Review

Mast cells and basophils are essential for allergies: mechanisms of allergic inflammation and a proposed procedure for diagnosis

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The current definition of allergy is a group of IgE-mediated diseases. However, a large portion of patients with clinical manifestations of allergies do not exhibit elevated serum levels of IgE (sIgEs). In this article, three key factors, *ie* soluble allergens, sIgEs and mast cells or basophils, representing the causative factors, messengers and primary effector cells in allergic inflammation, respectively, were discussed. Based on current knowledge on allergic diseases, we propose that allergic diseases are a group of diseases mediated through activated mast cells and/or basophils in sensitive individuals, and allergic diseases include four subgroups: (1) IgE dependent; (2) other immunoglobulin dependent; (3) non-immunoglobulin mediated; (4) mixture of the first three subgroups. According to our proposed definition, pseudo-allergic-reactions, in which mast cell or basophil activation is not mediated via IgE, or to a lesser extent via IgG or IgM, should be non-IgE-mediated allergic diseases. Specific allergen challenge tests (SACTs) are gold standard tests for diagnosing allergies *in vivo*, but risky. The identification of surface membrane activation markers of mast cells and basophils (CD203c, CCR3, CD63, etc) has led to development of the basophil activation test (BAT), an *in vitro* specific allergen challenge test (SACT). Based on currently available laboratory allergy tests, we here propose a laboratory examination procedure for allergy.

Keywords: allergy; mast cell; basophil; IgE; IgG; pseudo-allergic reaction; specific allergen challenge test; basophil activation test

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Introduction

Allergic diseases, which include allergic rhinitis, allergic asthma, allergic dermatitis, allergic conjunctivitis, anaphylaxis, food or drug allergic reactions, are major diseases involving approximately 22% of the world population^[1]. However, the current definition of allergic diseases is a group of diseases largely driven via immunoglobulin (IgE)-dependent mechanisms^[2], which is hardly applicable to the allergy patients in the 22% world population. Indeed, a majority of the allergy population has never undergone specific IgE (sIgE) testing. However, new terms, allergy-like reactions or pseudo-allergy, have been derived from allergy in the last two decades to describe a clinical syndrome much like allergy, with normal serum IgE levels^[3]. Although these patients are not diagnosed as allergies, these individuals are treated in exactly the same

manner as that for allergic patients. A majority of physicians prescribing anti-allergic medicine do not examine the serum IgE levels of these patients in daily clinical practice, suggesting that the term “allergy,” as a group of IgE-mediated diseases, might not cover all naturally occurring allergic disorders. Indeed, there might be some misunderstanding of allergy.

It has recently been reported that the diagnosis of immediate-type hypersensitivity begins with a thorough clinical history and physical examination, confirmed through an allergen extract skin prick and allergen sIgE measurement^[4]. This testing is a routine procedure used for diagnosing allergic disorders over the last several decades, consistent with the current definition of allergic diseases. Based on this definition, special attention has to be paid to serum level of IgE (sIgE). However, there is a great clinical disagreement between clinical manifestation (including skin prick tests) and sIgE measurement. For example, the predictive utility of serologic measures of sIgE for food and drug allergies and asthma is relatively poor^[4]. The consistency between the clinical manifestations of allergies and sIgE measurement was only 40% for 50487 clinical cases

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from 2008–2010 in the Allergy Department of Beijing Union Hospital^[5]. These clinical findings suggest that some patients with negative serologic levels of sIgE can still be diagnosed as an allergy.

According to the data from the Allergy Department of Beijing Union Hospital, 60% of patients with clinical manifestations of allergies do not have elevated serum sIgE levels. Thus, the current term “allergy” is not consistent with the understanding of millions of people, as allergists define “allergy” as a group of IgE-mediated diseases, which really should be considered as a subgroup of allergic diseases.

Basic pathogenesis of allergy

Allergic inflammation is a fundamental pathological change of an allergy, and type I hypersensitivity of the immune system is the basic mechanism of allergic inflammation^[2]. There are two phases in the basic process of allergic inflammation, as we previously described^[6]: the induction (sensitization) phase and the effector phase (Figure 1). The induction phase involves antigen presenting cells (APCs), T cells, Th2 cytokines, such as interleukin (IL)-4, IL-5 and IL-13, class switching of B cells, IgE secretion and binding to the high-affinity IgE receptor FcεRI on the membrane of mast cells and basophils, forming sensitized mast cells and basophils. The effector phase begins when same allergen cross-links two adjacent IgEs on sensitized mast cells or basophils; activated mast cells or

basophils subsequently released proinflammatory mediators or cytokines, thereby causing the clinical manifestations of allergy. Soluble allergens, sIgEs and mast cells or basophils are three key factors in the pathophysiological process of allergic inflammation, representing causative factors, messengers and primary effector cells, respectively. In contrast to primary effector cells, eosinophils and neutrophils are secondary effector cells, which can be accumulated and activated through the mediators released from mast cells or basophils.

Causative factors of allergies

Allergens are the causative factors of allergies. The current definition of aeroallergens is aerosols ranging from submicron particles to relatively larger pollen grains, fungal spores, animal emanations, and biogenic debris^[7].

Protein allergens

Based on the definition, multi-protein substances, including house dust mites, cat hair, *Aspergillus fumigatus* or short ragweed pollen, are called allergens. Accordingly, allergies caused by these substances are named after the allergic substance followed by the word “allergy.” For example, an allergy caused by house dust mite is called a house dust mite allergy.

However, since the identification of “the first indoor allergen” Fel d 1, purified from the cat (*Felis domesticus*)^[8], and “the first full sequence of allergen” Der p 1^[9], more than 300 protein molecules have been identified as “allergens”. The novel names of these allergens (such as Fel d 1–Fel d 7 from the cat; Asp f 1–Asp f 27 from *Aspergillus fumigatus*; Der p 1–Der p 14 from the house dust mite) appear to be in conflict with the traditional names of allergens (such as cat allergen, *Aspergillus fumigatus* allergen, or house dust mite allergen). To distinguish the novel name of an allergen from the traditional name of an allergen, we propose naming traditional allergens as “allergenic species” and novel name of allergens as “allergen.” For example, there are 14 allergens in house dust mite species. Because it is relatively easy to detect proteins in extracts, reservoir dust samples, and air-borne particulates using antibody-based immunometric assays, a growing number of protein allergens have been identified. There are at least three subgroups of allergens in the protein allergen group, which activate mast cells through different receptors, including IgE^[10, 11], IgG^[12, 13], and complement C3a, C5a receptors^[14, 15]. However, not all allergens are antigens; for example, large numbers of low molecular weight allergenic substances do not have antigenic activity, but these substances activate mast cells or basophils through direct, non-receptor-mediated mechanisms^[6].

Low molecular weight molecules (LMWMs)

There are huge numbers of LMWMs that cause allergies in the body and environment. For example, heparin induces anaphylactic and anaphylactoid reactions^[16], sphingosine-1-phosphate is emerging as a novel mediator of anaphylaxis^[17], and iodinated contrast agents have been shown to induce allergy-like reactions^[18]. These LMWMs should be included in the list of allergens. Therefore, the definition of allergens

Figure 1. Classical pathophysiological process of allergic inflammation. MC, mast cell; DC, dendritic cell; Eos, eosinophil; sIgE, specific IgE; mIgE, membrane binding IgE; TCR, T cell receptor; MHC II, class II major histocompatibility complex; PGD, prostaglandin D; LTC, leukotriene C; IL, interleukin; MBP, major basic protein. Source of mast cell images: http://proteopedia.org/wiki/index.php/PhI_p_2 and <http://findingtherootcause.blogspot.ca/2011/01/mast-cells.html>

should include substances that cause allergy regardless of the antigen, *ie*, a hapten, which needs to be bound to larger molecules to enhance antigenicity, or a LMWM, which does not stimulate the immune system to produce specific antibodies. This is, allergenic activity does not equal to antigenic activity, as antigenic activity stimulates the production of antibodies, whereas allergenic activity includes both antigenic activity and LMWM induced direct, non-receptor-mediated mast cell or basophil degranulation mechanisms. Based on the molecular size of allergens, there should be at least two different groups of allergens: large molecule allergens (molecular weight >10 kDa), including protein and non-protein allergens, and low molecular weight allergens, including haptens and other small molecule allergens.

Transmitters or messengers of allergy

Based on the previous definition of allergy, the mechanisms of IgE-mediated allergic inflammation have been extensively studied. As shown in Figure 1, all key cells and molecules involved in transmitting the biological message of allergen to primary effector cells are transmitters or messengers of an allergy, representing the most complicated process of an allergy, whose underlying mechanisms remain unknown. However, allergic inflammation reflects a complex interplay between several inflammatory cells, including mast cells, basophils, lymphocytes, dendritic cells, eosinophils, and neutrophils. These cells produce multiple inflammatory mediators, including lipids, purines, cytokines, chemokines, and reactive oxygen species^[19]. In the present review, the roles of some key cells and molecules in the transmission from biological messages of allergen to primary effector cells are summarized.

Cellular messengers of allergy

Dendritic cells (DCs) are major antigen presenting cells (APCs) specialized in the uptake, processing and presentation of antigens to T cells^[20]. Following allergen exposure, DCs act as reporters of the microenvironment, subsequently migrate to draining lymph nodes^[21] to activate naïve T cells to produce T helper (Th)2 cytokines^[14]. FcεRI-positive DCs are efficient stimulators of both primary and FcεRI/IgE-dependent secondary T-cell responses at low cell numbers^[22]. Susceptibility to airway hyperresponsiveness is associated with preferential myeloid DCs allergen uptake and production of Th17-skewing cytokines (IL-6 and IL-23)^[23]. Epidermal Langerhans cells (LCs) belong to the DCs family and represent the major APCs within the skin. The recruitment of CD1a+ LCs to the nasal mucosa during natural seasonal allergen exposure might contribute to local T-cell responses^[24]. Inflammatory dendritic epidermal cell-like DCs are a group of FcεRI-bearing APCs which might regulate inflammatory processes through the production of Th1/Th2-polarizing signals, proinflammatory cytokines and chemokines^[25].

Following allergen exposure, the interaction of DCs with CD4(+) T cells leads to the production of Th2 cytokines IL-4, IL-5 and IL-13. IL-4 and IL-13 play an important role in the pathogenesis of allergic diseases and are required for IgE

production in B-cells^[26]. However, Th2 cells are not the sole source of IL-4 and IL-13, other cell types, such as basophils^[27], mast cells^[28] and epithelial cells^[29], release relatively large quantities of IL-4 and IL-13. Indeed, allergic sensitization through the airway primes modest Th2 responses and strong Th17 responses that promote airway neutrophilia and acute allergen-induced airway hyperreactivity^[30]. Th17 cells are characterized by IL-17 (or IL-17A), IL-17F, IL-6, tumor necrosis factor, and IL-22 expression^[31]. Through IL-17, these cells promote neutrophil recruitment and are involved in allergic asthma, where neutrophils contribute to inflammation more than eosinophils. The identification of Th17/Th2 cells, producing both IL-4 and IL-17, in allergic asthma is consistent with the observation that different clinical phenotypes coexist in the same patient^[32]. Moreover, atopy might aggravate nasal polyposis through the stimulation of the Th17 population and increased IL-17A production^[33]. Regulatory T cells (Tregs) develop in the thymus from CD4(+) T cells (natural Tregs) and in the periphery through the conversion of naïve CD4(+) T cells (induced Tregs)^[34].

CD4⁺CD25⁺FOXP3⁺ Tregs and IL-10-secreting inducible type 1 Tregs inhibit the development of allergy^[35, 36]. Studies have shown that the numbers or function of both subsets might be deficient in the patients with atopic allergic diseases^[37].

The differentiation of B-lymphocytes into IgE-expressing cells depends on three types of signals. The first signal is delivered through the B-cell antigen receptor and is pivotal in determining the antigenic specificity of the response. The second signal is primarily provided through cytokines derived from Th2 cells, such as IL-4 and IL-13. Under tight regulation, these cytokines stimulate transcription through Ig constant region genes. The third signal is provided via the interaction between the constitutively expressed CD40 molecule on B-lymphocytes and CD154 (CD40 ligand), a molecule expressed on activated T-lymphocytes. Thus, the elevated levels of IgE observed in atopic individuals might reflect the preferential activation of Th2 cells^[38].

Molecular messengers of allergy

As shown in Table 1, lists the key molecules associated with the transmission of biological messages of allergens to primary effector cells. Notably, some of these messengers have been used as diagnosing tools for allergies. Although it seems likely that cytokines are essential for sensitization, IgE or IgG remain the key messengers of allergies. IgE molecules bind to high-affinity receptors on the surface of mast cells and basophils and the subsequent cross-linking of these molecules with the allergen releases preformed and newly synthesized mediators, causing the bronchoconstriction, lung inflammation and airway hyperresponsiveness observed in asthma (effector phase)^[14]. The antibody drug cetuximab, containing oligosaccharide, which stimulates the production of the oligosaccharide-specific IgE antibody, might serve as an emerging and clinically important IgE-mediated allergen^[39]. Recently, IgG has emerged as a key messenger of allergy, and the influence of IgG on mast cells and basophils has been summarized in a

Table 1. Key molecules related to transmission of biological messages of allergen to primary effector cells.

Molecule	Secreted from	Role in allergy
Immunoglobulin		
IgE	B cells	Bind to high affinity IgE receptor FcεRI forming sensitized MC and Bas. Cross links 2 adjacent IgEs on sensitized MC or Bas can activate them to release proinflammatory mediators or cytokines, which initiates clinical manifestation of allergy.
IgG1	B cells	Activating Bas to release histamine ^[153] . Aggregation of Fcγ3RI to activate human MC ^[13] .
IgG3	B cells	Activating Bas to release histamine ^[153] .
Cytokine		
TSLP	Bas ^[63] , MC ^[64] , DC ^[21]	Activation of Th2 cells, MC, DCs, Eos, and Bas, leading to inflammatory processes that define allergic disease ^[57] .
IL-3	MC ^[47] , T cells ^[155]	Provoke histamine, LTC4, IL-4, and IL-13 release from Bas ^[154] ; induce the rapid and specific expansion of Bas ^[43] ; stimulating generation of MC from CD133 ⁺ progenitor cells ^[44] .
IL-4 and IL-13	MC ^[51] , Bas ^[53] , EC ^[29] , Th2 cells ^[31]	Providing a first and crucial signal ^[49] for class switching in B cells to produce IgE.
IL-5	Eos, Th2 cells, MC, Bas ^[54]	Involved in the differentiation, maturation, migration, development, survival, trafficking and effector function of Eos ^[54] .
IL-17E (IL-25)	EC, Eos, Bas, MC ^[56]	Enhancing Th2 cytokine production ^[56] ; activation of Th2 cells, MC, DC, Eos, Bas, leading to allergic inflammation ^[57] .
IL-31	Th2 cells ^[60] , MC ^[61]	Coordinate the interaction of T-cells, MC, and Eos, with EC to release chemokines and other cytokines ^[61] .
IL-33	EC ^[21]	A ligand for ST2 receptor; inducing Th2 cytokine release from MC and polarized T cells; provoke Bas to produce IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, and GM-CSF ^[53] ; acting as a central molecule in allergic asthma via Bas, MC, Eos, and Th2 cells ^[62] .
GM-CSF	MC ^[65] , EC ^[21] , Bas ^[53] , Th2 cells ^[66]	Induction of IL-4 release from MC ^[67] ; stimulating the proliferation and differentiation of Eos in the bone marrow ^[68] and Eos chemotaxis and activation ^[69] .

IL, interleukin; GM-CSF, granulocyte/macrophage colony-stimulating factor; TSLP, thymic stromal lymphopoietin; LTC4, leukotriene C4; SCF, stem cell factor; EC, epithelial cells; MC, mast cell; Bas, basophil; Eos, eosinophil.

previous paper^[6]. Although the clinical implications remain obscure, elevated levels of beta-lactoglobulin-specific serum IgA and IgG4 have been associated with cow's milk allergy^[40]. Increased IgA levels have also been observed in the nasal lavage fluid of patients with allergic rhinitis^[41].

IL-3 stimulates the release of large quantities of histamine, LTC4, IL-4, and IL-13 from basophils^[42]. Because these molecules are major mediators of allergy and asthma, IL-3 is likely to play a role in allergy. IL-3 also plays an important role in the rapid and specific expansion of basophils^[43] and the generation of mast cells from CD133(+) progenitor cells in cord or peripheral blood^[44]. In the presence of stem cell factor (SCF) and IL-3, CD34(+)-enriched mononuclear cells from human blood are converted to FcεRI-expressing mast cells^[45], and rat bone marrow mononuclear cells (BMMCs) exhibit the characteristics of mucosal mast cells^[46]. Interestingly, mast cells secrete IL-3^[47], and mast cell-derived IL-3 selectively induces retinaldehyde dehydrogenase-II release from basophils via PI3-kinase and NF-κB pathways^[48], suggesting the self-amplification of mast cell activation and cross talk between mast cells and basophils.

IL-4 and IL-13 are key Th2 cytokines involved in allergy, providing the first crucial signal^[49] for class switching in B cells for the production of allergen-specific IgE antibodies that bind to specific receptors on mast cells and basophils^[31]. IL-4 production during antigen presentation to Th cells is critical

for the development of Th2 cells^[50]. Th2 cells^[31], mast cells^[51, 52] and basophils^[53], and EC^[29] release substantial quantities of IL-4 and IL-13.

IL-5 is a Th2 homodimeric cytokine involved in the differentiation, maturation, migration, development, survival, trafficking and effector functions of blood and local tissue eosinophils. The IL-5 receptor (IL-5R) consists of an IL-5-specific α subunit that interacts in conformationally dynamic ways with the βc subunit, an aggregate of domains that also have binding sites for IL-3 and GM-CSF. IL-5 and IL-5R drive allergic and inflammatory immune responses^[54].

IL-17 promotes neutrophil recruitment to the airways in neutrophilic asthma^[55], whereas IL-17E (also known as IL-25), produced in epithelial cells, eosinophils, basophils and mast cells, enhances Th2 cytokine production for the regulation of adaptive immunity^[56]. Upregulated IL-25 activity activates Th2 cells, mast cells, dendritic cells, eosinophils and basophils, leading to inflammatory processes that define allergic disease^[57]. Anti-IL-25 prevents the development of key features of asthma, suggesting the suppression of the Th2 response^[58].

IL-31 has recently been identified as a new member of the IL-6 family of cytokines. IL-31 signals through a heterodimeric receptor that stimulates JAK-STAT, RAS/ERK, and PI3K/AKT signal transduction pathways. The enhanced expression of IL-31 has been associated with a number of diseases, including allergy and inflammatory bowel disease^[59]. IL-31 coordinates

the interaction of T-cells, mast cells, and eosinophils with epithelial cells to release chemokines and other cytokines. IL-31 is primarily produced in Th2^[60] and mast cells^[61], suggesting a role in allergic diseases.

IL-33 is an IL-1 family member, recently identified as the ligand for the ST2 receptor, a member of the IL-1 receptor family. ST2 is stably expressed on mast and Th2 cells. IL-33 induces Th2 cytokine release from mast cells and polarized mouse T cells, leading to pulmonary and mucosal inflammation. Human blood-derived basophils express high levels of ST2 receptor and respond to IL-33 by producing several pro-inflammatory cytokines, including IL-1 β , IL-4, IL-5, IL-6, IL-8, IL-13, and GM-CSF^[53]. IL-33 also acts on the ubiquitously expressed IL-1 receptor accessory protein (ILRAcP) and might play a central role in allergic asthma, addressing various cascades of innate and adaptive immune responses in a unique fashion via basophils, mast cells, eosinophils and Th2 cells. DCs pre-treated with IL-33 were significantly more potent for the generation of allergen-specific Th2 cells with IL-5 and IL-13 production^[62].

TSLP (thymic stromal lymphopoietin), a member of the Th2 cytokine family, has recently emerged as an active participant in the pathogenesis of allergy. Unregulated TSLP activity activates Th2 cells, mast cells, DCs, eosinophils, and basophils, leading to inflammatory processes that define allergic disease^[57]. TSLP is secreted from basophils^[63], mast cells^[64] and DCs upon house dust mite exposure^[21], and the percentage of TSLP-positive mast cells in the total population of mast cells was significantly increased in asthmatic airways^[64].

Granulocyte/macrophage colony-stimulating factor (GM-CSF) is a hematopoietic growth factor produced in mast cells in response to IgE receptor-mediated activation^[65], epithelial cells upon house dust mite exposure^[21], basophils^[53] and Th2 cells^[66] for the induction of IL-4 release from mast cells^[67]. It played significant roles in the proliferation and differentiation of eosinophils in the bone marrow^[68], and the chemotaxis and activation of eosinophils^[69].

Primary effector cells of allergy

Mast cells and basophils are the primary effector cells of allergies^[70, 71], which directly respond to allergen challenge through immunoglobulin dependent or independent mechanisms^[72]. Upon activation, mast cells and basophils release three major groups of proinflammatory mediators causing pathological damages^[73] and clinical manifestations^[74, 75]. Symptoms of allergies occur after the activation of mast cells or basophils. Theoretically, the degranulation of mast cells and basophils is the definitive event in allergy, whereas IgE only serves as one of the key messengers.

Although mast cells and basophils play a decisive role in allergy, the cell types involved in the sensitization of primary effector cells are also essential for the occurrence of allergy. For example, an individual allergic reaction to alcohol, grass pollen, or certain foods requires long process to obtain sensitization to that specific allergen and not other allergens. This natural phenomenon suggests that mast cells or basophils

should be primed before activation, although the known activators are LMWMs.

Degranulated mast cells or basophils are definitely activated, but whether activated mast cells or basophils undergo the degranulation process remains unknown. Mast cells release three groups of mediators^[76], including preformed granule products, such as histamine, tryptase, chymase and heparin; newly synthesized arachidonic acid products, such as leukotriene C4 (LTC4) and prostaglandin D2 (PGD2)^[77]; and cytokines, such as IL-4, IL-13, and eotaxin^[78]. These products greatly contribute to pathological damage in different tissues (Table 2)^[79, 80].

Table 2. Key proinflammatory actions of major mast cell products.

Product	Secreted from	Action
Histamine	Granule	Induction of microvascular leakage ^[81] and vessel dilation; polarize DC into Th2 cell-promoting effector DC ^[82] ; induce Eos adhesion and accumulation ^[83] .
Heparin	Granule	A potent chemoattractant for Neu ^[92] ; increase vascular permeability ^[93] ; promote the storage of other granule-contained compounds; regulate the enzymatic activities of MC proteases ^[94] .
Tryptase	Granule	Induction of Eos and Neu accumulation ^[85] ; provoke the release of Eos peroxidase and beta-HSD from peripheral blood Eos ^[86] ; stimulate endothelial cells to release arachidonic acid and PAF and upregulate cell surface P-selectin expression ^[87] .
Chymase	Granule	Induction of Eos migration ^[88] , and stimulate mucin secretion from bronchial EC ^[90] .
MC-CPA	Granule	Regulating innate immunity responses ^[91] .
MMP9	Granule	A potent chemoattractant for Neu ^[95] .
LTC4	Membrane	Induction of Eos migration, increase in vascular permeability and bronchoconstriction ^[96] .
PGD2	Membrane	Induction of vasodilatation, increased permeability, migration of inflammatory cells, and production of cytokines ^[97] .
PAF	Membrane	Activate platelets, induction of bronchoconstriction, bronchial hyper responsiveness ^[98] , and chemotaxis of MC ^[99] .
TNF	Secretory vesicles	Stimulate migration of MC ^[107] ; promote cellular differentiation, survival, and production of inflammatory cytokines and chemokines ^[156] .
RANTES	?	Recruitment of Bas, Eos and MC ^[69] .
Eotaxin	?	Recruitment of Bas, Eos and MC ^[69] .
IL-6	Secretory vesicles	Stimulate migration of MC ^[105] .
IL-8	?	Stimulate migration of MC ^[106] .
IL-29	?	Induction of infiltration of MC ^[101] .

IL, interleukin; EC, epithelial cells; MC, mast cell; Bas, basophil; Eos, eosinophil; beta-HSD, beta-hexosaminidase; MC-CPA, mast cell carboxypeptidase A; TNF, tumor necrosis factor; RANTES, regulated upon activation normal T cell expressed and secreted; LTC4, leukotriene C4; PGD2, prostaglandin D2; PAF, platelet-activating factor; MMP9, matrix metalloproteinase-9.

Preformed granule products of mast cells

Histamine, apart from the induction of microvascular leakage^[81] and vasodilation, polarizes human DCs into Th2 cell-promoting effector DCs^[82] and induces eosinophil adhesion and accumulation^[83]. The activation of the histamine H4 receptor enhances LPS-induced IL-6 production in mast cells via ERK and PI3K activation^[84]. Tryptase induces eosinophil and neutrophil accumulation^[85], promoting the release of eosinophil peroxidase and beta-hexosaminidase from peripheral blood eosinophils^[86], and stimulating human coronary artery endothelial cells to release arachidonic acid and platelet-activating factor (PAF)^[87]. Chymase induces eosinophil migration^[88], which was mediated through the extracellular signal-regulated kinase pathway^[89], and stimulates mucin secretion from bronchial epithelial cells^[90]. While the exact contribution of mast cell carboxypeptidase A (MC-CPA) to allergy is unclear, this protease plays a role in regulating innate immunity responses, including the degradation of harmful substances, such as the vasoconstrictive factor endothelin 1 and snake venom toxins^[91]. Heparin is a potent chemoattractant for neutrophils^[92], which increases vascular permeability through a heparin-initiated bradykinin formation mechanism^[93]. Heparin plays an essential role in promoting the storage of other granule-contained compounds, including bioactive monoamines and different mast cell-specific proteases, and regulating the enzymatic activities of mast cell proteases^[94]. MMP-9 is a potent chemoattractant for neutrophils, which might be responsible for the crosstalk between mast cells and neutrophils^[95].

Newly synthesized arachidonic acid products of mast cells

LTC4 is an important mediator produced through the arachidonic acid pathway in the plasma membrane of mast cells and

basophils via 5-lipoxygenase, which promotes inflammation processes, including eosinophil migration, increased vascular permeability and bronchoconstriction^[96]. PGD2 is another major arachidonic acid product primarily produced in mast cells in allergic diseases, inducing vasodilatation, increased vascular permeability, inflammatory cell migration, and cytokine production^[97]. As a potent phospholipid mediator involved in anaphylaxis, PAF activates platelets and induces bronchoconstriction, bronchial hyper-responsiveness^[98], and mast cell chemotaxis^[99]. Interestingly, arachidonic acid products can be released alone from basophils without degranulation in response to allergen challenge^[100].

Mast cell-released cytokines

Cytokines, such as IL-4^[101], IL-6, vascular endothelial growth factor^[102], IL-13, and TNF^[103], are released from mast cells without causing degranulation. The cytokines released from mast cells act as potent proinflammatory factors to contribute to the pathogenesis of allergy^[6]. For example, the interactions of eotaxin, RANTES and MCP-1 with CCR3 (CD193) are responsible for the recruitment of basophils, eosinophils and mast cells^[104]. While IL-6^[105], IL-8^[106], and TNF^[107] stimulate mast cells migration^[108], and IL-29 induces mast cell infiltration via CD18- and intercellular adhesion molecule-1 (ICAM-1)-dependent mechanisms^[101].

Activation markers of mast cells and basophils

Mast cell-specific secretory products

Mast cell-specific secretory products, including histamine, tryptase, chymase, LTC4, PGD2 and beta-hexosaminidase, are activation markers for mast cells, and histamine, LTC4 and PGD2 are activation markers for basophils (Table 3). However, eosinophils release LTC4^[109] and DC secretes PGD2^[110].

Table 3. Activation markers of mast cells and basophils.

Marker	Property	Expression cell	Location	Type of marker
Histamine	Amine	MC, Bas	Granule	Degranulation
Heparin		MC, Bas	Granule	Degranulation
Tryptase	Protease	MC, little in Bas	Granule	Degranulation
Chymase	Protease	MC	Granule	Degranulation
MC-CPA	Protease	MC	Granule	Degranulation
beta-HSD	Enzyme	MC	Granule	Degranulation
LTC4	Lipid metabolite	MC, Bas, Eos	Membrane	Activation
PGD2	Lipid metabolite	MC, Bas, DC	Membrane	Activation
FcεR1	IgE receptor	MC, Bas, DC, Eos	Surface	Activation?
CD117	SCF receptor	MC, Bas, HSC, Mel	Surface	Constitutive
CCR3	Chemokine receptor 3	MC, Bas, T cells, Eos	Surface	Constitutive
CD63	Lysosomal-associated membrane protein	MC, Bas, Neu, DC, T cells, Eos	Surface	Degranulation
CD123	IL-3 receptor	MC, Bas, DC, Mon	Surface	Constitutive
CD200R3	Receptor	MC, Bas	Surface	Activation
CD203c	Phosphodiesterase	MC, Bas	Surface	Activation
CD300a	Inhibitory receptor	Bas	Surface	Degranulation

MC-CPA, mast cell carboxypeptidase A; beta-HSD, beta-hexosaminidase; HSC, hematopoietic stem cells; Mel, melanocytes; MC, mast cell; Bas, basophil; Eos, eosinophil; Mon, monocyte; SCF, stem cell factor; EC, epithelial cells; IL, interleukin.

In the last two decades, for the identification of surface membrane activation markers for mast cells and basophils has made promising progress.

Plasma membrane molecules

CD63 (gp53, lysosomal-associated membrane protein) has been identified as an activation marker for basophils^[111] and mast cells^[112], which is employed in flow cytometric basophil activation tests (BAT) for the diagnosis of allergy^[113]. CD63 expression is rapidly upregulated following allergen challenge and reaches a maximum after 20–30 min^[114]. However, as a lysosomal-associated membrane protein, CD63 is a non-specific marker of basophils, and the upregulated expression of this molecule has been observed in several other cell types, such as neutrophils^[115], DCs^[116], T cells^[117], and eosinophils^[118]. Therefore, the identification of a constitutive and constant expression marker for basophils, regardless of activation status, is essential for the specificity of BAT. Thus, CCR3^[119] and CD123 (IL-3 receptor α chain)^[120] have been selected as constant expression and identification markers for basophils to distinguish these cells from CD63, the activation marker. Because CCR3 has also been observed on eosinophils^[121] and a small proportion of CD4⁺ T cells^[122], this protein is not the unique marker for basophils. Similarly, CD123 has been identified on plasmacytoid DCs^[123] and plasmacytoid monocytes^[124]; thus, this protein is not a unique marker for basophils either. However, DCs and monocytes, but not basophils, express human leukocyte antigen (HLA)-DR, which could distinguish CD123-positive basophils from DCs and monocytes. Thus, basophils in the BAT can be identified as CD123⁺/HLA-DR-cells in flow cytometry analysis^[125], and CD63⁺ basophils in whole blood are located in the CD123⁺ HLA-DR-cell population^[126].

Anti-CD63 antibodies suppress IgE-dependent allergic reactions *in vivo* and the IgE-mediated degranulation of mast cells *in vitro*^[127], suggesting that CD63 is involved in the degranulation of mast cells in allergy. Cross-linking the IgE-receptors enhances the expression of both CD63 and CD203c (ectonucleotide pyrophosphatase/phosphodiesterase 3) on basophils^[128]. CD203c has also been recognized as a more specific surface marker for basophils than CD63^[129]. Basophil priming and degranulation-enhancing factors are not required for CD203c-based BAT^[114]. The spontaneous expression of CD203c is significantly higher on basophils from patients with exacerbated asthma than on those from patients with stable asthma or healthy subjects. In contrast, no differences in the spontaneous expression of CD63 or CD69 were observed among the three groups. The anti-IgE-induced expression of CD203c is significantly increased in basophils during asthma exacerbation^[130], suggesting that the increased expression of CD203c, but not CD63, is associated with asthma exacerbation.

Nevertheless, BAT is a widely validated and reliable tool, particularly for the diagnosis of hymenoptera venom^[131], nut^[132], grass pollen^[133] and rare allergies (such as drugs and exotic foods)^[113], and anaphylaxis^[134] and anaphylactoid reactions^[120]. BAT exhibited the highest sensitivity and specificity, with a significantly better ability than sIgE testing for the

identification of *Anisakis* species in the patients with acute urticaria, potentially supplementing current standardized procedures in both diagnosis and follow-up^[135]. Indeed, BAT has several advantages over the autologous serum skin test: no risk of accidental infection, no influence of antihistamines on the test results, quantifiable results, and potential for treatment monitoring^[136]. In addition, BAT can be dissociated from basophil histamine release^[137]. Nevertheless, there is currently no approach for mast cell and/or basophil marker testing or available optimal algorithm for the clinical application of this marker in allergy diagnosis.

The high-affinity IgE receptor Fc ϵ RI on the basophil membrane shows potential as a basophil activation marker. However, the IgE gating strategy has the highest variation, showing up to 80% of non-basophils in the selected gate in certain donors^[119]. This variation might reflect the large proportion of CD1c⁺ DCs^[138] and eosinophils^[139] expressing surface Fc ϵ RI. CD200R3, as a disulfide-linked dimer, has been identified on mast cells and basophils primarily in association with the ITAM-bearing adaptor DAP12. Cross-linking CD200R3 with antibodies induced mast cells degranulation and IL-4 production in basophils *in vitro*^[140]. In addition, CD117 (c kit) a receptor of SCF is expressed on the surface of all mast cells, independent of maturation and activation status^[141], suggesting that this receptor has potential as a surface marker for mast cells and basophils. However, the expression of CD117 on some hematopoietic stem cells, melanocytes, and Cajal cells of the gastrointestinal tract, and kit-positive tumors^[142] complicates the use of this receptor as a selection marker for mast cells and basophils. CD300a is expressed on human peripheral blood basophils and rapidly upregulated upon IgE/Fc ϵ RI cross-linking, showing potential as an activation marker for basophils^[143].

Properties and pathogenesis of pseudo-allergic reactions

Pseudo-allergic reactions are clinical manifestations, including urticaria, angioedema, conjunctivitis, rhinitis, asthma, and anaphylaxis, which mast cell or basophil activation is not mediated via IgE, or to a lesser extent via IgG^[144] or IgM. The main causes of pseudo-allergic reactions are food, additives and drugs. The diagnosis of pseudo-allergic reactions is characterized by the absence of sIgE for the suspected substances, and the treatment for this allergy is similar to that for allergic diseases, including antihistamine drugs, steroids, B2 agonists, and epinephrine (Table 4)^[3].

Non-IgE-mediated pseudo-allergic reactions

Non-IgE-mediated pseudo-allergic reactions resulting from drugs are called drug-induced immediate hypersensitivity reactions (DIIHSRs), which does not fit in Gell and Coombs' Type I category of drug allergies. The DIIHSRs are primarily caused by (1) certain liposomal formulations of intravenous drugs and imaging agents, (2) infusion liquids containing micelle-forming amphiphilic lipids or synthetic block-copolymer emulsifiers and (3) iodinated radiocontrast media with limited solubility in water^[145]. The mechanism of DIIHSRs

Table 4. Comparison of allergic and pseudo-allergic reactions.

		Characteristics
Allergic reactions		Pseudo-allergic reactions
Clinical manifestation	Urticaria, angioedema, conjunctivitis, rhinitis, asthma, anaphylaxis, etc.	Urticaria, angioedema, conjunctivitis, rhinitis, asthma, anaphylaxis, etc.
Diagnosis	Clinical manifestation with elevated specific serum IgE to allergens	Clinical manifestation without elevated specific serum IgE to allergens
Treatment	Antihistamine drugs, steroids, B2 agonists, epinephrine, etc.	Antihistamine drugs, steroids, B2 agonists, epinephrine, etc.
Main causes	Mites, pollens, animal debris, insect sting, etc.	Food, additives, drugs, etc.
Primary effector cells	Mast cells and/or basophils	Mast cells and/or basophils
Mediated by	IgE	IgG, IgM or others
Response to SIT	About 90% effective	N/A

SIT, specific immuno-therapy; N/A, information not available.

involves the activation of the complement system to generate anaphylatoxins C3a and C5a, and the latter activates mast cells and/or basophils, suggesting a subdivision of Type I allergies. DIIHSRs are largely under-reported, with a significantly higher risk in adult women than in men. Neuromuscular blocking agents remain the most frequently incriminated drugs. Reactions involving antibiotics, dyes, or nonsteroidal anti-inflammatory agents have been reported with increasing frequency^[146].

Pseudo-allergic reactions might also occur following administration of iodinated contrast media. Positive skin tests to contrast media have been reported, but the affinity of IgE towards contrast media is low^[18].

Anaphylaxis and anaphylactoid reactions

Anaphylaxis is a life-threatening allergic reaction primarily mediated through IgE antibodies as well as IgG or IgM antibodies (immune complex anaphylaxis), which interact with mast cells, basophils, or the complement system to liberate vasoactive mediators and recruit other inflammatory cells. The most common elicitors of anaphylaxis are foods in childhood, insect stings and drugs. In clear-cut IgE-mediated anaphylaxis, allergen-specific immunotherapy is an effective causal treatment, with success rates of 90% in insect venom anaphylaxis^[147]. Studies have reported cases with similar clinical symptomatology without detectable immunological sensitization, which were initially referred to as pseudo-allergic or anaphylactoid reactions, but are now called “non-immune anaphylaxis”, according to the World Allergy Organization (WAO). Indeed, anaphylaxis and anaphylactoid reactions are clinically indistinguishable^[18]. However, the distinction of different pathophysiological processes is important because non-immune anaphylaxis cannot be detected using skin tests or *in vitro* allergy diagnostic procedures. Thus, history and provocation tests are crucial^[148].

If we consider allergies as a group of mast cell and/or basophil-mediated diseases, pseudo-allergic reactions should be included in the category of allergy, as a group of non-IgE-

mediated allergic diseases. Thus, IgE-mediated allergy, as a subgroup of allergy, might be the largest subgroup, reflecting the fact that pseudo-allergic reactions are mediated through mast cells and/or basophils and the clinical symptomatology and treatment of these reactions are similar (if not the same) to those for allergic diseases.

Proposed definition and classification of allergic diseases

Allergic diseases are a group of diseases mediated through activated mast cells and/or basophils in sensitive populations. Allergic diseases include four subgroups: (1) IgE dependent; (2) other immunoglobulin dependent; (3) non-immunoglobulin mediated; and (4) mixture of the first three subgroups. Ideally, allergic diseases should include chronic allergic reactions, such as contact dermatitis, which most likely are not mast cell and/or basophil-mediated. Because the nature of allergy remains elusive, our proposal definitely requires further confirmation. Moreover, numerous issues, such as infection, autoimmune diseases, atherosclerosis, which might involve mast cell or basophil activation agents, should be further considered. Moreover, whether these issues affect the progress of allergy should be addressed in the near future.

Diagnosis procedure of allergic diseases

As for any other types of diseases, the diagnostic procedure of allergy must be based upon its definition and classification, beginning with a thorough clinical history and physical examination.

Specific allergen challenge test (SACT)

Once symptoms compatible with an allergic disorder have been identified, the SACT should be applied to provide confirmation of sensitization. SACTs are the most reliable and gold standard tests for diagnosing allergy, which include *in vivo* tests, such as skin provocation tests for medications, oral challenge tests for food allergens and bronchial challenge tests for aerosol allergens. The main procedure for *in vivo* SACT

is demonstrated in Figure 2. However, SACTs should be conducted under the supervision of experienced physicians because these procedures might cause adverse reactions, such as anaphylaxis^[149]; thus, these tests are not frequently used in daily clinical practice. The skin prick test (SPT) and atopy skin patch test are *in vivo* SACTs, which are safely employed in daily clinical practice. However, because the testing allergens of SPT and the atopy skin patch test are primarily located in the epidermis and have limited contact with mast cells, these tests are not as reliable as the other SACTs described above. To achieve safe and more reliable testing results, *in vitro* SACTs have been developed. The specific allergen-induced basophil histamine release test^[149] and BAT using flow cytometry^[150] are two tests available for clinical practice. Once fully developed, these tests should more accurately and reliably determine allergens than any current *in vitro* tests.

Figure 2. Main procedure and mechanism of the specific allergen challenge test. PGD, prostaglandin D; LTC, leukotriene C.

Allergen-specific immunoglobulin tests

Because the classical definition of allergy is a group of diseases largely driven through IgE-mediated mechanisms, allergen sIgE measurement has been the most popular allergy test used worldwide^[151]. In the current review, IgE-mediated allergy is only considered as a subgroup of allergy, therefore other types of allergen-specific immunoglobulins, such as IgG, IgA, or IgM, should be determined following positive SACTs. Ultimately, the patient's clinical history remains the principal arbiter to determine the final diagnosis of allergic disease. Positive serum immunoglobulin tests provide further information concerning the types of allergens and allergies the patients suffer from, such as IgE-mediated or IgG-mediated allergies.

Proposed laboratory diagnosis procedure of allergic diseases

Based on the proposed definition, the ideal laboratory examination procedure for allergy should begin with allergen extract skin prick and skin patch (small molecules) tests according to clinical history and physical examination (Figure 3). The test

Figure 3. Proposed procedure for the laboratory diagnosis of allergy. Non-IgE/IgG dependent, IgE-dependent or IgG-dependent allergies have been proposed in the current review. The gray arrows indicate the previous names of the diseases.

results will limit the number of allergens needed for the basophil histamine release test and BAT. BAT is more sensitive and specific than any other *in vitro* diagnostic techniques in drug allergy. The sensitivity of BAT to different drugs ranges between 36% and 97.7%, with a specificity of approximately 93%^[150]. There was a case that the SPT and serum sIgE to beef, pork and milk allergens showed negative results, but the BAT showed significant positive results^[152]. The positive SACTs will confirm the diagnosis of allergy, and the substances that the patients are allergic to. Ideally, serum sIgE or specific IgG measurement should be performed after positive SACTs to determine the subtype of allergy that the patients suffer, and alternatively this measurement can be performed simultaneously with SACTs.

Future work

With more than 2000 years of clinical practice, we are coming increasingly closer to understanding the nature of allergic diseases, and mast cells and basophils are unarguably essential cells for allergy. Fortunately, the proper tools have been created to breakthrough the diagnosis of these diseases. To further understand the nature of allergic diseases and examine the laboratory diagnosis procedure, the following work should be performed: 1) Investigating non-IgE mediated sensitization processes of mast cells or basophils; 2) Understanding the reason why different types of allergens cause different subtypes of allergy; 3) Investigating sensitized mast cells or basophils respond to a single type allergen or several types of aller-

gens; 4) Investigating the types of stimulation, the strength of stimulation and the mechanisms which cause mast cells selectively secrete different mediators; 5) Paying more attention to the LMWM-induced activation of mast cells or basophils; 6) Identifying the best antibody combination for BAT; 7) Developing a more reliable and low-cost allergen-specific basophil histamine release test; and 8) Characterizing other clinical conditions, such as infection, autoimmune diseases and arthrosclerosis, which might involve mast cell or basophil activation agents. Moreover, we should also investigate why these individuals do not suffer from allergies.

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