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A review on immunological mechanisms and clinical correlation of hypersensitivity reactions

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Abstract

Exaggerated or inappropriate immune responses, also known as hypersensitivity reactions, result in tissue injury and contribute to a wide spectrum of allergic, autoimmune, and inflammatory diseases. These reactions arise from dysregulated interactions among immune cells, antibodies, and inflammatory mediators following prior sensitization to specific antigens. Gell and Coombs classified hypersensitivity reactions into four types that is Type I (IgE-mediated immediate hypersensitivity), Type II (antibody-mediated cytotoxic reactions), Type III (immune complex-mediated reactions), and Type IV (T-cell-mediated delayed hypersensitivity). The immunological mechanisms underlying each type, including the roles of immunoglobulins, complement activation, immune complexes, cytokine networks, and effector immune cells are discussed. Furthermore, Type II and Type IV hypersensitivity reactions are subdivided to highlight the functional diversity of immune-mediated tissue injury. Understanding the mechanistic basis of hypersensitivity reactions is essential for accurate diagnosis, effective management, and the development of targeted therapeutic strategies.

Keywords: Autoimmunity, food allergens, hypersensitivity, immune reactions, mediators

1. Introduction

The immune system protects the body from harmful microorganisms through a coordinated network of defenses known as immune system. It functions mainly through two arms: humoral immunity and cellular immunity. Humoral immunity is mediated by B-lymphocytes, which produce five major classes of immunoglobulins IgG, IgA, IgM, IgD, and IgE that help neutralize and eliminate pathogens. Cellular immunity is carried out by T-lymphocytes, which recognize antigens and release lymphokines that guide other immune cells to destroy these harmful agents. When immune responses become dysregulated, they may trigger hypersensitivity reactions and contribute to various disease conditions [15]. Hypersensitivity is defined as an abnormal or harmful immune reaction directed against foreign or even self-antigens [10]. It usually occurs after prior exposure to the antigen and represents an altered state of responsiveness, a condition commonly described as “allergy” [8]. The concept of “allergy” was first introduced by von Pirquet to describe immune responses that could either protect or potentially injure the host [4]. Similarly, the term “hypersensitivity” originally denoted a state in which an organism, after exposure to an infectious agent, reacted more strongly upon re-exposure. Over time, both terms have become more closely associated with harmful immune reactions.

Building on this understanding, Gell and Coombs proposed a widely used classification system for hypersensitivity reactions [7]. They categorized these reactions into four types based on the underlying mechanism of tissue injury: type I (immediate, IgE-mediated), type II (cytotoxic, IgG/IgM-mediated), type III (immune-complex mediated), and type IV (delayed, T-cell mediated). Further subtypes have since been added to types II and IV to better represent the diversity of disease mechanisms. In clinical practice, however, these categories may overlap, and a patient can exhibit features of more than one type simultaneously. Reactions that do not fit neatly into a single category particularly those triggered by medications are often classified as mixed drug reactions.

Practically, such reactions may be easier to describe based on the organ system involved. It is also well established that several drugs, including penicillins, can provoke multiple types of hypersensitivity reactions ^[14].

2. Classification of hyper sensitivity reactions

2.1 Type I Hyper Sensitivity Reactions

IgE antibodies are produced in response to parasitic infections and, together with eosinophil activity, play an essential role in eliminating these parasites. Type 1 hypersensitivity is a classic allergic reaction in which the immune system mounts an exaggerated response to normally harmless substances called allergens. This reaction is categorized as an immediate or IgE-mediated hypersensitivity, as it involves the rapid release of inflammatory mediators upon re-exposure to the specific allergen. The sensitization phase begins when individuals predisposed to Type 1 hypersensitivity encounter an allergen for the first time and subsequently produce IgE antibodies ^[1, 20]. These IgE molecules bind to high-affinity IgE receptors on mast cells and basophils. During subsequent exposure, allergens crosslink the bound IgE, activating these cells and inducing the release of potent mediators including histamine, leukotrienes, and cytokines ^[1, 9, 19, 21]. The sudden release of these mediators results in various clinical features of allergy, ranging from mild symptoms such as itching, sneezing, and localized swelling to severe, life-threatening reactions like anaphylaxis ^[1, 2].

A wide range of allergens can provoke Type 1 hypersensitivity. Common sources include environmental allergens such as pollen, dust mites, and animal dander; food allergens like nuts, shellfish, and eggs; and triggers such as insect stings, certain medications, and latex ^[16]. These allergens are recognized as foreign by the immune system, and repeated exposure leads to heightened responsiveness and intensified allergic manifestations ^[12]. Examples of immediate hypersensitivity reactions include anaphylaxis ^[18], characterized by vasodilation and airway constriction and often triggered by food allergens such as nuts and milk; bronchial asthma ^[13], resulting from recurrent immediate and late-phase reactions in the airways; and urticarialn ^[3] which presents as a wheal-and-flare response in the skin.

2.2 Type II Hypersensitivity Reactions

Type II hypersensitivity reactions, also called antibody-mediated cytotoxic reactions, occur when IgG or IgM antibodies mistakenly bind to self-antigens present on the surface of host cells. Under normal circumstances these antibodies help defend the body by binding to microbial surfaces, but when directed toward endogenous antigens, they initiate immune mechanisms that damage or alter the function of the host's own cells. The antigens targeted in these reactions are usually located on circulating blood cells such as red blood cells, neutrophils, and platelets, or on epithelial cells and basement membranes in mucosal and glandular tissues. The tissue injury in type II hypersensitivity arises through a few well-recognized immunologic processes ^[6]. When antibodies bind to antigens on cell surfaces, they may opsonize the cells directly or activate complement, leading to deposition of complement fragments that further opsonize these targets. Opsonized cells are subsequently removed and destroyed by phagocytes bearing receptors for the Fc portion of antibodies and complement components, as seen in autoimmune hemolytic anemia and autoimmune thrombocytopenic purpura. In other situations, antibodies

become deposited in specific tissues such as basement membranes, where they attract neutrophils and macrophages; the release of inflammatory mediators from these cells results in localized tissue injury, a mechanism characteristic of antibody-mediated glomerulonephritis. Antibody-dependent cell-mediated cytotoxicity also contributes to type II injury, where effector cells like NK cells and eosinophils bind to the Fc regions of cell-bound antibodies and release cytotoxic molecules; in helminth infections, for example, eosinophils attach to IgE-coated parasites and discharge granules that damage them.

Based on the nature of the immune reaction, type II responses are categorized into type IIa and type IIb subtypes. Type IIa reactions primarily involve cytolytic immune responses in which antibodies lead to the destruction of target cells, such as in autoimmune hemolytic anemia. In contrast, type IIb reactions involve antibodies that alter cellular function rather than cause cell death. These include conditions like graves disease, where stimulating antibodies target the TSH receptor and promote excess thyroid hormone production, and chronic idiopathic urticaria, in which antibodies are directed against the high-affinity IgE receptor (FcεRI) or against IgE itself ^[11].

2.3 Type III Hypersensitivity Reactions

Type III hypersensitivity reactions occur when IgG or IgM antibodies form immune complexes with circulating antigens. These antigen-antibody complexes may persist in the bloodstream and eventually become deposited in various tissues, where they trigger complement activation and subsequent inflammatory damage. The sites most commonly affected include small blood vessels, renal glomeruli, and synovial membranes, and deposition in these locations leads to vasculitis, glomerulonephritis, and arthritis respectively ^[5]. Importantly, the clinical features of type III reactions are determined by where the immune complexes accumulate, rather than the origin of the antigen itself. The antigens participating in these reactions may be self-derived, as seen in autoimmune disorders such as systemic lupus erythematosus, or exogenous, such as in serum sickness caused by exposure to therapeutic proteins like thymoglobulin or to certain small-molecule drugs including penicillin or procainamide.

2.4 Type IV Hypersensitivity Reactions

Type IV hypersensitivity reactions arise from the activity of sensitized T lymphocytes rather than antibodies. The classical delayed-type hypersensitivity described by Gell and Coombs involves CD4⁺ Th1 cells and is now categorized as type IVa. In this response, antigen-specific T cells release cytokines that activate macrophages, and the resulting inflammatory mediators including lysosomal enzymes, reactive oxygen species, nitric oxide, and various pro inflammatory cytokines produce tissue injury and may induce fibrosis through chronic cytokine and growth factor secretion. Delayed-type hypersensitivity contributes to the pathology of several autoimmune and inflammatory diseases. For example, in type 1 diabetes, T cells and macrophages participate in the destruction of pancreatic β-cells; in multiple sclerosis, T cells recognize myelin-derived antigens and drive central nervous system inflammation; and in rheumatoid arthritis, T-cell dependent synovial inflammation plays a significant role. As more T-cell subsets have been defined, type IV hypersensitivity has been divided into four subcategories IVa, IVb, IVc, and IVd based on cytokine patterns, participating immune cells, and mechanisms of tissue injury ^[17].

3. Conclusions

Hypersensitivity reactions represent a failure of immune regulation in which protective immune mechanisms become pathogenic and cause tissue damage. The Gell and Coombs classification provides a valuable framework for understanding the various immunological pathways involved in these reactions, although overlapping mechanisms can be observed in clinical practice. Type I hypersensitivity demonstrates the rapid consequences of IgE-mediated mast cell activation, while Type II and Type III reactions demonstrate antibody-driven cytotoxicity and immune complex-mediated inflammation, respectively. Type IV hypersensitivity reveals the critical role of T lymphocytes and cytokine-mediated cellular responses in delayed tissue injury, with distinct subtypes contributing to different clinical outcomes. A thorough understanding of these mechanisms is crucial for interpreting disease pathogenesis, recognizing mixed or atypical hypersensitivity patterns, and guiding therapeutic interventions. Continued research into immune regulation and molecular pathways involved in hypersensitivity reactions will further enhance diagnostic precision and improve patient management across allergic, autoimmune, and drug-induced immune disorders.

Conflict of Interest

Not available

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Reference

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