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POSITION PAPER

Nomenclature of allergic diseases and hypersensitivity reactions: Adapted to modern needs: An EAACI position paper

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Abstract

The exponential growth of precision diagnostic tools, including omic technologies, molecular diagnostics, sophisticated genetic and epigenetic editing, imaging and nanotechnologies and patient access to extensive health care, has resulted in vast amounts of unbiased data enabling in-depth disease characterization. New disease endotypes have been identified for various allergic diseases and triggered the gradual transition from a disease description focused on symptoms to identifying biomarkers and intricate pathogenetic and metabolic pathways. Consequently, the current disease taxonomy has to be revised for better categorization. This European Academy of Allergy and Clinical Immunology Position Paper responds to this challenge and provides a modern nomenclature for allergic diseases, which respects the earlier classifications back to the

Abbreviations: ACD, allergic contact dermatitis; AD, atopic dermatitis; ADCC, antibody-dependent cellular cytotoxicity; AERD, aspirin-exacerbated respiratory diseases; AGEP, acute generalized exanthematous pustulosis; APC, antigen-presenting cell; AR, allergic rhinitis; ARC, allergic rhinoconjunctivitis; B, B lymphocytes; BAS, basophil; CRS, chronic rhinosinusitis; DRESS, severe drug reaction with eosinophilia and systemic symptoms; EoE, eosinophilic oesophagitis; EOS, eosinophil; FPIES, food protein-induced enterocolitis syndrome; HDM, house dust mite; IFN-γ, interferon-gamma; IgE/G/M/A, immunoglobulin type E/G/M/A; IL, interleukin; ILC1/2/3, innate lymphoid cells type 1/2/3; MC, mast cell; MO, monocyte; Mφ, macrophage; NEU, neutrophils; NK, natural killer cell; NK-T, natural killer T cell; NSAID, nonsteroidal anti-inflammatory drugs; sIgE, allergen-specific IgE; SJS, Stevens-Johnson syndrome; T1/T2/T3, type 1/2/3 immune response; Tc1/2/17, T cytotoxic lymphocyte type 1/2/17; TEN, toxic epidermal necrolysis; Tfh, T follicular helper cells; Tfr, follicular regulatory T cells; TGF-β, tumour growth factor-beta; Th1/2/9/17/22, T helper lymphocyte type 1/2/9/17/22; TLSP, thymic stromal lymphopoietin; TNF-α, tumour necrosis factor-alpha; TSLP, thymic stromal lymphopoietin.

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early 20th century. Hypersensitivity reactions originally described by Gell and Coombs have been extended into nine different types comprising antibody- (I-III), cell-mediated (IVa-c), tissue-driven mechanisms (V-VI) and direct response to chemicals (VII). Types I-III are linked to classical and newly described clinical conditions. Type IVa-c are specified and detailed according to the current understanding of T1, T2 and T3 responses. Types V-VI involve epithelial barrier defects and metabolic-induced immune dysregulation, while direct cellular and inflammatory responses to chemicals are covered in type VII. It is notable that several combinations of mixed types may appear in the clinical setting. The clinical relevance of the current approach for allergy practice will be conferred in another article that will follow this year, aiming at showing the relevance in clinical practice where various endotypes can overlap and evolve over the lifetime.

KEYWORDS
allergic diseases, EAACI position paper, hypersensitivity, nomenclature, pathophysiology and mechanism

1 | INTRODUCTION

The rapid growth of technology, including molecular diagnostics, omics technologies, genetic and epigenetic editing, nano-technologies, imaging and many more, generated in-depth knowledge of disease pathogenetic pathways (endotypes), allowing more detailed disease descriptions. The disease nomenclature usage of this new information set allowed a shift from a mere pathomechanistic approach, with symptoms and organ dysfunction as the primary descriptors, to recognition of a more established network of immunological and metabolic pathways described by various biomarkers, ideally validated. New disease endotypes, defined by distinct pathophysiological mechanisms, are now described for asthma,[1–4] allergic rhinitis (AR),[5–7] chronic rhinosinusitis (CRS),[8,9] atopic dermatitis (AD),[10,11] and food,[12] venom[13] and drug allergy.[14] However, the current disease taxonomy does not cover this information, so categorising diseases becomes more complicated, thus necessitating revision. A new nomenclature was needed describing diseases based on a combination of their intrinsic biology and traditional 'signs & symptoms', leading to a better understanding of aetiology, mechanisms, prevention, diagnosis and treatment. It should also be flexible, allowing easy incorporation of subsequently developing evidence into existing knowledge, and ideally, its implementation into daily practice should be effortless.

During the last two decades, high throughput technologies and analysis of multi-omics datasets have significantly contributed to increasing the resolution in identifying the triggers and pathomechanisms of diseases.[15] In addition, the introduction of precision medicine, the concepts of disease endotypes, genotypes, theratypes and regiotypes have helped to stratify patients based on disease mechanisms to optimize the management of allergic diseases.[16–18]

Artificial intelligence (AI) and machine learning have emerged as powerful tools for analysing complex datasets delivered by the new precision diagnostic tools, identifying patterns that may not be readily apparent to human researchers. In the context of allergic diseases, AI can potentially support unbiased patient characterization based on their endotypes and more accurately predict responders and non-responders to targeted interventions or immune-modulating therapies. By uncovering novel biomarkers and identifying subgroups of patients with distinct immunological profiles, AI can facilitate the development of personalized treatment strategies (biologicals and small molecules/allergen immunotherapy and other immune-modulatory interventions), ultimately improving patient outcomes and achieving disease modification and targeted prevention.[19]

1.1 | Historical perspective

The term 'allergy' was first coined by Clemens von Pirquet in 1906. He derived the word from the Greek words '*allos*' (meaning 'other' or 'different') and '*ergon*' (meaning 'work' or 'reaction'). An allergy is an unexpected abnormal or exaggerated reaction to an exogenous stimulus involving the immune system.[20]

The term 'atopy' and the concept of atopic diseases were first proposed by the physicians Arthur F. Coca and Robert A. Cooke in the early 20th century. Atopy (or atopic) is a term derived from the Greek word '*topos*', which means 'place', '*atopos*' meaning 'out of place' or 'strange'. In 2001, Johansson et al. defined atopy as a personal or familial tendency to develop asthma, rhinoconjunctivitis or dermatitis due to sensitization to allergens. Individuals with atopy tend to have higher levels of immunoglobulin E (IgE) antibodies.[21]

The designation 'hypersensitivity' was introduced first in 1951 by Phillip Gell and Isabel Hinde referring to tuberculin reaction.[22–24] In 1963 Gell together with Robin Coombs defined hypersensitivity as an undesirable, uncomfortable or damaging response that arises from an overreaction of the adaptive immune response. It encompasses both allergies, which are triggered by external stimuli, and

autoimmunity, which arises from intrinsic stimuli. Typically, hypersensitivity reactions are a secondary immune response occurring in a host with a pre-sensitized (immune) state. According to Gell and Coombs, hypersensitivity reactions were classified into four types: type I: immediate (IgE-mediated), type II: cytotoxic (antibody and Fc receptor-mediated, cellular), type III: immune complex-mediated and type IV: delayed-type (T-cell-mediated).[25]

In 2001, the European Academy of Allergy and Clinical Immunology (EAACI) nomenclature task force led by Johansson et al. published the nomenclature for allergy. This document divides hypersensitivities into the following categories: IgE-mediated reactions that include atopic, and non-atopic conditions (insect sting, food allergy, drugs, helminths); non-IgE-mediated disorders, which are cell-mediated reactions that involve T-lymphocytes (contact dermatitis), IgG-mediated (allergic alveolitis) and other immune cells, for example, eosinophils (gastroenteropathy); non-allergic reactions that do not have the immune mechanisms involved.[21,26]

In the 1990s, several scientists translated the Mossman and Coffman murine Th1-Th2 model to human allergy and asthma.[27–29] In the late 1990s Werner Pichler proposed a further subdivision of type IV hypersensitivity reactions, based on the key cells, cytokines and chemokines. Type IVa (tuberculin reaction) are those reactions where monocytes (MOs) and macrophages (Mφ) are preferentially activated and recruited (with the subvariant of a granulomatous reaction); type IVb, where eosinophils and T helper lymphocytes type 2 (Th2) cells are preferentially activated and recruited; type IVc is mediated by cytotoxic functions of $CD8^+$ T-cells; and type IVd, where neutrophils (NEU) are preferentially activated and recruited.[30–32] Due to the current understanding that $CD8^+$ T-cells can be very diverse and analogous to $CD4^+$ T-cell subsets: $CD8^+$ subset 1 (Tc1), $CD8^+$ subset 2 (Tc2), $CD8^+$ subset 17 (Tc17), $CD8^+$ regulatory subset (–Treg), we have further modified the concept in this article – see below.

1.2 | Advances in immunology and allergy research

Given the advances in the understanding of immune mechanisms and novel therapeutic options, this EAACI Position Paper provides a necessary update of previous EAACI and World Allergy Organization nomenclature. The new nomenclature of allergic diseases is described in Figure 1.

In brief, the novel concept described in this article is based on the understanding of distinct characteristics and functions of type 1, type 2 and type 3 complex immune responses and tissue-driven responses, which play crucial roles in immune-related disorders such as allergies or autoimmunity. *Type 1 immune responses (T1)* are directed towards intracellular pathogens such as *Mycobacterium tuberculosis* or viruses. $CD4^+$ T cells (Th1), type 1 innate lymphoid cells (ILC1), natural killer cells (NK), natural killer T cells (NK-T) and type 1 $CD8^+$ cytotoxic lymphocytes (Tc1) detect and kill infected cells and their contents. Interferon-gamma (IFN-γ) is the main effector cytokine, and IgG1, IgG2 and IgG3 are the main antibodies. These cells interact among each other and tissue cells through the activation of Mφ and NEU to eliminate intracellular pathogens. *Type 2 immune responses (T2)* protect against helminths (large protozoan infections), poisons and venoms. Key players are Th2, ILC2 and Tc2 cells, IgE and effector cells such as basophils, eosinophils and mast cells (MCs) with interleukin (IL)-4 and IL-5, IL-9, IL-13 as the main effector cytokines.[33] *Type 3 immune responses (T3)* are directed against extracellular bacteria and fungi characterized by Th17 cells, ILC3 and Tc17, with IL-17 as the main effector cytokine and NEU as the primary effector cells.[34] Mutations in involved genes, defects and deviation of these immune responses may lead to immune deficiencies, autoimmunity, cancer, abortions and allergies.

The modern definition of allergy should reflect the pathophysiological complexity of these conditions. They include conditions caused by hypersensitivity of the immune system elicited by otherwise harmless environmental substances. Although classically, the mechanisms of allergies are associated with T2 responses, recent discoveries showed endotypes of allergic diseases related to T1 or T3-driven activation pathways,[34–36] which were originally assumed to be involved in a variety of immune-mediated diseases including autoimmunity characterized by mechanisms distinct from allergies.[37]

Allergy is an abnormal or exaggerated reaction to exogenous stimuli which involves various types of hypersensitivity reactions engaging antibodies, immune cell-mediated, tissue-driven or metabolic mechanisms resulting in the development of respiratory, skin, eye, gastrointestinal and other symptoms, including anaphylaxis. Anaphylaxis is a serious systemic allergic reaction that is usually rapid in onset and is sometimes fatal.[38,39] The term atopy, although deeply rooted, has limited use today as it is based mainly on the symptomatic definition of diseases and does not represent the current understanding of the pathophysiology.

2 | MECHANISMS OF THE MOST IMPORTANT ALLERGIC DISEASES

2.1 | Type I or immediate response

Type I, IgE-dependent reactions occur in patients with AR, allergic rhinoconjunctivitis (ARC), asthma, AD, acute urticaria/angioedema, food, venom and drug allergy (Figure 2).[40]

Classical allergens initiating type I hypersensitivity are pollens (trees, grasses and weeds), house dust mites (HDM), mould spores, cockroaches, animal dander, saliva and urine (e.g. cats, dogs, hamsters, guinea pigs), insect venoms (e.g. bees, wasps, ants), foods (e.g. peanuts, tree nuts, milk, eggs, fish, shellfish, soy, wheat, fruits, vegetables), latex (e.g. gloves, balloons and condoms) and drugs (e.g. penicillin and other beta-lactam antibiotics, serums and vaccines, insulin, monoclonal antibodies and other protein medications).

Type I response includes two phases. The *sensitization phase* depends on T2 cell signals (related to the hypersensitivity type IVb-described below) which regulate allergen-specific immunoglobulin E

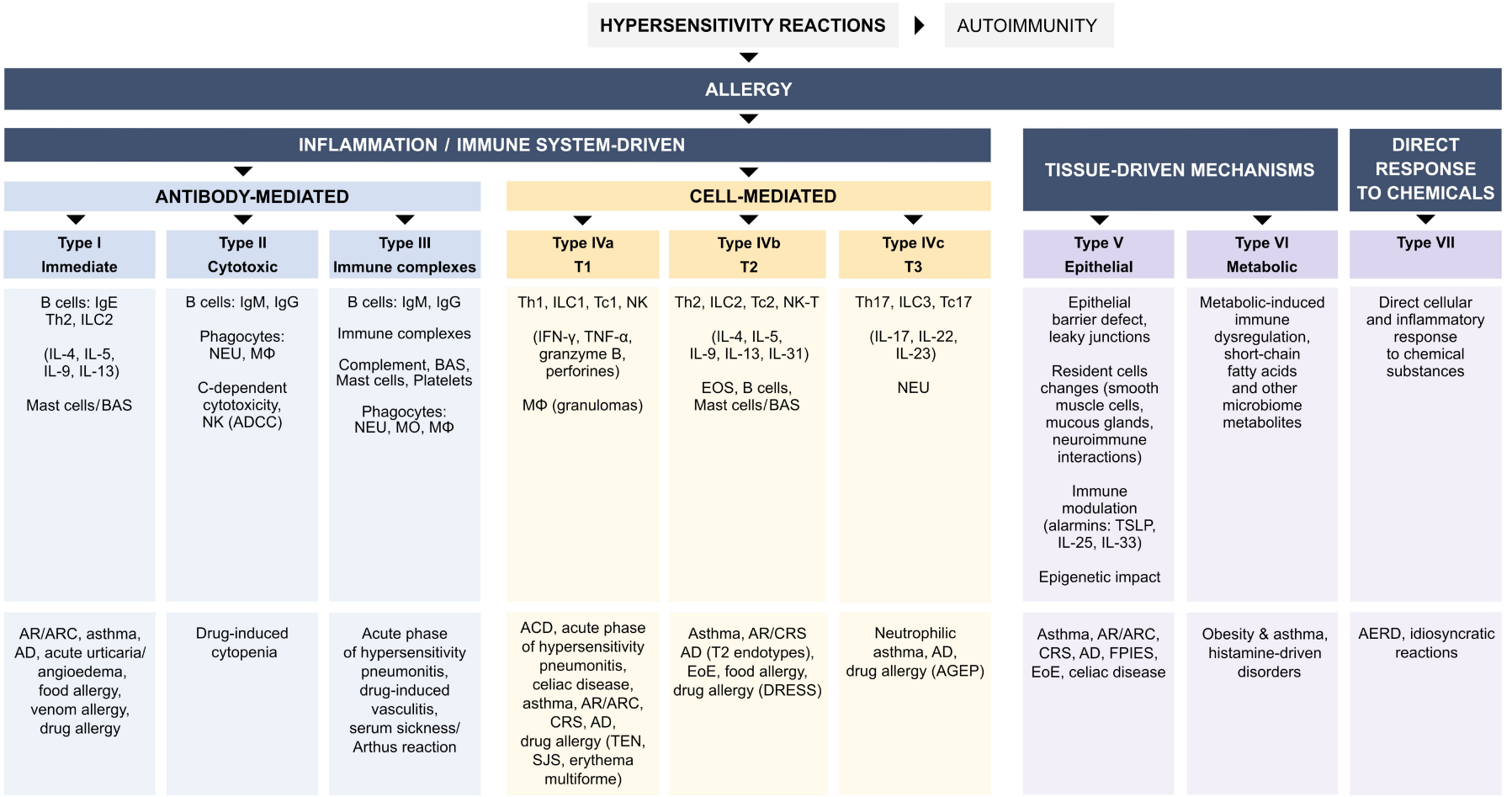


FIGURE 1 New nomenclature of allergic diseases. Hypersensitivity refers to an undesirable, uncomfortable or damaging response that arises from a tissue cell dysfunction or immune system overreaction. Allergy is an abnormal or exaggerated reaction to exogenous stimuli which involves various types of hypersensitivity reactions engaging antibodies, immune cell-mediated, tissue-driven or metabolic mechanisms resulting in the development of respiratory, skin, eye, gastrointestinal and other symptoms, including anaphylaxis. ACD, allergic contact dermatitis; AD, atopic dermatitis; ADCC, antibody-dependent cellular cytotoxicity; AERD, aspirin-exacerbated respiratory diseases; AGEP, acute generalized exanthematous pustulosis; AR, allergic rhinitis; ARC, allergic rhinoconjunctivitis; B, B lymphocytes; BAS, basophil; CRS, chronic rhinosinusitis; DRESS, severe drug reaction with eosinophilia and systemic symptoms; EoE, eosinophilic oesophagitis; EOS, eosinophil; FPIES, food protein-induced enterocolitis syndrome; IFN-γ, interferon-gamma; Ig (E, G, M), immunoglobulin (type E, G, M); IL, interleukin; ILC1/2/3, innate lymphoid cells type 1/2/3; MO, monocyte; Mφ, macrophage; NEU, neutrophils; NK, natural killer cell; NK-T, natural killer T cell; SJS, Stevens-Johnson syndrome; T1/T2/T3, type 1/2/3 immune response; Tc1/2/17, T cytotoxic lymphocyte type 1/2/17; TEN, toxic epidermal necrolysis; Th, T helper lymphocytes; TLSP, thymic stromal lymphopoietin; TNF-α, tumour necrosis factor-alpha.

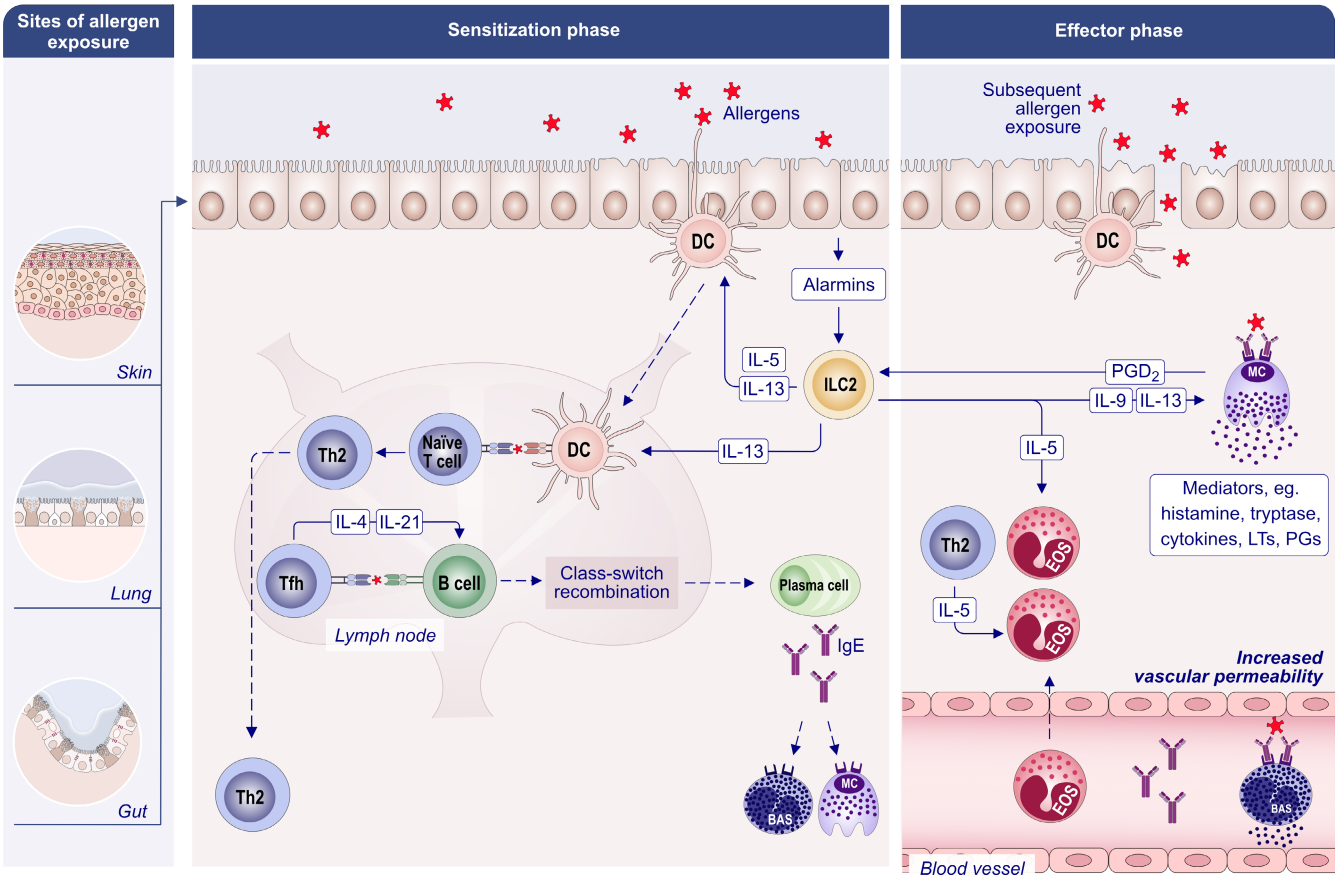


FIGURE 2 Mechanisms of type I hypersensitivity in AR, ARC, asthma, AD, acute urticaria/angioedema, food, venom and drug allergy. The allergen is deposited on the epithelial cells, in the respiratory tract, gut or skin. The sensitization phase occurs after the first contact with the allergen, APCs, for example, DCs, present the antigen to the naïve Th. ILC2 are activated by cytokines released by epithelial cells (called alarmins), such as IL-25, IL-33 and TSLP. Upon activation, they produce large amounts of type 2 cytokines, including IL-5, IL-9 and IL-13, further supporting the T2-cell response. Tfh help B cells to maturate and produce high-affinity sIgE. MC and BAS possess the high-affinity receptor for the Fc fragment of sIgE (FcεRI) and are coated with sIgE, thus concluding the sensitization phase. The effector phase occurs upon subsequent exposure to the same allergen. The allergen crosslinks sIgE bound to MC and BAS, triggering degranulation. MCs are located in various tissues throughout the body, while BAS circulate in the blood. Preformed mediators inside MC and BAS, like histamine, induce symptoms upon release into the microenvironment, like vasodilation, bronchial muscle contraction and increased mucus secretion. Eosinophils play a significant role in the delayed allergic response and the persistence of inflammation, engaging mechanisms related to type IVb hypersensitivity. Therefore, the mutual interaction between type I and IVb-related processes is vital to both the sensitization and the chronic phase. Asthma, AR, ARC and AD endotypes can show T2-type cytokine overexpression (IL-4, IL-5 and IL-13) and high serum sIgE levels. Food/venom/drug allergy can be induced directly by a trigger with a potentially life-threatening anaphylactic reaction. Acute urticaria/angioedema can be induced by allergens (e.g. foods, medications, insect bites or stings). B, B lymphocyte; BAS, basophil; DC, dendritic cell; EOS, eosinophil; IL, interleukin; ILC2, type 2 innate lymphoid cell; LT, leukotrienes; MC, mast cell; PG(D_2), prostaglandin (D_2); sIgE, allergen-specific immunoglobulin E; Tfh, T follicular helper cell; Th naïve/2, T helper lymphocyte naïve/type 2; TSLP, thymic stromal lymphopoietin.

(sIgE) production. The mechanism involves a complex interplay between the adaptive and innate immune systems. The process begins when an individual is exposed to an allergen for the first time. The allergen is internalized by antigen-presenting cells (APCs) such as dendritic cells (DC), B lymphocytes (B) and Mφ, which process and present the allergen peptides on their surface, linked to major histocompatibility complex class II (MHC class II) molecules to naïve T cells. DCs are shown to be the strongest activator of naïve T cells. However, B cells and Mφ can also contribute to naïve T-cell differentiation. Specific cytokines produced by APCs can vary depending on factors such as the nature of the antigen/allergen they encounter, the local cytokine environment and the activation state of the APCs themselves.[41] DCs surface molecules, secreted metabolites and cytokines promote the activation and differentiation of naïve T-cells into various immune cell subsets, such as Th1, Th2, Th17, Tc1, Tc2, Tc17 and regulatory T cells. DCs do not secrete a typical type 2 immune response polarizing cytokines. Early IL-4 is produced by MCs and basophils, while ILC2s amplify and sustain the response. They are activated by cytokines released by epithelial cells (alarmins), such as IL-25, IL-33 and thymic stromal lymphopoietin (TSLP).[42] ILC2s can also be directly activated by environmental toxins.[43] Upon activation, ILC2 produce large amounts of type 2 cytokines, including IL-5,

IL-9 and IL-13, further supporting the T2 cell response, eosinophil recruitment and mucus production. There is limited data showing that ILC-2 produce IL-4, but this has not been fully elucidated.[44,45] This leads to the differentiation of naïve T cells into Th2 and Tc2 cells; IL-4 and IL-13 promote the immunoglobulin class-switch and thus the production of sIgE by B cells and increase the tissue migration of Th2 cells. Additionally, ILC2-derived cytokines can promote local tissue repair and remodelling, contributing to chronic inflammation and tissue damage in cases of persistent allergen exposure.[35,46] T follicular helper cells (Tfh) are a subset of $CD4^+$ Th cells that play a critical role in the development and maturation of B cell responses, including the production of high-affinity antibodies. Tfh cells provide signals to B cells in the germinal centres, including cytokines (such as IL-4 and IL-21) and costimulatory molecules (such as CD40L). These signals help B cells undergo class-switch recombination, which results in the production of IgE.[47]

In many sensitized individuals, the clinical signature does not appear. The type I hypersensitivity response occurs due to deficient immune regulatory response, in ILC regulatory (ILCregs) cells, Tregs, Bregs and follicular regulatory T cells (Tfr).[48–53]

The *effector phase:* MCs and basophils express the high-affinity IgE receptor (FcεRI) for the Fc region of IgE. sIgE, the least-abundant member of the antibodies, irreversibly binds to FcεRI on the surface of MCs and basophils, sensitizing these cells to the allergen. As a result, MCs, both mucosal and connective tissue subtypes, and basophils are coated with sIgE. Upon subsequent exposure to the allergen, the allergen crosslinks two adjacent IgE on the cell surface, causing the cells to degranulate. The degranulation process releases pre-stored mediators such as histamine, heparin, proteases (e.g. tryptase) and some cytokines, as well as newly generated such as prostaglandins, leukotrienes and adenosine nucleotides. Upon activation, a MC can either slowly release (piecemeal degranulation) or rapidly release (anaphylactic degranulation) mediators or cytokines and chemokines that induce inflammation, from storage granules into the local tissue microenvironment.[54] These mediators cause the characteristic symptoms of an allergic reaction, including vasodilation, increased vascular permeability, smooth muscle contraction, stimulation of sensory nerves and mucus production.[55] IgE further upregulates the FcεRI on MCs allowing more IgE to bind to receptors and increase the mediator release upon allergen crosslinking. In addition, MCs can be activated by other non-IgE-related MC stimuli, described in section type VII.

Decreased levels of IgE and increased specific IgG4 can occur as part of the immune system's adaptive response to avoid allergic reactions after repetitive exposure to high concentrations of allergens, as in allergen immunotherapy (AIT). AIT can shift the immune response from a T2 cell-dominated response favouring IgE production to a T1 or Treg response, which supports the production of other immunoglobulins like IgA and IgG4.[56] Class-switching is associated with different cytokines, such as IFN-γ, IL-10 and tumour growth factor-beta (TGF-β). IgA and IgG4 can compete with IgE for allergen binding (blocking activity) without causing MCs or basophils activation. IgG4 can also suppress the production of IgE by B cells, either directly or by inhibiting the activity of Th2 cells. IgA in mucosal secretions can bind to allergens, forming immune complexes that prevent the allergens from crossing the mucosal barrier and entering the circulation (immune exclusion). IgA can neutralize allergens' biological activity by binding to them and preventing them from inducing an immune response.[57,58]

Activation, migration and prolonged life span of eosinophils contribute to the late-phase allergic reaction and chronicity of inflammation, involving hypersensitivity type IVb mechanisms.[59] Thus reciprocal regulation of type I and type IVb-related mechanisms is crucial in allergy development during the sensitization and chronic phase of allergic disease.

2.2 | Type II or antibody-mediated cellular cytotoxicity reaction

Type II reactions are typically drug-induced reactions which are considered a cause of allergic cytopenia. However, type II reactions are an essential pathogenetic event in several autoimmune diseases, such as immune thrombocytopenia, autoimmune haemolytic anaemia (AIHA), autoimmune neutropenia, Biermer's disease, Goodpasture syndrome, haemolytic disease of the foetus and the newborn (erythroblastosis fetalis), myasthenia gravis, pemphigus and transfusion reactions involving mismatched blood types.[60–63]

In a drug-dependent type II *allergic reactions*, a drug or its metabolite first binds to proteins on the cell membrane. Subsequently, anti-drug antibodies and drug-membrane protein complex bind and activate complement or are being bound by the Fc fragment gamma receptor (FcγR) on the effector cell such as an NK cell, eosinophil, Mφ or neutrophil, finally inducing cytolysis (Figure 3). The mechanisms of sensitization leading to the development of IgG are unclear and might potentially be due to molecular mimicry. Similarly, in type II *autoimmune reactions*, complexes of drug/anti-drug antibodies bind to the cell membrane on self-antigens and activate the complement or an effector cell via the Fc receptor, which results in cytolysis.

The primary antibodies involved in type II allergic reactions are IgG and IgM. The immunoglobulins damage cells by several mechanisms: (1) Activation of the classical way of the complement system generating the cytolytic membrane attack complex C5b-9. (2) Antibody-dependent cellular cytotoxicity (ADCC) mainly via NK cells and CD16 expressing $CD8^+$ T cells.[64] In ADCC, the IgG recognize antigens (drugs) bound to the target cell surface and then are bound by the FcγR on the effector cells. The effector cell releases cytotoxic substances, such as perforin and granzymes, that induce regulated cell death mechanisms, including apoptosis, necroptosis and pyroptosis.[65,66] (3) Opsonization of the drug-target cell by C3b and iC3b complement fragments or antibodies and phagocytosis by Mφ and NEU. (4) Activation of eosinophils through FcγR, and release, for example, major basic protein (MBP) or reactive oxygen species (ROS).[59,67]

The activation of the complement system and the recruitment of immune cells lead to the release of inflammatory preformed and

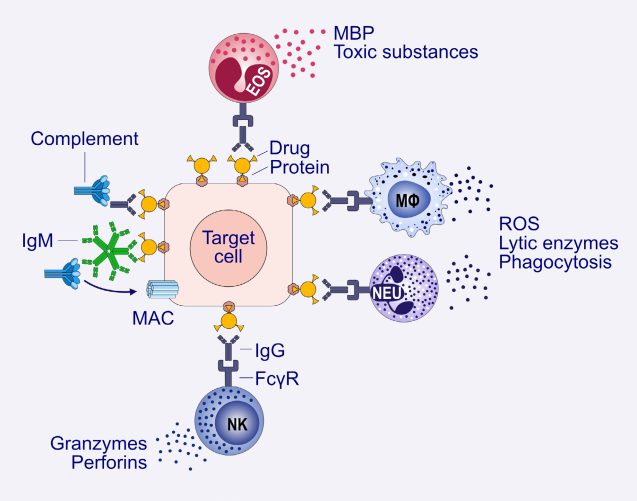


FIGURE 3 Mechanisms of type II hypersensitivity, that include allergic cytopenia. The drug binds to the cell membrane proteins, and subsequently, an anti-drug antibody (IgM or IgG), bind to the complex drug-cell membrane. This leads to complement activation and cell membrane lysis. IgG can be bound by FcγR on Mφ and NEU, which activates phagocytosis, ROS and enzymes production. IgG can be also bound by FcγR on EOS and cause the release of MBP or ROS. ADCC can be executed by NK or $CD8^+$ cells. The activation of complement and the recruitment of immune cells contribute to tissue damage. ADCC, Ab-dependent cellular cytotoxicity; EOS, eosinophil; FcγR, Fc fragment gamma receptor; IgG/M, immunoglobulin class G/M; MAC, membrane-attack complex; Mφ, macrophage; MBP, major basic protein; NEU, neutrophil; NK, natural killer cell; ROS, reactive oxygen species.

newly generated mediators, and proteolytic enzymes, contributing to further tissue damage.

2.3 | Type III or immune complex-mediated reactions

Type III *allergic reactions* include the acute phase of hypersensitivity pneumonitis (also referred to as extrinsic allergic alveolitis), drug-induced vasculitis, serum sickness and Arthus reaction. Type III reactions are associated with several *autoimmune diseases*, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and post-streptococcal glomerulonephritis.[68]

Type III allergic hypersensitivity reactions are mediated by IgM and IgG antibodies that bind soluble antigens, for example, drugs, venoms or other allergens, to form antigen–antibody complexes. As a result of the reduced clearance due to decreased function of the MOs activating system or increased production of antigen–antibody complexes (such as in chronic infections, autoimmune or neoplastic diseases), immune complexes deposit in various tissues throughout the body, such as small blood vessels, capillaries, joint synovium, kidney glomeruli and lung alveoli which are porous and permit the immune complexes to enter the tissues and cause inflammation. This leads to the extravascular activation of the complement system, which releases chemotactic agents that attract NEU, causing inflammation and tissue damage (Figure 4).[68]

Complement activation stimulates a local inflammatory response, which causes the symptoms. In addition, complement-independent pathways involve the immune complexes with FcγR on immune cells, such as NEU, undergoing pathologic frustrated phagocytosis. However, some research studies suggest that complement may play a minimal role in the actual process of allergic type III reactions.[69] Arthus reaction is only slightly reduced in mice with intact Fc signalling whose complement is decreased. In this case, MC degranulation appears to drive the entire reaction.[70–72] Complement, specifically the anaphylatoxin C5a, might indirectly drive the reaction by altering the ratio of activating to inhibitory Fc receptors on effector cells.[73] Subsequent aggregation of immune complex-related events may result in local fibrinoid necrosis with ischemia-aggravating thrombosis in tissue vessel walls.

2.4 | Type IV or cell-mediated reactions

Memory T lymphocytes interacting with ILCs, NK-T cells, NK cells, NEU, eosinophils and Mφ drive type IV reactions. Historically, these reactions were called delayed-type, due to the observation that symptoms develop several hours to days after exposure. Various T-cell subsets mediate Type IV responses through different specific pathways, displaying a high degree of heterogeneity reflecting the distinct phenotypic features of memory lymphocytes. Some disease mechanisms can be only explained by the cooperation of several subtypes of type IV hypersensitivity.

2.4.1 | Type IVa – T1 immune response

Typical clinical manifestations of type IVa reaction are allergic contact dermatitis, the chronic phase of hypersensitivity pneumonitis (also referred to as extrinsic allergic alveolitis) and celiac disease. Type IVa reactions can also be essential for non-T2 endotypes of asthma, AR, CRS or AD. These mechanisms also explain non-immediate allergic reactions to drugs, which occur after the haptenization of the drug with a carrier protein.[74]

Type IVa reactions are considered to be T1 responses, mediated by memory Th1 and Tc1 cells, which acquire their phenotype upon exposure to IL-12, IL-23 and IFN-γ provided by APC.[75] Th1 cells produce high amounts of IFN-γ, lymphotoxin and tumour necrosis factor-alpha (TNF-α), which contribute to many disease mechanisms, including granuloma formation, synthesis of IgG1 and IgG3 by B cells and the activation of T-cell cytotoxicity.[76] The memory immune response in type IVa reactions is amplified by innate immune cells, including ILC1 and classically-activated Mφ (M1 Mφ), among others.[77] Activated Mφ release various inflammatory mediators, such as ROS, proteases and pro-inflammatory cytokines, contributing to tissue damage at the site of antigen exposure. The tissue damage leads to the clinical manifestations of type IVa hypersensitivity, which can vary depending on the specific antigen and the affected tissue (Figure 5A).

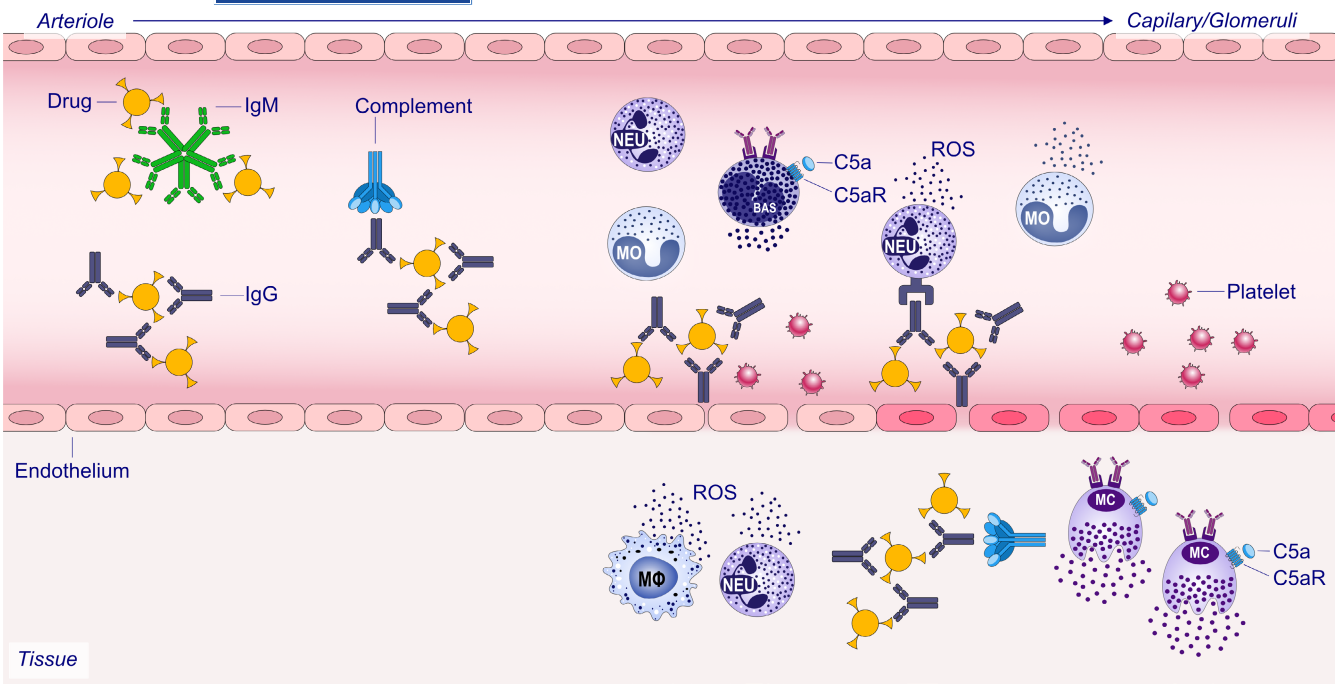
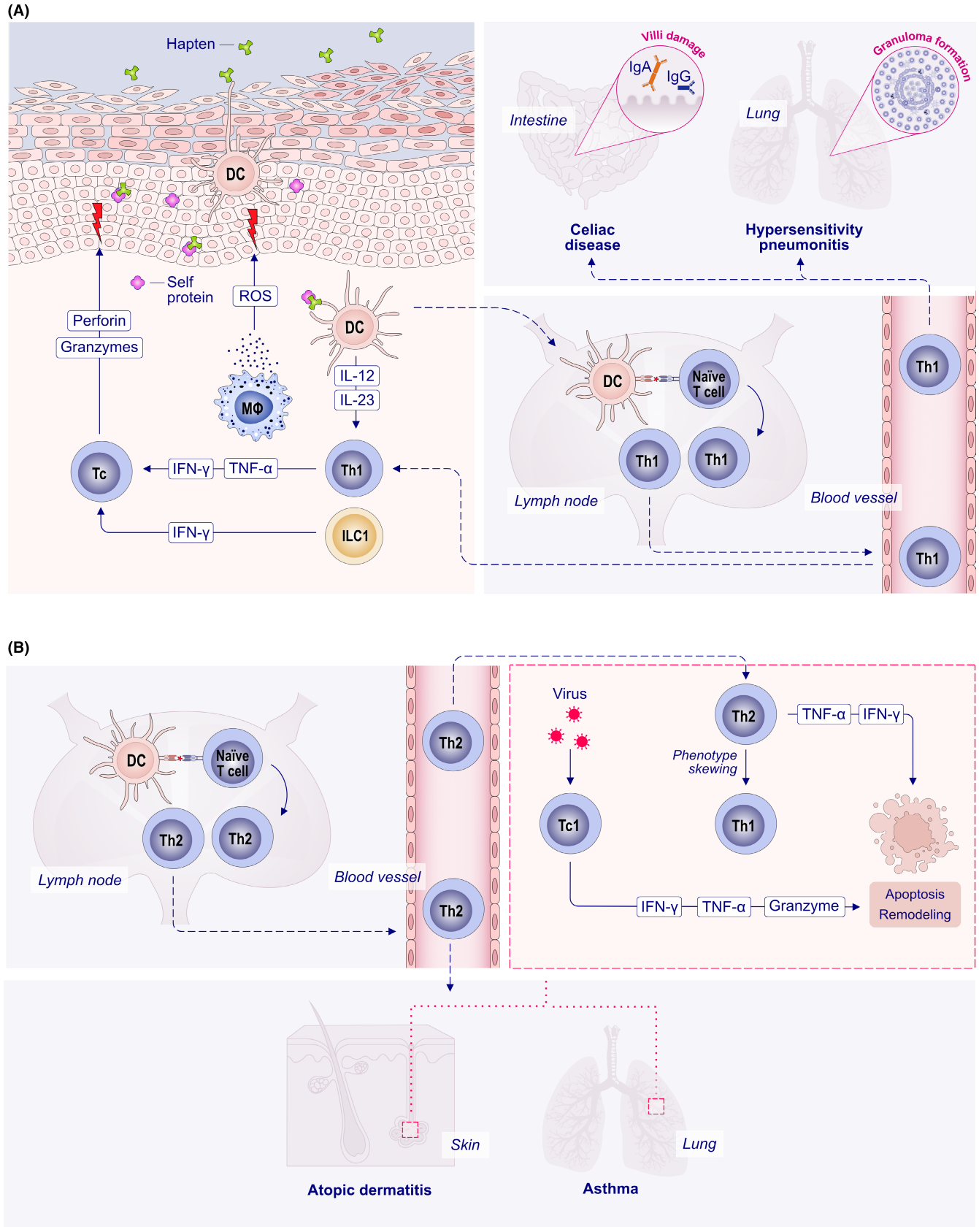


FIGURE 4 Mechanisms of type III hypersensitivity, including the acute phase of hypersensitivity pneumonitis, drug-induced vasculitis, serum sickness and the Arthus reaction. These reactions involve the formation of antigen–antibody complexes through the interaction of IgM and IgG antibodies with soluble antigens (e.g., drugs or venoms). These immune complexes are deposited in various body tissues, including blood vessels, joint synovium, kidney glomeruli and lung alveoli, due to impaired clearance by the Mφ activating system. This triggers the complement system and increases vascular permeability, leading to cell chemotaxis. Recruiting NEU and MO cause inflammation through the release of enzymes and RO. BAS and MC release inflammatory mediators through binding the complement C5a fragment by C5aR. A cascade of events may ultimately lead to local fibrinoid necrosis, thrombosis and vasculitis. BAS, basophil; C5a(R), complement component 5a (receptor); MO, monocyte; MC, mast cell; Mφ, macrophage; NEU, neutrophil; IgG/M, immunoglobulin class G/M; ROS, reactive oxygen species.

In addition, in T2-dependent asthma or AD, (hypersensitivity type VIb), after migrating to the bronchi or skin, Th2 cells can change their phenotype to produce T1 effector cytokines: IFN-γ, TNF-α and express Fas-ligand and other apoptotic death signals that can induce bronchial epithelial or keratinocyte apoptosis followed by remodelling (Figure 5B).[78,79]

$CD8^+$ cytotoxic memory Tc1 cells also engage in type IVa reactions, especially in non-immediate allergic reactions to drugs.[74] Memory cytotoxic T cells usually differentiate upon exposure to IFN-γ released by APC and Th1 cells.[80] Tc cells produce high amounts of IFN-γ, mediating many inflammatory mechanisms.[81] The activation of memory Tc cells differs from that of memory Th cells.

FIGURE 5 Mechanisms of type IVa hypersensitivity, including (A) ACD, chronic phase of hypersensitivity pneumonitis and celiac disease, (B) but also including non-T2 endotypes of asthma or AD. APC presents antigen/hapten to Th1 memory cells, which acquire their phenotype upon cytokine exposure, leading to the activation, proliferation and production of IFN-γ and TNF-α. These cytokines recruit and activate immune cells, leading to inflammation and tissue damage. Mφ are producing ROS, Tc and NK cells release granzymes and perforins. Innate immune cells, especially ILC1s, amplify the response by producing a large amount of IFN-γ. Clinical manifestation of type IVa reaction is typical in ACD, where the triggering hapten is a small molecule which needs to associate with a host protein (e.g., an epidermal protein) to become immunogenic in a process called harmonization. In the intestine, celiac disease is mediated by gliadin-specific Th1 cells inducing intestinal inflammation upon the intake of wheat and other cereals. Chronic intestinal inflammation with damage of villi is associated with the generation of IgA and IgG antibodies against tissue proteins: anti-tissue transglutaminase Ab (tTG-IgA), anti-endomysial Ab (EMA-IgA), anti-deamidated gliadin peptides Ab (DGP-IgA and DGP-IgG), which turns the disease into a mixed allergic-autoimmune condition. The chronic phase of hypersensitivity pneumonitis is directed against airborne allergens that mediate inflammation in the lung parenchyma, ultimately leading to lung granuloma formation and scarring (fibrosis) of the lung tissue. (B) Th2 cells that migrate to the asthmatic bronchi, nasal mucosa or atopic skin often skew to additionally producing T1 effector cytokines: IFN-γ, TNF-α and Fas-ligand (death signals) that can induce bronchial epithelial or keratinocyte apoptosis followed by remodelling. The $CD8^+$ T cells (Tc1), which respond to viral infections, can contribute to tissue inflammation and remodelling. Viruses activate Tc1 cells, which produce IFN-γ, granzyme, etc. and induce airway hyperreactivity. ACD, allergic contact dermatitis; AD, atopic dermatitis; DC, dendritic cell; IFN-γ, interferon-gamma; IgA/G, immunoglobulin A/G; IL, interleukin; ILC1, type 1 innate lymphoid cell; Mφ, macrophage; ROS, reactive oxygen species; Th naïve/1/2, T helper lymphocyte naïve/1/2 type; Tc, cytotoxic lymphocyte; TNF-α, tumour necrosis factor-alpha.



Whereas Th cells can only be reactivated at the sites of inflammation by APCs expressing MHC-II molecules presenting exogenous antigenic peptides, Tc cells can be reactivated locally by any cell expressing MHC-I molecules presenting endogenous antigenic peptides, including stromal cells.[82] Upon activation, memory Tc1 cells increase the expression of perforin and granzyme B, thus mediating

the lysis of the cell expressing the antigen in the context of MHC-I molecules.[80] In addition, TNF-α, Fas-ligand, TNF-like weak inducer of apoptosis (TWEAK) and TNF-related apoptosis-inducing ligand (TRAIL) signalling play a role in tissue injury, particularly epithelial cell apoptosis.[83,84] It has been shown that $CD8^+$ T cells, which play a crucial role in the antiviral immune defence can also trigger chronic allergic inflammation and remodelling. Rhinovirus, respiratory syncytial virus (RSV), influenza virus, parainfluenza virus, human metapneumovirus or coronaviruses (Sars-Cov-2) activate Tc1 cells, which produce IFN-γ, granzyme etc., leading to tissue damage and can also induce airway hyperreactivity.

2.4.2 | Type IVb – T2 immune response

The most characteristic expression of a type IVb hypersensitivity reaction can be observed in the classical allergic reaction with chronic airway inflammation in AR, CRS, asthma and AD (T2 endotype), food

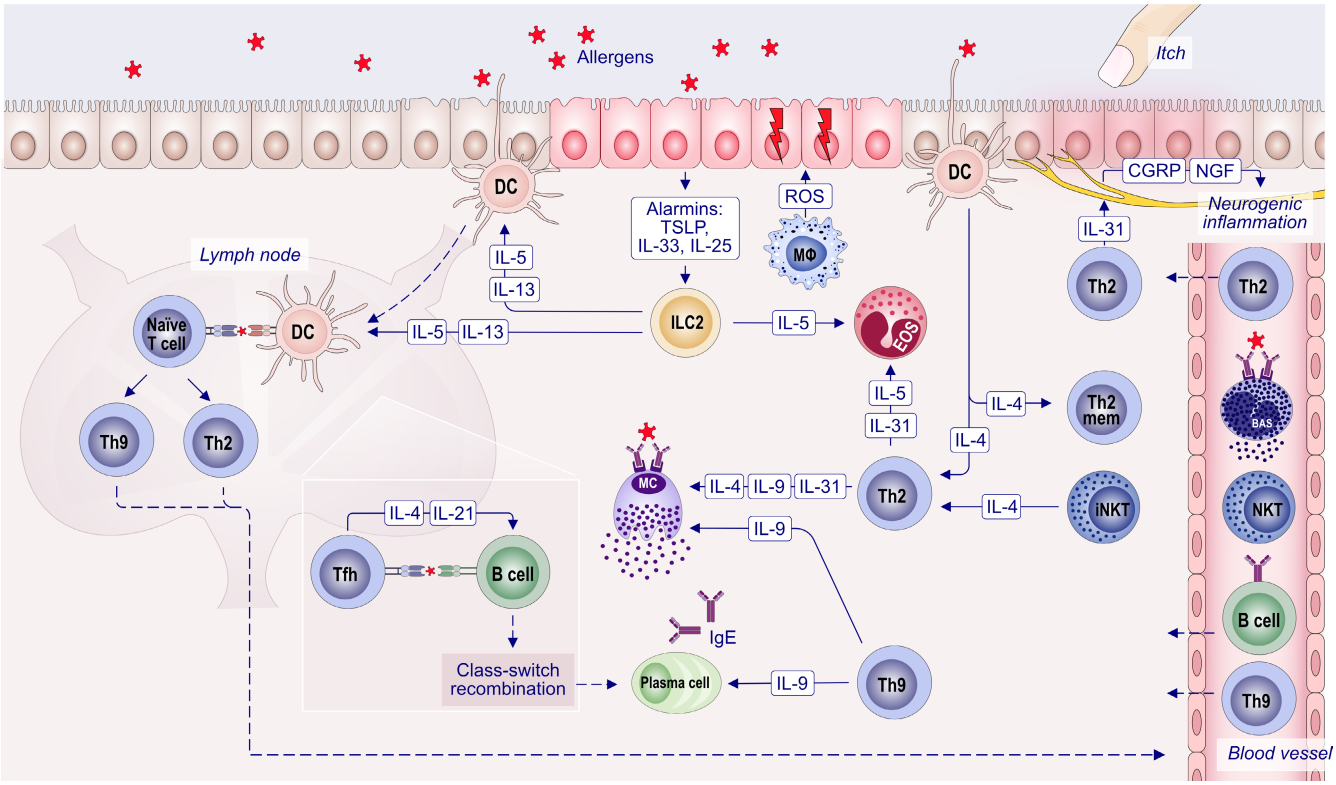


FIGURE 6 Mechanisms of type IVb hypersensitivity, including AR, AD, chronic rhinosinusitis with nasal polyposis and asthma (T2 endotype), but also EoE and food allergy. In Type IVb hypersensitivity reactions, Th2 cells play a central role, driven by cytokines such as IL-4, IL-13, IL-5, IL-9 and IL-31. These cytokines stimulate B cells to class switch to IgE (IL-4 and IL-13) and mediate eosinophilia (IL-5), causing inflammation and tissue damage. IL-31 mainly produced by Th2 cells, activates IL-31 receptors on sensory neurons, which release CGRP and NGF causing neurogenic inflammation and itch. Th9 cells, which differentiate with IL-4 and TGF-β, contribute significantly to this response, enhancing sIgE synthesis and promoting MC growth. The response is further complicated by the ILC2 cells, MC and alternatively activated Mφ. ILC2, DC and Th2 cells, activated by IL-25, IL-33 or TSLP, cooperate, producing cytokines and affecting epithelial barriers. They facilitate eosinophil and basophil recruitment and modulate APC function, contributing to the chronicity of Type IVb reactions. iNK-T cells contribute to this response by producing IL-4 and IL-13, which induce alternative activation in Mφ and promote inflammation. Eosinophils migrate to inflammatory sites, activate various cytokines and chemokines and release cytotoxic granules contributing to tissue damage, cell death and chronic inflammation. At the final stage when IgE synthesis is triggered, type IVb and I overlap. T2-high asthma is characterized by eosinophilic airway infiltrates and Th2-dependent cytokine overexpression (IL-4, IL-5 and IL-13). In AD, the most common endotype is characterized by high serum IgE levels and a strong association with other allergic diseases such as asthma and AR. Both IgE-dependent and IgE-independent pathways characterize mixed food allergy. Atopic manifestations arising from IgE-independent factors include delayed food-allergy-associated atopic dermatitis (6–48 h post-exposure) caused by the T2 cells (hypersensitivity type IVb), and eosinophilic gastrointestinal disorders, such as EoE. The oesophageal epithelium is the source of the IL-1 cytokine family members (IL-33, IL-36) and TSLP, involved in the balancing of pro- and anti-inflammatory responses. AD, atopic dermatitis; AR, allergic rhinitis; APC, antigen-presenting cell; B, B lymphocyte; BAS, basophil; CGRP, calcitonin gene-related peptide; DC, dendritic cell; EOS, eosinophil; EoE, eosinophilic oesophagitis; (s)IgE, (allergen-specific) immunoglobulins class E; ILC2, type 2 innate lymphoid cell; IL, interleukin; (i)NKT, (invariant) natural killer T cells; Mφ, macrophage; MC, mast cell; Mf, macrophage; NGF, nerve growth factor; ROS, reactive oxygen species; Th0/2/9, T helper lymphocyte naïve/type 2 or 9; T2, type 2 immune response; Tfh, T follicular helper cell; TGF-β, tumour necrosis factor beta; Th mem, Th memory cells; TSLP, thymic stromal lymphopoietin.

allergy, eosinophilic oesophagitis (EoE) or protein-contact dermatitis. Th2 cells, ILC2, NK-T cells, eosinophils and a subset of Mφ are the main players in the Type IVb – T2 immune response.

Type IVb reactions are mediated by Th2 cells, which acquire their phenotype upon exposure to IL-4, basophils or NK-T cells.[85] Th2 cells produce high amounts of IL-4, IL-5, IL-9, IL-13, IL-31 and eotaxins I-III. IL-4 and IL-13 are the key cytokines of type IVb hypersensitivity and induce a class switch to IgE in B cells by direct (from IgM) and indirect (from IgG1) mechanisms.[86] IL-13 is responsible for the tissue remodelling accompanying chronicity in type IVb hypersensitivity, whereas IL-5 mediates the bone marrow expansion of eosinophils, circulating eosinophilia and recruitment of eosinophils to the sites of inflammation and their survival in the tissues; eosinophils degranulate releasing their endogenous proteases into the microenvironment causing further tissue injury, chronic tissue damage and barrier disruption.[87] IL-31 is the main cytokine playing a role in itch. It is mainly produced by Th2 cells but also by Mφ and DC. Its receptor is expressed on sensory neurons, epithelial cells or keratinocytes.[88,89] Th2 immune responses are often accompanied by allergen-specific Th9 cells, which differentiate upon exposure to IL-4 and TGF-β.[90] Th9 cells can be considered substantial players in type IVb hypersensitivity. They produce IL-9, which enhances IL-4-mediated synthesis of IgE by B cells and is an important growth factor for MC precursors in the bone marrow, eosinophils and basophils.[91] The memory immune response in type IVb reactions is amplified by the activation of innate immune cells such as MCs, basophils, ILC2, eosinophils or alternatively-activated Mφ, among others (Figure 6).[92]

ILC2 cells can produce type 2 cytokines, particularly IL-5, IL-13, IL-9 and amphiregulin to mediate T2 immune protection against helminths, causing tissue inflammation and tissue homeostasis. ILC2 are activated in response to IL-33 and/or IL-25 from epithelial cells. They crosstalk with T2 pathways, play a role in the recruitment of eosinophils and basophils and activate APCs that support a T2 response.[93] ILC2s, together with Th2 cells, open epithelial barriers via IL-13 and play a role in the resolving of tissue inflammation.[94,95]

MCs and basophils, and possibly ILC-2, provide the early source of IL-4 involved in Th2 cell differentiation.[96,97] In addition, IL-4 is produced by a unique subset of invariant natural killer T (iNK-T) cells (NK-T2), contributing to the activation of $CD4^+$ and $CD8^+$ T2 cells and the initiation and ongoing T2 inflammation via IL-4. In addition, a small fraction of IL-13-producing T2 NK and NK-T cells have been shown in the non-IFN-γ secreting group.[98] IL-4 and IL-13 induce an alternative activation program in Mφ that become suppressors of T1-linked cellular activities. A subset of Mφ governs T2 functions at the interface of immunity, and tissue homeostasis and can produce IL-13.[99]

Eosinophils are the main players in all type IVb-T2 immune responses and contribute to chronic allergic inflammation. Mature eosinophils circulate in the blood and migrate to tissue sites of type IVb inflammation and helminth infection. Eosinophils are activated by various cytokines (such as IL-5) released by immune cells like Th2 and MC.[100] Eosinophils are also activated in response to chemokines like eotaxin-1 (CCL11), eotaxin-2 (CCL24), C-C motif chemokine ligand 5 (CCL5 or RANTES), 5-hydroxy eicosatetraenoic acid and 5-oxo-eicosatetraenoic acid and certain leukotrienes like leukotriene B4and MO chemoattractant proteins. IL-13 stimulates eosinophilic exit from the bone marrow. Activated eosinophils release cytotoxic granules containing proteins like major basic protein (MBP), eosinophil cationic protein, eosinophil-derived neurotoxin and eosinophil peroxidase.[59] Eosinophils can undergo cytolysis, where granules are directly exposed to the extracellular environment, which allows them to exert pronounced direct effects on surrounding tissues.[101] These proteins can cause tissue damage and contribute to the inflammation and symptoms associated with allergic reactions. Activated eosinophils produce extracellular traps (EET) that cause cellular damage due to their eosinophilic toxin content.[102]

Type IVb and type I hypersensitivity overlap at the very final stage when IgE synthesis is triggered. T2 cells, through the released cytokines (IL-4, IL-13) induce IgE synthesis. However, the major type IVb-related effector mechanism involves eosinophil activation through IL-5. In addition, type IVb and type V hypersensitivity overlap in epithelial cell activation and opening of the epithelial barriers and drainage of the inflammation towards the bronchial lumen.[95]

2.4.3 | Type IVc – T3 immune response

Th17, Tc17, ILC3 and other IL-17A- and IL-17F-producing cells have been implicated in neutrophilic inflammation and the pathogenesis of AD and neutrophilic asthma.

In type IVc responses, Th17 cells, which belong to the helper T-cell lineage, produce IL-17 family cytokines that regulate innate effectors and orchestrate local inflammation by inducing the release of proinflammatory cytokines and chemokines capable of recruiting NEU and enhancing Th2 cytokine production. Memory Th17 cells acquire their phenotype upon exposure to IL-6, IL-21, IL-23 and TGF-β provided by APCs. The main effector cytokines produced by Th17 cells are IL-17A, IL-17F, IL-21, IL-22 and granulocyte-Mφ colony-stimulating factor.[103] IL-17A and IL-17F are produced by $CD4^+$ and $CD8^+$ T cells, gamma delta T cells and NK cells in response to IL-1β and IL-23. Their default role is protective immunity against fungi and bacteria by promoting antimicrobial peptide production, neutrophil recruitment and enhanced epithelial barrier function.[104] IL-17A and IL-17F activate ILC3 and stromal cells to produce IL-8, which recruits NEU to the sites of inflammation.[105] Thus, tissue infiltration by NEU is the hallmark of type IVc hypersensitivity. In addition to the 'respiratory burst'and enzyme release, which cause necrosis, neutrophil extracellular traps (NETs) can be associated with host damage. NETs are networks of extracellular fibres, primarily composed of DNA (Figure 7).[106] Similar mechanism, extracellular traps – EET, have eosinophils (see above – type IVb).

The T3 response can be amplified by innate immune cells, especially ILC3. Type IVc inflammation often accompanies type IVa

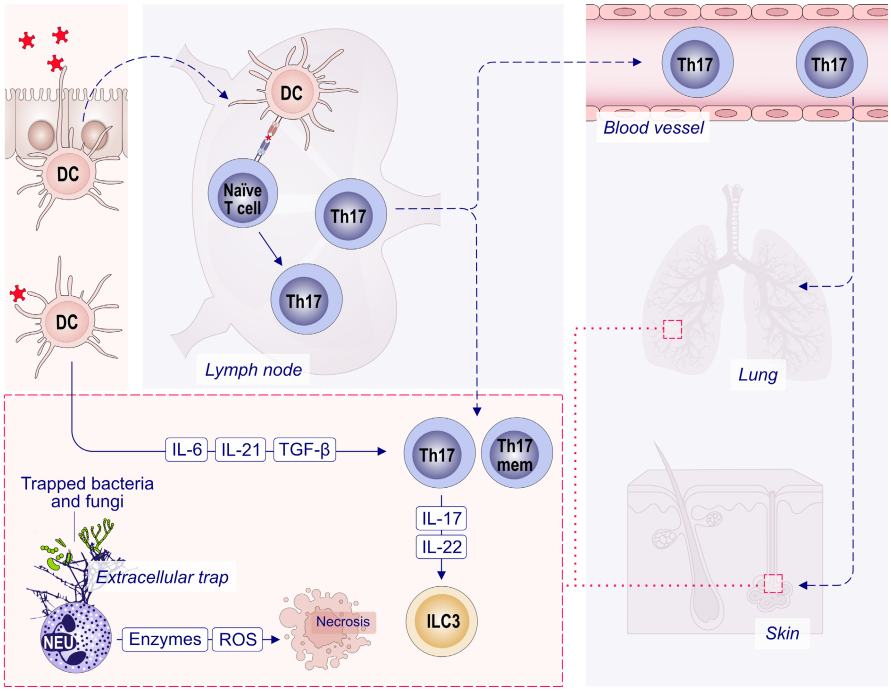


FIGURE 7 Mechanisms of type IVc hypersensitivity, in the pathogenesis of AD, chronic rhinosinusitis with nasal polyposis and neutrophilic asthma. In type IVc hypersensitivity, Th17 cells and ILC3 play a key role by producing IL-17 family cytokines, which induce neutrophil recruitment and enhance Th2 cytokine production, leading to inflammation. Certain bacterial and fungal components can promote Th17 responses. These responses can result in tissue damage via 'respiratory burst', enzyme release or NETs. NETosis is an important part of anti-bacterial and -fungal response, by trapping and killing various pathogens. This mechanism is particularly relevant to conditions like AD and neutrophilic asthma. Normal serum IgE levels might characterize the AD endotype with a more diverse immune profile involving Th1, Th17 and Th22 cells. The skin barrier dysfunction in AD is more severe, and these patients are more susceptible to irritant contact dermatitis. AD, atopic dermatitis; DC, dendritic cell; IgE, immunoglobulin E; IL, interleukin; ILC3, type 3 innate lymphoid cell; NET, neutrophil extracellular trap; NET, neutrophil extracellular trap; NK, natural killer cell; ROS, reactive oxygen species; TGF-β, tumour necrosis factor-beta; Th naïve/2/17/22, T helper lymphocyte naïve/2/17/22 type; Th17 mem, memory Th17.

reactions. However, in some pathologies, the activation of memory Th17 cells prevails.[107]

2.4.4 | Other possible types of type IV hypersensitivity

The p-i concept (=pharmacological interaction with immune receptors) postulates that some drugs can bind directly and reversibly (non-covalently) to immune receptors and thereby stimulate the cells. A certain drug may bind to a particular T-cell receptor (TCR) or bind directly to a certain HLA-molecule, which would explain the striking HLA associations of some drug hypersensitivity reactions. This drug binding suffices - together with TCR interactions with the HLA - to stimulate the T-cell to secrete cytokines, increase, and exert cytotoxicity.[108]

[Correction added on 3 November 2023, after first online publication: In section 2.4.4 Other possible types of type IV hypersensitivity, the preceding paragraph and reference no. 108 have been added to this version.]

More subtypes of IV reactions could be described based on the driver effector T cells. These can include, for example, Th9 or Th22 cells.[109,110] IL-9 is the prototypic cytokine that influences various target cells such as T cells, B cells, MCs and airway epithelial cells by activating members of the signal transducer and activator of transcription (STAT) proteins 1, STAT3 and STAT5. Th9 cells may promote immune tolerance in some models[111] and protect against parasitic infections,[112] they also trigger allergic inflammation and asthma,[113] which highlight their pleiotropic role in the immune system. $CD4^+$ T-cell subsets (Th17, Th9), MCs and ILC2s, can produce IL-9. Among other effects, IL-9 is a key cytokine for Th17 and Treg differentiation,[114] increases IL-4-mediated production of IgE and IgG by B cells,[115] and enhances the growth of bone marrow MCs and MC progenitors together with stem cell factor.[116] Th22 cells play a tissue-protective role at the early stages of asthma and AD, and are involved in tissue remodelling at the chronic phase.[117–119] The prototypic cytokine is IL-22. IL-22 primarily targets nonhematopoietic epithelial and stromal cells promoting proliferation and playing a role in tissue regeneration. In addition, IL-22 regulates host defence at barrier surfaces. In contrast, a proinflammatory role of IL-22 in the skin has also been proposed, as the severity of AD is associated with increased levels of $CD8^+$ IL-22-secreting cells.[120]

2.5 | Type V – epithelial barrier defect

In recent years, significant progress has been made in understanding the different phenotypes and endotypes of mucosal/cutaneous

inflammatory diseases such as chronic AR/ARC, CRS, AD, asthma or food protein-induced enterocolitis syndrome, EoE and celiac disease. This revealed that these conditions are not homogeneous diseases but are instead defined by a constellation of symptoms which may result from different pathological mechanisms.[121] In some cases, the inflammatory process appears to reflect altered barrier function of the skin or mucosa, rather than from a primary immune dysregulation.[122] The impairment of the epithelial barrier function facilitates the activation of the underlying immune system and subsequently leads to chronic inflammation. Barrier loss can result from defects in several essential components, including stratum corneum structural elements in skin, tight junction proteins in skin and mucosa, protective antiproteases, expression of antimicrobial products, transport of ions, protons, water or antimicrobial materials and other mechanisms. The activation of sensory nerves, which contributes to the development of allergic symptoms, is also associated with the loss of barrier (Figure 8).[123] Intestinal barrier dysfunction may also occur via mucus erosion through low fibre-containing nutrition/diet.[124,125] This accounts for the rationale to introduce type V hypersensitivity to point out the peculiarities of the pathological processes and due to their importance in the view of personalized and precision approaches to endotype and biomarkers characterization and rapidly developing biological treatment, especially with anti-alarmins.

Mutations in filaggrin, a keratin-binding protein essential for epidermal homeostasis, significantly predispose to AD, in individuals with and without IgE-sensitization to allergens.[126] It has been suggested that filaggrin mutations could exert a similar effect on mucosa and predispose to diseases like asthma.[127,128] The impairment of the epithelial barrier can also arise from inflammatory phenomena.[95] It has been shown that IL-13 derived from Th2 cells and ILC2s markedly disrupts epithelial tight junctions.[94,129] The activation and tissue migration of ILC2 and Th2 cells strongly depend on epithelial-derived alarmins, especially IL-33, IL-25 and TLPS.[130] Interestingly, the protease activity of some aeroallergens, like HDM, might account for the activation of airway epithelial cells, the release of IL-33, the stimulation of ILC2, the production of IL-13 and the ultimate disruption of epithelial tight junctions.[131] These linked phenomena can occur without lymphocytes or activation of adaptive immunity.[95] It has been shown that the tight junctions in the airway mucosa of patients with allergic rhinitis and asthma are also disrupted. This illustrates how the barrier defect can also occur in classical type IVb hypersensitivity.[132] These data demonstrate the intricate relationship between different hypersensitivity mechanisms in the skin and mucosa: epithelial integrity can be dampened by intrinsic defects, but inflammatory phenomena can also cause an impairment of the barrier function, which further activates the immune system.

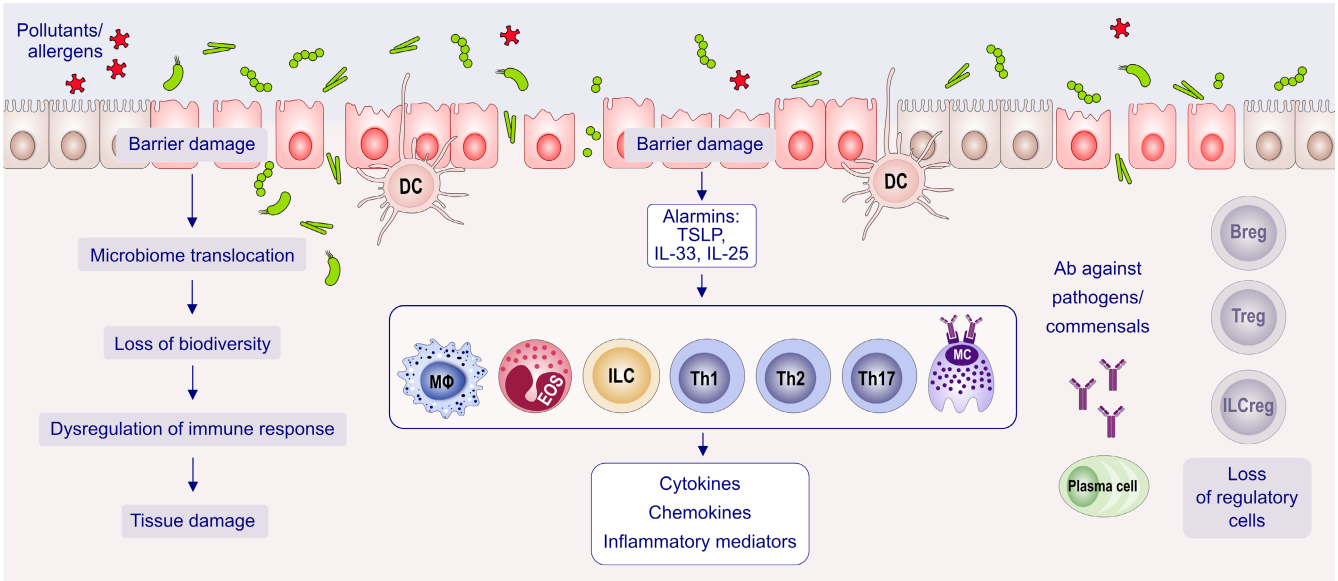


FIGURE 8 Mechanisms of type V hypersensitivity; include asthma, chronic AR/ARC, CRS, AD, FPIES, EoE and celiac disease. The epithelial barrier defect and microbial dysbiosis lead to dysregulation of the immune response, including extensive activation of T1, T2 and T17 responses combined with the loss of Treg, Bregs and ILCregs. Additionally, formation of sIgE to inhaled or ingested allergens, activation of Mφ, MC and BAS and release of proinflammatory cytokines, chemokines and inflammatory mediators (histamine, leukotrienes, ROS). The sequence of events eventually leads to tissue damage that can be seen in asthma, chronic AR/ARC, CRS, AD, FPIES, EoE and celiac disease. Immune response to opportunistic pathogens and commensals, for example, *Staphylococcus aureus* (microbiome translocation) leads to IgE antibody production against them. Ab, antibody; AD, atopic dermatitis; AR/ARC, allergic rhinitis/rhinoconjunctivitis; BAS, basophil; Breg, B regulatory cells; CRS, chronic rhinosinusitis; DC, dendritic cell; EOS, eosinophil; EoE, eosinophilic oesophagitis; IL, interleukin; ILC, innate lymphoid cell; ILCreg, ILC regulatory cells; MC, mast cell; Mφ, macrophage; FPIES, food protein-induced enterocolitis syndrome; ROS, reactive oxygen species; sIgE, allergen-specific immunoglobulins class E; Th1/2/17, T helper lymphocyte type 1/2/17; Treg, T regulatory cells; TSLP, thymic stromal lymphopoietin.

As an important factor in type V hypersensitivity, the direct involvement of environmental factors that directly disrupt epithelial barriers has been recently demonstrated in several models and human tissues.[43] Direct exposure to air pollutants, chemicals and other environmental factors in the exposome can disrupt the epithelial barriers and affect the microbiome and immune system. Many of the chemical agents found in common consumer products (including toothpaste, shampoo, detergents and processed foods), are known to damage these critical barriers, increasing permeability to bacteria, toxins, pollutants and allergens.[133] When epithelial barriers are disrupted (or 'leaky'), substances and microbes can pass into deeper tissues, where they normally do not belong and trigger an immune/inflammatory response that can initiate or aggravate many chronic inflammatory diseases via inflammasome pathways.[134] Epithelial barrier defects have been demonstrated not only in T2 responses but also in non-T2 responses in chronic rhinosinusitis with nasal polyposis (CRSwNP) and non-T2 asthma. Recent exposure studies in mouse models of eosinophilic lung inflammation in asthma and eosinophilic esophagitis development in response to sodium lauryl sulphate and detergents demonstrate that asthma and (EoE)-like inflammation start with only epithelial cell activation and barrier leakiness-induced with toxic substances.[43,135]

As a direct example of chemical cytotoxicity, individuals with leaky epithelial barriers exhibit local inflammation in their epithelial cells, referred to as 'epithelitis'. Epithelitis is the initial event that attracts proinflammatory cells to the damaged epithelial barrier area. It starts with environmental insults (pollutants and toxic substance exposure), viral infections and enzymes in allergens. Mainly the alarmins, IL-25, IL-33 and TSLP and numerous proinflammatory chemokines are released by the epithelial cells inviting the immune system, into the area, particularly the Type IVb and players of the T2 response.[122]

Microbial dysbiosis takes place in areas of leaky inflammation epithelial barrier. A healthy microbiota on the surface of the mucosal barrier regulates numerous aspects of the barrier homeostasis. However, reduced biodiversity and alterations in the composition and metabolism of gut and skin microbiota are associated with various inflammatory conditions, including asthma, allergic diseases, inflammatory bowel disease, type 1 diabetes and obesity.[136] Dysbiosis refers to an imbalance in the microorganisms residing in our tissues, with microbial dysbiosis and bacterial translocation linked to the development and exacerbation of allergic and autoimmune diseases.[137]

2.6 | Type VI – metabolic-induced immune dysregulation

Concurrent with a general increase in the rates of obesity, the number of obese patients with asthma has also risen dramatically during the last few years.[138] Obesity is a distinguishing variable for clustering and classifying asthma subtypes. The obese asthmatic, more likely to be female with adult-onset asthma, and more likely to become corticosteroid resistant, has a higher risk of being hospitalized and more frequently presents with severe disease.[139] Obesity can influence asthma by altering chest wall dynamics. It can influence inflammatory responses directly (e.g. via the release of inflammatory mediators from adipose tissue) or indirectly (e.g. due to the typical dietary changes associated with obesity, such as high levels of processed fats and low levels of fibre).[140] Increasing body mass index (BMI) is associated with increased levels of circulating inflammatory mediators and increased blood neutrophil and eosinophil counts.[141] Obesity is associated with increased levels of circulating serum acute phase reactants, ROS, chemokines and innate proinflammatory cytokines as well as those directly derived from adipose tissue (e.g. leptin),[142] but usually with no increase in serum cytokines associated with T-cell polarization, such as T_H2 cytokines. While stressed and hypoxic adipocytes contribute to the pool of inflammatory mediators observed in serum, activated tissue Mφ are particularly important to inflammatory responses and metabolic dysfunction associated with obesity.[143]

In obese asthmatics, there is an additive effect of asthma and obesity on increased release of pro-inflammatory mediators and airway (allergic) inflammation, as well as modification of the gut, nasal, oral and lung microbiome, closely linked with inflammatory responses.[144] While IL-5 levels are elevated in the bronchoalveolar lavages (BALs) of obese and non-obese asthmatics, only obese asthmatic BALs and lung tissue biopsies display increased activation of innate inflammatory pathways and enhanced activation of pathways associated with airway remodelling, which were not observed in the non-obese asthmatic lung. The obese asthmatic displays immune and inflammatory features associated with both asthma and obesity. Metabolic dysregulation in diabetes and obesity is linked to epithelial barrier leakiness. Immune cells activated at leaky barrier sites, particularly in the gut, can migrate to distant organs, causing inflammation in those areas. Moreover, increased inflammatory mediators in the circulation, namely, 'circulating microinflammation', consisting of acute phase reactants, chemokines and cytokines, can be detected and cause a metabolic burden.[145] In parallel with metabolic changes, perturbation of the intestinal microbiota, together with a persistent low-grade inflammatory response in the gut and fat tissue, is observed in obesity.[146]

The role of the microbiome and bacterial-derived mediators such as histamine in metabolic-induced immune dysregulation has been postulated. The imbalance in the gut microbiome, known as dysbiosis, can lead to a deviated immune response and increase the risk of chronic disease, including allergies or autoimmunity. Histamine, a mediator of inflammation, has been shown to regulate the immune response and is synthesized by certain bacteria, such as Lactobacillus and Escherichia, in the gut microbiome.[147,148] Histamine type 2 receptor plays a crucial role in modulating Th2- and Treg-cell activity.[149] Multiple novel immune modifying metabolites (e.g. tryptophan metabolites, short-chain fatty acids) have been recently identified and dysregulated secretion of these immunomodulators may also contribute to the development of allergies.[150]

2.7 | Type VII – direct cellular and inflammatory response to chemical substances

Type VII reactions occur in patients with AR, ARC, asthma, AD, acute urticaria/angioedema and drug allergy.

Idiosyncratic reactions include cross-reactive hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs). These reactions include at least three different phenotypes depending on the presence or absence of underlying respiratory or cutaneous disease: NSAIDs-exacerbated respiratory disease, in patients with rhinitis and/or asthma with or without nasal polyposis; NSAIDS-exacerbated cutaneous disease, in patients with underlying chronic spontaneous urticaria; and NSAIDs-acute urticaria/angioedema, in otherwise healthy individuals.[151] Recently, other phenotypes consisting of the simultaneous presence of cutaneous and respiratory symptoms after intake of NSAIDs have been extensively described.[152] The underlying mechanism in these reactions was linked to the inhibition of cyclooxygenase (COX)-1 and the release of eicosanoid mediators in susceptible individuals and has also been recently proposed for NSAID-induced acute urticaria/angioedema.[153]

Aspirin-exacerbated respiratory disease (AERD), also called NSAID-exacerbated respiratory disease (N-ERD) and previously called Samter's disease, is a chronic inflammatory condition characterized by the triad of asthma, recurrent nasal polyps and hypersensitivity to aspirin and other NSAIDs.[154] Arachidonic acid is a fatty acid that serves as a precursor for the synthesis of various eicosanoids, including prostaglandins (PG) and leukotrienes.[155] In AERD, there is an imbalance in the metabolism of arachidonic acid, leading to an overproduction of cysteinyl leukotrienes and a decrease in anti-inflammatory PG.[156] Aspirin and other NSAIDs inhibit the COX-1 and COX-2 enzymes responsible for synthesizing PG and leukotrienes. This inhibition further exacerbates the imbalance, resulting in a more pronounced inflammatory response. Cysteinyl leukotrienes (LTC4, LTD4 and LTE4) are potent inflammatory mediators crucial in AERD pathogenesis.[157] They cause bronchoconstriction, increased vascular permeability, mucus production and recruitment of inflammatory cells. Platelets are more easily activated in AERD patients, releasing various inflammatory mediators, such as thromboxane A2 and platelet-activating factor. The imbalance between Th2 cells and regulatory Tregs causes Th2 cells to secrete cytokines that promote eosinophilic inflammation, while Tregs help suppress excessive immune responses.[158] Airway epithelial remodelling in AERD is more than goblet cell metaplasia, resulting in a network of dysregulated inflammatory pathways and epithelial MC changes that sustain T2 inflammation.[159]

Examples of pharmacological interactions are represented by reactions mediated by G protein-coupled receptors (GPCR) expressed in MCs. A novel GPCR known as Mas-related GPCR X2 (MRGPRX2) has been recently described, which is activated in an Ab-independent manner by a range of cationic ligands (secretagogues) and is thought to be responsible for anaphylactoid reactions. These ligands include inflammatory peptides and drugs associated with allergic-type reactions, such as non-depolarizing neuromuscular blockers (atracurium, mivacurium, tubocurarine and rocuronium) and fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin and ofloxacin), among others. Anti-fungal antibiotics, aminoglycosides and sulphonamides induce MC degranulation through this receptor.[160] In addition, MRGPRX2 expression is increased in the skin of patients with severe chronic urticaria.[161] Representative members of each evaluated drug group led to the release of histamine, TNF, PGD2 and b-hexosaminidase from MCs in leukocyte adhesion deficiency type 2 subjects.[162]

In addition, MCs can be activated by various compounds through their associated G-protein coupled receptors (e.g. morphine, radiocontrast media) by ion channels or, in the case of mucosal MCs, by hyperosmolar stimuli (as in exercise-induced asthma or by physical injury through pattern recognition receptors (PRR) that are triggered by damage-associated molecular patterns, by microbial pathogens through PRRs for pathogen-associated molecular patterns. Furthermore, complement components can also activate membrane receptors on MCs to exert various functions as well.[163,164]

3 | CONCLUSIONS

The dissemination and acceptance of the new nomenclature of allergic diseases proposed herein is important for the progress in the entire field. This approach is based on disease mechanisms and endotypes rather than phenotypes and enhances insight into the link between different (allergic) diseases that can coexist in one individual, simultaneously or at different timepoints during a human's life. Endotype-driven thinking can lead to the development of new diagnostic tools, improved therapeutic strategies and better disease management, as well as guide future translational and clinical research into more innovative strategies. These will include new biologics, more effective forms of AIT or even strategies to alter the microbiome and environmental exposures to reduce the risk of allergies. The key discoveries considered in this novel systematology include the role of T-cell subsets, the discovery of the innate mechanisms of non-T2 responses in tissue remodelling and chronicity, the role of virus-induced exacerbations, the epithelial barrier disfunction, advances in immune metabolism and its consequences on immune polarization contributing to allergic responses. As shortly mentioned above, a combination of different hypersensitivity reactions occurs and develops a mixed type, such as the combination of type I, type IVb, type V and type VI simultaneously. In addition, a conditional skew between different type IV hypersensitivity reactions takes place when there are bacterial, fungal or viral infections over a T2 inflammation in the skin, lung and upper respiratory tissues.

The major advantage of this immune response and tissue-based allergy nomenclature approach is helping move the field towards precision and personalized medicine. The final goal is to tailor the management of individual patients based on their specific immune responses, allergen sensitivities and other factors, including the individual's exposome and metaexposome.[165]

This work will continue to provide advice for clinical practice, which will be conferred in followed-up articles. On top of the

straightforward model shown in this article, the mixed endotypes will be presented and critically discussed because many individuals can express more than one overlapping endotype, which can be a dynamic process over their lifetime.

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[Correction added on 3 November 2023, after first online publication: the sequence and citations of references # 55 to 165 were incorrect and have been renumbered throughout the article and references in this version.]

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