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New Mechanistic Advances in FcεRI-Mast Cell–Mediated Allergic Signaling

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Abstract

Mast cells originate from the $CD34^+/CD117^+$ hematopoietic progenitors in the bone marrow, migrate into circulation, and ultimately mature and reside in peripheral tissues. Microbiota/metabolites and certain immune cells (e.g., Treg cells) play a key role in maintaining immune tolerance. Cross-linking of allergen-specific IgE on mast cells activates the high-affinity membrane-bound receptor FcεRI, thereby initiating an intracellular signal cascade, leading to degranulation and release of pro-inflammatory mediators. The intracellular signal transduction is intricately regulated by various kinases, transcription factors, and cytokines. Importantly, multiple signal components in the FcεRI-mast cell–mediated allergic cascade can be targeted for therapeutic purposes. Pharmacological interventions that include therapeutic antibodies against IgE, FcεRI, and cytokines as well as inhibitors/activators of several key intracellular signaling molecues have been used to inhibit allergic reactions. Other factors that are not part of the signal pathway but can enhance an individual's susceptibility to allergen stimulation are referred to as cofactors. Herein, we provide a mechanistic overview of the FcεRI-mast cell–mediated allergic signaling. This will broaden our scope and visions on specific preventive and therapeutic strategies for the clinical management of mast cell–associated hypersensitivity reactions.

Keywords FcεRI · Mast cell · Immunoglobulin · IgE · Degranulation · Mediator · Cofactor · Allergy · Allergen · Treg cell

Abbreviations

AMPK	Adenosine monophosphate–activated protein kinase
BMMC	Bone marrow–derived mast cell
BLT1	Leukotriene B4 receptor 1
COX	Cyclooxygenase
CRAC	Calcium release–activated calcium
DAG	Diacylglycerol
DARPin	Designed ankyrin repeat protein
DC	Dendritic cell
ER	Endoplasmic reticulum
GPCR	G-protein-coupled receptor
HDAC3	Histone acetylase 3
HRF	Histamine-releasing factor
Ig	Immunoglobulin
IL	Interleukin
IP3	Inositol 1,4,5-triphosphate
ITAM	Immunoreceptor tyrosine–based activation motif
Lck	Lymphocyte-specific protein kinase
LT	Leukotriene
MITF/TFE	Microphthalmia-associated transcription factor/transcription factor E
NOS	Nitricoxide synthase
NSAID	Non-steroidal anti-inflammatory drug
PAF	Platelet activator factor
PAF-AH	Platelet activator factor-acetyl hydrolase
PAFR	Platelet activator factor receptor
PDH	Pyruvate dehydrogenase
PI	Phosphatidylinositol
PG	Prostaglandin
PLC	Phospholipase C
SCF	Stem cell factor

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SCFA	Short-chain fatty acid
SFK	Sarcoma family kinase
sGC	Soluble guanylate cyclase
SH2	Sarcoma homology 2
SHIP1	Sarcoma homology 2 domain–containing inositol phosphatase 1
Siglec	Sialic acid–binding immunoglobulin-type lectin
SNARE	Soluble N-ethylmaleimide-sensitive factor attachment protein receptor
Src	Sarcoma
Syk	Spleen tyrosine kinase
TGF	Transforming growth factor
TI	Transcription infidelity
Treg cell	Regulatory T cell
TSLP	Thymic stromal lymphopoietin

Introduction

Hypersensitivity reactions represent a series of exaggerated immune/inflammatory responses that are often associated with unfavorable outcomes in genetically predisposed individuals. There are four types of canonical hypersensitivity reactions, i.e., types I, II, III, and IV [1]. Mast cells and basophils are the main effector cells of Type I hypersensitivity reactions (also known as allergic reactions). Both these cell types originate from the basophil-mast cell common progenitors ($CD34^+/CD117^+$) in the bone marrow and migrate into circulation. Through the cell surface–expressing integrins (e.g., α4β7, α4β1, and α6β1), the mast cell progenitors migrate from the circulation into peripheral tissues in a tissue-dependent manner where they proliferate, survive, and differentiate into mature cells after binding of the stem cell factor (SCF) to its cell surface receptor, KIT [2–5]. Other important modulators for mast cell differentiation and maturation include nerve growth factor, transforming growth factor (TGF)-β, interleukins (ILs, e.g., IL-4 and IL-33), IgE, and histamine [2, 6]. Functionally mature mast cells are classified into mucosal-type cells (key effector cells of food allergy) and connective tissue–type cells, based on their tissue localization. Alternatively, mast cells can be classified into those producing only tryptase, and those producing tryptase, chymase, and carboxypeptidase, according to the nature of granule proteases [2, 4]. Basophils are resident immune cells in circulation [4, 5]. The functions of mast cells/basophils are versatile and highly environment-dependent, and both these cell types are physiologically responsible for allergic or anaphylactic reactions [4, 5]. However, the contribution of basophils alone is difficult to evaluate, as these cells typically participate in allergic reactions in consort with mast cells [7].

Mast cells express a variety of membrane-bound receptors, including FcεR, FcγR, Toll-like receptor, and G-protein-coupled receptor (GPCR, e.g., MRGPRX2) [8]. Activation of these receptors can initiate both IgE-mediated and non-IgE-mediated hypersensitivity reactions [9]. Among these, the most studied receptor is FcεR, which is an inherent receptor for IgE binding, and has two known subtypes, the high-affinity FcεRI and low-affinity FcεRII (CD23) [10]. Activation of FcεRI can be attained by micromolar concentration of allergens, which makes this receptor a highly efficient and primary activator of allergic reactions [11]. Over the past two decades, allergic diseases have shown an increasing trend across the globe [12]. For example, the first 15 years of this century have witnessed a 5–sevenfold increase in the frequency of hospital admissions due to anaphylaxis [13]. The increase is particularly notable in western countries, but not insignificant in developing countries, such as China [14]. In this context, in-depth research of the molecular or cellular mechanisms of allergic reactions, in particular those mediated by the FcεRI-mast cell pathways, is a key imperative. The aim of this review article is to provide a current overview of the mechanistic studies on the allergen-IgE-FcεRI interplay, intracellular signal transduction, and degranulation in mast cells, as well as the cofactors involved in allergic reactions.

Allergens and the Allergenicity

Signaling of the FcεRI-mast cell axis begins with an antigen that has breached immune tolerance in genetically predisposed individuals [12]. There are a growing number of established allergens, such as food, pollens, insect venom, fungal spores, house-dust mites, drugs, latex, hormones, and vaccines [15, 16]. More recently, the coronavirus-2019 vaccine as a new allergen has gained attention [17]. Indeed, these allergens can initiate different types of immune reactions depending on the individual circumstances. For example, wheat can elicit gluten sensitivity, wheat allergy, and celiac disease. While wheat allergy is mediated by an IgE-mediated mechanism (mainly type I hypersensitivity) characterized by production of IgE antibodies specific to wheat or ω-5 gliadin, auto-antibodies to gluten/gliadin concurrent with local or systematic autoimmune reactions (mainly type II, III, or IV hypersensitivity) are the underlying mechanisms of celiac disease; gluten sensitivity, on the other hand, is mediated by neither of these mechanisms, but rather by innate immune abnormalities [18]. However, the precise mechanisms that drive specific immune reactions remain largely obscure.

The allergenicity is dependent on the unique IgE determinants of the native molecules. In addition, some transcription

errors can enhance allergenicity. For example, transcription infidelity (TI) is a naturally occurring error that generates RNA gaps (e.g., single base omissions) and translational frame-shifts, causing protein alterations and diversity. Recombinant TI proteins of the peanut allergen rather than the canonical allergen itself can induce IgE class switch, increase production of variant protein-specific IgE antibodies, and thus promote development of allergic reactions in mice [19]. In recent studies, various chemical modifications were used to reduce allergenicity and generate "hypoallergens" [20, 21]. Currently, allergen-specific immunotherapy is the most effective approach for allergic diseases [22, 23]; this approach requires an eligible allergoid with weakened allergenicity, but retained immunogenicity, which can prompt signaling internalization but provoke no degranulation. In this regard, artificial modifications of allergen is actively pursued for allergoid preparation [24].

Generation of Allergen-Specific IgE (Allergic Sensitization)

The "dual allergen exposure hypothesis" describes how an allergen induces development of allergic sensitization and responses [12, 25]. In brief, oral entry in early life is exclusively involved in the development of tolerance, while impairment of skin barrier (e.g., as a result of *Filaggrin* gene mutation) allowing the entry of environmental allergens in the body (first exposure) leads to failure of development of tolerance [25, 26]. Several epithelial cytokines (e.g., IL-25, IL-33, and TSLP) serve as alarmins, facilitating pro-allergic development [12, 25]. Recent studies have revealed the TSLP is regulated by tryptase-protease activated receptor 2 and IL-1 pathways in humans and mice [27]. Some cytokines, mainly the Th2 cell-derived IL-4 and IL-13, may fuel class switching of IgE [28, 29]. Hence, targeting these two cytokine receptors may prevent the development of allergic sensitization and diseases [30, 31]. However, recent studies suggested that a subset of the T follicular helper cells, but not the Th2 cells, produces IL-4 and IL-13 for the class switching of IgE [32, 33]. Subsequently, B and plasma cells initiate the production of allergen-specific IgE antibodies (a process known as allergic sensitization) that bind to the FcεRIs on mast cells, thereby establishing Th2 memory [12, 25, 34].

The role of epicutaneous sensitization in the development of allergic diseases has been documented in animal studies. Epicutaneous injuries were found to induce expansion of intestinal mucosal mast cells and aggravation of allergic intestinal symptoms [35, 36], while remission of the epicutaneous inflammation by local use of glucocorticoids attenuated the intestinal symptoms [36]. Recent work extends the allergenic gateway to airway [37]. The process of allergen re-exposure (the second exposure) is exemplified here by oral food challenge studies. In mesenteric lymph nodes, the dendritic cell (DCs), after identifying the trans-epithelial translocated allergens, were shown to prime the immune reactions toward a Th2-skewed state concurrent with IgE production in an individual with allergic sensitization, as described previously [12, 25]. These allergens ultimately bind to the IgE antibodies that have been bound to FcεRIs on mast cells, resulting in cross-linking of these receptors.

Serum allergen-specific IgE is a key biomarker of the disease severity [38, 39]. Many clinically relevant serum IgE antibodies are known to exist throughout the lifetime, but the source of this serological memory is debatable. While Asrat and Kaur [40] purported that the specific long-lived IgE-bearing plasma cells generated in bone marrow by chronic allergen exposure harbor the serological memory, Rodrigo et al. [41] argued that the lifelong IgE antibodies are sustained by specific long-lived memory B cells that replenish the IgE-bearing plasma cell compartments. Concurrent with the production of allergen-specific IgE are specific IgA and IgG antibodies. The latter two isotypes can compete with IgE for binding to the allergens and prevent the development of allergic reactions [42]. Of note, the IgG4 antibodies compete for binding to the same sequential epitopes as IgE isotypes [43] and hamper the development of peanut allergy in subjects with peanut-sensitive HLA alleles [44].

Structure and Synthesis of the FcεRI Complex

FcεRI is an inherent receptor for IgE (the Fc fragment of IgE antibody) with high binding affinity (K_D: 10^{-10} M) [45, 46]. Human FcεRIs are mainly expressed on mast cells and basophils [10, 11, 45]. The FcεRI complex on human mast cell surface is a tetramer composed of one α subunit, one β-subunit, and 2 γ-subunits (αβγ2) [11, 45, 47]. Among these, the α-subunit has two extracellular Ig superfamily domains (α1 and α2), both of which are responsible for the ligand (Fc fragment of the IgE antibody) binding [10], while the β- and γ-subunits contain immunoreceptor tyrosine–based activation motifs (ITAMs) that provide binding sites for many intracellular signal molecules via their Sarcoma (SRC) homology 2 (SH2) domains [11, 48, 49].

Synthesis of the constitutive chains and subsequent assembly of the FcεRI complexes occur in endoplasmic reticulum (ER) in mast cells [11]. In brief, the core protein of α-chains is synthesized by an individual signaling pathway, and then undergoes signal-peptide cleavage, and glycosylation in the ER [11]. Concurrently, both β- and γ-chains are co-translated by respective signaling pathways and participate in the α-chain modifications [11, 47]. Subsequently, protein folding ensues, which is guided by several chaperones (e.g., calnexin and calreticulin), leading to formation

of proper tertiary and quaternary structures [47]. The full maturation of the FcεRI complex is finally completed by terminal glycosylation in the golgi apparatus prior to its transportation to the mast cell surface [11]. Abnormalities at any stage in the synthesis, modification, and export of FcεRI complex can affect FcεRI expression on cell surface and the amplitude of allergic responses. Hence, specific interventions targeting the synthesis of FcεRI represent a viable therapeutic approach for desensitization.

Increasing evidence has demonstrated the indispensability of α, β, and γ subunits for signal transduction. Recent studies have shown that β-subunit hypofunction (by exon skipping) and hyperfunction (by an enhancer named MS4A4A) can either hamper or boost the development of allergic diseases, respectively [50, 51]. Due to its core role, the FcεRIβ is a primary target of many therapeutic interventions for allergic diseases [49]. In addition, interaction of HDAC3 with a series of microRNAs can modulate the FcεRI activity and mediate passive anaphylaxis by deacetylating the histones [52].

Activation of FcεRI by IgE

The Fc fragment of IgE antibody can asymmetrically bind to the two Ig-like extracellular domains of the FcεRIα (α1 and α2) on mast cells through two hydrophobic regions in the Cε3 domain of the antibody at a 1:1 stoichiometry with high affinity [10, 45]. The resultant IgE-FcεRI complexes diffuse freely on the surface of mast cells as do the unoccupied FcεRIs, exhibiting a dynamic state under resting circumstances [45]. In the absence of allergens, the binding of monomeric IgE to FcεRI promotes survival, inhibition of Fas/FasL-independent apoptosis, and increased membrane-bound FcεRI expression, but not degranulation of mast cells [6]. This highlights the importance of anti-IgE antibodies in the treatment of allergic diseases. In addition, interventions against the allergen-binding sites on IgE-Fab fragments may have important therapeutic significance for allergic diseases. Formation of a multivalent allergen-IgE-FcεRI complex is followed by redistribution and cross-linking concurrent with immobilization of the IgE-FcεRI complexes [45]. Indeed, the IgE-FcεRI aggregates remain in a highly mobile condition until the allergen concentration reaches a threshold [53]. FcεRI immobilization induced by high allergen levels is a trigger for receptor internalization, but not required for signaling transduction [45, 53]. Importantly, the cross-linking of FcεRI complexes can form an aggregation, namely "signaling patches." These non-functional small patches coalesce till the formation of functional large patches that promote robust degranulation in mast cells [54].

Several properties of the allergen-IgE-FcεRI axis affect the effector responses of mast cells with respect to affinity and valency. The relationship between allergen concentration/dose and mast-cell effector responses exhibits a bell-shaped curve with the peak effector responses corresponding to a medium allergen concentration [55, 56]. The underlying mechanism for this phenomenon is not completely clear, but presumably the FcγRIIb phosphorylation maintained by Lyn and Sarcoma homology 2 domain–containing inositol phosphatase 1 (SHIP1) collaboration rather than the IgG-dependent signaling renders an inhibitory signal on the effector responses when the allergen concentration is at a supra-optimal level [55, 57]. High-affinity binding (e.g., DNP) can lead to Lat1 signaling that favors degranulation, and promotes release of inflammatory cytokines (e.g., TNF-α and IL-6) and further recruitment of neutrophils to the site of allergy, leading to stronger effector responses. On the other hand, low-affinity binding (e.g., 2NP) can shift the signaling from Lat1 to Lat2, and promote release of chemokines (e.g., CCL2-4) concurrent with recruitment of monocytes/macrophages, leading to weaker effector responses [58]. This highlights the distinct signatures of effector cells, signaling molecules, and response grades between the high- and low-affinity stimuli.

Typically, the multivalent allergens tend to form large and immobile IgE-FcεRI clusters and prompt more pronounced allergic responses than do the monovalent allergens [54]. Moreover, the multi-valency is able to prompt IgE-FcεRI cross-linking despite presence of low-affinity interaction [59]. The IgE-FcεRI cluster size is an important parameter for signal internalization and initiation of allergic inflammation. Theoretically, there exists an optimal FcεRI cluster size that corresponds to the mast cell desensitization but not causes effector responses; however, in an in vitro study, the optimal size was found to vary, depending on the allergenicity [60]. These properties together with the number of FcεRI occupied with IgE and allergens, IgE specificity, specific IgE/total IgE ratio, allergen-IgE avidity, and allergen diversity [56, 61] collectively determine the overall amplitude of effector responses.

Intracellular Signaling Transduction in Mast Cells

The activation of FcεRI by allergen-specific IgE initiates intracellular signal cascade in mast cells, resulting in the release of preformed or newly synthesized allergic mediators (also known as degranulation). In brief, the intracellular signaling cascade starts with activation of two Src family kinase (SFK) members, Lyn and Fyn, both of which immediately phosphorylate the FcεRIβ-ITAMs and facilitate the binding of Zap70 family member Spleen tyrosine kinase (Syk) to the FcεRIγ-ITAMs. Recent work has provided revealing binding details between the SFK members

and FcεRI complex. The Lyn-FcεRI binding is mediated actually not by the transmembrane tyrosine phosphatases, but by an initial lipid-based interaction that allows for Lyn access, followed by a protein-based interaction and subsequent phosphorylation [62]. In addition, the Y130 phosphorylation in the Syk interdomain A and the distance between FcεRIγ-ITAM pairs determine cis or trans binding of the Syk-FcεRIγ complex [63]. The resultant phosphorylation of some downstream signal molecules, e.g., TRAP, LAT, NTAL, and SLP-76, in combination with the Tec family member Btk promotes activation of phospholipase Cγ (PLCγ), which then catalyzes the phosphatidylinositol 4,5-biphosphate hydrolysis to generate diacylglycerol (DAG) and inositol 1,4,5,-triphosphate (IP3). While DAG prompts the activation of PKC, driving a calcium-dependent mediator release, IP3 binds to its receptors on ER membrane and promotes efflux of the ER Ca^{2+} [2, 4, 11, 29]. Differential use of BTK and PLC can discriminate the IgE-FcεRI from SCF-KIT signaling [64]. These non-receptor tyrosine kinases are indispensable communicators of the allergic signaling. Inhibition of Lyn and Fyn can weaken the IgE-mediated allergic responses [65]. Replacement of the tyrosine within Syk SH2 domains by glutamic acid was found to inhibit Syk-FcεRIγ binding and impair allergic inflammation [66]. The Syk in collaboration with SHIP1 underlies the memory-like phenomena of allergic responses in mast cells [67]. In addition, inhibition of the Tec family member Btk kinase was shown to protect against IgE-mediated anaphylaxis [68]. Nevertheless, orchestration of signal transduction is a complex and well-coordinated process. Although Lyn knockdown disrupts phosphorylation of Syk kinase as well as the downstream signaling molecules (e.g., Lat and SLP-76), which is suggestive of proximal signaling impairment, the distal signaling molecule, e.g., Erk, is enhanced, leading to FcεRI-initiated degranulation in sensitized rat RBL-2H3 basophilic cells [69]. The secretory granules that contain allergic mediators are synthesized by individual signaling pathways in the rough ER and modified post-translationally in the Golgi apparatus, forming unit granules that bud from the trans-Golgi region of mast cells. The post-Golgi granules transform to pro-granules, immature granules, and mature granules after constant fusion before the formation of allergic granules that are stored in the cytoplasm [4, 70] (Fig. 1).

The activated PLCγ-DAG axis as described above can signal PKC, prompting the release of matured allergic mediator granules, a biological process referred to as exocytosis [4, 11]. Many components involved in this process heavily rely on the intracellular calcium concentrations that are refilled by the efflux of ER calcium and influx of extracellular calcium. For example, calcineurin Aα that contributes to the release of allergic mediators in activated mast cells is calcium-dependent [71]. The calcium sensor, cation

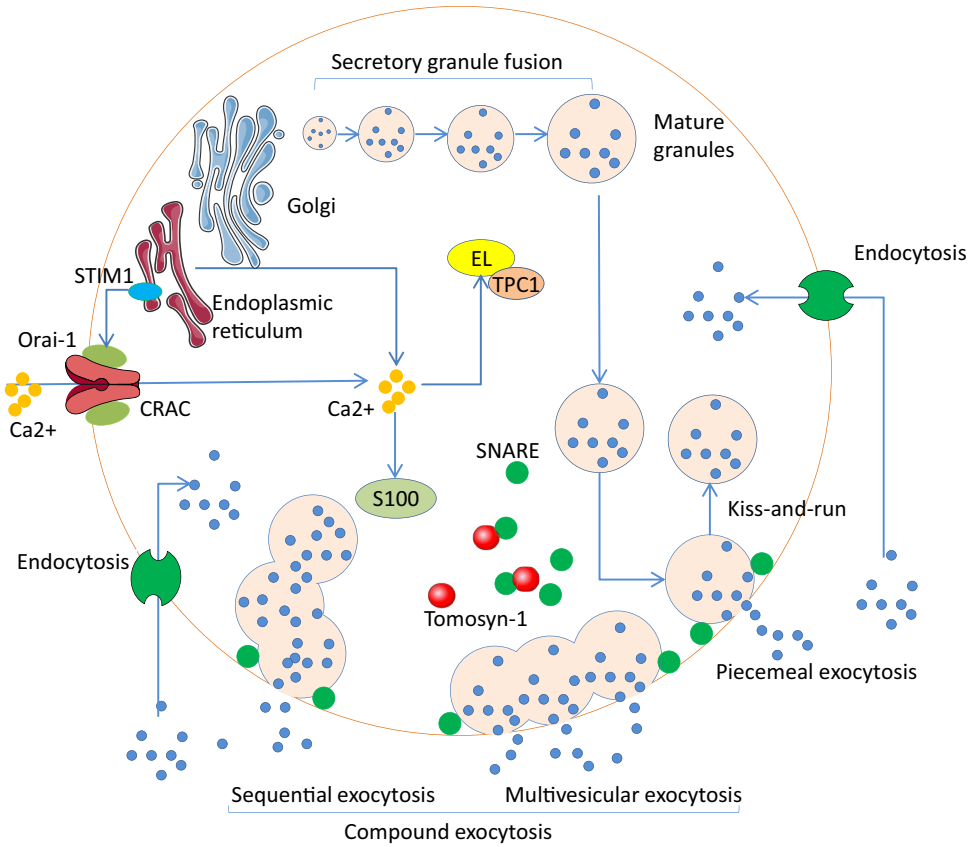

Fig. 1 Synthesis, exocytosis, and endocytosis of allergic mediators. Abbreviations: CRAC, calcium release–activated calcium; EL, endolysosomal; STIM1, stromal interaction molecule 1; TPC1, two-pore channel 1

channels, and calcium-binding proteins (e.g., S100) are all involved in maintaining the intracellular calcium concentrations (Fig. 1). On one hand, the PLCγ-IP3 axis can induce ER Ca^{2+} efflux by activating the IP3 receptor. On the other hand, calcium depletion in the ER may activate calcium sensor stromal interaction molecule (STIM) 1, which then opens the calcium release–activated calcium (CRAC) channels/store-operated channels [72]. As the key constituents of CRAC channels, the Orai family members Orai1 and Orai2 play an important but antagonistic role in this process. Orai-1 inhibition can reduce the calcium influx, leading to weakened mediator release [73], while Orai-2 deletion can open CRAC channels, and increase Ca^{2+} concentrations in mast cells, leading to enhanced anaphylaxis [74]. In addition, the intracellular Ca^{2+} concentrations are also regulated by the two-pore channels that are engaged in inducing endolysosomal calcium uptake and ER calcium filling [75], and by the calcium-binding protein S100A4 whose depletion is associated with decreased serum allergen-specific IgE and pro-inflammatory cytokines [76].

Releasing patterns of the mediators, including "piecemeal exocytosis" (e.g., "Kiss-and-run") and "compound exocytosis" (e.g., sequential or multivesicular), are stimuli-dependent [2, 4, 29]. Prior to the exocytosis, several soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs) and their binding proteins are necessary for the fusion of the granules with plasma membrane. In this regard, the SNARE protein SNAP23 is involved in constitutive exocytosis and anaphylactic reactions in connective tissue mast cells [77]; the SNAP23 regulates the exocytosis of mast cells via the association of its cysteine-rich domain with the plasma membrane [78]. As a special SNARE protein, the Syntaxin 3 plays a primary role in mediating the compound exocytosis in mast cells [79]. In contrast, the SNARE-binding protein Tomosyn-1 interacts with syntaxins, serving as a negative regulator of the mast cell degranulation in a PKCδ-dependent manner [80]. Mast cells can regulate the release of mediators through paracrine, endocrine, and autocrine loops [29]. Moreover, an exocytosis-coupled endocytosis process (e.g., kiss-and-run, slow, and bulk endocytosis) enables mast cells to retrieve the extracellular mediator granules, and thus maintain the cell integrity [4, 81]. The synthesis, exocytosis, and endocytosis of allergic mediators are illustrated in Fig. 1.

Regulation of the FcεRI-Mast Cell–Initiated Intracellular Signaling

Intraceullar signaling of FcεRI-mast cell is highly orchestrated to either upregulate or downregulate the allergic responses through various mechanisms. SHIP1 can negatively regulate the IgE-FcεRI signaling through suppressing Lyn kinase, hydrolyzing phosphatidylinositol (PI)-3,4,5-P3 to PI-3,4-P2, and decreasing cytokine production [57]. The Src kinase–like adapter protein (SLAP) binds to the FcεRIβ and downregulates its expression, blocking the signal to the downstream kinases (e.g., Syk, Akt, and Erk) [82]. The adenosine monophosphate–activated protein kinases (AMPKs) serve as a negative regulator of the IgE-mediated allergic reactions in that the core subunit AMPKα2 can phosphorylate FcεRIβ, thus blocking the IgE-induced recruitment of signaling proteins to the FcεRI complex [83]. Consistently, AMPK inhibition mediated by activation of either Lyn-Syk-Akt axis or orphan nuclear receptor NR4A1, both as a result of FcεRI activation, can fuel the allergic inflammation [83, 84]. Recently, Chang, et al. examined the intracellular signal molecule alterations in mast cells in response to several ligands, including allergen-IgE, SCF, HSP70, and CCL3. They found that Lat phosphorylation by lymphocyte-specific protein kinase (Lck) was critical for the stimulation of these ligands [85]. This indicates a central role of Lck kinase in the regulation of intracellular signaling cascade.

Transcriptional factors are also important regulators in allergic signaling pathways. The Gata family members modulate the activity of signaling molecules by binding to their DNA consensus sequence (T/A)GATA(A/G) [48]. Gata1 and Gata2 are involved in modulating the tryptase and protease gene expression in mouse bone marrow–derived mast cells (BMMCs) and increasing the mediator production [86, 87]. Of note, Gata-2 binds to the super-enhancer regions of many target genes that maintain the mast cell potentials in response to allergen stimulation [88]. Moreover, Gata-2 has an indirect impact on several other transcription factors; for example, Gata-2 was shown to bind directly to the promoter of *C/EBPα* gene and prevent RUNX1 and PU.1 from binding to the neighboring regions in mouse BMMCs [89]. The microphthalmia-associated transcription factor/transcription factor E (MITF/TFE) family includes a group of transcription factors with basic helix-loop-helix leucine zipper (b-HLH-LZ) that recognizes the E-box motifs in the target gene promoters [48]. The MITF expression in mast cells is regulated by Gata-2. Importantly, these two factors modulate the expression of histidine decarboxylase gene in mast cells that encodes a key enzyme for catalyzing histidine to histamine in mice and humans [90]. In addition, the TFE member TFEB is involved in promoting the biogenesis and exocytosis of secretory granules observed in interferon-α/β receptor subunit 1–deficient mice [91]. As a hematopoietic cell–specific transcription factor, PU.1 can enhance the IgE-mediated allergic responses by transactivating the Syk promoter and inducing the FcεRIβ expression in mice and humans [92]. This suggests that PU.1-based intervention may be a potential treatment for FcεRI-mast cell–mediated allergic diseases.

Finally, mitochondria also play a role in IgE-FcεRI-mediated intracellular signaling. The Erk1/2 kinases in the cytoplasm of mast cells phosphorylate amino acid residue Serine73 on MITF and amino acid residue Serine727 on Stat3, prompting their translocation to the mitochondria; these two transcription factors in consort with phosphorylated pyruvate dehydrogenase (PDH) exert important regulatory effects on the mast cell intracellular signaling transduction [93, 94]. Notably, the mitochondrial MITF is associated with mast cell degranulation, cytokine production, and oxidative phosphorylation [94]; the mitochondrial Stat3 can affect electron transport chain activity, production of reactive oxygen species, and intra-mitochondria/intracellular calcium concentrations [93]; and the mitochondrial PDH that is regulated by MITF can affect mast cell degranulation [95]. However, further work is required to elucidate the detailed mechanisms by which the mitochondrial molecules affect the intracellular signaling transduction.

In both humans and mice, mast cells can release soluble isoform of FcεRIs that blocks the IgE-FcεRI binding, leading to weakened intracellular signaling [96]. Similar effects and mechanisms of the exosomes have also been observed in mice [97]. Suppression of protein disulfide isomerase activity in mast cells can exert an inhibitory effect on allergic signaling, leading to decreased FcεRI expression, Th2 cytokine production, and degranulation in mice [98]. Extracellular HSP70 can induce degranulation via phosphorylation of Lat [99]. In addition, microbiota-derived SCFA butyrate can suppress the FcεRI-IgE-mediated allergic signaling in human and mouse cells, via inhibition of the histone deacetylases, but not the SCFA receptors. Moreover, butyrate can downregulate the expression of signaling molecules Btk, Syk, and Lat [100]. All of these molecules are potential therapeutic targets in the context of allergic diseases. A summary of the regulatory factors involved in intracellular allergic signal transduction is presented in Table 1.

Allergic Mediators and the Signaling Pathways

A vast number of allergic mediators are derived from mast cells, including proteases (e.g., tryptase, chymase, and carboxypeptidase), cytokines (e.g., IL-4, TSLP, and TNF-α), chemokines (e.g., CCL-3, CCL-5, and CX3CL-1), and growth factors (e.g., TGF-β1, SCF, and VEGF). These mediators are either preformed (e.g., histamine, tryptase, and chymase) or newly synthesized (lipid mediators, e.g., PAF, cysteinyl leukotrienes [CysLTs], and prostaglandin [PG]) [4,

Table 1 A summary of the regulatory factors of allergic signal transduction in mast cells

Regulatory molecules	Mechanisms of action	References
SHIP1	A negative regulator of Lyn and cytokine production (especially at supra-optimal allergen concentrations); hydrolyzing PI-3,4,5-P3 to PI-3,4-P2	[57]
CSK	A negative regulator of degranulation and chemotaxis; a positive regulator of adhesion to fibronectin and cytokine production	[145]
SLAP	A negative regulator of allergic signaling by binding to FcεRIβ and Cbl-b	[82]
AMPK	Disrupting the FcεRI complex by blocking recruitment of signal proteins to the FcεRI	[83]
NR4A1	An enhancer of allergic signaling by inhibiting AMPK	[84]
Lck	An enhancer of allergic signaling by phosphorylating Lat	[85]
Gata2	An enhancer of allergic signaling by binding to the super-enhancer regions of target genes	[88]
MITF/TFE	A group of enhancers of allergic signaling with basic helix-loop-helix leucine zipper that recognizes the E-box motifs in the target gene promoters	[48]
PU.1	An enhancer of allergic signaling by transactivating Syk promoter and inducing FcεRIβ expression	[92]
Mitochondrial molecules	Stat3 phosphoralation prompts mast cell activation through augmenting ATP production, decreasing reactive oxygen species roduction, increasing calcium concentrations, and inhibiting mitophagy	[93]
	MITF phosphoralation facilitates mast cell degranulation and cytokine production; PDH enhances mitochondrial OXPHOS activity and mast cell degranulation; mitochondrial MITF regulates PDH activity	[94, 95]
sFcεRI	A negative regulator of allergic signaling by blocking IgE-FcεRI binding	[96]
Exosome	A negative regulator of allergic signaling by binding to IgE via FcεRI	[97]
PDI	An enhancer of allergic signaling by augmenting FcεRI expression, Th2 cytokine production, and degranulation	[98]
HSP70	An enhancer of allergic signaling by phosphorylating Lat	[99]
Butyrate	A negative regulator of allergic signaling by downregulating Btk, Syk, and Lat	[100]

AMPK adenosine monophosphate–activated protein kinase, *CSK* C-terminal Src kinase, *HSP70* heat shock protein 70, *Lck* lymphocyte-specific protein kinase, *MITF/TFE* microphthalmia-associated transcription factor/transcription factor E, *PDI* protein disulfide isomerase, *PDH* pyruvate dehydrogenase, *SHIP1* src homology 2 domain–containing inositol phosphatase-1, *SLAP* Src kinase–like adapter protein

12, 29]. Here, we focus on several typical allergic mediators and the signaling pathways.

Histamine is one of the most studied vasoactive amines involved in allergic reactions. The release of histamine is regulated by histamine-releasing factor (HRF) [101, 102]. Mechanistically, some IgE/IgG antibodies can bind to the two binding sites (N19 and H3) within HRFs through their Fab fragments, followed by formation of disulfide-linked HRF dimmers that promote cross-linking of Ig-FcεRI complex concurrent with release of histamine [101, 103]. Recently, two synthesized inhibitors targeting N19 (anti-N19 monoclonal antibody and N19-PEG) that block the Ig-HRF binding have been developed for treatment of food allergy in an animal model [103]. In mast cells, membrane-resident phospholipid can be converted to arachidonic acid by phospholipid A2 (PLA2), leading to production of several CysLTs (e.g., LTB4 and LTE4) that exert pro-inflammatory effects in cooperation with their receptors [104, 105]. Recent work has identified the involvement of a distinct subset of DCs with differentiated expression of LTB4 receptor 1 (BLT1) in allergic inflammation [106]. Targeting of the LTB4-BLT1 pathway in lung eptithelial cells was found to hamper allergic inflammation by reducing IL-33 production, and suppressing the innate lymphoid cell-2 activation [107]. On the other hand, arachidonic acid can be converted by cyclooxygenase (COX) into a series of prostaglandins (PGEs) [108]. Of note, PGE2 can attenuate mast cell activation, and protect against anaphylaxis through binding to its receptor EP2/4, while relative PGE2 deficiency predisposes to anaphylaxis in humans and mice [109]. PGE2 exerts anti-allergic effects by hindering phosphorylation of PLCγ-1 and Erk rather than a COX-inhibiting mechanism [109]. Logically, pharmacological agonism of the PGE2 receptor EP2 is an effective intervention to suppress the IgE-mediated activation of mast cells in human and mouse mast cells [109, 110].

Platelet-activating factor (PAF) is a potent lipid mediator involved in allergic reactions which is released from various immune cells such as basophils, eosinophils, and mast cells. PAF is synthesized by lysophosphatidylcholine acyltransferase and degraded by PAF-acetyl hydrolase (PAF-AH) that binds to the PAFR on effector cells. Antagonists of PAFR that show a synergistic effect with epinephrine were found to improve the therapeutic outcome of allergic shock in a rat model [111]. The activity of PAF is mainly regulated by PAF-AH, which degrades the PAF into inactive lysoPAF, and regulates the half-life of PAF [112, 113]. Thus, the severity of anaphylactic reactions is inversely related to the PAF-AH activity [112]. Histamine and PAF can activate constitutive endothelial nitric oxide synthase (eNOS), and thus promote synthesis of NO through a PI3Kinase-Akt pathway in endothelial cells [29]. In addition, estrogen can induce the expression of tissue NOS that prompts NO synthesis and anaphylactic development [114]. Activation of soluble guanylate cyclase (sGC) by NO leads to the conversion of GTP to intracellular second messenger cGMP [115], and potent vasodilation and bronchodilation effects [29, 116]. Pharmacologically, sGC agonists are thus potential bronchodilators in the setting of asthma [116].

These mediators have a diverse range of physiological effects. These can increase vascular permeability, bronchial smooth muscle contraction, circulatory collapse, or cardiac arrest directly (e.g., proteases) or by activating the mediator receptors. It is plausible that these mediators can cause target tissue damage, resulting in death/apoptosis of epithelial or endothelial cells. Studies have shown that proteases can impair the bronchial epithelium integrity; tryptase and chymase can disrupt epithelial cell junctions, impair barrier function, inhibit lesion repair, and exacerbate airway damages in human bronchial epithelial cells [117–119]. In addition, studies have shown altered gene expression in skin lesions in patients with chronic spontaneous urticaria [120], and in tryptase- and/or chymase-treated human bronchial epithelial cells [119]. In-depth characterization of the mediator-triggered alterations, as well as the underlying mechanisms for these alterations, is essential for the development of pharmacological interventions for allergic reactions.

Anti-Allergic Strategies and the Mechanisms of Action

The FcεRI-mast cell–mediated allergic signaling represents a set of distinct allergen-activated immune responses. Interventions targeted at components in this machinery are logical clinical management strategies against allergy, as discussed elsewhere in this paper or other reviews [121–123]. Here, we focus on several promising therapeutic strategies and their related mechanisms.

Omalizumab and ligelizumab are humanized IgG1k monoclonal antibodies against the IgE Cε3 domain, both of which bind to free IgE in a 2:1 stoichiometry [124–126]. Recently, Gasser et al. [46] demonstrated that these two therapeutic monoclonal antibodies bind to different but somewhat overlapping epitopes in the IgE Cε3 domain; ligelizumab has higher affinity for IgE, stronger inhibitory effects on circulating basophil activation and IgE production, but lower dissociation than omalizumab; ligelizumab but not omalizumab can remove the IgE-Fc3/4 fragments from FcεRIα and suppress the IgE synthesis despite incapacity of eliciting the cross-linking of FcεRIα-bound IgE-Fc3/4 fragments. Other therapeutic anti-IgE antibodies including Quilizumab, MEDI4212, and UB-221 have also been studied [121, 126, 127].

Designed ankyrin repeat proteins (DARPins) are a group of small-molecule non-antibody protein scaffolds that are designed for neutralizing the target proteins with high affinity and specificity. Anti-IgE DARPins not only prevent free IgE from binding to FcεRI, but dissociate pre-formed IgE-FcεRI complexes, conferring fast and potent suppressive effects on the development of allergic reactions [121]. Although the allergen-IgE binding is highly specific, low-affinity (but high-avidity) binding may allow for allergen cross-reactivities [128]. Mouse anti-human IgE monoclonal-antibodies can serve as low-affinity allergic response inhibitors that interfere with the allergen-human IgE binding and attenuate the IgE-mediated systemic responses in human FcεRIα transgenic mice [129]. Allergen-specific IgG antibodies can suppress allergic symptoms by competitively blocking the allergen-IgE binding [130]. This is in agreement with the counteractive effects of IgG, in particular IgG4, against IgE [42].

Inhibitory signaling against the FcεRI complex is an effective therapeutic approach that is mediated by inducing cross-linking of the inhibitory IgG receptor (FcγRIIb/

Table 2 A summary of current anti-allergic therapeutic agents and mechanisms of action

Therapeutic categories	Agents	Mechanisms of action	References
Anti-IgE	Omalizumab	Neutralizing free IgE antibodies; normalizing allergic inflammation–related genetic expression; reducing mast cell releasability; depleting allergen-reactive effector T cells in combination with allergen-specific immunotherapy	[46, 120, 146, 147]
	Ligelizumab	Similar to omalizumab; conferring higher affinity, stronger inhibitory effects on circulating basophil activation and IgE production, but lower dissociation than omalizumab; removing the IgE-Fc3/4 fragments from FcεRIα, and suppressing the IgE synthesis	[46]
	E2_79	Serving as DARPin; neutralizing free the IgE antibodies; dissociating pre-formed IgE-FcεRI complexes	[121, 148]
	LARI	Downregulating the expression of both FcεRI and IgE on mast cells; inhibiting the phosphorylation of several intracellular signaling molecules; promoting partial mediator depletion	[129]
	Allergen-specific IgG	Competitively blocking the allergen-IgE binding	[130]
	Receptor-destroying enzyme	Modulating specifically the branched glycans on IgE, thereby hindering IgE-FcεRI binding	[149]
Anti-FcεRI	Anti-FcεRIα mAb	Neutralizing FcεRIα	[131]
	Allergen-specific IgG	IgG-FcγRIIb binding prompts cross-linking of FcγRIIb with FcεRI, and elicits an inhibitory signaling	[121]
Inhibitors of Tyrosine kinases	WZ3146	Serving as inhibitor of Lyn and Fyn kinase	[65, 121]
	GSK2646264	Serving as inhibitor of Syk kinase	[3]
	Fostamatinib	Serving as inhibitor of Syk kinase	[121]
	Fenebrutinib/Remibrutinib	Serving as inhibitor of Btk kinase	[3]
	Ibrutinib/acalabrutinib	Serving as inhibitor of Btk kinase	[121]
Activator of negative regulators	AQX-1125	Serving as activator of SHIP1	[121, 150]
Anti-siglec	Anti-siglec-6/anti-siglec-7/anti-siglec-8 (Lirentelimab)	Binding to the siglecs on mast cells counteracts the effects of intracellular tyrosine kinases, thereby hindering development of IgE-FcεRI allergic signaling	[121]
Anti-cytokine/cytokine receptor	Dupilumab	Blocking IL-4/IL-13 signaling (anti-IL-4Rα mAb)	[3, 122, 123]
	Lebrikizumab/Tralokinumab	Blocking IL-13 signaling (anti-IL-13 mAb)	[122]
	Secukinumab	Blocking IL-17 signaling (anti-IL-17A mAb)	[3]
	Nemolizumab	Blocking IL-31 signaling (anti-IL-31RA mAb)	[122]
	Etokimab	Blocking IL-33 signaling (anti-IL-33 mAb)	[122]
	Tezepelumab	Blocking TSLP signaling (anti-TSLP mAb)	[122]

DARPin designed ankyrin repeat protein, *HRF* histamine-releasing factor, *LARI* low-affinity allergic response inhibitor, *mAb* monoclonal antibody, *SHIP1* src homology 2 domain–containing inositol phosphatase-1

CD32b) with FcεRI [121]. In addition, bispecific antibodies against both FcγRIIb and FcεRI or Fcγ-Fcε fusion proteins can prevent allergic reactions [121]. Anti-FcεRIα monoclonal antibody is an effective desensitization approach, which suppresses the allergic signaling more rapidly than omalizumab or ligelizumab [131]. With regard to safety, the monovalent anti-FcεRIα monoclonal antibodies and IgG4 variants are superior to divalent and IgG1 variants, respectively, as low interaction with FcεRs promotes mild FcεRI cross-linking reactions [132].

In addition, other anti-allergic approaches have also been examined for blocking allergic signaling by inhibiting the crucial intracellular signal molecules (e.g., Syn, Fyn, Btk, and Syk) [121]. Sialic acid–binding immunoglobulin-type lectin (siglec) is a transmembrane receptor on mast cells, and the siglecs once bound by sialic acid–containing ligands can counteract the effects of tyrosine kinases in IgE-FcεRI signaling; anti-siglec monoclonal antibodies that activate the siglecs can potentially hamper allergic signaling [121]. Neutralization of some alarmins or Th2 cytokines (e.g., IL-25, TSLP, IL-4, IL-13, and IL-17) or cytokine receptors (e.g., IL-4α receptor and IL-33 receptor) with therapeutic monoclonal antibodies have been studied for their efficacy in suppressing the development of allergic reactions [3, 123, 133]. Other potential strategies include CD33 (siglec-3) recruitment, elimination of IgE-bearing B cells, and IgE-HRF-binding inhibitors [103, 134, 135]. A summary of these anti-allergic strategies and the related mechanisms is presented in Table 2, and the action sites of several important therapeutic agents are illustrated in Fig. 2.

Cofactors and the Mechanisms of Action

In addition to biomolecules and signaling pathways, some other factors can also affect the development of FcεRI-mast cell–mediated allergic inflammation. These factors include exercise, alcohol, drugs, biological factors (e.g., sex), and cold, which are collectively referred to as cofactors. These cofactors can render certain individuals at an increased risk of developing allergic reactions. However, the long-standing notion that cofactors can modulate the severity of allergic reactions [136] has been challenged by a recent study which showed that the cofactors in mild-to-moderate allergic reactions are not associated with the reaction severity [137].

Food-dependent exercise-induced anaphylaxis is a representative allergic syndrome with exercise being the cofactor. In wheat-dependent exercise-induced anaphylaxis, the omega-5 gliadin and high molecular weight glutenin of wheat are the main allergens [138, 139]. Exercise itself does not facilitate absorption of these allergens in healthy individuals; however, in individuals with hypersensitivity or damaged intestinal epithelium, exercise can facilitate absorption by inducing redistribution of blood flow, enhancing activity of tissue transglutaminase, and increasing plasma osmolality and acidosis [139]. The underlying mechanisms of alcohol that serves as a cofactor are associated with an increase in histamine levels by

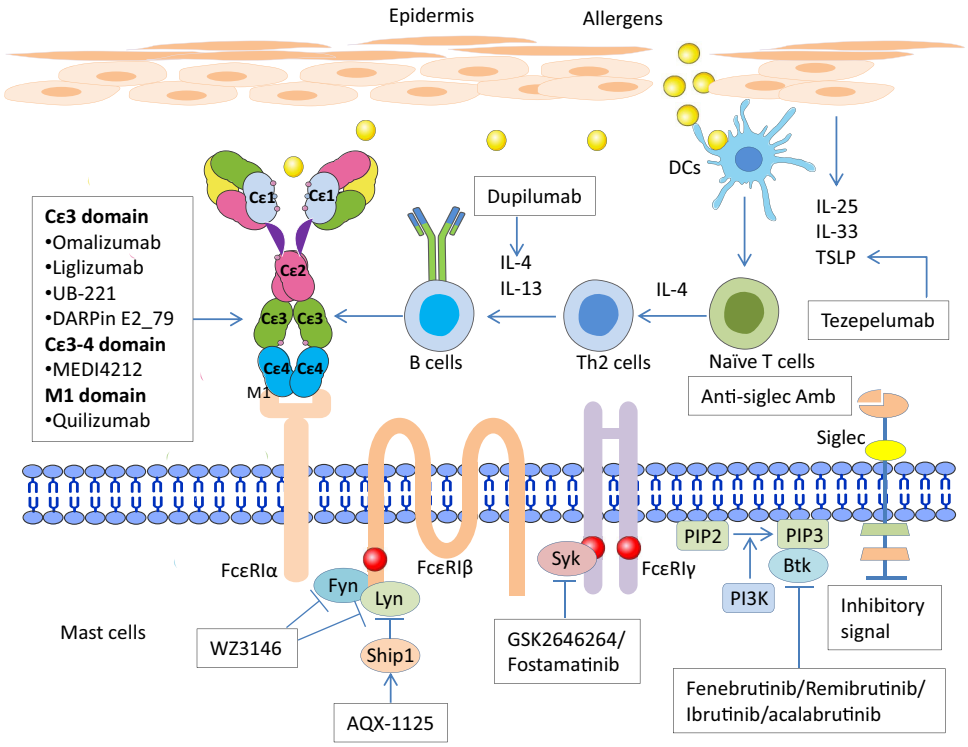

Fig. 2 A graphic illustration of the binding sites for several anti-allergic agents. Abbreviations: DCs, dendritic cells; Ship1, Sarcoma homology 2 domain–containing inositol phosphatase 1; PIP2, PtdIns (4,5) P2; PIP3, PtdIns (3,4,5) P3; PI3K, phosphoinositide 3-kinase; siglec, sialic acid–binding immunoglobulin-type lectin

inhibition of the diamino oxidase as well as an increase in extracellular adenosine by inhibition of its uptake [140].

Drugs can induce the allergic reactions through IgE- or IgG-mediated mechanism, or by direct activation of the GPCR, e.g., MRGPRX2, as discussed elsewhere. Alternatively, certain drugs can also serve as a cofactor. For example, non-steroidal anti-inflammatory drugs (NSAIDs) may be a cofactor in omega-5 gliadin allergy (also known as wheat-dependent NSAID-induced anaphylaxis) [141]. NSAIDs (e.g., aspirin) potentiate the development of allergic reactions by inhibiting cyclooxygenase and reducing the production of protective PGE2, facilitate the release of adenosine that binds to adenosine receptor 3, and enhance FcεRI-mast cell–mediated degranulation [136, 140]. Other examples of drugs acting as a cofactor include angiotensin-converting enzyme inhibitors, β-blockers, and lipid-lowering drugs [136, 137]. Sex serves as an important cofactor of the allergic reactions, which can be explained partly by the estrogen-related effects, e.g., elevated serum estradiol and estrogen receptor levels, increased endothelial NOS and NO production, impaired integrity and increased permeability of the intestinal mucosa [114]. Cold urticaria is an example of allergic reaction in which cold acts as a cofactor [142]. A possible mechanism is that the cold stress can elicit Th2 inflammation and development of allergic reactions by inducing the epithelial alarmin IL-33 release [143].

The search of cofactors remains actively in progress with candidates such as proton pump inhibitors, consumption of large amounts of unprocessed foods, and fasting [144]. Clarification of these cofactors and the mechanisms of action may facilitate more favorable therapeutic outcomes for allergic diseases.

Conclusions and Future Perspective

Mast cells are key effector cells of allergic/anaphylactic reactions with its membrane-bound FcεRI complex serving as a high-affinity inherent receptor for the allergen-specific IgE. Here, we provide an overview of the new mechanistic advances in the composition and regulation of FcεRI-mast cell signaling cascade that represents a classic paradigm of the allergic reactions. The allergic signaling cascade starts with an allergen which induces the production of specific IgE antibodies (allergic sensitization) through a mechanism known as "dual allergen exposure hypothesis." Extensive effort for allergen modifications is crucial for allergoid preparation and for further development of allergen-specific immunotherapy. When the tolerance is lost in a topic individual, activation of FcεRI on mast cells by allergen-specific IgE initiates intracellular signal transduction, and ends with degranulation, leading to a series of clinical phenotypes. This process is highly complex and closely regulated by many kinases, transcription factors, cytokines, and bioactive molecules. Over the years, much effort has been directed on the development of therapeutic strategies for allergic diseases. Of these, interventions targeting the IgE antibodies (e.g., anti-IgE monoclonal antibodies and anti-IgE DARPins) have led to appreciable success. Nevertheless, several unmet goals remain. The underlying mechanisms for loss of immune tolerance are still a mystery. The structural and genetic alterations to epithelium/endothelium by allergic mediators are not well characterized. In-depth understanding of the underlying mechanisms and cofactors involved in the development of FcεRI-mast cell–mediated allergic signaling are necessary for identifying new pharmacological targets and therapeutic designs against mast cell–mediated allergic responses.

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Declarations

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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