyte. Sensitized CD8+ type2 T-lymphocyte (also called T cytotoxic (Tc) type 2 cells) may also participate	Cytotoxic CD8+ T lymphocytes recognize fragments of antigen on the surface of target cells	Direct stimulate mast cells or basophils
Antigen	Soluble	Cell-associated	Cell-associated	Soluble	Soluble	Soluble	Cell-associated	Variable
Examples in humans	• Acute symptoms of allergic rhinitis • General and local anaphylaxis • Early-phase allergic reactions (in experimental models of atopic allergic disease)	• Certain allergic drug reactions (e.g. penicillin) • Incompatible transfusion reactions • Autoallergic "autoimmune") hemolytic anemia	• Chronic urticaria (Anti-FceRIa Ab- agonist) • Graves disease (Thyroid stimulating Ab - agonist) • Myasthenia gravis (Anti-acetylcholine receptor Ab- antagonist)	• Serum sickness • Extrinsic allergic alveolitis • Antigen-Ab complex "immune complex") glomerulonephritis	• Tuberculin reaction • Contact dermatitis • Rheumatoid arthritis	• Chronic asthma • Chronic allergic rhinitis • Atopic eczema • Late-phase allergic reactions (in experimental models of atopic allergic disease)	• Early-onset, insulin -dependent diabetes • Graft rejection	• NSAID, radio-contrast hypersensitivity
Related test in clinical laboratory	• Skin prick (intradermal) test, • Allergen(food, drug, aeroallergen) provocation test		• Autologous serum skin test (?)	• Arthus reaction	• Skin patch test	• Induced sputum • FENO		• Drug, exercise provocation test

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