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Allergy, Anaphylaxis, and Nonallergic Hypersensitivity: IgE, Mast Cells, and Beyond

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Highlights of the Study

- The prevalence of allergies has been increasing steadily, currently affecting up to 30% of people worldwide.
- While classical type I IgE-mediated hypersensitivity reactions are still the major underlying mechanisms, other pathways and cells mediating the release of hypersensitivity-induced mediators have emerged recently; these are discussed from a mechanistic viewpoint.
- Current allergy diagnosis tests in clinical practice are discussed.

Keywords
Allergy · Anaphylaxis · IgE · Mast cells · Nonallergic hypersensitivity

Abstract
IgE-mediated type I hypersensitivity reactions have many reported beneficial functions in immune defense against parasites, venoms, toxins, etc. However, they are best known for their role in allergies, currently affecting almost one third of the population worldwide. IgE-mediated allergic diseases result from a maladaptive type 2 immune response that promotes the synthesis of IgE antibodies directed at a special class of antigens called allergens. IgE antibodies bind to type I high-affinity IgE receptors (FcεRI) on mast cells and basophils, sensitizing them to get triggered in a subsequent encounter with the cognate allergen. This promotes the release of a large variety of inflammatory mediators including histamine responsible for the symptoms of immediate hypersensitivity. The development of type 2-driven allergies is dependent on a complex interplay of genetic and environmental factors at barrier surfaces including the host microbiome that builds up during early life. While IgE-mediated immediate hypersensitivity reactions are undoubtedly at the origin of the majority of allergies, it has become clear that similar responses and symptoms can be triggered by other types of adaptive immune responses mediated via IgG or complement involving other immune cells and mediators. Likewise, various nonadaptive innate triggers via receptors expressed on mast cells have been found to either directly launch a hypersensitivity reaction and/or to amplify existing IgE-mediated responses. This review summarizes recent findings on both IgE-dependent and IgE-independent mechanisms in the development of allergic hypersensitivities and provides an update on the diagnosis of allergy.

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Introduction

Type I hypersensitivity reactions, as initially defined by Coombs and Gell [1], refer to the IgE-triggered release of inflammatory mediators such as histamine by mast cells and basophils. Type I hypersensitivity reactions play a crucial role in the development of allergies manifesting such as allergic anaphylaxis, allergic rhinitis, food allergies, atopic dermatitis, and allergic asthma that affect up to 30% of people in Western countries [2–4]. They are caused by the inappropriate response of individuals to certain antigens (called "allergens") driven by a T helper type 2 (Th2) immunity, leading to the production of allergen-specific IgE antibodies [5, 6]. These IgE antibodies bind to high-affinity IgE receptors (FcεRI) expressed on mast cells and basophils, sensitizing them to get activated in a subsequent encounter with the allergen [7, 8]. This adaptive IgE-driven pathway of mast cell and basophil activation represents the major component of classical type I hypersensitivity reactions responsible for the development of allergic disorders. However, recent data have provided a wealth of new information on hypersensitivity reactions and other effector cells. To take into account this ever-evolving complexity, a task force was created by the European Academy of Allergology and Clinical Immunology (EAACI) with the goal to standardize the nomenclature of allergies at the beginning of the 21st century. It came up with a position paper [9, 10] providing a new definition of allergic and nonallergic hypersensitivities as mediated respectively by adaptive immune responses (allergen-specific antibodies or lymphocytes) and by other (innate) mechanisms. The concepts have been continuously updated and have also been integrated into the clinical context for improved diagnostics and therapeutic interventions [4]. The classification of allergic and nonallergic hypersensitivity is presented in Figure 1.

The purpose of this review is to discuss type I immediate hypersensitivity and also the emerging mechanisms involved in other immediate allergic and nonallergic hypersensitivities and summarize their clinical implications. In particular, we will provide insight into recent advances related to the development of IgE-driven type I hypersensitivity reactions, the role of environmental factors such as exposure to microbiota in early life, and the role of barrier surfaces. We will discuss the immunological processes of allergic hypersensitivities relating to IgG and complement-mediated allergies, which besides mast cells and basophils, may involve other immune effector cells such as neutrophils, macrophages, and even platelets [11–13]. New data explain certain types of innate and IgE-independent allergies to chemical compounds and drugs as well as physical stimuli involving a new set of receptors such as Mas-related G protein-coupled receptor-X2 (MRGPRX2) [14] and adhesion G protein-coupled receptor (ADGRE2) expressed on mast cells [15]. Hence, it is now well established that in addition to the well-described IgE receptor [7, 8, 16], mast cells express many other receptors that can initiate hypersensitivity-like responses or at least contribute as cofactors in their enhancement [17]. Some recent reviews have summarized the various receptors involved [17, 18]. Furthermore, consensus statements and guidelines have been issued for optimal diagnosis and management of mast cell-related conditions such as mast cell activation syndrome (MCAS) and hereditary α-tryptasemia (HαT) [19–21]. Indeed, a high proportion of hypersensitivity reactions observed in clinics actually does not involve mast cell-triggered responses and are often misdiagnosed, calling for consensus clinical guidelines [22–24]. In this context, it can also be mentioned that recent data have helped elucidate connections between hypersensitivities and triggering compounds emanating from the peripheral nervous system [25].

IgE-Dependent Allergies and Anaphylaxis

It is well established that IgE-dependent allergies are Th2-driven. The Th2 branch of the adaptive immune system favors $CD4^+$ Th2 cells, eosinophils, basophils, mast cells, type 2 innate lymphoid cells, as well as the production of cytokines such as IL-4, IL-5, IL-9, and IL-13 and humoral antibody responses of the IgE isotype [5, 6, 26]. Originally destined to cope with extracellular bacteria and parasites, new data have highlighted its role in the inactivation of venoms and toxins and the repair responses of lesioned tissue [27–29]. Although these responses are clearly beneficial for the host, Th2-mediated immune responses may also lead to uncontrolled or maladaptive inflammatory reactions, i.e., the generation of IgE antibodies to allergens and the development of allergic diseases [3, 28].

Th2 Immunity and the Environment in Early Life

Besides genetic factors, Th2-mediated pathologies and IgE-mediated allergic diseases are the result of a complex interplay with the environment [30]. It became

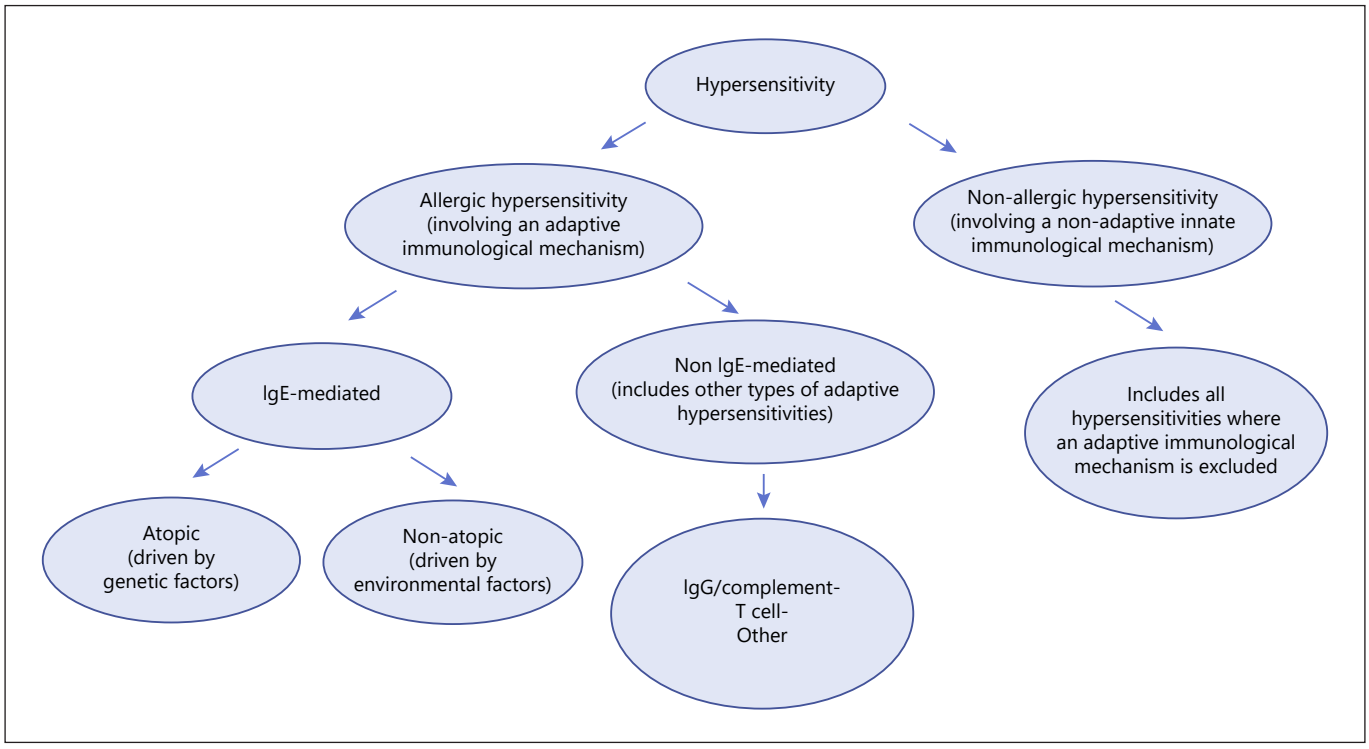

Fig. 1. Hierarchy of hypersensitivity reactions involved in immediate hypersensitivity responses (adapted and modified from references [9] and [10]).

evident that allergies have been steadily increasing since the middle of the last century in developed countries. One explanation put forward was the hygiene hypothesis, stating that the increased cleanliness, use of antibiotics, and subsequently altered diversity of microbial exposure are linked to the observed growth of global allergy prevalence [31, 32]. It is already featured in some older studies that have compared West and East German populations before and after the 1990s reunification [33]; a more recent study in this context has compared Amish and Hutterite children in the USA. While these populations share genetic ancestry and similar lifestyles, the use of distinct farming practices (traditional for the Amish, industrialized for the Hutterites) leads to an about 4 to 5-fold lower prevalence of asthma and allergy in the Amish population [34, 35]. Additional experimental proof of this "farming effect" came from the examination of house dust probes from the Amish (with a 7-fold higher endotoxin content than from the Hutterites), which were sufficient to protect mice against allergic asthma phenotypes via innate immune mechanisms [35, 36]. Importantly, the human microbiome of the lung, gut, and skin epithelia and associated metabolites that builds up during early life from environmental challenges may play an important role in controlling allergic sensitization through sequential, nonredundant steps of imprinting and educating the immune responses, named the so-called "neonatal window of opportunity" [37–40].

Role of Epithelial Barriers in the Development of Th2-Mediated Immunity

A critical component in the generation of allergic-type Th2-mediated immune responses is the altered (leaky) epithelial barrier, which supports allergen exposure by a combination of genetic and environmental factors (e.g., air pollution, protease activity of allergens, microbial dysbiosis) [41, 42]. Consequently, barrier tissues such as the skin and mucosal tissues such as the gut or lungs, upon antigen challenge, mount an innate immune response characterized by the production of typical chemokines/cytokines and alarmins (IL-1, IL-25, IL-33, TSLP). These products then activate type 2 innate lymphoid cells to produce type 2 cytokines such as IL-4 and IL-13, thereby contributing to the orchestration of a prototypical Th2 response [28]. Recent research has also highlighted the

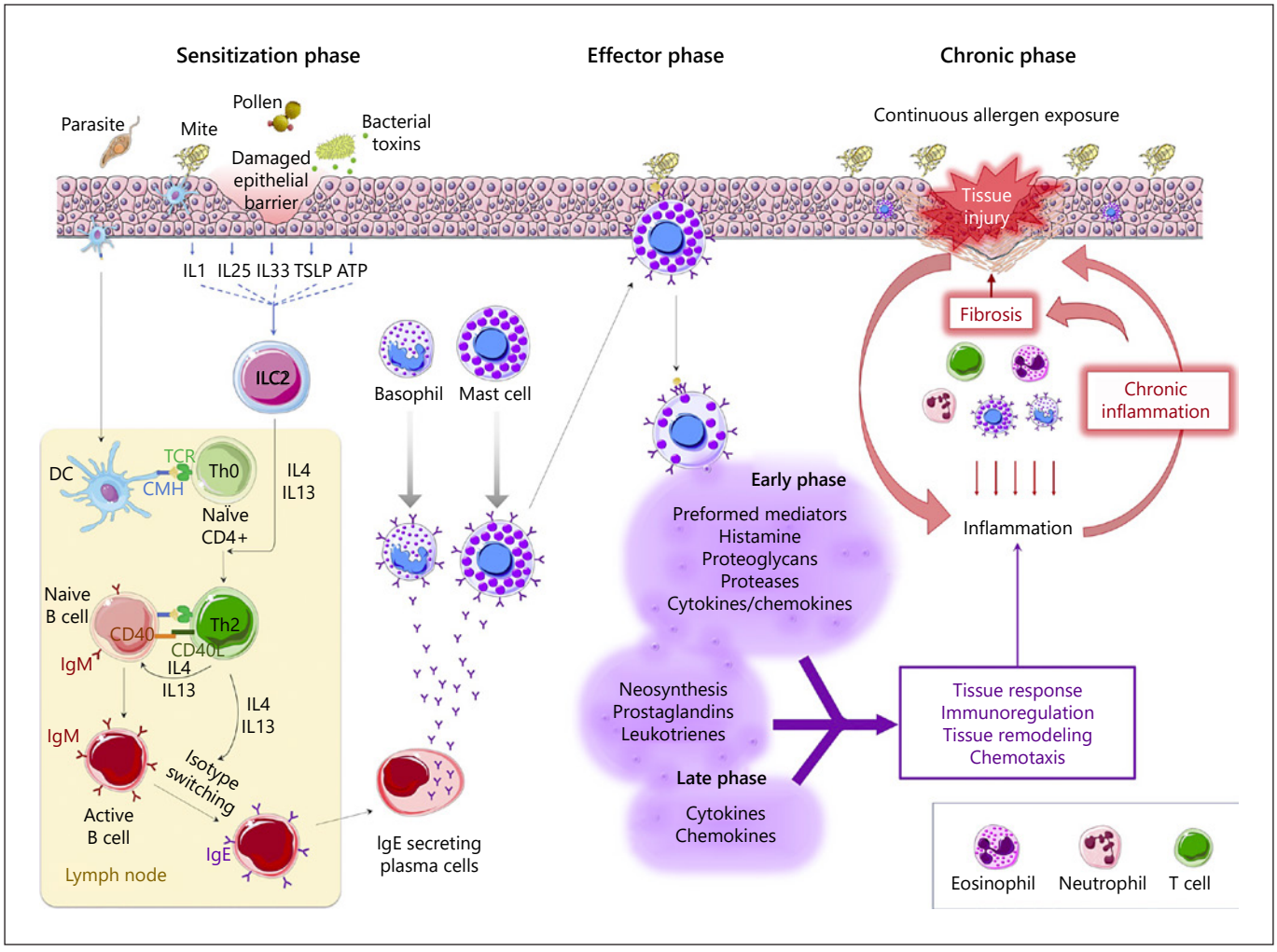

Fig. 2. Mechanisms of allergic inflammation. During the sensitization phase in a Th2-favorable environment, barrier epithelial cells respond to allergen challenge. This engenders cytokines that activate type 2 innate lymphoid cells and dendritic cells (DCs). DCs present allergenic peptides to naive T cells, under which the influence of type 2 innate lymphoid cell-secreted cytokines differentiate into IL-4/IL-13-producing Th2 cells. They contact naive B cells via a CD40/CD40L interaction and inducing their switch to IgE-secreting plasma cells. IgE binds to FcεRI present on mast cells and basophils, thereby enhancing its expression. Upon a subsequent allergen encounter, mast cells and blood basophils degranulate, releasing allergic mediators stored in granules and newly synthesized lipid compound (prostaglandins, leukotrienes) responsible for early phase allergic symptoms (vasodilatation, vascular permeability, bronchoconstriction, etc.). In a more delayed phase, they also secrete a whole variety of newly synthesized chemokines/cytokines. Together, they drive an inflammatory response and infiltration of other immune effector cells. When allergen exposure and ensuing epithelial injury persist, a chronic state of tissue injury and remodeling develops.

role of the microbiome present at these barrier surfaces in the development of allergic pathology [38]. While a healthy microbiome will essentially engender anti-inflammatory homeostatic responses, dysbiosis at these surfaces will support an uncontrolled Th2 response, favoring the development of allergies [38, 43]. E.g., increased dermal *Staphylococcus aureus* colonization combined with barrier defects has been shown to favor atopic dermatitis development [44]. Likewise, twin studies have evidenced that the microbiome and metabolome in the gut exhibit important differences in healthy versus food-allergic subjects [45]. Although the lung has traditionally been viewed as a sterile organ, new evidence clearly indicates that an altered airway microbiome or certain viral infections favor the development of asthma [46, 47]. Why certain antigen products are more prone to induce aller-

gies and IgE responses remains a subject of intense research. This includes, e.g., certain structural parameters revealed by the analysis of their three-dimensional structure [48], particular enzymatic (e.g., proteolytic) activities that might impact epithelial barriers [49], the crosstalk between sensory neurons and mast cells promoting activation of the latter [50], and the association with certain HLA class II alleles [51].

IgE-Mediated Activation of Mast Cells and Basophils

Following allergen encounters at epithelial barriers, the Th2-mediated immune response is put into place through the interaction of antigen-presenting dendritic cells with naive CD4 cells, generating IL-4- and IL-13-secreting Th2 cells (Fig. 2). They then interact with B cells (through CD40L and CD40) to promote isotype switching and production of allergen-specific IgE, which binds to FcεRI expressed on mast cells and basophils. In a second encounter with the allergen, receptor-bounded IgE will get crosslinked, launching a signaling cascade that culminates within minutes in the release of preformed mediators such as histamine, proteoglycans (heparin), and various mast cell-specific proteases, such as tryptase, chymase, and carboxypeptidase A3 [7, 52]. Histamine, in particular, is responsible for the immediate vasoactive effects that, in the worst case, may provoke anaphylaxis and even death [53]. This is rapidly followed (within 15 min) by the new synthesis and secretion of lipid mediators including certain prostaglandins and leukotrienes (LTB4 and LTC4) with multiple proinflammatory functions such as the chemoattraction of additional inflammatory effector cells and bronchoconstriction [54]. It is well known that mast cells and basophils also secrete a number of chemokines and cytokines, some of which (e.g., TNFα) are released from prestored sources in mast cell granules, promoting an immediate effect on the attraction of other immune effector cells [55]. Hence, these mediators contribute to the participation of neutrophils and eosinophils following the allergic stimulus [3]. In case of continuous non-seasonal allergen exposure, mast cells and basophils, together with these other inflammatory cells, participate in the chronic inflammatory process, contributing to the maintenance of a persistent inflammatory response with ongoing tissue injury and remodeling and eventually fibrosis development and loss of parenchyma such as in the airways [3].

Beneficial Roles of Allergy

Although IgE-mediated type I hypersensitivity responses generally initiate a sustained inflammatory response, it should be noted that, as for the inflammatory process in general, they clearly have beneficial functions for the host, notably in the defense against various types of microbial pathogens [56–58]. Still, nowadays, about 1.5 billion people are infected with soil-transmitted helminth infections worldwide. Mast cells clearly have a protective role in such infectious diseases [58, 59], while, e.g., basophils can play a central role in the defense against tick bites [60, 61]. The importance of IgE-mediated type I hypersensitivity reactions has also been demonstrated in the defense against a number of venoms from various organisms, ranging from snakes to reptiles to arthropods [27, 62, 63]. These protective actions involve mast cell proteases such as chymase, tryptase, and caboxypeptidase A3 stored in granules and able to rapidly degrade and inactivate the noxious peptides [64]. Most importantly, a series of elegant studies by the laboratory of Steve Galli has shown that even a bona fide IgE-mediated allergic response can contribute to an acquired resistance to potential lethal effects of venoms such as honeybee venom-induced anaphylactic reactions. While in certain "unlucky" individuals such a response can be deadly, it can also contribute to the protection of the host inactivation of the venom by released proteases [65–67].

IgG-Dependent Allergies and Anaphylaxis

Although allergies and anaphylaxis are classically caused by IgE antibodies in humans, evidence has been accumulating that under certain circumstances, IgG-dependent mechanisms may also be at the origin of such responses [11, 13]. This may be the case for certain drug-induced allergies ranging from small chemical compounds to large biologicals such as humanized antibodies [12, 13]. Evidence for an IgE-independent anaphylactic mechanism came initially from experimental studies in mice where active anaphylaxis was induced after immunization with antigen and subsequent challenge in mice deficient for IgE and FcεRI [68, 69]. Passive IgG-mediated anaphylaxis experiments injecting IgG immune complexes promoting an immediate drop in body temperature in mice were then conducted to identify IgG receptors involved. These experiments showed that all three murine activating FcγR, i.e., FcγRI, FcγRIII, and FcγRIV can play a role depending on the allergen-specific IgG

isotype (murine IgG1 binds only to FcγRIII) with FcγRIII having a predominant role [69, 70]. Analysis of relevant mediators responsible for IgG-mediated anaphylaxis revealed that the biological effect was not due to histamine but was rather associated with platelet-activating factor (PAF) and could be attenuated with PAF receptor antagonists [71–74]. Major PAF-producing cells such as neutrophils, monocytes/macrophages, and basophils have been implicated in IgG-mediated anaphylaxis, with the relative contribution being dependent on the experimental model used [72, 73, 75]. As FcγR differ between mice and humans, the contribution of human FcγRs (hFcγR) was also investigated in FcγR-humanized mice using either single or complete hFcγR knock-in mice [76]. Initial data showed that the knock-in mice reproduced the expression profile of FcγR isoforms in humans [76, 77]. Among hFcγRs, hFcγRI did not seem to be implicated [77], while hFcγRIIA appears to be the major contributor. Expressed on neutrophils and monocytes/macrophages it plays a prime role by activating PAF release despite the robust expression of the inhibitory receptor hFcγRIIB [76, 77]. These studies established that platelets can also contribute to anaphylaxis and increase its severity. Indeed, hFcγRIIA is expressed on human platelets contrasting with the absence of any FcγR on mouse platelets [76, 77]. Under these conditions, in addition to PAF, serotonin secreted by activated platelets was shown to play a role in anaphylaxis increasing its severity [13, 18, 74]. Analysis of IgG subclass specificity in mice showed that all subclasses (IgG1, 2a, 2b) except IgG3 were capable of inducing anaphylaxis, while the subclass specificity in humans has not yet been examined [13, 75]. Yet, it is known that IgG4 acts as a suppressor of allergic responses, building up notably during allergen-specific immunotherapy [78].

It remains a fact that in all IgG-induced models, relatively high doses of allergen-specific IgG antibodies as well as high doses of allergen were required to induce IgG-mediated anaphylaxis, largely exceeding those relevant for IgE-dependent allergies [11–13]. Hence, this has made clear that bona fide IgG-mediated anaphylactic responses may occur only under certain circumstances in which high concentration of IgG against the allergen are achieved in the absence of detectable IgE antibodies. This seems to be the case in a small proportion of allergic reactions to drugs that include, e.g., humanized therapeutic antibodies or small molecular weight compounds that may get bound to carrier proteins such as certain quaternary amines present in neuromuscular-blocking agents (NMBAs) [11–13]. A recent study by Jönsson et al. [79] has directly examined the possibility of IgG-induced anaphylaxis in a cohort of 86 patients with suspected anaphylaxis to NMBAs during general anesthesia. They found that concentrations of anti-NMBA IgG and markers of FcγR and neutrophil activation as well as PAF release correlated with anaphylaxis severity [79]. In fact, 49% of the patients with high concentrations of anti-IgG Abs to quaternary amines did not have detectable IgE Abs. In these patients FcγRIIA was internalized by neutrophils expressing significantly elevated activation markers such as CD11b, CD18, and CD66b. At the same time, their PAF-acetylhydrolase activity was decreased, which is indicative of elevated plasma PAF concentrations. Ex vivo, patient-derived purified anti-NMBA IgG when complexed to NMBA-bounded human serum albumin could directly activate neutrophils to produce reactive oxygen species. Hence, this study clearly points to the possibility that IgG-dependent anaphylactic reactions can occur in humans even when allergen-specific IgE remains undetectable [79]. Yet, they require high IgG and allergen concentrations as is the case for certain drug-induced allergies. In this context, it should be mentioned that the principle of allergen-specific immunotherapies, which have been described more than a century ago [80], is to induce blocking IgG-specific antibodies [81]. In the case of low allergen concentrations, they prevent allergen access to cell-bound IgE antibodies, eventually involving high concentrations of inhibitory IgG4. They can also co-crosslink the IgE bound to FcεRI with the IgG-binding inhibitory receptor FcγRIIB expressed on mast cells and basophils. It should be noted, however, that this latter receptor is more highly expressed in mice than in humans [71, 78, 82, 83]. Only when allergen concentrations are exceptionally (unphysiologically) elevated, e.g., upon parenteral administration of drugs or biological drugs, an unwanted IgG-mediated hypersensitivity reaction may occur.

Complement-Induced Allergies

Other hypersensitivity-inducing products that can derive from an immunological process are complement fragments produced by the classical pathway [84]. Studies in the 1950s by Z. Ovary [85] on hypersensitivity phenomena in guinea pigs and rats, using the passive cutaneous anaphylaxis (PCA) test, revealed the role of complement in the formation of anaphylatoxin, a term coined in 1909 by E. Friedberger [86] to define the activity in serum able to induce anaphylaxis. Two proteolytic complement fragments known as C3a and C5a were found to induce

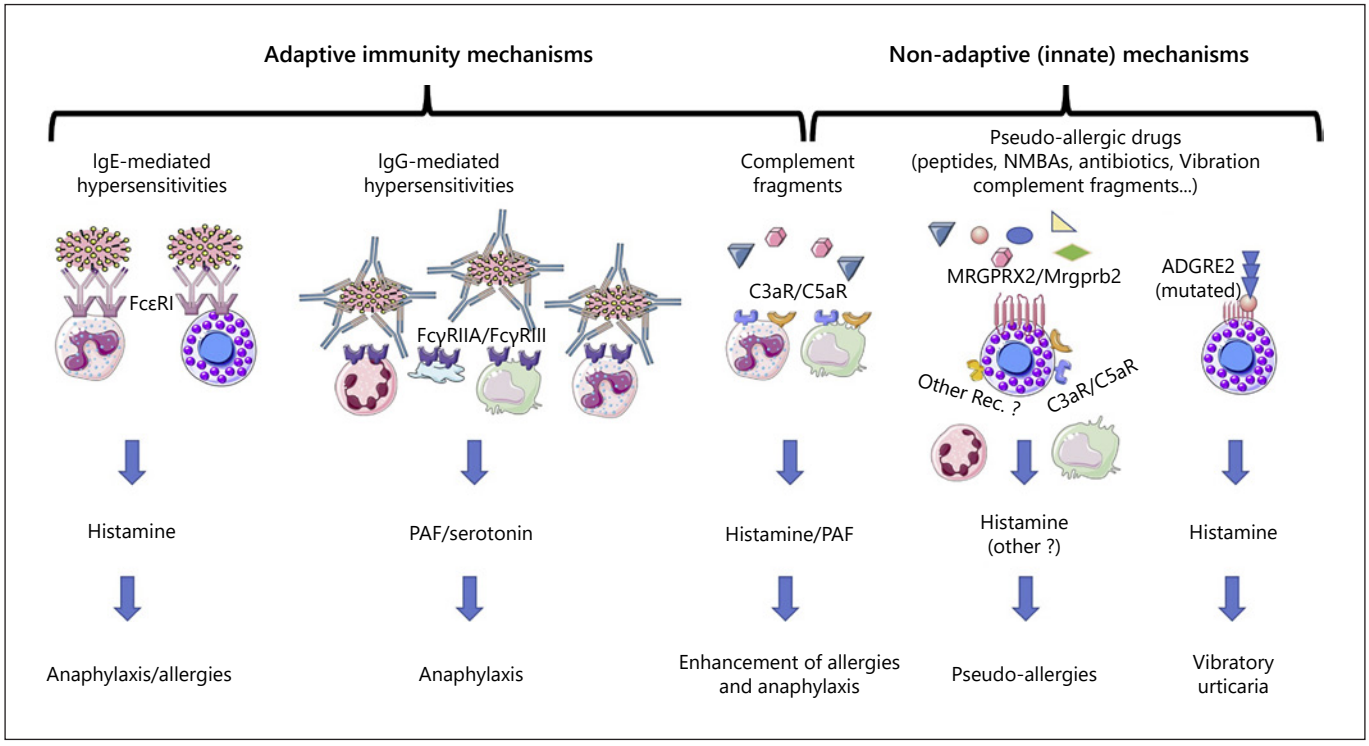

Fig. 3. Summary of described hypersensitivity mechanisms. The classical IgE-dependent type I hypersensitivity response involves mast cells and basophils that release histamine, promoting anaphylaxis and allergies. Under specific conditions where the allergen and allergen-specific IgG antibodies reach very high concentrations, several cell types in the circulation (neutrophils, monocytes/macrophages, basophils, and platelets) are activated by immune complexes through FcγRIIA and FcγRIII to release PAF and serotonin (platelets) causing anaphylaxis. Complement fragments generated by classical (adaptive) and nonclassical innate pathways can activate mast cells and monocytes/macrophages which can enhance allergies and anaphylaxis. A large variety of positively charged drugs and peptides can interact with various innate receptors such as MRGPRX2/Mrgprb2 receptors and provoke so-called "pseudo-allergic" responses. Physical stimuli such as vibration can activate the ADGRE2 adhesion receptor to cause local hypersensitivity reactions (vibratory urticaria) in the skin.

histamine release by rat mast cells, supporting the notion that these products can have a role in immediate allergic-type hypersensitivities [87], although the degranulation ability of C5a in human mast cells is somewhat disputed [88]. Receptors for C3a and C5a are also found on neutrophils and macrophages with the activation being correlated to release PAF [89, 90]. Studies in mast cell-deficient mice that had been reconstituted with mast cells deficient for C3a and C5a receptors confirmed C3a- or C5a-induced PCA reactions following their intradermal injections. These products were also able to enhance IgE receptor-induced PCA responses, revealing an important crosstalk [91]. In humans, increased C3a and/or C5a levels have been reported in patients undergoing immediate hypersensitivity reactions, often locally, e.g., in the heart or in skin [92–94], with anaphylatoxin levels appearing to be correlated with the severity of symptoms [95, 96]. The risk of associated severity of symptoms, however, seems lower than the risk associated with increased levels of mast cell tryptase or histamine [97]. It therefore appears that these fragments play a role in local allergic reactions and may eventually also enhance anaphylaxis or asthma [98]. Certain clinical applications or drugs that are able to directly generate C3a and C5a independent from an immunological process using the alternative pathway of complement activation such as cellulose membranes used for hemodialysis, contrast agents, etc., may also play a role in complement-induced anaphylaxis [95, 99]. However, in each of these cases of human anaphylaxis, definite proof of the involvement of complement needs careful examination of other potential effector mechanisms as IgG and IgE antibodies to these products have also been found [11, 99].

Hypersensitivities Induced by Nonadaptive Innate Mechanisms

As indicated above, it is now evident that, besides adaptive hypersensitivity responses, nonadaptive innate stimulation of effector cells via a variety of receptors may provoke similar symptoms and therefore have been called pseudo-allergic reactions [100–102]. In particular, mast cells as sentinel cells at the contact with the external environment are known to express a large variety of receptors, many of which can initiate mast cell degranulation and histamine release upon activation [17] (Fig. 3). Even physical stimuli such as vibration or UV light have been described as potential effector mechanisms [103]. Thus, mast cells via diverse mechanisms can promote hypersensitivity reactions and MCAS that are not necessarily dependent on an adaptive immune process.

Role of the Mast Cell Specific Receptor Mas-Related G Protein-Coupled Receptor-X2 (MRGPRX2)

A receptor which has received much attention in this context is the MRGPRX2 or its murine homolog Mrgprb2 [14, 104, 105]. They are part of a larger family of 50 members in mice and 8 members in humans, initially shown to be expressed in nociceptive neurons of the dorsal root ganglia [104, 106, 107]. One member of this family, MRGPRX2 (or Mrgprb2 in mice), was also found to be expressed in the hematopoietic system, notably in human and mouse mast cells of the connective tissue type [104, 108, 109]. Recent evidence has shown that these receptors are also expressed on human basophils and eosinophils, although the function in these cells is still a subject of controversy [110, 111]. MRGPRX2/Mrgprb2 can be activated by a highly diverse group of basic molecules, ranging from neuropeptides such as substance P, vasointestinal peptide, wasp venom-derived peptides such as mastoparan, antimicrobial host defense peptides such as β-defensin, cathelicidin, etc., small cationic molecule drugs (e.g., NMBAs) such as atracurium, cisatracurium, etc., antibiotics such as fluoroquinolones, vancomycin, opioids, the cationic polymer compound 48/80, etc [14, 100, 112]. This opens up the possibility that mast cell activation through this receptor may be responsible for acute hypersensitivity reactions that occur in the absence of an immunization process. Yet, this should be approached with caution as, e.g., the inability to detect IgE to certain drugs may not necessarily mean that IgE is not present as it can be below the limit of detection. On the other hand, as all human subjects express the MRGPRX2 receptor on certain types of mast cells, acute adverse reactions to such drugs may actually be more common as previously appreciated. In this respect, evidence shows that mild-to moderate allergic-type events to various chemical compounds can be very frequent, while severe anaphylactic events are much more rare [101, 113]. The reason for these milder reactions may relate to the fact that the plasma concentrations achieved, even after parenteral administration of MRGPRX2-binding drugs/compounds, may be below the EC50 values, preventing a full-blown activation of this receptor [101]. Another possible reason relates to the fact that only certain types of mast cells express the receptor. In particular, it is known that this receptor reaches high levels of expression on skin mast cells, and it is therefore possible that skin rashes occur when local concentrations of the drug are high, e.g., when applied topically [114]. More severe reactions may also be provoked by genetic gain-of-function variants of this receptor [115]. Based on the location of mast cells close to nerve endings, another important role of the MRGPRX2 receptor represents its ability to participate in the interaction of mast cells with the neurosensory system, initiating a neuroinflammatory crosstalk [50, 112]. Indeed, certain nociceptive or pruriceptive stimuli as well as certain allergens via their inherent cysteine protease activity, e.g., Der f 1 or Der p 1 from *Dermatophagoides* house dust mites, can directly stimulate nerve endings to release neuropeptides such as substance P that are MRGPRX2 ligands, which in turn stimulate mast cells for mediator release [25]. In this context, Serhan et al. [116] using an atopic dermatitis-like mouse model (repeated epicutaneous exposure to HDM *Dermatophagoides farinae* and the bacterial exotoxin SEB from *Staphylococcus aureus*) revealed an important neuro-immune crosstalk. Such allergenic stimulation induced nociceptor functional knots to release substance P, which in turn activates mast cells to degranulate, a key early event regulating the development of allergic skin inflammation [116].

Role of the Mast Cell Specific Receptors ADGRE2 in Vibratory Urticaria

Another recently described innate receptor involved in mast cell-mediated hypersensitivity reactions is the ADGRE2 GPCR (also known as EMR2). It is expressed on myeloid cells such as neutrophils and macrophages, but recently it has also been found to be expressed in human mast cells [103, 117]. In these cells, a gain of function mutation (C492Y) in ADGRE2 has been linked to patients presenting with autosomal dominant vibratory urticaria, a clinical manifestation distinct from dermographism and other physical urticarias [15]. These patients

have localized hives similar to other vibratory urticarias, but they are due to local stimulation of frictional nature in the skin in particular. Skin mast cells in these patients are attached to the ADGRE2 ligand dermatan sulfate (the predominant extracellular matrix glycosaminoglycan in the skin) [118] and degranulate upon application of a vibratory stimulus due to the mutant's ability to enhance the magnitude of the signaling response on a per cell basis and the number of responding cells [117]. Enhanced signaling was found to be due to a destabilization of the interaction between the extracellular N-terminal fragment (NTF) and the GPCR-like 7 transmembrane C-terminal fragment by the ADGRE2 mutant, which favors dissociation of NTF upon application of a physical force and signaling [117]. Interestingly, this receptor seems also to be responsible for the activation of ADGRE2 in patients with hereditary α-tryptasemia (hHαT) [119]. Here the ADGRE2 receptor gets activated by cleavage of the NTF through α- and β- tryptase heterotetramer released by human mast cells. These heterotetramers between α- and β- tryptase present specificity and biochemical properties distinct from those of the active tryptase β-homotetramer and are found more frequently in these patients [119]. Physiologically, it is possible that limited activation of mast cells by physical forces in the microenvironment may serve to mediate pain and itching in the skin and recruit local immune cells for tissue repair.

In this context, it is clear that ADGRE2 may not be the only receptor responding to physical forces, as it is well known that mast cells and basophils respond to physical stimuli including thermal, mechanical friction, electromagnetic radiation, UV light, etc., some of which are relevant to the pathophysiology of urticaria [120–124]. Receptors involved in this include ion channels such as TRPV2, which are expressed in mast cells [123, 125] and respond to mechanical, osmotic, thermal, and laser light stimulation [122, 123], and NOX2 which are involved in the initiation of a calcium response upon stimulation with UVA irradiation [126].

Other Receptors Expressed in Mast Cells Implicated in Allergic Hypersensitivity Responses

In addition to the receptors mentioned above, mast cells express many other receptors, some of which can potentially activate these cells to initiate hypersensitivity reactions either through adaptive (as discussed before) or nonadaptive processes. The latter include ST2 receptors activated through the alarmin IL-33 [127–129], P2X1, P2X4, and P2X7 receptors activated by the alarmin ATP released during an inflammatory process [125, 130, 131]. These receptors, while not necessarily causing a full-blown anaphylactic-type of response, may contribute to an allergic-type inflammatory reaction that is associated with various diseases including neurologic, digestive, respiratory, cardiovascular, cutaneous, and musculoskeletal inflammation [18, 103]. Some of these may also be relevant to the so-called MCAS, a clinical condition in which patients present with spontaneous episodic signs and symptoms of anaphylaxis, concurrently affecting at least two organ systems and resulting from secreted MC mediators [23].

Allergy-Related Inflammatory Responses

Besides immediate hypersensitivity responses induced by mast cells, basophils, and other cells, similar symptoms may also be due to other inflammatory processes. For example, various types of food allergies such as eosinophilic esophagitis or eosinophilic gastrointestinal disorders are characterized by esophageal/intestinal dysfunction and hypersensitivities with a predominant infiltration of eosinophils [132, 133]. The pathophysiology remains poorly understood and multifactorial and is thought to involve type 2 immunity fostered by a combination of genetic, host, and environmental factors [133–135]. Other hypersensitivities, many of which develop during early childhood, are dependent on sensitivity to protein components in food and include protein-induced enterocolitis syndrome, food protein enteropathy, and food protein-induced allergic proctocolitis [133]. Again, although it is generally possible to identify the proteins that induce these types of hypersensitivity, the pathophysiology remains poorly understood, and manifestations often resolve during childhood [133]. It is therefore crucial to clearly define the pathological mechanism behind the symptoms for each individual patient. In this category, it can also be integrated with delayed-type allergic hypersensitivities mediated by allergen-reactive T cells, e.g., allergic contact dermatitis and certain drug-induced reactions [136].

Diagnosis of Allergy and Anaphylaxis in Clinical Practice

In clinical practice, hypersensitivity reactions may affect virtually any organ, leading to patients consulting not only allergists but also general practitioners, emergency medicine doctors, pediatricians, pulmonologists, dermatologists, ear, nose, and throat specialists, or anesthesiologists, among others. Therefore, basic education in allergology is mandatory across all fields of medicine.

Patients seeking medical attention because of a history of possible hypersensitivity reactions must be offered a three-step diagnostic procedure: a detailed questionnaire about the clinical characteristics of the culprit reaction, a thorough physical examination, and IgE sensitization using skin tests, in vitro tests, or a combination of both [137, 138]. A diagnosis of IgE-dependent allergy is founded on the association of a convincing clinical history and proven sensitization to the culprit allergen. The gold standard for allergy diagnosis is a positive challenge test reaction to a culprit allergen, e.g., nasal allergen challenge or oral food allergen challenge test [139–141]; a positive test, i.e., yielding a reaction to the culprit allergen, is a reliable proof of genuine allergy. However, challenge tests bear a non-negligible risk of severe allergic reactions and therefore can only be performed by specialized medical staff in appropriate settings with high costs and lengthy delays [142].

Multiple in vitro tests are available for diagnosis of allergy. IgE measurements are done either as a "total IgE" quantification, which is nowadays used as an atopy test, or an "allergen-specific IgE" test, which will provide evidence for sensitization to a specific allergen [138]. Shortly after the discovery of IgE [143, 144], the first serological test for evaluating allergen-specific IgE was a radioactive test (due to the low concentrations of IgE in serum) termed the radioallergosorbent test (RAST) [145], later replaced by tests based on immunofluorescence. The advent of recombinant allergens has also enabled microarray-based (multiplex) allergy diagnosis tests that enable the screening of hundreds of allergens including specific epitopes [146]. Assessment of functional effects of IgE sensitization in specialized laboratories can be obtained by basophil activation tests (BAT) [147] or mast cell activation tests (MAT) [148, 149]. While the BAT requires access to fresh patient blood, the MAT can be performed on patient serum. Both assays evaluate activation of allergen-specific IgE-sensitized cells by flow cytometry (externalization of CD63) by a culprit allergen [147, 150]. Tryptase, a protease almost exclusively produced by mast cells, exhibits level variations informing on mast cell numbers, activity, and degranulation [151]. In the clinical situation, while the measurement of histamine as a sign of mast cell activation is difficult due to its short half-life, the diagnosis of anaphylaxis can be done using paired tryptase samples: one taken during the degranulation event ("acute tryptase") and the other taken either prior to the event, or, more often, once the anaphylaxis symptoms and signs have resolved ("baseline tryptase") [152]. Tryptase determination is currently available for in vitro diagnosis as a "total tryptase" test, providing a cumulative result for all isoforms and all activation states. A transient elevation of serum tryptase, with acute tryptase levels exceeding 1.2 × baseline level + 2 (μg/L), confirms mast cell degranulation and therefore anaphylaxis [153]. Baseline tryptase levels greater than 8 μg/L are potentially linked to hereditary α-tryptasemia (HαT), a genetic trait found in 5–8% of Caucasian populations associated with an increased prevalence of anaphylaxis, while baseline tryptase levels greater than 20 μg/L constitute a minor criterion of systemic mastocytosis [151].

Further biomarkers which are useful for the diagnosis or management of allergic reactions are allergen-specific IgG4, which increase during successful allergen immunotherapy (desensitization) [78, 154], eosinophil activation biomarkers such as eosinophil cationic protein or eosinophil-derived neurotoxin [155] and various mast cell mediators such as histamine metabolites, or leukotrienes [156]. Delayed-type hypersensitivity reactions, mainly drug-induced, can be investigated using lymphocyte activation or proliferation tests [157].

Among all these tests, allergen-specific IgE and tryptase are by far the most common. A so-called top-down approach consists usually in anamnesis followed by allergen-specific IgE determination, meaning that clinical data will point to one or a small number of potential culprit allergens, which will be assayed as singleplex allergenic extracts in diagnostic tests. If specific IgE to extracts is demonstrated, a second level of investigation will address specific IgE to specific allergenic molecules in the extract, aiming at more precise diagnosis, assessment of severity and allergen cross-reactivity, prognostic and therapeutic evaluation. Multiple methods are available for allergen-specific IgE determination using singleplex or multiplex approaches and providing qualitative or quantitative results [138, 146].

A few examples among the many currently unmet needs in the diagnosis of allergy are assessment of MRGPRX2 activation, as tryptase determination does not discriminate between IgE-induced and MRGPRX2 mechanisms [158], investigation of allergenicity [159], and efficient harnessing of biomarkers for precision medicine applied to allergy and anaphylaxis [160].

Conclusions

The purpose of this review was to summarize recent data on hypersensitivity responses implicated in the development of allergies, focusing on both adaptive immu-

nological and nonadaptive innate triggering of mast cells and other cells. Although bona fide type I hypersensitivity reactions in humans are caused by the crosslinking of IgE antibodies bound to mast cells and basophils, engendering the release of histamine as one of the major mediators, it has become clear that alternative mechanisms to induce immediate hypersensitivity reactions exist (Fig. 3). These include other adaptive immunological mechanisms that are not necessarily Th2-driven such as the generation of IgG antibodies to certain drugs or antibodies, under which certain specific conditions (high concentrations of both antibodies and antigen) may generate immune complexes able to activate neutrophils, macrophages, and platelets to release PAF and/or serotonin as anaphylaxis-causing agents. Other alternative types of activation may appear more local and milder due in part to incomplete activation or restricted expression of receptors to certain mast cell subtypes, as, e.g., described for complement receptors or the recently described MRGPRX2 receptors. It seems likely that many of the milder local allergic reactions may be caused by immediate hypersensitivity reactions; however, on some occasions, other more delayed types of hypersensitivities also occur. Still, the study of hypersensitivity needs to take into account the ever-evolving complexity, as exemplified by the recent discovery of the MRGPRX2 receptors and the connections with the sensory nervous system [14, 50]. Hence, it will be important in the clinical context to clearly define the underlying pathophysiological mechanisms in order to design the appropriate therapeutical strategy.

Statement of Ethics

No human or animal subjects were used for writing this review.

Conflict of Interest Statement

Joana Vitte reports speaker and consultancy fees in the past 5 years from Meda Pharma (Mylan), Novartis, Sanofi, Thermo Fisher Scientific, and AstraZeneca outside the submitted work. The other authors declare no competing interests.

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Author Contributions

All authors contributed to the writing of the review and design of the figures. Writing was coordinated by Ulrich Blank.

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