Mast Cells

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Keywords
Mast cells • Tryptase • Chymase • IL-13 • Glucocorticoid • FcεRI

Abbreviations

CPA3	Carboxypeptidase A3
cys-LT	Cysteinyl leukotriene
FcεRI	High-affinity receptor for IgE
GC	Glucocorticoid
GM-CSF	Granulocyte-macrophage colony-stimulating factor
IL	Interleukin
MCs	Mast cells
MC_T	T-type mast cells
MC_{TC}	TC-type mast cells
MIP	Macrophage inflammatory protein
NFAT	Nuclear factor-activated T
NF-κB	Nuclear factor-κB
PAF	Platelet-activating factor
PGD_2	Prostaglandin D_2
SCF	Stem cell factor
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor
TSLP	Thymic stromal lymphopoietin

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Core Message
Mast cells trigger not only the immediate-type allergic reactions in an IgE-mediated manner but also the late-phase allergic response and chronic allergic inflammation.

5.1 Introduction

Mast cells (MCs) serve as essential effector cells for acute IgE-mediated allergic reactions by releasing histamine and other vasoactive mediators, as seen in allergic rhinitis, for example. MCs are also recognized as important source of a variety of cytokines and chemokines. Thus, MCs trigger not only the immediate-type allergic reactions in an IgE-mediated manner but also the late-phase allergic response and chronic allergic inflammation, thereby regulating the function of other immune cells. MCs are present throughout connective tissues and mucosal surfaces, particularly at the interface with the external environment such as the skin and respiratory tract (Hawrylowicz et al. 2006). The nasal mucosa is the first barrier of the entire respiratory tract that encounters various pathogens or allergens. In this review, I will summarize the roles of MCs in allergic airway diseases by focusing on the role of human MCs in the airways.

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5.2 Origin and Distribution of MCs

MCs originate from hematopoietic progenitors. Kitamura et al. discovered two different mice strains genetically lacking MCs: *Sl/Sl*^{d} mice lacking SCF, which was turned out to be the mast cell growth factor, and *W/W*^{v} mice lacking KIT, which is the receptor for SCF. By using these "natural" MC deficient mice, it was established that immature MC progenitors can migrate from bone marrow into the tissue through blood circulation, unlike immature granulocytes which are kept in bone marrow. Then, these cells undergo maturation in the tissues under specific factors like stem cell factor (SCF) present within the microenvironment (Kitamura et al. 1977, 1978; Kitamura and Go 1979).

Phenotypically distinct subsets of MCs are present in rodents, based on their distinct staining characteristics, T-cell dependency, and functions, namely, connective tissue MCs and mucosal MCs (Befus et al. 1982; Pearce et al. 1982). Regarding T-cell dependency, it is well established that mucosal MCs can grow in the presence of interleukin (IL-)3 (Ihle et al. 1983). However, human MCs do not grow when hematopoietic cells are cultured with IL-3 (Saito et al. 1988). Although human IL-3 has a significant sequence homology with murine IL-3, the degree of homology between human and murine IL-3 was almost similar (approximately 26–28 % at amino acid sequence) to that between human IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF). Also, receptor structure for IL-3 is distinct between human and mouse. While human has a common β-subunit of the receptors for GM-CSF, IL-3, and IL-5, the mouse has two distinct β-subunits; one is specific for the IL-3 receptor and exists only on MCs, and the other is equivalent to the human common β-subunit (Miyajima 1992).

Regarding human MC phenotypes, two types of MCs have been recognized based on the neutral proteases they express. TC-type MCs (MC_{TC}) contain tryptase together with chymase, and other neutral proteases, whereas T-type mast cells (MC_T) contain tryptase but lack the other neutral proteases present in MC_{TC} (Irani et al. 1986). Also, MC_{TC} preferentially dwell in the connective tissue such as skin, while MC_T are often found in mucosa such as airway epithelium. In allergic rhinitis and asthma, MCs are known to accumulate within the epithelial compartment of the target organ. In fact, there is a selective increase of MC_T in the epithelial compartment of the nasal mucosa of the patients with allergic rhinitis (Enerback et al. 1986; Pawankar and Ra 1996).

Asthma can be divided into two subgroups ("Th2 high" and "Th2 low" asthma) based on epithelial cell gene signatures for the activity of Th2 cytokines such as IL-13 (Dougherty et al. 2010). The patients with Th2 high asthma have more infiltration of MCs into the airway epithelium. These subgroups can be diagnosed based on the level of serum periostin, which production is specifically induced by IL-13, and that the patients with Th2 high asthma subtype are more sensitive to anti-IL-13 therapy (Corren et al. 2011). These intraepithelial MCs express both tryptases and carboxypeptidase A3 (CPA3) but not chymase (Dougherty et al. 2010). According to classical definition (Irani et al. 1986), MC_T were not supposed to express CPA3. However, according to the recent data (Nakajima et al. 2004; Kashiwakura et al. 2004), all types of MCs and basophils seem to express CPA3. Therefore, we can consider these epithelial MCs at least as a sort of MC_T. MCs exposed to conditioned media from IL-13-activated epithelial cells showed downregulation of chymase but no change in tryptase or CPA3 expression (Dougherty et al. 2010). This may relate to the reason why MC_T are preferentially found in the mucosa and are deficient in primary immunodeficiency patients (Hawrylowicz et al. 2006).

As shown in Table 5.1, MC_{TC} can respond to various non-immunological stimuli such as C5a or substance P, while MC_T do not (Hawrylowicz et al. 2006). Kajiwara et al. recently reported that MC_T, but not MC_{TC}, express functional receptor for platelet-activating factor (PAF). It was found by searching preferentially expressed genes in lung MCs (MC_T) compared to skin MCs (MC_{TC}). Interestingly, these MC phenotypes, i.e., expression of chymase and receptors for these

Table 5.1 Characteristics of two phenotypes of human mast cells

Phenotype	MC_{TC}	MC_T
Proteases	Tryptase (+++) Chymase (+) Carboxypeptidase A3 (++) Cathepsin G (+)	Tryptase (++) Chymase (–) Carboxypeptidase A3 (+?)
Distribution	Skin (++) Intestinal submucosa (+) Intestinal mucosa (–) Alveolar wall (++) Bronchial subepithelium (+) Dispersed lung mast cells (–) Tonsils (++) Nasal mucosa (–)	Skin (–) Intestinal submucosa (++) Intestinal mucosa (++) Alveolar wall (–) Bronchial subepithelium (+) Dispersed lung mast cells (++) Tonsils (++) Nasal mucosa (++)
Relation to pathology	Increased in fibrotic diseases Unchanged in allergic and parasitic diseases Unchanged in chronic immunodeficiency diseases	Increased around the site of T cell aviation Increased in allergic and parasitic diseases Decreased in chronic immunodeficiency diseases
Response to non-immunological stimuli	Substance P (+) C5a (+) PAF (–)[a]	Substance P (–) C5a (–) PAF (+)[a]

Adapted from reference Hawrylowicz et al. (2006)

[a]Kajiwara et al. (2010)

non-immunological stimuli, are retained over weeks even when these MCs are cultured in the standard MC culture condition (supplemented with SCF and IL-6) (Kashiwakura et al. 2004; Kajiwara et al. 2010). This is contrasting to the results showing that MCs lose chymase by the factor(s) produced in the IL-13-activated epithelial cells (Dougherty et al. 2010). It would be interesting to know whether MCs, which have lost chymase by the IL-13-activated epithelial cell-derived factor(s), respond to substance P or PAF.

5.3 Role of MCs in Acute Allergic Reactions

MCs express more than 10^5 high-affinity IgE receptor (FcεRI) per cell. When MCs that have been sensitized with some specific IgE antibody are challenged with the specific allergen, they are activated by cross-linking of FcεRI molecules. Thus, activated MCs evoke immediate-type reaction by releasing their granules in which histamine, neutral proteases, and heparin had been stored. Then, lipid mediators such as cysteinyl leukotriene (cys-LT) or prostaglandin D_2 (PGD_2) are synthesized on their membranes and are released into microenvironment within several minutes.

Released histamine and lipid mediators cause acute allergic symptoms such as nasal discharge, bronchospasms, and urticaria. Histamine plays an essential role in acute skin allergic reactions, whereas cys-LT plays a pivotal role in bronchoconstriction. MCs almost exclusively express PGD_2 synthase compared to all other cell types. Although the role of PGD_2 in immediate-type reaction is unclear, it serves as chemoattractant for eosinophils, basophils, and Th2 cells.

Human MCs also exclusively express tryptase, one of the neutral proteases, among all human cell types. Tryptase constitutes 10 % of the MC by protein weight (Hawrylowicz et al. 2006). Proteoglycan (human MCs use "eosinophil" major basic protein instead of proteoglycan molecules) serves as a core protein in the crystalloid structure of the MC granules by binding to heparin and neutral proteases (Nakajima et al. 2002). The MC tryptase acts as trypsin-like

enzyme and thereby causes tissue remodeling such as abnormal proliferation of airway smooth muscles (Brightling et al. 2002).

5.4 Role of MCs in Allergic Inflammation

MCs secrete a variety of cytokines and chemokines several hours after allergen-induced degranulation via transcription of these genes. The representative cytokines/chemokines which are produced by activated human MCs are Th2 cytokines such as IL-5, IL-13, and GM-CSF and CC chemokines such as CCL1/I-309, CCL2/monocyte chemoattractant protein-1, CCL3/macrophage inflammatory protein (MIP-)1α, and CCL4/MIP-1β. Activated human MCs also secrete a substantial amount of CXCL8/IL-8 (Nakajima et al. 2002; Bischoff 2007). MCs can store and release some of cytokines such as tumor necrosis factor (TNF)-α during degranulation process. Regarding IL-4 production, it seems reproducible using mouse MCs. However, only a few groups succeeded to immunohistochemically demonstrate the presence of IL-4 on human MCs (Bradding et al. 1992; Pawankar et al. 1997). In any case, at least in human, basophils are more potent producers of IL-4. Instead, IL-4 potently activates human MC function and maturation. Human MCs can produce a substantial amount of another Th2 cytokine, IL-13, in response to IgE-mediated stimuli, and the IL-13 production is markedly enhanced by preincubation with IL-4 (Bischoff 2007). However, these cytokines and chemokines are not unique to MCs and are produced by other cell types. During antigen stimulation, more Th2 cytokines would be produced by proliferating T cells. We should consider the relative role of MCs in the allergic or innate-type inflammation by understanding cytokines/chemokines produced by other immune cell types and epithelial-mesenchymal tissues. For example, epithelial-mesenchymal tissue-derived thymic stromal lymphopoietin (TSLP) and IL-33 are now recognized as most important cytokines for both innate-type and allergic inflammation occurred in allergic diseases such as asthma. These two cytokines and CC chemokines such as CCL17 and CCL23 are produced in response to external stimuli and Th2 cytokines such as IL-13 and stimulate the chemotaxis and development of Th2 cells and the function of MCs. Other than Th2 cytokines and CC chemokines, tryptase, cys-LT, and TNF-α also stimulate epithelial-mesenchymal tissue (Hawrylowicz et al. 2006; Oboki et al. 2010; Takai 2012; Ito et al. 2012) (Fig. 5.1).

Although human MCs do not normally produce cytokines in response to other cytokines such as IL-4 without FcεRI cross-linking, it should be noted that IL-33, which are released during necrosis of epithelial-mesenchymal tissue, alone stimulate MCs to release a variety of cytokines such as IL-13 (Iikura et al. 2007). Regarding other innate immune responses, mouse MCs are proven to play an essential role in protection against microbial infection via Toll-like receptor (TLR)s (Supajatura et al. 2002; Nakajima et al. 1997; Krämer et al. 2008). Human MCs can express functional TLR4 after preincubation with IFN-γ. These MCs can produce more TNF-a, CCL5, CXCL10, and CXCL11 compared to IgE dependently activated MCs (Okumura et al. 2003).

Topical use of glucocorticoid (GC) is the first line therapy for allergic diseases such as asthma and allergic rhinitis. Although GC do not block the degranulation of MCs, these drugs downregulate the gene expression of FcεRI in MCs and thereby downregulate IgE-mediated activation of MCs. More notably, glucocorticoid can inhibit gene expression of a variety of cytokines in MCs. Even in short time incubation, GC blocks the nuclear factor-κB (NF-κB)-dependent gene expression of cytokines, such as IL-13, CXCL8/IL-8, and GM-CSF. On the other hand, GC does not inhibit nuclear factor-activated T (NFAT)-dependent gene expression of cytokines, such as CCL1, CCL3, and CCL4.

Interestingly, an immunosuppressive agent, FK-506 inhibits NFAT-dependent-, but not NF-κB-dependent-, gene expression (Kato et al. 2009). If these drugs are added simultaneously into the reaction buffer for MC activation, the expression of cytokines is almost completely

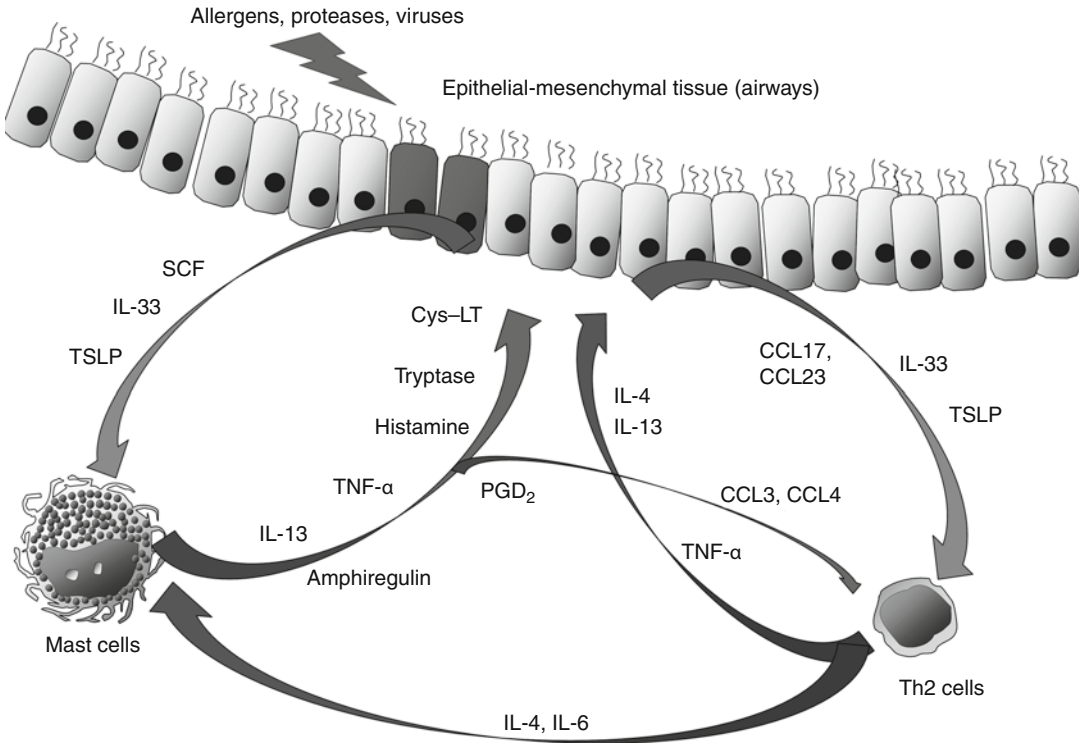

Fig. 5.1 Mutual stimulatory effect of mast cells, Th2 cells and epithelial-mesenchymal tissue on chronic allergic inflammation. These cell types are stimulating each other by releasing cytokines and mediators to form allergic inflammation in the airway. Among such cytokines, IL-13, IL-4 and IL-33 play a key role

blocked (http://www.ncbi.nlm.nih.gov/geo/, dataset number = GSE15174, submitted by Atsushi Kato). Among cytokine or growth factor genes, only IgE-mediated amphiregulin gene upregulation was not blocked by preincubation with GC and FK-506. Amphiregulin acts on airway epithelial cells to produce mucin and is upregulated in asthmatic airways (Okumura et al. 2005). It also relates to lung-tissue homeostasis, i.e., repair of the lung epithelia injured by viruses (Monticelli et al. 2011).

Conclusion

MCs trigger not only the immediate-type allergic reaction in an IgE-mediated manner but also the late-phase allergic response and chronic allergic inflammation, thereby regulating the function of other immune cells. While histamine, tryptase, and PGD_2 released in the immediate-type reaction are unique to MCs (or basophils), most cytokines and chemokines are produced by other cell types as well as MCs. It is necessary to determine the relative role of MCs in the allergic or innate-type inflammation by understanding cytokines/chemokines produced by other immune cell types and epithelial-mesenchymal tissues. The expression of these cytokines is almost completely blocked when GC and FK506 are added simultaneously into the reaction buffer for MC activation. It would be difficult to overwhelm this effect even if we could develop a new anti-MC drug.

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