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Review article

Mast cell and atopy

Reem A. El-Feky
Lecturer in Pediatrics, Ain Shams University, Cairo

INTRODUCTION

During the first 100 years after Paul Ehrlich discovered them, mast cells were believed to be a component of connective tissue that was derived from undifferentiated mesenchymal cells.[1] However, Kitamura and co-workers [2] demonstrated that mast cells (MCs) arise from multipotent hematopoietic progenitors in bone marrow. These cells took their name from the Greek word mastzellen, meaning well-fed as Paul observed the granular nature of the cells.[3]

MCs are usually perivascular. They are generally noted to be particularly abundant in tissues that are exposed to the environment.[4,5] Committed MC progenitors are rare in bone marrow suggesting they are rapidly released into the blood where they circulate and move out into the peripheral tissues. This migration is controlled in a tissue specific manner. Basal trafficking to the intestine or the lung requires expression of α4β7 integrin and the chemokine receptor CXCR2 by the MC progenitors and expression of VCAM-1 in the intestinal and pulmonary endothelium.[6] In humans, MCs have been described to reach densities of up to 500 to 4,000 per mm3 in the lungs, 7,000 to 12,000 per mm3 in skin and 20,000 per mm3 in the gastrointestinal tract.[7] These densities have been noted to increase in the skin of humans that is not covered by clothing, suggesting that regions that experience continual environmental exposure respond by either recruiting more MCs or inducing their local proliferation.[8]

Since their discovery in 1878, MCs have primarily been regarded as effector cells promoting harmful IgE mediated allergic reactions following secondary exposure to allergens.[9] However, in the last decade they were being increasingly recognized for their key role in pathogen recognition, and in initiating primary protective innate and adaptive immune responses.[9,10] To function as immune surveillance cells, MCs must be able to interact with incoming pathogens. MC activation usually occurs through at least 3 mechanisms of pathogen recognition: (i) direct binding of pathogens or their components by pathogen associated molecular pattern (PAMP) receptors located on the MC surface; (ii) binding of opsonized bacteria or their products by complement receptors or immunoglobulin receptors, or (iii) recognition of endogenous peptides produced by infected or injured host cells. One class of PAMP receptors are the Toll like receptors (TLRs).[11] Each TLR binds a specific component of different pathogens. Human MCs have been shown to express TLR-1,-2,-3,-4,-5,-6,-7 and -9 under certain conditions.[12,13]

Mast cell and initiation of allergic sensitization

In atopic patients, allergens are recognized, processed and presented by antigen presenting cells such as dendiritic cells, in association with MHC II and co-stimulatory molecules, to naïve T cells. Naïve T cells that recognize the allergen as foreign then differentiate into Th2 type T cells which produce cytokines that enhance allergen specific IgE synthesis by B cells. This primary immune response is termed allergen sensitization and has been previously thought to occur without involvement of mast cells.[14] (figure 1).

However, new evidence suggested that MCs might coordinate and drive a Th2 immune response to innocuous agents particularly when these innocuous agents are encountered in the setting of endotoxin exposure. Endotoxins are common contaminants in the environment and can act on MCs via TLRs. When an individual encounters allergen and low doses of endotoxin in the environment together, MC activation through TLR signaling may lead to MC secretion of cytokines such as TNFα into the local environment. TNFα induces the expression of E–selectin on vascular endothelial cells which induce dendiritic cell chemotaxis. Dendiritic cells then migrate to the lymph node leading to an inappropriate Th2 immune response to the innocent allergen in a "bystander phenomenon" resulting in B cell production of a specific IgE with subsequent induction of MC FcεRI to this specific IgE and so allergen sensitization.[15,16,17]

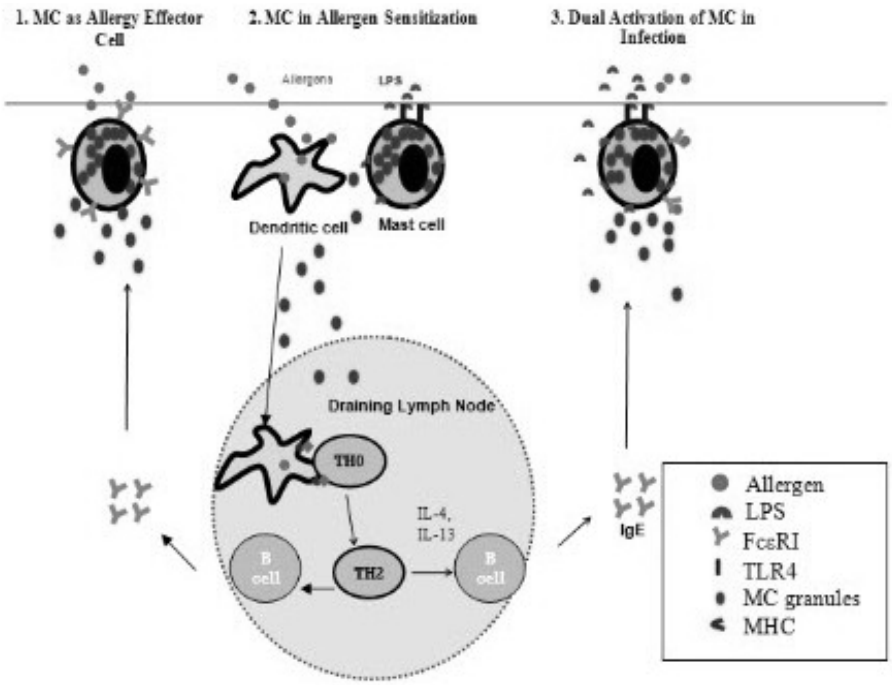
In a mouse model of asthma, intranasal administration of low dose Lipopolysaccharide (LPS) and antigen resulted in markedly enhanced eosinophil accumulation in the lung upon antigen re-challenge as compared to mice that were sensitized with antigen only or sensitized with high

dose LPS and antigen.[15,17] In addition, serum antibodies in mice treated with low dose LPS and antigen showed a Th2 pattern (high IgE and IgG1) as opposed to those from mice treated with high dose LPS and antigen (high IgG2a-Th1 pattern).[15] When this experiment was performed in MC deficient mice, eosinophilic infiltration was markedly low and was restored when MC deficient mice underwent MC repletion prior to exposure to LPS and allergen thereby indicating that MCs were important in the process of allergen sensitization.[15,17]

Once allergen sensitization has occurred, MCs expressing allergen specific IgE may amplify the allergic response by acting as antigen presenting cells to further drive allergen specific Th2 proliferation.[14]

Mast cell and early phase allergic reaction

Mast cells and basophils are the two major cell populations that express high affinity FcεRI and the number of surface FcεRI is up-regulated by increased concentrations of immunoglobulin. Aggregation of only a small fraction of mast cells' FcεR1 is sufficient to trigger mast cell activation and mediator release.[18] This FcεRI-dependent mast cell activation response results in rapid release (in minutes) of preformed cytoplasmic granule-associated mediators (such as histamine, heparin, tryptase and other proteoglycans, proteases as MC chymases) and certain cytokines (TNFα, VEGF and other ILs) together with the secretion of de novo-synthesized lipid mediators (including cysteinyl leukotrienes [LTs] and prostaglandins [PGs]).[18,19,20]



1. MCs degranulate when allergen binds to IgE on the MC surface. 2. MCs play a key role in allergen sensitization when allergen exposure occurs in the presence of bacterial byproducts. 3. Allergen and bacterial products act synergistically to increase MC granule release.

Quoted from (Hofman and Abraham, 2010)[14].

Figure 1. Mast cell roles in allergic diseases.

Mast cell and late phase allergic reaction

Late phase reaction is mainly produced by cells of the immune system. Mast cells produce, with a prolonged kinetics, many cytokines, chemokines and growth factor.[17,18,19] Among these cytokines are IL-1, IL-3, IL-4, IL-5, IL-13, TNF-a, and GM-CSF, and chemokines; including IL-8, eotaxin, regulated upon activation normal T cell expressed and secreted (RANTES), and monocyte chemotactic protein-1(MCP-1)[21]. IL-2 usually serves as an important eosinophil chemoattractant. IL-3, IL-5, and GM-CSF delay the apoptosis of eosinophils for a minimum of 12–14 days, whereas in their absence, the life-span of these cells does not exceed

48 hours.[22,23] They also cause eosinophils to express large numbers of receptors for cytokines, immunoglobulins, and complement[22]. IL-5 induces eosinophil differentiation in the bone marrow and also stimulates eosinophil precursors to synthesize granule proteins.[24] In addition to selective differentiation of eosinophils, IL-5 is responsible for their mobilization and release from bone marrow into the bloodstream.[22,25,26] IL4 up-regulates FcεR1 and allows eosinophil recruitment.[27] RANTES is a strong chemoattractant and induce histamine release from basophils. MPC recruits monocytes-macrophage lineage cells. [21]

Recent studies have identified a "Th2 cell- mast cell- eosinophil axis". Stem cell factor (SCF) produced from eosinophils allows MC proliferation and activation. In return, MCs regulate SCF release. Th2 cytokine- stimulated MCs express more inflammatory mediators that can activate eosinophils.[28,29]

Many studies tried to elicit the role of MC in allergy. Mouse models of asthma showed that MCs and MC derived TNFα contribute to both airway hyperactivity and inflammation.[30] LTB4 produced on MC activation induces airway inflammation by recruiting effector CD8 and CD4 T cells.[31] MCs also contribute to a model of Th17 cell-dependent neutrophils-associated lung inflammation in ovalbumin (OVA), OVA-specific T-cell receptor transgenic mice.[30]

In a rodent model of atopic dermatitis (AD), MC degranulation was correlated with the severity of AD.[32] In a study comparing the serum levels of soluble growth factor for MCs; SCF and its receptor KIT in AD patients versus patients with psoriasis, the level of SCF and soluble KIT were elevated only in AD patients especially those with severe disease. These studies indicated that MCs might serve as a marker of severity in AD.[33] There has been a number of reports on the association of AD with polymorphism of mast cell-related genes as polymorphism in the chain of high affinity of IgE receptor and genetic variants of MC chymase.[34,35]

Mast cell and exacerbation of the allergic reaction

Infection exacerbates allergic diseases particularly, asthma and atopic dermatitis through different mechanisms. Multiple studies detected circulating IgE antibodies to staphylococcal superantigens, including enterotoxin A (SEA), staphylococcal enterotoxin B (SEB), and toxic shock syndrome toxin-1, in almost 30- 50% of patients with atopic dermatitis (AD).[36,37] In chronic rhinosinusitis, S. aureus enterotoxin B shifts the cytokine pattern toward Th2 and induces polyclonal IgE production, which might contribute to severe inflammation via the activation of the mast cells.[38] In a recent study on 73 patients with moderate to severe AD, the investigators found a high prevalence of IgE antibodies to Malassezia furfur and Alternaria alternara.[39]

Toll-like receptors (TLRs) on MCs play an important role in allergy exacerbation. Activation of TLR signaling in addition to FcεRI signaling in the setting of infection and allergen exposure causes enhanced MC activation and worsening of established allergic disease. Peptidoglycan (PGN) from S. aureus stimulated mast cells in a TLR2-dependent manner to produce TNFα, IL-4, IL-5, IL-6, and IL-13. The intradermal injection of PGN in a mouse model induced skin vasodilatation and inflammation through the TLR2-dependent activation of MCs.[40] In bronchial asthma, dual activation of TLR4 or TLR2 on the MC surface by lipopolysaccharides (LPS) of gram negative bacteria or PGN of Gram positive bacteria, in association with FcεRI stimulation by an allergen acted synergistically to increase cytokine production by MCs. In the setting of dual TLR-FcεRI signaling, MCs produced augmented amounts of IL-6, IL-13, and TNFα.[41] IL-6 and TNFα have been shown to recruit neutrophils into the site of MC activation while IL-13 promoted a Th2 response in T cells and initiated IgE class switching, all of which served to exacerbate allergic asthma. Some viruses, such as Respiratory Syncytial Virus (RSV), a known asthma trigger, contain proteins such as HsP60 and F-protein which can activate TLR4.[42] In theory, dual activation of TLR 4 and FcεRI on MCs in the setting of simultaneous allergen exposure and RSV infection could lead to increased cytokine production and TNFα release by MCs thereby worsening asthma symptoms.[14]

MCs can also amplify the allergic response in the uninfected host through acting as antigen presenting cells in the setting of allergen re-exposure after sensitization. MCs have the ability to phagocytose antigens that bind to surface receptors and to process and display them on the MC surface in the setting of MHC I or even, perhaps, MHC II under certain conditions. MCs bearing MHC allergen complexes could then stimulate CD 8+ or CD 4+ effector T cells located in peripheral sites such as the skin or lungs where MCs are naturally found leading to expansion and proliferation of the particular allergen specific T cell line. Increased numbers of allergen specific CD8 T+ cells and CD

4 T+ cells contributed to exacerbations of allergic diseases especially asthma.[43]

Mast cells and tissue remodeling

There is a controversy whether MCs induce or prevent tissue remodeling in chronic inflammation. In a mouse model of asthma, MCs increased the numbers of mucus-producing goblet cells in the airway epithelium and increased collagen deposition.[44] In another model, mice lacking the MC chymase exhibited more substantial increase in airway reactivity to metacholine, more airway inflammation and thickening of bronchial smooth muscle than the wild mice strain.[45] This might indicate that at least one product of the mast cell might help to limit the pathology associated with allergic inflammation.[9] In AD model, MC degranulation was evident in acute stage without any increase in number, yet the chronic stage was characterized with an increase in the number of MCs especially at areas with severe lymphocytic infiltrates in the papillary dermis.[46]Theses MCs were found to produce growth factors and angiogenic factors that induce skin thickening and fibrosis.[47]

Mast cells and anaphylaxis

Although anaphylaxis is considered a systemic event, the presence and activation of mast cells in specific organs may play a critical role in the severity. Within the heart, mast cells are located between myocardial fibers, around blood vessels and in the arterial intima. Activation of these critically positioned mast cells may directly contribute to cardiopulmonary failure. Cardiac mast cells *in vitro* release many of the classic mast cell mediators of anaphylaxis including PAF.[48,49] PAF is thought to be a critical factor in the development of anaphylactic shock through its ability to induce hypotension and cardiac dysfunction .[50] PAF-induced anaphylactic shock in mice appears directly dependent on phosphoinositide-3 kinase (PI3K) and endothelial nitric oxide synthase (eNOS)-derived nitric oxide (NO) which functions as a potent vasodilator.[51]

The overall number of mast cells may also be relevant in anaphylaxis. It is known that individuals with recurrent anaphylaxis tend to have more dermal mast cells than those without anaphylaxis. Mastocytosis, a disease characterized by the pathologic accumulation of mast cells in tissues, is often associated with spontaneous episodes of hypotension and has served as a unique disease model. Activating mutations in the tyrosine kinase Kit, such as D816V, are strongly associated with mastocytosis.[52] Identification of this mutation suggests that additional yet unidentified genetic polymorphisms or mutations may potentially account for an increase in mast cell numbers, which may predispose individuals to recurrent anaphylaxis.[53]

Novel directed treatment to the mast cell

Mast cell therapeutics may be broadly classified into those directed at cell membrane targets (membrane receptors), to intracellular targets (cell signaling, gene expression) or to extracellular targets (released mediators); Table 1. Often treatment selection is tailored to include one or more of these agents depending on the individual patient and the specific allergic disease. Some are in clinical use as mast cell stabilizers, corticosteroids, omalizumab and antihistamines. [53]

As previously shown, MCs rely critically on TLR binding for activation in both allergic sensitization and exacerbations of allergic disease as well as in initiation of innate and adaptive immune responses. One possible future treatment for allergic diseases may be antibodies that act as decoys and bind LPS and PGN thereby preventing them from binding to TLR4 and TLR2 on the MC surface. Although this may effectively prevent the induction of Th2 responses to allergens encountered in the presence of LPS or PGN, this strategy is unlikely to affect innate and adaptive immune responses to pathogens because pathogens are recognized via multiple mechanisms and receptors on MCs and other cell types.[54]

Another treatment strategy for allergic diseases is inhibition of the mediators released by MCs. One novel treatment incorporating this concept is the ongoing clinical investigations of TNFα blockade to treat severe refractory asthma. Several clinical trials have investigated the efficacy of different TNFα inhibitors in severe and moderate asthma with varying results. In an initial open label investigation of the TNFα blocker, etanercept, for treatment of severe asthma, improvement in metacholine airway hyperresponsiveness as well as improvement in lung functions and asthma symptoms was found.[54,55] A randomized, double blind placebo controlled trial of etanercept in patients with severe asthma showed a small but significant improvement in asthma control[55]. However another clinical trial of a human monoclonal antibody against TNFα, golimumab, showed no clinical benefit.[56]

There are many clinical trials in progress assessing the safety and efficacy of different IL4 and IL13 inhibitors in the treatment of asthma and allergic rhinitis. These include studies of a

monoclonal antibody against IL13, monoclonal antibody inhibitors of the IL4 and IL13 receptors, and a recombinant human IL4 variant which inhibits IL4 and IL13 receptors.[57] One preclinical study of an anti- IL13 antibody in allergic macaques showed decreases in allergic inflammation upon allergen exposure but had no effect on lung function.[58] The human clinical trials of these agents for therapy of asthma and allergic rhinitis are ongoing.[14]

As our understanding of mast cell signaling has evolved, potential new intracellular targets have been identified. A Syk tyrosine kinase inhibitor, R112, which disrupts mast cell IgE–FcεRI signaling has displayed promising results in some clinical trials and may represent a new class of allergy therapeutics.[59,60]

CD63 is a tetraspanin present on the surface of mast cells that interacts with b1 integrins and modulates adhesion. Anti-CD63 monoclonal antibodies have shown the ability to decrease FcεRI-induced degranulation via impairment of the Gab2–PI3K pathway, suggesting a potential therapeutic application.[61]

Table 1. Mast cell directed treatment.

Mast cell Target	Therapeutic class	Mechanism of action	Stage of development
Cell membrane	Chromones	Potential disruption of calcium influx, chloride ion transport and exocyctic processes	Clinical use
	B_2 antagonists	Increase cytosolic cAMP levels through binding of B_2receptors	Clinical use
	Omalizumab	Monoclonal antibody to free IgE resulting in decreased Fc€RI membrane expression	Clinical use
	CCR3 antagonists	Block chemotaxis and degranulation	Clinical trials
	Ca^{2+} & K^+ channel antagonists	Disruption of ion influx with attenuation of degranulation and chemotaxis	Pre-clinical
	Anti- CD63 antibody	Monoclonal antibody to CD63 which interferes with cellular adhesion to β1 integrins and blocks Fc€RI-induced degranulation via impairment of Gab2-PI3K pathway	Pre-clinical
Intracellular	Glucocorticoids	Regulate transcription of numerous inflammatory genes	Clinical use
	Syk Kinase inhibitors	Block IgE- Fc€RI mediated downstream signaling (phosphorylation)	Clinical trials
	MAPK inhibitors	Block the phosphorylation of multiple intracellular proteins (including transcription factors) that are involved in cellular proliferation, differentiation, survival and chronic inflammation	Clinical trials
	PDE4 inhibitors	Blocks hydrolysis of cAMP to 5' AMP	Clinical trials
Extracellular	5-LO inhibitor	Blocks the conversion of arachidonic acid to LTA_4 which subsequently prevents CysLT formation	Clinical use
	Tryptase inhibitors	Block the protease activity of tryptase	Pre-clinical
	CysLTR 1 antagonists	Block the binding to and effects of CysLT on target organs	Clinical use
	$H_{1\text{-}4}$ receptor antagonists	Blocks the binding to and effect of histamine on target cells	H_1, H_2;clinical use, H_3; clinical trials, H_4; pre-clinical
	PAR-2 antagonists	Block PAR-2 receptor signaling following activation by proteases (e.g. Tryptase)	Pre-clinical
	DP and CRTH-2 receptor antagonists	Block the binding to and effects of PGD_2 on target cells	Pre-clinical

MAPK, mitogen-activated protein kinases, PI3K; phosphoinositoide-3 kinase, PDE; phosphodiestrase, 5-LO; 5-lipooxygenase, PAR-2; proteinase activated receptor 2, CRTH-2; chemoattractant receptor homologue on T-helper 2 cells, DP, D prostanoid

Quoted from (Brown et al, 2008)[53].

CONCLUSION

MCs are one of the frontier cells in allergic diseases. They are involved in all steps of allergy. New treatment targeting these cells might help allergic patients in conquering their allergy.

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