

Exploring the Role of Mast Cells in Eosinophilic Esophagitis

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KEYWORDS

• Mast cells • Eosinophils • Esophagitis • Mediators

For most of the last 125 years, since its identification, the mast cell has been narrowly viewed in the context of immediate-type hypersensitivity, as seen in allergic reactions and parasite infections. Over the last decade, it has become increasingly clear that mast cells are involved in a wide variety of important biologic processes, including innate immunity and host defense, adaptive immunity, nonimmunologic inflammation, tissue remodeling, and homeostasis. Moreover, several lines of evidence suggest that, under certain circumstances, mast cells act to limit inflammation and tissue damage.¹ Thus, traditional dogma about the proinflammatory role of mast cells must now be reconsidered to take into account the versatility and complexity of the cell's biologic potential.²

This article considers the role of mast cells in eosinophilic esophagitis (EoE). The biologic diversity of the cell is discussed and the evidence implicating mast cells in this condition is reviewed. The evidence to date is still indirect and inconclusive, but several mechanisms by which mast cells could potentially contribute to the pathogenesis of EoE are explored.

THE MAST CELL

Mast cells are found in virtually all vascularized tissues and are particularly abundant at host–environment interfaces, such as the skin or mucosal surfaces like the gastrointestinal tract. They are derived from hematopoietic progenitor cells in the bone marrow but their maturation and differentiation occur in tissues under the influence of several growth factors, such as interleukin (IL)-3, -4, -6, -9, -10, nerve growth factor, and prostaglandin E₂ (in the gastrointestinal tract). However, a critical cytokine in the growth, differentiation, survival, and function of mast cells is stem cell factor, derived from stromal cells and other sources.³

Mast cells do not represent a homogenous population of cells but rather, have morphologic, biochemical, and functional differences based on the factors seen in the microenvironment. Human mast cells are classified into two types based on their

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protease content: tryptase-containing mast cells (MC_T), and mast cells with tryptase and chymase within the cytoplasmic granules (MC_{TC}).⁴ Human MC_T are located predominantly in mucosal tissues, such as the intestine and respiratory tract, whereas human MC_{TC} are mainly found in connective tissues such as the skin but are also in the submucosa and muscularis propria of the intestinal tract. Mast cells are a significant component of the gastrointestinal tract, making up as much as 1% of cells in the submucosa and 2% to 3% of the cells in the lamina propria.⁵

Mast cells are normally found in the mucosa and submucosa of the esophagus, but rarely in the muscularis.⁶ The expansion of mast cells into the muscularis has been reported in esophageal leiomyomatosis, in conjunction with diffuse eosinophilic infiltration.⁷ But our understanding of the numbers and distribution of mast cells in EoE has been limited by several factors. The esophagus has long been thought to be little more than a conduit for food, with little interest from an immunologic perspective, until recently. As a result, we still have only a rudimentary understanding of the immunology of this portion of the gastrointestinal tract. Most of what we know comes from biopsies obtained at the time of endoscopy, which are typically superficial and therefore do not give us a complete picture. With regard to the mast cells in the human esophagus, the subsets of cell types have not been described in detail either, but the assumption is that, because the esophagus is composed of squamous epithelium, MC_{TC} type mast cells would be predominant.

Mast cell activation with the release of mediators can occur through several mechanisms (**Box 1**). The most extensively studied is antigen cross linking of IgE antibodies on the surface of the mast cell, leading to degranulation and mediator release. Although this mechanism may be relevant in some cases of EoE, it is probably a minority. But many alternative pathways can induce mast cell mediators independent of IgE. These include stem cell factor, complement fragments (C3a and C5a), neuropeptides, adenosine, and cell wall components of bacteria (see **Box 1**). Particularly relevant to EoE is the ability of eosinophil-derived proteins to induce mast cell degranulation. Other mechanisms that can induce mast cell mediator release in the gastrointestinal tract include acid reflux⁸ and bile acids.⁹ Thus, several classic immunologic and alternative mechanisms may be involved in the activation of esophageal mast cells during inflammation.

At one time, it was thought that mast cell activation/mediator production was synonymous with degranulation. However, it is now clear that the production of mediators is specific to the eliciting stimulus and may be independent of the process of degranulation. A now well-studied example is the interaction of bacterial lipopolysaccharide and other components of bacteria with Toll-like receptors expressed on the mast cell.¹⁰ These interactions result in cytokine production (eg, tumor necrosis factor- α [TNF- α] and IL-6) in the absence of degranulation. This dissociation of mast cell mediator release and degranulation makes it difficult to assess mast cell participation in any condition solely on a histologic evaluation of mast cell degranulation. Equally important is the evolving concept that without knowledge of the activating stimulus, the finding of mast cell degranulation alone does not provide insight into the specific mediators being produced.

Mast cells contain, and can synthesize, various biologically potent mediators, as depicted in **Fig. 1**. Within the cytoplasmic granules of the mast cell are a panel of pre-formed mediators, including histamine, neutral proteases, TNF- α , and others.¹¹ Mast cells can also produce newly synthesized mediators, such as leukotrienes, platelet-activating factor, and a host of cytokines and chemokines (see **Fig. 1**). Cytokines such as IL-5 and IL-13 are particularly important because they have been implicated in the etiopathogenesis of EoE.¹²

Box 1**Relevant potential pathways involved in the activation and release of mediators from mast cells in eosinophilic esophagitis***Antibody receptors*

IgE

IgG₁

Superantigens

Cytokines/mediators

Stem cell factor

Tryptase

IL-1, IL-12

Adenosine

Prostaglandin E₂

Tumor necrosis factor

Granule-associated products of eosinophils

Major basic protein

Eosinophil cationic protein

Fragments of complement activation

C3a, C5a

C3b, C4b

Endogenous peptides

Neuropeptides: substance P, calcitonin gene-related peptide, neurotensin, vasoactive intestinal polypeptide

Nerve growth factor

Endothelin-1

Antimicrobial peptides (source: neutrophils)

Bacterial products

Lipopolysaccharide

Peptidoglycan

CpG-DNA

This list of mast cell activating agents is incomplete. The particular agents involved and their precise contribution in EoE is unknown. The response of mast cells to each agent may differ, depending on the species (rodent versus human) and mast cell population (mucosal versus connective tissue) examined. See Ref. ²⁶ for a more comprehensive review of this topic.

The production of these mediators by mast cells can have several direct or indirect effects (ie, they may interact directly with eosinophils or resident cells to elicit a response, or indirectly by recruiting additional immune cells into the esophagus).

EVIDENCE OF MAST CELL PARTICIPATION IN EOSINOPHILIC ESOPHAGITIS

Much of the data implicating mast cells in the pathogenesis of EoE is indirect and inferential. An increased number of mast cells have been noted in esophageal biopsies

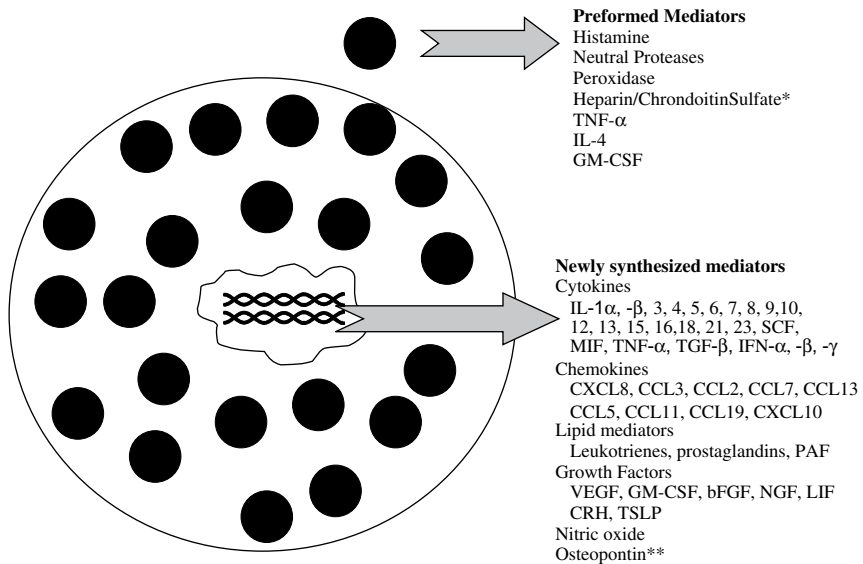


Fig. 1. Mast cell activation can lead to release of preformed mediators contained within cytoplasmic granules or newly synthesized mediators. *Matrix proteoglycan differs in connective tissue and mucosal mast cell populations. **To date, osteopontin has only been identified as a product of murine connective tissue-type mast cells. bFGF, basic fibroblast growth factor; CRH, corticotropin-releasing hormone; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; LIF, leukemia inhibitory factor; MIF, macrophage inhibitory factor; NGF, nerve growth factor; PAF, platelet-activating factor; SCF, stem cell factor; TGF, transforming growth factor; TSLP, thymic stromal lymphopoietin; VEGF, vascular endothelial growth factor.

from patients who had EoE,^{13–17} with as many as 20 times the normal number of mast cells found in the mucosal layer of the esophagus.¹⁷ An increase in mast cell numbers correlates with the degree of esophageal eosinophilia and the number of mast cells diminishes with effective treatment.^{17–19} However, studies differ in being able to find evidence of mast cell degranulation.^{14,15} Elevated levels of mast cell-specific/associated genes have been reported,¹⁴ including a 13-fold and 6-fold increase in the genes carboxypeptidase A3 and tryptase, respectively, and a 4-fold increase in the gene for the high affinity receptor for IgE, Fc ϵ RI.¹⁴

The significance of these findings remains to be determined but taken together, they suggest that mast cells are an active cellular component of the pathology associated with EoE.

POTENTIAL MECHANISMS OF MAST CELL INVOLVEMENT IN EOSINOPHILIC ESOPHAGITIS

Mast cells can contribute to the pathogenesis of EoE through several possible mechanisms.

Mast cells can have several direct and indirect interactions with eosinophils. They may be involved in eosinophil activation or survival through the production of IL-4, -5, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-13, and eotaxin-1. Mast cell release of tryptase may also activate eosinophils by way of protease-activated receptor 2 (PAR₂) expressed on their cell surface, which can induce eosinophil granule protein release, superoxide generation, and cytokine secretion.²⁰ Mast cells can promote

eosinophil recruitment by their ability to synthesize and release eosinophil-selective chemokines and leukotrienes (see **Fig. 1**). The release of mast cell-granule-associated proteoglycans, like heparin from connective tissue mast cells, can potentiate the action of chemokines such as eotaxin, an eosinophil-specific chemokine.²¹ Some of the cationic proteins contained by eosinophils, particularly eosinophil-derived major basic protein, can induce mast cell degranulation and TNF- α production,⁷ which represents a potential positive feedback loop augmenting the inflammatory response.

The release of mediators, such as histamine, leukotrienes, TNF- α , and eosinophil chemoattractants, can act to augment edema, inflammatory cell recruitment, and smooth muscle contractility, and enhance adaptive immune responses. Mast cells are also a source of transforming growth factor-beta (TGF- β) and IL-5, which have been implicated in various conditions associated with tissue fibrosis, including EoE.²² The effect of mast cell mediator production could be to augment inflammation, alter esophageal motility, and promote stricture formation.

However, some aspects of mast cell involvement in EoE may act to limit the inflammatory response. Several products of mast cells, such as TGF- β , histamine, IL-4, and IL-10 can have anti-inflammatory effects or the potential to down-regulate aspects of acquired immune responses. Mast cells can also produce mediators that degrade proinflammatory molecules. For example, mast cell tryptase can cleave and inactivate calcitonin gene-related peptide, and some mast cell proteases can degrade endothelin-1.

In patients who have esophageal achalasia, a primary motility disorder, mast cell numbers expand in the esophagus and the mast cells seem to associate with the interstitial cells of Cajal (ICC),²³ which are important in motor activity in the gastrointestinal tract. This association appears to correlate with survival of the ICC,²³ implying

Box 2

Theoretic consideration of mast cell functions in eosinophilic esophagitis (effector and immunomodulatory roles)

Proinflammatory

Alter vascular endothelium (eg, histamine, leukotrienes, tryptase, vascular endothelial growth factor, platelet-activating factor, nitric oxide, corticotropin-releasing hormone)

Recruit eosinophils and other immune cells (eg, chemokines, IL-8, TNF- α , leukotrienes)

Promote proliferation of eosinophils and other immune cells (eg, IL-5, GM-CSF, IL-3, and other growth factors)

Activate eosinophils (eg, tryptase activation of PAR₂ receptors)

Promote tissue remodeling/fibrosis (eg, TGF- β , tryptase, IL-5)

Promote T helper-1 response (eg, histamine, osteopontin)

Anti-inflammatory

Promote clearance of pathogens by phagocytosis, secretion of antimicrobial peptides

Degrade potential toxic endogenous peptides (eg, protease inactivation of endothelin-1)

Release anti-inflammatory peptides (eg, somatostatin)

Suppress adaptive immune responses (eg, IL-10)

Promote antigenic tolerance (eg, IL-10)

Suppress T helper-1 and T helper-2 cell activation (eg, histamine)

These roles include direct and indirect action of mast cell mediators on immune targets and on "nonimmune" cells, such as vascular endothelial cells, fibroblasts, nerve cells, and muscle cells.

a protective function for mast cells with regards to enteric nerves. This protective function of the mast cell for ICCs has also been suggested in Crohn's disease.²⁴

It can also be argued that the proinflammatory and anti-inflammatory actions of mast cells are not mutually exclusive. Inflammation is a dynamic process composed of phases, including initiation, augmentation, and resolution. It is certainly possible that mast cells could make a proinflammatory contribution during the initiation and augmentation phases and play an anti-inflammatory role in the resolution phase (**Box 2**).

SUMMARY

Current evidence suggests that mast cells are involved in EoE, and several potential mechanisms were suggested for how mast cells might contribute to this condition. However, the precise role of the mast cell in EoE remains unknown. Further research will be necessary to define the mast cell populations in EoE, the relevant biologic triggers inducing mast cell activation, the specific "panel" of mediators produced, and the net contribution of mast cells to the pathophysiology of this condition. This research will require intense basic investigation, which should be facilitated by animal models, particularly mast cell-deficient mice, in which it is possible to isolate the mast cell as an experimental variable.²⁵ Although a proinflammatory component to the involvement of mast cells in EoE appears to exist, it will be important to keep an open mind and explore all possibilities.

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