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Mast Cell-Mediated Orchestration of the Immune Responses in Human Allergic Asthma: Current Insights

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Abstract

Improving the lung function after experimental allergen challenge by blocking of mast cell (MC) mediators and the capability of MC mediators (including histamine, prostaglandin (PG) D2, and leukotriene (LT) C4) in induction of mucosal edema, bronchoconstriction, and mucus secretion provide evidence that MCs play a key role in pathophysiology of asthma. In asthma, the number of MCs increases in the airways and infiltration of MCs in a variety of anatomical sites including the epithelium, the submucosal glands, and the smooth muscle bundles occurs. MC localization within the ASM is accompanied with the hypertrophy and hyperplasia of the layer, and smooth muscle dysfunction that is mainly observed in forms of bronchial hyperresponsiveness, and variable airflow obstruction. Owing to the expression of a wide range of surface receptors and releasing various cytoplasmic mediators, MCs orchestrate the pathologic events of the disease. MC-released preformed mediators including chymase, tryptase, and histamine and de novo synthesized mediators such as PGD2, LTC4, and LTE4 in addition of cytokines mainly TGFβ1, TSLP, IL-33, IL-4, and IL-13 participate in pathogenesis of asthma. The release of MC mediators and MC/airway cell interactions during remodeling phase of asthma results in persistent cellular and structural changes in the airway wall mainly epithelial cell shedding, goblet cell hyperplasia, hypertrophy of ASM bundles, fibrosis in subepithelial region, abnormal deposition of extracellular matrix (ECM), increased tissue vascularity, and basement membrane thickening. We will review the current knowledge regarding the participation of MCs in each stage of asthma pathophysiology including the releasing mediators and their mechanism of action, expression of receptors by which they respond to stimuli, and finally the pharmaceutical products designed based on the strategy of blocking MC activation and mediator release.

Keywords Airways · Asthma · Mast cells · Mediators · Remodeling

Abbreviations

AEC	Airway epithelial cell
ASM	Airway smooth muscle
BAL	Bronchoalveolar lavage
bFGF-2	Basic fibroblast growth factor-2
BHR	Bronchial hyperresponsiveness
BM	Basement membrane
BSM	Bronchial smooth muscle
EB	Eosinophilic bronchitis
ECP	Eosinophil cationic protein
HLMC	Human lung mast cell
ICAM-1	Intercellular adhesion molecule-1
LT	Leukotriene
PAR	Protease-activated receptor
PDGF	Platelet-derived growth factor
PG	Prostaglandin
SCF	Stem cell factor
VCAM-1	Vascular cell adhesion molecule-1
CRTH2	Chemoattractant receptor-homologous molecule expressed on TH2 cells

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Introduction

Asthma is characterized by chronic airway inflammation, and hyperresponsiveness (AHR) accompanied by mucus

hypersecretion [1]. Triggers of allergic asthma include allergens, fungus (such as Aspergillus fumigatus [2]), viruses (mainly human rhinoviruses (HRV) [3]), and pollutants (including polycyclic aromatic hydrocarbons [4]) [5]. They interact with the airway epithelial cells to initiate the inflammatory response across the airways by releasing of cytokines, particularly IL-25, IL-33, and TSLP [5]. Synergistically with IL-1 and TNF, TSLP stimulates the production of high levels of Th2 cytokines by human MCs [6]. In uncontrolled asthma, MC infiltration to the peripheral airways including the alveolar interstitium occurs. Unlike the healthy subjects, MCs in individuals with asthma express FcεRI and surface bound IgE [7]. The increase in number of MCs in asthmatics is associated with evidence of TH2-skewed inflammation [8] and remodeling with interstitial fibrosis [9]. The participation of MCs in pathogenesis of asthma is supported by the results of tissue biopsies obtained from infants dying of viral bronchiolitis that revealed the presence of large number of tissue resident MCs. It has been reported that these MCs unlike those seen in adult asthmatic individuals did not express surface FcεRI. Development of asthma in children commonly requires both allergic sensitization and viral infection. Considering that sensitization to airborne allergens rarely occurs within the first year of life, there should be a link between MC and viral infection as a predisposing factor for later asthma development [7]. MCs develop from CD34+/CD117+ pluripotent progenitor cells that originate in the bone marrow [10, 11]. The progenitors release into circulation by which access the peripheral tissues via a well-organized integrin/receptor-mediated trafficking. Within the residing tissues, the progenitors differentiate and mature to MCs under the influence of local growth factors, mainly stem cell factor (SCF) [12, 13]. Other MC growth and survival modulators include nerve growth factor (NGF), TGF-β, CXCL12, IL-3, IL-4, IL-9, IL-10, and IL-33 [13]. Human MCs found in connective tissues contain tryptase, chymase, carboxypeptidase, and cathepsin (MC_{TC}), while majority of MCs found in lung and gut express only tryptase (MC_T) [14]. Upon IgE-FcεRI-mediated MC activation, subsequent degranulation and release of bioactive mediators occur [15]. MCs produce a wide range of mediators including biogenic amines (histamine and serotonin), serglycin, proteoglycans, proteases (mainly chymase and tryptase), and lipid mediators (platelet-activating factor (PAF), leukotrienes (LTs), and prostaglandins (PGs)) [16]. Additionally, activated MCs release a broad range of pre-stored or de novo synthetized cytokines including GM-CSF, TNFα, IL-3, IL-4, IL-5, IL-6, IL-10, IL-13, and IL-17, chemokines such as CCL2, CCL3, CCL5, and CXCL8, and growth factors including bFGF, NGF, VEGF, TGF-β, and SCF of which the latter acts as the main growth factor for these cells [15]. During immediate allergic reaction (occurring within 10–20 min following allergen exposure), MC released histamine and serotonin cause airway smooth muscle contraction, mucus hypersecretion, and plasma extravasation within the airway wall, that finally result in airway narrowing. The next phase of MC activation occurring within 20–40 min postallergen exposure is determined by the release of the newly produced mediators mainly PGs and LTs that cause further enhancing the allergic airway response [15].

Innate Immune Cells in Asthma (Recruitment and Function)

Both innate and specific immune cells actively participate in pathogenesis of asthma. Allergen exposure results in releasing cytokines from airway epithelium mainly IL-33, IL-25, and TSLP which activate ILC-2 cells to proliferate and secrete IL-4 and IL-5 that play a role in induction of IL-13 by Th2 and eosinophil recruitment and activation [17]. ILC2 cells are able to produce IL-13 in an Th2-independent pathway for instance under influence of basophil-derived IL-4 [18, 19]. MC released PGD2 has been reported to activate ILC-2 cells via acting on CRTH2 receptor through which induces the production of type 2 cytokines [20]. T2 cytokines mainly IL-4 and IL-13 cause reduction in junctional complex structure and function of airway epithelial cells in a JAK-dependent manner [21]. Disrupted barrier function possibly promotes allergen sensitization within the airways by accelerating and facilitating the uptake of allergens by subepithelial DCs [21]. Acting via ST2 receptor and MyD88-dependent signaling pathway, IL-33 activates MCs and induces their proliferation [22]. IL-25 acts directly on fibroblasts and endothelial cells to promote airway remodeling and angiogenesis and contributes to production of TSLP and IL-33 in the lung [23]. Eosinophils after being recruited to airways secrete toxic proteins stored in intracellular granules mainly major basic protein (MBP), eosinophil cationic protein(ECP), and reactive oxygen species, which are capable of damaging tissue during allergic inflammation [24, 25]. MBP is known to induce MC degranulation. Moreover, eosinophil released pro-inflammatory mediators mainly LTC4 and LTB4 promote vascular permeability, mucus secretion, and smooth muscle contraction [24]. Several eosinophil surface proteins including CD9, CD11a, CD16, CD25, CD45RO, CD48, CD89, and CD137 have been reported to upregulate in asthma [26]. Eosinophil-released mediators including IL-1, IL-3, IL-5, IL-6, TGF-α, TGF-β, and GM-CSF contribute to airway inflammation. Furthermore, eosinophil-released LTC4, PAF, and 15-HETE (15-hydroxyicosatetraenoic acid) induce acute hyperresponsiveness and ASM hypertrophy [27]. HLMCs activate ILC-2 cells by releasing LTD4 and PGD2 [17]. In return, ILC-2 cells produce IL-9 that is a MC growth factor and promotes IL-4-driven antibody production by B cells and can also induce goblet cell metaplasia [17, 28]. IL-13 induces airway hyperresponsiveness and, in concert with IL-9, promotes mucus production [29]. HLMCs not only release IL-13 but also

express the receptor IL-13Rα1. Interestingly, IL-13Rα1 overexpression is reported in asthmatics. IL-13/IL-13Rα1 interaction promotes FcεRI expression on MCs which leads to increased histamine release, MC proliferation, and activation in asthma in an autocrine fashion [30]. Airway epithelial cells contribute in DC recruitment and activation by releasing CCL20 and CCL2 [27]. Moreover, ILC-2-derived IL-13 facilitates the migration of activated lung $CD11b^{+}$ cDCs to the draining mediastinal lymph nodes (LNs), where they induce Th2 responses [17]. Immature DCs after uptaking the inhaled antigens become mature and migrate to regional LNs to present antigens to naïve T cells which results in differentiation of CD4+ T cells into Th2 cells involved in allergic asthma [31]. Interestingly, some helper T cells capable of producing IL-21 adopt a follicular helper T cell (T_{FH}) subset [17]. T_{FH} cells contribute to producing IL-4 and IL-21, that, along with Th2 cell-derived IL-4, promote class switching in B cells in favor of producing IgE [32]. $CD11c^{hi}$ DCs recruit effector Th2 cells to airways through secreting CCL17 and CCL22 [17]. During respiratory syncytial virus (RSV) infection, RSV-infected airway epithelial cells release TSLP which promotes the activation of DCs [33] (Fig. 1).

Mast Cell Progenitors from Bone Marrow to Airways: Production and Homing

While SCF, CCL5, CXCL8, CXCL10, CCL11, and CXCL12 are predominant chemokine in MC recruitment to airway epithelium, chemokines including SCF, TGFβ1, CXCL8, CXCL9, CX3CL1, CXCL10, CCL11, and CXCL12 play a role in recruitment of MCs to HASM [34]. Additionally, CXCL9, CXCL10, and CXCL11 act through CXCR3, the most highly expressed HLMC chemokine receptor, and induce a rise in cytosolic-free $Ca2^{+}$, actin reorganization, and chemotaxis [35, 36]. Human-activated lung MCs release LTB4 that actively attracts the immature MCs via BLT1 receptor to inflammation sites [37]. LTB4-mediated chemoattraction results in MC hyperplasia through which MC progenitors are supplied in the lung tissues [38]. Conversely, PGE2/E-prostanoid (EP)-2 receptor interaction results in inhibiting human lung MC migration [34]. SCF is produced predominantly by epithelial and mesenchymal cells. SCF-CD117 binding induces immature cell proliferation, promotes their chemotaxis to variety of anatomical sites, and suppresses mature MC apoptosis [34]. MCs after being recruited to airways benefit largely from adhesion molecules mainly CADM1 to adhere to human parenchymal lung fibroblasts and HASM cells through homophilic CADM1-CADM1 and CADM1-nectin-3 binding respectively. Human ASM bound SCF mediates MC adhesion via binding to KIT receptor (CD117) [34]. Bronchial smooth muscle (BSM) is infiltrated by MCs upon releasing mediators including TGF-β1, SCF, CXCL10, and CX3CL1 which possess MC chemoattracting activity [39] (Fig. 2, Table 1).

Role of MC Mediators in Allergic Asthma

Interactions of Mast Cells with Airway Epithelial Cells, Mucous Glands, and Epithelial Goblet Cells

AECs are activated through direct enzymatic activity of the exposed allergens or through activation of a wide range of pattern recognition receptors (PRRs) including TLRs, RIG-I-like receptors (RLRs), NOD-like receptors (NLRs), and C-type lectins. Upon exposure to inhaled allergens, AEC released CCL17 and CCL22 attract and recruit ILC2s, basophils, Tregs, and Th2 through acting on CCR4. Eosinophils and Th2 cells are recruited by AEC released eotaxins CCL11, CCL24, and CCL26 that act via CCR3 receptors. Additionally, AECs are capable of attracting basophils, ILC2s and Th2 cells through releasing PGD2 that binds to CRTH2 receptor [61]. MC-released IL-4 and IL-13 promote the capability of cytokine production by AECs [53]. Both MCs and AECs are able to produce TSLP. AECs owing to expressing TLRs mainly 3, 6, 7, 8, and 9 are able to sense inhaled antigens and in respond to their presence release TSLP. TSLP which is overexpressed in the asthmatic airway promotes the release of Th2 cytokines including IL-4, IL-5, and IL-13 [53]. MCs after localize into the submucosal mucous glands release mediators and cytokines including histamine, PGD2, LTC4, TNFα, chymase, IL-4, IL-6, and IL-13, that consequently promote mucous hypersecretion by hyperplastic submucosal cells and epithelial goblet cells [53]. MC-released IL-13 is the predominant cytokine associated with mucous secretion that promotes the secretion of airway mucus in asthmatics [62]. Excess mucus observed in asthma and COPDs is due to increased biosynthesis of the secretory MUC5AC which is the dominant macromolecule in chemical composition of mucus secreted by airways [63]. IL-13/IL-4Rα interaction activates cytokine receptor-associated Janus kinases (JAKs) which supports the phosphorylation of STAT6. Following dimerization, translocation of phosphorylated STAT6 to the nucleus occurs that suppresses the expression of FOXA2, a transcriptional repressor of MUC5AC [62, 64]. IL-13 signaling promotes transdifferentiation of ciliated to goblet cells [64]. TNFα also is considered as a MC mediator that plays a role in induction of mucous secretion. TNFα/TNFR1 interaction supports receptor trimerization followed by recruitment of multiple signaling proteins to the cytoplasmic domains of TNFR1. TNFR1-associated death domain-containing protein (TRADD) acts as a scaffold for the assembly of downstream signaling complexes, of which receptor-interacting protein1 (RIP1) and TNFR-associated factor2 (TRAF2) are major components. Both RIP1 and TRAF2 are involved in IκB kinase (IKK) activation. IKK promotes the phosphorylation of IκB, after which IκB becomes marked to undergo ubiquitination and degradation by the 26S proteasome. This process is dependent to

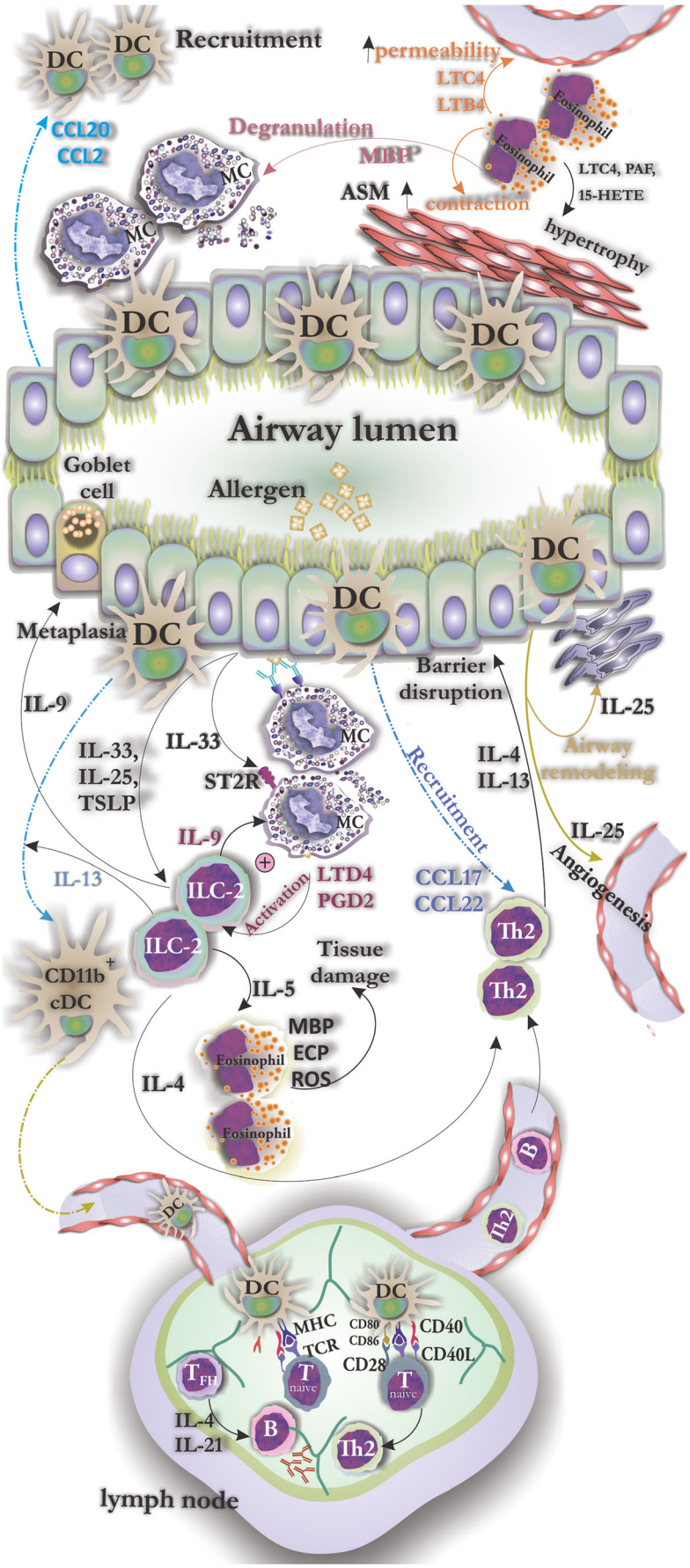


Fig. 1 Upon allergen exposure, air way epithelial cells release IL-25, IL-33, and TSLP and activate ILC-2. DCs after being recruited to lymph nodes act in favor of differentiation of naïve T cells to Th2 cells. T_{FH} cells contribute to Ig class switching in B cells and production of IgE. Antigen-specific IgE molecules sensitize MCs via binding to FcεRI. Further allergen exposures result in MC activation and degranulation. Innate immune cells including eosinophils and DCs are recruited to airways by chemoattractants released by other immune cells

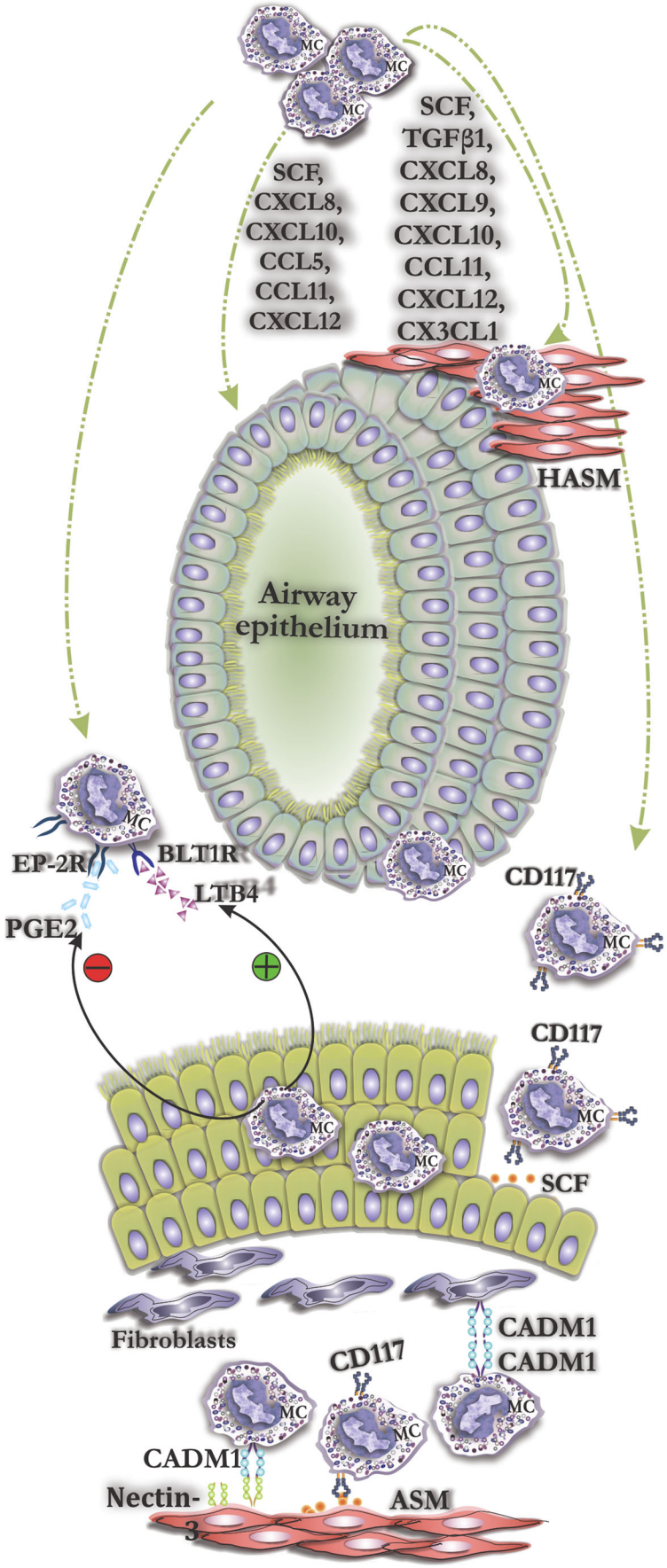


Fig. 2 Different chemoattractants are responsible for recruiting MCs to epithelium and ASM. MCs attach to fibroblasts and ASM using homo/heterotypic CADM1, and SCF/CD117 bindings

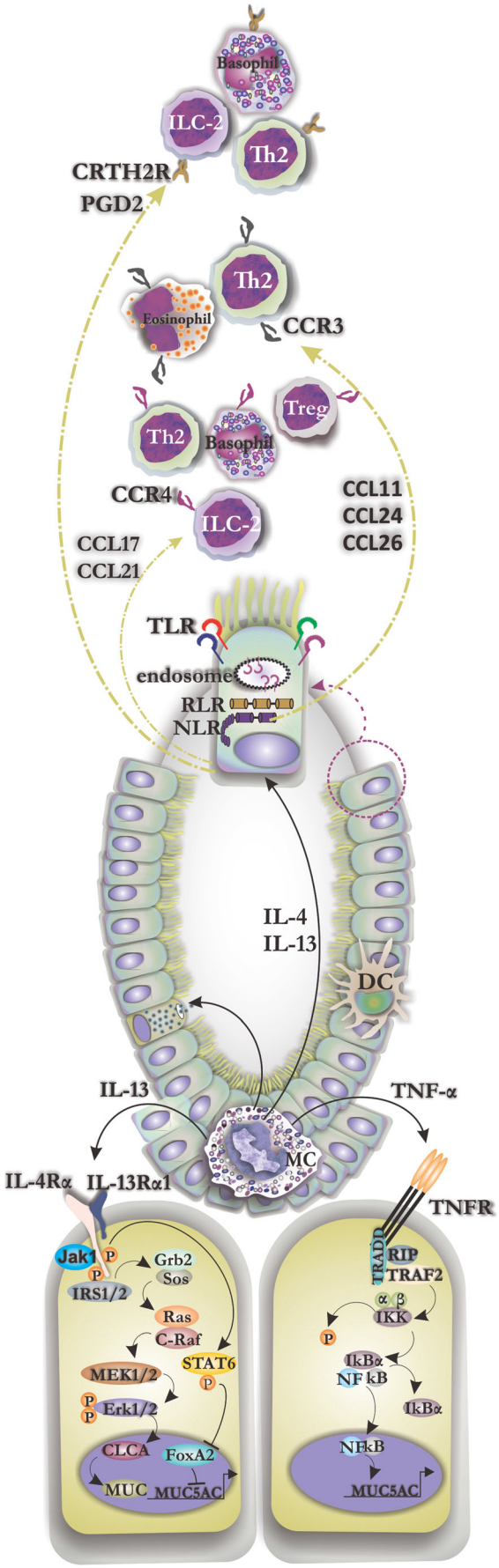
Table 1 Role of three classic groups of MC mediators in allergic asthma

Preformed mediators		
Chymase	Activates MMP-9, consequently degradation of the ECM and basement membrane (BM), migration of endothelial cells into the interstitial space, and endothelial cell proliferation and differentiation into mature blood vessels occur. It generates mature forms of IL-33 by acting on full-length IL-$33_{1–270}$ to activate ILC2s and eosinophils in vivo.	[40] [41]
Histamine	Upon MC degranulation, histamine causes immediate bronchoconstriction via H1 receptors. The levels in the BAL fluid directly correlate with the severity of asthma.	[42]
Tryptase	Tryptase induces AHR by activating ASM expressed PAR-2 and has been implicated in bronchoconstriction through release of neurokinins from afferent neurons in the airways. It promotes tissue remodeling and fibrosis. Upon releasing from MCs, it induces HASM to release TGFβ1 which promotes the expression of α-smooth muscle actin (α-SMA) by HASMC and induces the contractility.	[43] [44] [45]
De novo synthesized mediators		
PGD2	PGD2 is a chemoattractant for HASM when acts on CRTH2/DP2 receptor (expressed by eosinophils, basophils, and epithelial cells in addition of HASM) and may promote ASM migration toward the subepithelial BM. Additionally, when released from MCs, PGD2 acts as bronchoconstrictor. PGD2/DP2 interaction facilitates the trafficking of inflammatory cells into cite of inflammation by increasing smooth muscle relaxation, vasodilation, vascular permeability, and production of CCL22 by epithelial cells.	[46] [47] [47]
LTC4	Acting through Cys-LT1, LTC4 promotes variety of physiopathologic reactions in airways mainly acute bronchoconstriction, eosinophil chemotaxis and activation, mucus hypersecretion, hyperplasia, and contraction of ASM.	[48, 49]
LTE4	LTE4 induces airflow obstruction and MC activation when acts on CysLT1 receptor.	[50]
PAF	PAF an important pro-inflammatory mediator causes bronchial hyperactivity, increased vascular permeability, and accumulation of inflammatory cells.	[51]
Released cytokines		
IL-4	IL-4 as a pleiotropic cytokine acting via the IL-4R on majority of lung cells is associated with remodeling of epithelium and lamina propria. It also supports smooth muscle cell contractility. IL-4 supports the expression of FcεRI on MCs and basophils. In addition to MCs, other immune cells including Th2 cells, eosinophils, basophils, and ILC-2 are capable of producing and releasing IL-4.	[52] [52]
IL-13	IL-13 expression promotes inflammatory cell release, production of eotaxin and FeNO, mucus hypersecretion, and supports subepithelial fibrosis.	[53–55]
TSLP	MCs express the TSLP receptor, and TSLP/TSLP receptor interaction results in expression of Th2 cytokines. MCs are known to produce high levels of TSLP, upon IgE-mediated activation.	[56]
TGFβ1	TGFβ1 along with bFGF and PAF is a key mediator in fibrotic pathways. These mediators are associated with differentiation of the myofibroblasts which act as the key cell type involved in pulmonary fibrosis. TGFβ is well known for its profibrotic mediating properties in the lung which supports collagen synthesis.	[57] [9]
IL-33	IL-33 enhances IgE/Ag-, monomeric IgE-, C5a-, SCF-, and NGF-mediated cytokine production in human MCs, and HMC-1.	[58]
VEGF	MC and eosinophil-derived VEGF act as angiogenic factor in the asthmatic submucosa.	[59]
bFGF-2	Acts as a profibrogenic cytokine during airway remodeling.	[60]

unmasking a nuclear localization signal and permits subsequent nuclear import of NF-κB [62] (Fig. 3).

Mast Cell—Airway Smooth Muscle Interactions in Allergic Asthma

The presence of MCs in ASM is considered as a key feature in asthma pathogenesis [65] which is associated to the development of ASM hypertrophy and hyperplasia, ASM dysfunction expressed as BHR, and presence of variable obstruction in airflow [66]. Unlike submucosa residing MCs, the population located in the ASM bundles are always tryptase and chymase positive (MCTC) and their number has been linked to the severity of asthma [59, 67]. Interestingly, MC proteases show different properties when studied in isolation on ASM function. For example, while β-tryptase induces ASM cell proliferation, chymase dramatically reduces it [68]. ASM secretes the three CXCR3 ligands CXCL9, CXCL10, and CXCL11 capable of binding to MC expressed receptor CXCR3 that actively recruit them. SCF/CD117 and TGF-β/TGF-βR also play a role in recruitment of MCs to ASM [66]. Moreover, ASM secreted CXCL10 and CCL5 have a role in the recruitment of MCs via MC expressed CXCR3 and both CCR1 and CCR3, respectively [69]. MC surface expressed CADM-1 facilitates homotypic adhesion between MCs and also

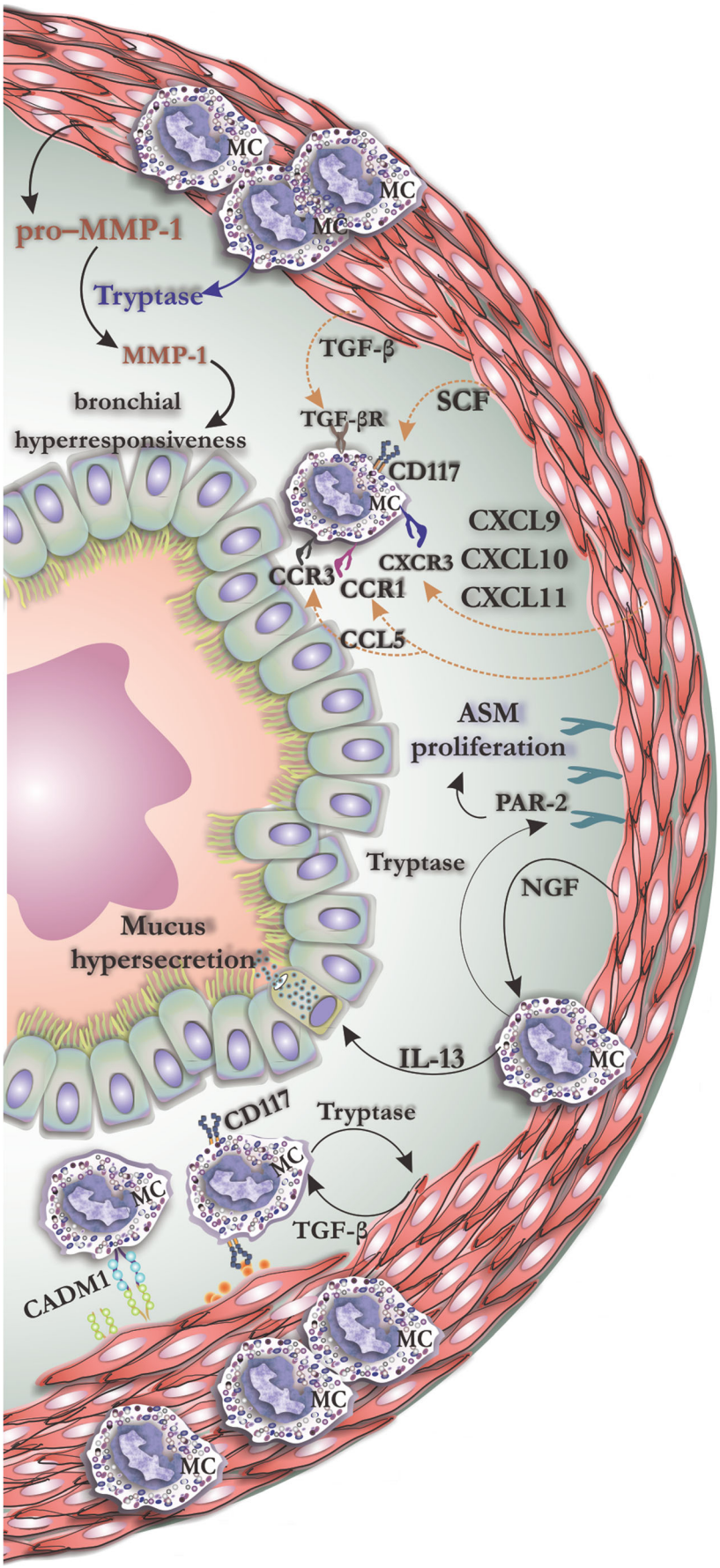


◀ **Fig. 3** Upon allergen exposure, AECs are activated by variety of receptors and release chemoattractant mediators and recruit variety of immune cells to airways. IL-13 and TNF play a crucial role in inducing the mucus production by goblet cells. Both IL-13 and TNF signaling pathways are illustrated

heterotypic adhesion with ASM. CADM-1 promotes MC survival and proliferation even in the absence of SCF and is thought to corporate with CD117 in promoting MC survival [57]. CADM-1-mediated MC-ASM adhesion results in ASM activation by MC tryptase, with secretion of TGFβ1 from ASM cells, that upregulates ASM contractile protein expression [57]. PGE2 a lipid mediator of MCs after releasing induces bronchial contractions through interaction with EP1 receptors and relaxations through acting on EP2 or EP4 receptors [70]. Under the function of HLMCs expressed EP2 or EP4 receptors, the concentration of cyclic-AMP raises through activation of adenylyl cyclase. It has been reported that PGE2 works via EP2 receptors to stabilize MCs [71]. Additionally, ASM cells overexpress PAR-2 in asthma. The consequences of PAR-2/MC-derived tryptase include inducing of the calcium mobilization, contraction, and proliferation of human ASM cells [72]. Relatively, overexpression of functional PAR-2 receptors by asthmatic BSM cells accounts for the increased calcium response to PAR-2 stimulation. Repeated PAR-2 stimulations by MC released tryptase promote the proliferation capacity of asthmatic BSM cells [73]. ASM released nerve growth factor (NGF) acts as a MC survival factor that promotes bronchial hyperresponsiveness [74]. Interestingly, ASM release a variety of inflammatory and angiogenic mediators, including eotaxin, GM-CSF, IL-1β, IL-2, IL-5, IL-6, IL-8, IL-10, IL-11, bFGF, PDGF-BB, and VEGF [59]. Recently, it has been reported that ASM-generated pro-MMP-1 after being proteolytically activated by MC-released tryptase plays a role in bronchial hyperresponsiveness. MMP-1 is capable of processing ASM-derived extracellular matrix that enhances ASM proliferation [60]. ASM-derived MMP-1 is induced by collagen I and tenascin C [75] (Fig. 4).

Mast Cells and Airway Remodeling in Asthma

In asthma, ASM layer infiltration by MCs and secretion of pro-inflammatory and profibrotic mediators are widely accepted to contribute to airway remodeling. Thickening of the asthmatic basement membrane occurs in response to increased deposition of collagen I and III, tenascin, and fibronectin, likely produced by activated myofibroblasts [59]. Subepithelial fibrosis which is another feature of airway remodeling in asthma occurs in the lamina reticularis just below the BM and results in thickening of the BM just below the epithelium [76]. MCs play a


MC
MC
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pro–MMP-1
Tryptase
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bronchial
hyperresponsiveness
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SCF
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CD117
MC
CXCL9
CXCL10
CXCL11
CXCR3
CCR3
CCR1
CCL5
ASM
proliferation
PAR-2
Tryptase
NGF
Mucus
hypersecretion
IL-13
MC
CD117
Tryptase
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TGF-β
CADM1
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◀ **Fig. 4** ASM released mediators actively attract MCs to airways. MCs benefit largely from CADM1 and CD117 to attach to ASM. MC Tryptase plays a role in converting pro-MMP-1 to MMP-1 which contributes in bronchial hyperresponsiveness. Tryptase also induces the ASM proliferation, in return ASM-derived TGFβ activates MCs

predominant role in developing of chronic airway inflammatory changes and remodeling by releasing mediators. Mitogenic properties of MC released tryptase on fibroblasts and to stimulate the synthesis of type 1 collagen in these cells have been reported. Both tryptase and histamine are able to induce ASM proliferation [42]. During airways remodeling TGFβ, another dominant MC mediator involved in airway remodeling promotes epithelial changes and induces subepithelial fibrosis, ASM remodeling, and microvascular changes. TGFβ after being released promotes the differentiation of fibroblasts to myofibroblasts and induces the release of cytokines including fibroblast growth factor-2 (FGF-2) and connective tissue growth factor (CTGF). The latter cytokine enhances the production and deposition of ECM proteins [77]. A number of MC mediators including VEGF, histamine, bFGF, metalloproteinases, IL-8, and proteases are involved in MC-mediated angiogenesis during asthma [40]. MC-derived chymase activates MMP-9 that facilitates the degradation of the ECM and BM, migration of endothelial cells into the interstitial space, and endothelial cell proliferation and differentiation into mature blood vessels [78]. MC-derived proteases, mainly tryptase, and MMPs boost inflammatory responses and airway remodeling in asthma. In turn, ASM-derived mediators, including TGF-β, PGE2, and soluble and membrane-bound SCF modulate the activation state of infiltrating MCs [78].

Mast Cell-Targeted Treatment in Allergic Asthma

There are different therapeutic strategies to target MC-related airway inflammation:

Neutralizing IgE (anti-IgE) and Prevent the Antibody from Linking to the FcεRI

Omalizumab, a clinically approved therapeutic humanized antibody, inhibits the IgE/FcεRI interaction via binding to the Cε3 region on free IgE, prevents MC and basophil activation, and blocks IgE binding to CD23 on B cells and APCs [15, 79, 80]. Moreover, MeDI4212 an antibody with high affinity binds specifically to IgE Cε3 domain and prevents IgE binding to its receptors (FcεRI and CD23) [81].

Neutralizing MC Activator Mediators via Blocking MC Surface Receptors

MCs express a number of receptors that regulate their activation [82]. Tezepelumab (AMG-157) is a fully human neutralizing IgG2 anti-TSLP monoclonal antibody. Tezepelumab inhibits both the early and late allergic responses to a whole long allergen challenge and reduces the number of eosinophils in both blood and sputum of patients with asthma [83, 84]. C-Kit is a surface receptor of SCF expressed on most MCs. It is widely used as a surface marker to identify MCs in tissue. Masitinib is a new kinase inhibitor designed to inhibit c-Kit kinase. It has proven to be effective in mastocytosis and is in a phase III program on patients with severe asthma [85].

Blocking the Signaling Pathways

It is well stablished that cross-linking at FcεRI activates spleen tyrosine kinase (Syk). According to the structure and function, Syk is classified as a ZAP70 family member that is required to mediate MC activation and de novo synthesis of eicosanoids, chemokines, and cytokines [86, 87]. Considering that Syk is located upstream in the cell signaling pathway of multiple immune receptors in human MCs, therapies with Syk inhibitors possibly may be more efficient than drugs that inhibit a single downstream event. In this regard, the Syk inhibitor R343 (Rigel) previously known for its capability to abrogate FcR and BCR signaling has been evaluated by inhaled route in clinical trials for asthma [88].

Blocking the Receptors of Mediators

Blocking the receptors of MC-released mediators could be an effective strategy of controlling the inflammatory effects of MCs in asthma. LTD4 receptor antagonists including "montelukast," "zafirlukast," and "pranlukast" are well documented in both asthma and allergic rhinitis [15]. Additionally, the PGD2 receptor "CRTH2" antagonist setipiprant has been reported effective in reducing the late phase reaction after allergen challenge [15]. The pro-inflammatory effects of PGD2 could be observed when it binds to CRTH2 receptor. The receptor is selectively expressed on variety of immune cells including Th2 cells, eosinophils, and basophils [89]. Blocking CRTH2 results in suppressing PGD2 chemotactic activity by which PGD2 recruits effectively circulating eosinophils and basophils to the site of inflammation [89]. Phase 1 clinical trial has revealed the safety selective H4R antagonists including UR-63325, JNJ-39758979, and PF-3893787 in human [27]. Imatinib, a potent inhibitor of c-Kit discoidin domain and platelet-derived growth factor receptors (PDGFR), has been reported to decrease airway hyperresponsiveness, MC counts, and tryptase release in patients with severe asthma [90, 91].

Discussion and Conclusion

It is still not clear why airway remodeling develops in asthma and how such changes contribute to alterations of airway function. In proportion to adult asthma, we also have a poor knowledge regarding childhood asthma. Surprisingly, the frequencies of MCs in the subepithelial mucosa and in the ASM of children who wheeze and with severe asthma as controls show no significant alteration [65]. Moreover, efforts should be done to clarify the exact role of newly discovered MC expressed receptors and released mediators. As an example, mice MC-derived neurotrophin 4 (NT4) has been reported to be in association with persistent changes in ASM innervation and AHR in mice; however, the role of human MC-derived NT4 has been poorly understood in pathogenesis of asthma [92]. Additionally, IFN-γ2 (IL-28A) beyond its role in autoimmunity has been reported to modulate lung DC function to promote T1 immune skewing and suppresses allergic airway after being released from airway MCs in patients with combined rhinitis with asthma [93]. Targeting MC progenitor recruitment may offer an upstream checkpoint to reduce tissue recruited MCs, and the consequences of their presence. The exact molecular mechanism of such recruitment remains unclear most likely it involves integrins and perhaps CADM1, that binds to endothelial CADM1 [48]. Interestingly, the use of IL-37 that binds to IL-18Rα as an anti-inflammatory biological cytokine in suppressing inflammatory cytokines involved in asthma pathogenesis is under investigation. IL-37 capability of suppressing the secretion of pro inflammatory cytokines released from MCs including IL-1, IL-6, IL-8, and TNF-α makes it a promising cytokine to control the MCs [94]. It also increases activated Treg, APC, activated antigen sensitized T cells, and naïve T cells [94]. In humans, the KCa3.1 which is an intermediate conductance $Ca2^+$ activated K+ channel is activated following FcεRI-dependent activation and enhances the influx of $Ca2^+$ (via Orai 1 channels) and histamine release in HLMCs. KCa3.1 blockers such as TRAM-34 have been investigated in mice models of asthma, but still their effectiveness in human asthma has not been proven [57]. Interestingly, attention has been given to immune modulating properties of TLRs especially TLR9 to redirect allergic Th2 responses by triggering Th1 response via TLR activation to control and treat asthma [95]. In recent years, IL-18, a pro-inflammatory cytokine, was introduced as an IFN-γ-inducing factor. IL-18 is emerging to be involved in the pathogenesis of asthma through promoting the production of Th2 cytokines by T cells, NK cells, basophils, and MCs in mice models. Although IL-18 levels have been reported to elevate in patients with asthma, and that human MCs express IL-18R, the exact role of IL-18 with the focus to MCs needs to be investigated in human [96, 97]. Most recently, lysosomotropic agents mainly mefloquine or siramesine that induce the HLMCs apoptosis via permeabilizing the secretory granules of HLMCs and releasing the contents of the granules into the cytosol have been reported to be promising in targeting HLMCs in asthma [98]. Upon acute inflammatory reaction ATP levels increase and adenosine forms through ATP breakdown. ATP and adenosine are capable of activating HLMCs expressed P2Y, P2X, and adenosine receptors [99]. P2X7 selective antagonists possibly could be used for the treatment of MC-mediated chronic inflammatory diseases mainly asthma [99]. One aspect of asthma pathogenesis in human that should be investigated precisely is the role of TLR signaling which has been extensively studied in mice models of asthma. For instance, mediatory role of the BLT2 ligand–BLT2 axis in LPS/TLR4 signaling in producing Th2 cytokines especially IL-13 has been reported [100]. It has been reported that combined stimulation of FcεRI and TLR induces a synergistic cytokine response in MCs, suggesting a contributory role of MCs to allergic exacerbations in the presence of pathogens [101]. Interestingly, in a human in vitro model using LAD2 cells, lipoteichoic acid is reported to reduce the surface expression of FcεRI through TLR2. Yoshioka et al. concluded that TLR2 ligands may be used as a therapy for controlling allergic disorders [102]. Finally, considering the similarities between MCs and basophils including their ability of releasing histamine, leukotrienes, and Th2-related cytokines following IgE-dependent stimulation and the fact that basophils increase in number in tissue and sputum of patients with asthma, investigations should be done to clarify their overlapping roles with MCs in asthma [103]. Investigations to determining the exact role of MCs in pathogenesis of asthma have limitations as any other MC related study; first, unlike animal model, obtaining tissue samples from human airways is limited to postmortem samples or specimen obtained through surgical treatment. Additionally, unlike mice models, there is no transgenic or genetically knockdown human models to participate in MC investigations. MC activation syndrome or mastocytosis may provide opportunity to investigate the role of MCs in pathogenesis of asthma when compared with normal individuals. Although, it seems logical to assume that patients with mastocytosis will tend to have bronchial hyperresponsiveness due to high burden of infiltrated MCs in airway, surprisingly, very few cases have been reported [104].

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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

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