Mast Cells and Allergic Rhinitis

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ABSTRACT

That mast cells play a role in acute allergic inflammation by releasing various inflammatory mediators, including histamine, leukotrienes (LT), such as LTC₄ and LTD₄, and prostaglandins (PG), such as PGD₂, is well known. Additionally, mast cells contribute to the development of allergic inflammation also through the release of multifunctional cytokines. The incidence of intraepithelial mast cells (IEMC) is found to be greater in nasal mucosa exposed to an allergen, and the cells are thought to play an important role in producing the immediate allergic reaction. Lamina propria mast cells (LPMC) are known to be the dominant source of TH₂ cytokine and are responsible for development of the late phases of an allergic reaction. They may upregulate the expression of adhesion molecules on the endothelial cells and induce basophil and eosinophil recruitment. Based on these considerations, it can be proposed that mast cell is a initiating cell of allergic reaction in target organ and IEMC and LPMC have capacity to make major contribution to both immediate or late phase reaction of allergic rhinitis.

KEY WORDS: Allergic rhinitis · Mast cells · Chemical mediators · Cytokines · Adhesion molecules.

INTRODUCTION

In an atopic individual, specific IgE is bound as Fc fragments to Fc receptors on the surface of mast cells. The binding of antigen to the cell surface-bound IgE initiates the process of mast cell activation and the secretion of chemical mediators. These mediators are responsible for most of the early events that characterize allergic reactions in the various organs. It has recently been established that mast cells contribute to the chronic inflammatory events of allergic disease by secreting cytokines.

The nose is a potential site for allergic inflammation. Allergic rhinitis (AR) is an IgE-mediated atopic disease characterized by symptoms of sneezing, rhinorrhea and nasal obstruction, an increased level of serum specific IgE and nasal eosinophilia. Previous studies have shown that there is an increase in the number of mast cells in the epithelial compartment of the nasal mucosa of patients with allergic rhinitis and that the increase correlates with the severity of the disease. However, the responsibility for the initiation and perpetuation of allergic inflammation does not lie with any single cellular element and occurs as result of a cascade of events involving a variety of cells.
may also be cultured from rodent bone marrow in the presence of IL-3 and IL-4. Such cultured mast cells resemble mucosal mast cells based on granule content of chondroitin sulfate and low levels of histamine. Moreover, the presence of mucosal mast cells in vivo appears to depend on T cells, the presumed source of IL-3 and IL-4 since they are absent in athymic mice. Bone marrow-derived mucosal mast cells can be changed to a connective tissue mast cell phenotype by co-culture with fibroblasts. Recent repopulation experiments in mast cell-deficient mice further suggest that the mucosal and connective tissue phenotypes are not fixed and that bi-directional changes may be possible in suitable microenvironments. However, it is likely that in normal development there is a maturational sequence from bone marrow precursor to mucosal type mast cell to connective tissue mast cell. The key point is that the precise nature of the mast cell and the mediators it can produce vary with its anatomic location.

In humans, the factors that regulate mast cell growth and development are less well defined. Human T cell-independent connective tissue mast cells and T cell-dependent mucosal mast cells appear to share similar patterns. In addition, mast cells phenotypes are not as clearly differentiated in humans as they are in mice. The major differences between the types of human mast cells are in the composition of the serine proteases found in the granules (trypsin-like or chymotrypsin-like in substrate specificity) and in the ultrastructural morphology of the granules. Nevertheless, it does appear that in humans as well as in mice the pattern of mediators produced by mast cells varies with anatomic location.

The event that initiates immediate hypersensitivity is the binding of antigen to IgE on the mast cell or basophil surface. Mast cells are activated by the cross-linking of FcεRI molecules, which is thought to occur by the binding of multivalent antigens to the attached IgE molecules. Experimentally, antigen binding can be mimicked by polyvalent anti-IgE or by antigens to the attached IgE molecules. Experiments performed with monomeric protease of around 130 kDa which is stored in the cell membranes and 3) the mast cells initiate transcription, translation, and secretion of cytokines. Basophils also undergo degranulation and synthesize lipid mediators it is not yet known whether basophils synthesize cytokines.

The mechanisms of granule exocytosis are partly understood, largely from studies of rat mast cell and basophil leukemia cell lines. The cross-linking of FcεRI results in the activation of a G protein that, in turn, activates membrane-bound phospholipase C to catalyze the breakdown of phosphatidyl inositol bisphosphate into inositol triphosphate (IP3) and diacylglycerol (DAG). IP3 causes the elevation of cytoplasmic calcium, and DAG activates protein kinase C. The effect of the elevated calcium is less clear, but the binding of calcium to calmodulin leads to the activation of myosin light chain kinase, which phosphorylates myosin light chain at distinct amino acid residues from protein kinase C.

Mast cells may be activated by mechanisms other than the cross-linking of FcεRI. For example, mast cells or basophils respond to interleukin-8 (IL-8) and other mononuclear phagocyte-derived cytokines produced as part of natural immunity, as well as in undefined T cell-derived cytokines produced as part of cell-mediated immunity, and to complement-derived anaphylatoxins, such as C5a, produced during humoral immune responses. Mast cells may also be recruited into inflammatory reactions and activated by neutrophil granule contents or by neurotransmitters such as norepinephrine and substance P. These latter agents are potentially important as links between the nervous system and the immune system.

**Preformed mediators from mast cells**

The mediator most readily associated with the mast cell is the simple dopamine, histamine. It is synthesized in the mast cell granule by the decarboxylation of histidine, mainly by histidine decarboxylase, dopa decarboxylase. Histamine is stored in the acid proteases. Once in the extracellular environment, histamine exerts potent effects, which include contraction of the bronchial smooth muscle, increased mucus production, vasodilatation and contraction of post-capillary venular endothelial cells, which increases vasopermeability.

The backbone of the crystalline mast cell granule is proteoglycan which, in human mast cells is mainly heparin, which constitutes some 75% of the proteoglycan, with a mixture of chondroitin sulphates. The mast cell protease, present in all mast cells regardless of sub-type (Table 1), is tryptase. Tryptase is a tetrameric serine protease of around 130 kDa which is stored in a fully active form in the granule. It is a mitogen for fibroblasts and in a human epithelial cell line may induce its proliferation, stimulate it to release the granulocyte chemoattractant IL-8 and up-regulate its expression of ICAM-1.

Chymase, which is present only in the MC\textsubscript{TC} subset, is a monomeric protease of 30 kDa which is stored in the same secretory granules as tryptase. Like tryptase, chymase is stored within the granule in its fully active form, so that it needs

<table>
<thead>
<tr>
<th>Table 1. Distribution of neutral proteases in mast cells sub-types</th>
<th>MC\textsubscript{C}</th>
<th>MC\textsubscript{TC}</th>
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<tbody>
<tr>
<td>Tryptase</td>
<td>Tryptase</td>
<td>Tryptase</td>
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<tr>
<td>Tryptase</td>
<td>Chymase</td>
<td>Carboxypeptidase</td>
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<tr>
<td>Carboxypeptidase</td>
<td>Gathepsin G</td>
<td>Carboxypeptidase</td>
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no further processing before release. The enzymatic activities of chymase (Table 2) include the degradation of neurotensin,\(^{10}\) substance P or VIP\(^{11}\) and the cleavage of angiotensin I to an-
trictor effect, PGD\(_2\) is chemokinetic for human neutrophils,
ndable contraction of smooth muscles, contraction of arter-
nal smooth muscles, enhanced permeability of post-capillary
ules and enhanced mucus secretion, most of which, in the
th of IL-4 and the stimulation of secretion from cultured subm-
ucosal gland cells.

**Newly generated mediators from mast cells**

The immunological activation of mast cells induces the li-
eration of arachidonic acid within the membrane. This pho-
spholipid is then rapidly oxidized down one of two pathways: the cyclo-oxygenase pathway, to form PGD\(_2\) or the lipoxigenase pathway, to form LTC\(_4\). These are the only two eicosanoids made by the human mast cell. PGD\(_2\) is a potent bronchocon-
trictor agent which is rapidly degraded to another bronchoco-
strictor agent, 9\-glutamine transpeptidase to yield LTD\(_4\), in addition to its broncho-
strictor effect, PGD\(_2\) is chemokinetic for human neutrophils, augments LTBD\(_2\)-induced neutrophilia in the epithelium and is a
powerful inhibitor of platelet aggregation.

Leukotriene C\(_4\) is produced by a variety of inflammatory
cells including mast cells and eosinophils. In the extracellular
environment, glutamine is removed from the glutathione resi-
due of LTC\(_4\) by \(-\)glutamine transpeptidase to yield LTD\(_4\), from which glycine is then removed by LTD dipeptidase to yield LTE\(_4\). The physiological effects of the leukotrienes include
potent contraction of smooth muscles, contraction of arter-
tial smooth muscles, enhanced permeability of post-capillary
ules and enhanced mucus secretion, most of which, in the
ways, are mediated by LTD\(_4\).\(^{12}\)

**Biological properties of human mast cell cytokines**

It is now established that mast cells are a source of several
multifunctional cytokines. Each of the cytokines so far ident-
ified as human mast cell products are likely to be involved in
the pathogenesis of allergic mucosal inflammation. IL-4 act-
vates B cells for Ig secretion through up-regulation of cell-
surface MHC class II antigen,\(^{19}\) CD23 and CD40\(^{40}\) and plays
pivotal role in the isotype switching of B cells to IgE syn-
thesis. IL-4 specifically increases expression of vascular cell
adhesion molecule-1 (VCAM-1) involved in the very late
agent (VLA)\(-4\)-dependent recruitment of T cells\(^{15}\) and eos-
phinophils,\(^{16}\) and induces the expression of low-affinity IgE
receptors (F\(_c\)RII, CD23) on monocytes. In addition, IL-4
induces fibroblast chemotaxis and collagen secretion.\(^{17}\) Possi-
ably the most important effect of IL-4 comes from its ability
to induce the development of the TH2 phenotype of T cells,
an action that produces IL-4, IL-5 and IL-6, as reviewed by
Romagnani.\(^{18}\) The presence of IL-4 at the onset of an immu-
nological response may therefore dictate whether a cell-med-
iated or humoral response develops.

The effects of IL-5 in humans are almost exclusively limited
to eosinophils. IL-5 is a growth and differentiation factor\(^{19}\)
and activator for eosinophils\(^{20}\) and in addition prevents their programmed cell death to prolong survival.\(^{11}\) IL-5 promotes eosinophil adhesion to vascular endothelium through a CD11/CD18-dependent mechanism,\(^{22}\) and primes eosinophils for chemotaxis in response to other mediators as well as being
directly chemotactic itself.\(^{23}\) As a consequence, IL-5 is cons-
idered to be a pivotal cytokine in allergen- and parasite-med-
iated eosinophilic responses.

IL-6 activates a wide range of cellular processes, including
those of T-cells, and the stimulation of Ig production in B
cells, and thus it enhances IL-4-dependent IgE synthesis. IL-6
is also the most important cytokine responsible for the pro-
duction of acute-phase proteins by hepatocytes during inflam-
matory responses. IL-8 belongs to the intercine family of
cytokines and is secreted by a wide variety of cells, including
T cells, macrophage/monocytes, endothelium and epithelial
cells.\(^{24}\) It is a potent chemoattractant for neutrophils and is
also chemotactic for eosinophils after priming with IL-3, IL-5
or GM-CSF.\(^{25}\)

TNF-\(\alpha\) (cachectin) is another cytokine implicated in the
pathogenesis of asthma. When administered by inhalation or
intravenously in animals, TNF-\(\alpha\) increases airway responsi-
veness.\(^{26}\) It is a chemoattractant for neutrophils and monocytes,
increases microvascular permeability, and enhances both the
release of mast cell mediators\(^{27}\) and the cytotoxicity eosinoph-
ils.\(^{28}\) In addition, it has the capacity to up-regulate the leuk-
ocyte endothelial cell adhesion molecules (CAM) E-selectin,
VCAM-1 and ICAM-1 involved in the recruitment of neut-
rophils, eosinophils, monocytes and T cells into inflammatory
zones. TNF-\(\alpha\) also stimulates fibroblast proliferation and the
secretion of matrix proteins, collagenase and cytokines, in-
cluding IL-6.\(^{29}\)
Heterogeneity of mast cells in allergic rhinitis

Since Enerback’s reports on the heterogeneity of rat intestinal and peritoneal mast cells, which classify them into mucosal mast cells and connective tissue mast cells, further studies have showed the heterogeneity of the cells. Human mast cells are classified into at least two phenotypically distinct subpopulations based on the basics of the type of neutral protease they contain: MC1 (those mast cells that contain only tryptase) and MC2 (those mast cells that contain both tryptase and chymase). MC1 are found predominantly located at mucosal surfaces, increase in number in allergic disease and are reduced in number in acquired and chronic immunodeficiency syndromes. In contrast, MC2 are found predominantly in submucosal and connective tissues, and are not increased in number in areas of heavy lymphatic infiltration. Furthermore, the tissue-specific heterogeneity of mast cells, their heterogeneity in response to various antagonists and their heterogeneity in cytokine expression are well documented.

Although Kitamura has demonstrated tissue-specific heterogeneity in mice and switching from one subtype to another, there is no such clear evidence in human beings. Recently Barddding et al. reported heterogeneity in mast cells based on cytokine expression. Pawankar compared the expression of cytokines in nasal epithelial (IEMC) and lamina propria mast cells (LPMC), and also found heterogeneity in the extent of cytokine expression between IEMC and LPMC. She also observed that the expression of FcRI was differentiated in that the nasal mast cells of AR patients expressed increased levels of FcRI as compared to the nasal mast cells of chronic rhinitis (CR) patients and that the expression of FcRI in mast cells was upregulated by IL-4. These findings suggest that, even within the same tissue, local microenvironmental factors play a crucial role in modulating the immunophenotypic characteristics of mast cells.

Chemical mediators in allergic rhinitis

The reagent on an anaphylactic mechanism refers to the events that follow the combination of antigen with IgE molecules specific for it on the surface of mast cells. This involves the release of various mediators, like histamine, leukotriene, chemotactic factors and platelet activating factors. In atopic patients, nasal insufflation with an allergen to which they are sensitive induces immediate itching, sneezing, and rhinorrhea, with nasal blockade developing over 30 to 40 minutes after the challenge and persisting for up to two hours depending on the strength of the immunological challenge. During this immediate nasal response, the lavage of the nasal cavity demonstrated increased local concentration of histamine, kinins, prostaglandins D2, LTs (C4, D4 and E4) and tryptase. The findings of increased levels of both PGD2 and tryptase in the lavage suggests a mast cell origin. And Gomez et al. has observed these results also by nasal biopsy, after inducing mast cell granulation in the nose by antigen challenge and forcing the elevation of the mediator after the challenge in the nasal tissue.

Allergen nasal challenge in patients, especially pediatric patients, is also reported to be associated with late nasal reaction. There is a less constant finding in the nose than in the lower airways after an allergen challenge. The level of histamine, Kinins, and LTC4 has been found to recover and elevate during this late response. But there is no evidence of elevation of PGD2. Leukotrienes are derived from the metabolic oxidation of arachidonic acid by the lipogenase pathway in which the unstable 5-hydroperoxyeicosatetraenoic acid (HPETE) is converted initially to LTA4, which depending on the cell concerned, either metabolites to LTC4, LTD4 or LTE4. The latter process occurs in various granulocytes and it is possible that at least two cell types are required for the full expression of leukotriene synthesis. Histamine, and these peptide leukotrienes, which enhance vascular permeability, lead to fluid extravasation and tissue edema.

Cytokines from mast cells in the nasal mucosa of allergic rhinitis

In both AR and CR patients, cells expressing IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-13, GM-CSF, IFN-γ and TNF-α can be detected in the nasal mucosa. When the expressions of the cytokines are compared in the nasal mucosa between AR and CR, up-regulation of the expression of IL-4 gene clusters is found in AR patient. These include IL-4, IL-5, IL-6, IL-13 and GM-CSF. By contrast, an increased number of cells expressing IL-8, IFN-γ and TNF-α are noted in the nasal mucosa of CR patients.

A variety of inflammatory cells such as mast cells, eosinophils, T lymphocytes and macrophages as well as resident epithelial cells contribute as sources of these cytokines (Table 3). However, mast cells and T lymphocytes constitute the predominant source of Th2-type cytokines, excluding IL-5, which is expressed by lymphocytes, mast cells and eosinophils. Bradding et al. report that in their study mast cells accounted for >90% of IL-4- and IL-6-expressing cells and 50% of IL-5-expressing cells in In contrast, Ying et al. report that CD4 T lymphocytes were the predominant source of IL-4 in AR, counting for >70% of IL-4-expressing cells. Altho-ugh it is well agreed that mast cells are an important source of IL-4, IL-5 and IL-6, this discrepancy in the relative contribution of mast cells as cytokine-expressing cells may be the consequence of the different experimental techniques used. Whatever the case, the numerical predominance of cytokine-expressing cells cannot be equated to the amount of cytokine produced, and further
Expression of very late antigens in nasal mast cells

Several types of cell surface molecules are involved in the recruitment of inflammatory cells into the specific sites of inflammation. Lymphocytes and mast cells in the tissues are surrounded by other cells like fibroblasts and mucosal cells as well as by extracellular matrix protein (e.g. collagen, fibronectin and laminin). Therefore, it may be thought that the interaction of these inflammatory cells with fibroblasts and extracellular matrix is important in the perpetuation of chronic inflammation. It has been demonstrated that β1 integrins, such as very late antigen-4 (VLA-4) and very late antigen-5 (VLA-5), and the vitronectin receptor integrins of cytokine expression in mast cells play a role in cell survival. Pawankar has detected the expression of VLA-4 and VLA-5 in the nasal mast cells of AR patients. Furthermore, they also found up-regulation of the expression of VLA-4 and VLA-5 in nasal mast cells of these patients.

VCAM-1 and intercellular adhesion molecule-1 are counterreceptors of ligands for β1 and β2 integrins, respectively. Studies have shown increased expressions of ICAM-1 and VCAM-1 in the nasal mucosa of AR. A striking feature of the inflammation is the selective accumulation of activated eosinophils and basophils, without increased numbers of neutrophils. Lee et al. have demonstrated that ICAM-1 expresses in the nasal mucosa of AR and that the expression was not up-regulated after stimulation with antigen in contrast VCAM-1 in the nasal mucosa may result in the accumulation of activated eosinophils and basophils without increasing the number of neutrophils. It is known that IL-4 and IL-13 can up-regulate VCAM-1 expression in endothelial cells; thus mast cells and lymphocytes may indirectly contribute to the recruitment of eosinophils and basophils through the IL-4- and IL-13-induced up-regulation of VCAM-1 expression in the nasal mucosa.

FcεRI-expressing cells in the nasal mucosa of allergic rhinitis

The cross-linking of allergen-specific IgE bound to the high-affinity IgE receptors (FcεRI) on the surface of mast cells with multivalent allergens results in the release of inflammatory mediators, which produces clinical symptoms. The expression of FcεRI in mast cells is therefore important for the development of allergic diseases. However, the precise relation

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**Table 3. Cytokine profile in the nasal mucosa**

<table>
<thead>
<tr>
<th>Type of cell</th>
<th>Allergic rhinitis</th>
<th>Chronic rhinitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial cells</td>
<td>IL-1, IL-6, IL-8, IL-10, GM-CSF</td>
<td>TNF-α, IL-1, IL-8</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10</td>
<td>IL-1, IL-2, IL-3, IL-5, IL-7, IL-8, IL-10, GM-CSF, TNF-α</td>
</tr>
<tr>
<td>Mast cells</td>
<td>IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-13, GM-CSF, IFN-γ</td>
<td>IL-8, TNF-α</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>IL-5, IL-6, GM-CSF</td>
<td></td>
</tr>
<tr>
<td>Macrophages</td>
<td>IL-1β</td>
<td>IL-1β</td>
</tr>
</tbody>
</table>

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**Fig. 1.** Possible roles of nasal mast cells in early-phase and late-phase allergic reactions.
between the Fc ε RI and atopy is unclear. It has been reported that eosinophils and monocytes also express Fcε RI. Mor-phologically, Fcε RI+ cells in the nasal mucosa of AR patients are either mast cells or basophils. However, basophils co-constitute <6% of the total number of Fcε RI+ cells. Occasionally a few Fcε RI+ cells with monocyte-like morphologic features are detected. Neither eosinophils nor macrophages demonstrate in the nasal mucosa of AR patients. In a comparison of the number of Fcε RI+ cells in the nasal mucosa of AR and CR patients, an increased number of Fcε RI+ cells are demonstrated in the nasal mucosa of AR patients.

Role of nasal mast cells in allergic rhinitis

After the cross-linking of allergen-specific IgE on the surface of mast cells with multivalent antigen, a series of the reactions occurs (Fig. 1). First, several morphologic changes, including swelling of the cytoplasmic granules, widening of the fenestra on the cell surface, and subsequent solubilization of its granule contents, occur in the mast cells. Histamine, tryptase, PGD2, and LTC4 are among the mast-cell products that can be elaborated from the cells immediately after exposure to allergens. Histamine induces vasodilatation, increased vascular permeability, and increased glandular secretion in the ipsilateral and contralateral sides through neural reflexes. Sneezing results from the action of histamine on H1 receptors present on the sensory nerve endings of the trigeminal nerve. Of particular importance is the action of histamine on the subepithelial blood vessels, which causes vasodilatation, hypervenemia, and mucosal edema. Prostaglandins such as PGD2 also cause edema by vasodilatation and increased vascular permeability. The precise role of tryptase is not yet known. The physiologic effects of newly synthesized leukotrienes including LTC4, LTD4, and LTE4 are mediated by increased vascular permeability, vasodilatation, and induction of mucus secretion. It is well known that the number of IEMC (mucosal mast cells) increases in the nasal mucosa on exposure to allergens and that these cells play a crucial role in allergic inflammation through the allergen- and IgE-dependent release of these inflammatory mediators. And LPMC are known to be the predominant source of Th2-type cytokines in AR. It is therefore proposed that both IEMC and LPMC play important but diver-ses roles in perpetuating allergic inflammation.

In short, it can be thought that IEMC contribute to the development of the immediate or acute phases of allergic reaction through the release of inflammatory mediators including tryptase, histamine, PGD2, and LTs, whereas LPMC are responsible for the development of the late phase of allergic reaction by up-regulating the expression of adhesion molecules including VCAM-1 and ICAM-1 (IL-4, IL-13, and TNF-α) on endothelial cells and by contributing to basophil and eosinophil recruitment (IL-4, IL-13, and TNF-α). LPMC may also be important in promoting chronic allergic inflammation by regulating the growth, differentiation, and IgE isotype switching of B cells (IL-4, IL-6, and IL-13) by maintaining the levels of VCAM-1 and ICAM-1 expressions on endothelial cells (IL-4, IL-13, and TNF-α) and by promoting eosinophil development and survival (IL-3 and IL-5). In view of the substan-tial number of B cells present in the nasal mucosa and based on the evidence that mast cells in AR patients induce IgE synthesis in B cells, it is speculated that mast cells promote chronic aller-gic inflammation by amplifying and maintaining IgE synthesis locally in the target organ.

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