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REVIEW

The role of mast cells in allergic inflammation

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Summary
The histochemical characteristics of human basophils and tissue mast cells were described over a century ago by Paul Ehrlich. When mast cells are activated by an allergen that binds to serum IgE attached to their FcεRI receptors, they release cytokines, eicosanoids and their secretory granules. Mast cells are now thought to exert critical proinflammatory functions, as well as potential immunoregulatory roles, in various immune disorders through the release of mediators such as histamine, leukotrienes, cytokines chemokines, and neutral proteases (chymase and tryptase). The aim of this review is to describe the role of mast cells in allergic inflammation.

Mast cells interact directly with bacteria and appear to play a vital role in host defense against pathogens. Drugs, such as glucocorticoids, cyclosporine and cromolyn have been shown to have inhibitory effects on mast cell degranulation and mediator release. This review shows that mast cells play an active role in such diverse diseases as asthma, rhinitis, middle ear infection, and pulmonary fibrosis.

In conclusion, mast cells may not only contribute to the chronic airway inflammatory response, remodeling and symptomatology, but they may also have a central role in the initiation of the allergic immune response, that is providing signals inducing IgE synthesis by B-lymphocytes and inducing Th2 lymphocyte differentiation.

Abbreviations: AA, allergic asthma; APC, antigen presenting cell; BAL, bronchoalveolar lavage; CTMC, connective tissue mast cell; ECM, extracellular matrix; ELAM-1, endothelial-leukocyte adhesion molecule-1; FcεRI, high-affinity IgE receptors I; ICAM-1, intercellular adhesion molecule; INF-γ, interferon-gamma; IL, interleukin; LTs, leukotriences; MC, mast cell; MMC, Mucosal mast cell; PGs, prostaglandins, platelet-activating factor; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule.

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Contents

Introduction

Mast cells are found in the skin and in all mucosal tissues at homeostasis, and numbers are elevated in asthmatics lungs[1] and gastrointestinal tract of inflammatory bowel disease. Mast cells were first described by Ehrlich in his 1878 doctoral thesis on the basis of their unique staining characteristics and large granules, that gave them their name, "Mastzellen" which means well-fed cells, because their cytoplasm was stuffed with granular material. Mast cells are now considered to be part of the immune system. The mast cell was identified as a mesenchymal cell which is stained metachromatically with some blue dyes and it was recognized several years later that these cells contained in their granules the majority of the body's histamine.[2] Mast cells play a central role in inflammatory and immediate allergic reactions. They are able to release potent inflammatory mediators, such as histamine, proteases, chemotactic factors, cytokines and metabolites of arachidonic acid that act on the vasculature, smooth muscle, connective tissue, mucous glands and inflammatory cells.[3] Histamine is not only released when the body encounters a toxic substance, it is also released when mast cells detect injury. It causes nearby blood vessels to dilate allowing more blood to reach the site of the injury or infection. Mast cells are localized in the connective tissue and do not usually circulate in the blood stream.

The aim of this review is to discuss the effects of different Th2 cytokines on mast cell development, and the contribution of these cells to the chronic airway inflammatory response, tissue remodeling and symptomatology, and also to understand the role of these cells at the initiation of the allergic immune response, where they provide signals inducing IgE synthesis by B-lymphocytes and Th2 lymphocyte differentiation.

Mast cell development and differentiation

Mast cells arise in the bone marrow where maturation is influenced by stem cell factor binding to the receptor c-kit and by other cytokines such as interleukin (IL)-3, IL-4, IL-9, and IL-10. These cytokines promote differentiation and proliferation of both human and mouse mast cells.[4–7] The SCF receptor (c-kit) plays an important role in the hematopoiesis during embryonic development. Mast cell is the only terminally differentiated hematopoietic cell that expresses the c-Kit receptor. In addition, SCF promotes mast cell adhesion, migration, proliferation, and survival.[8] SCF also promotes the release of histamine and tryptase, which are involved in the allergic response. Mast cell progenitors leave the bone marrow and settle in various tissues dependent of stimulation.[9] Two types of mast cells, mucosal and connective tissue mast cells, were reported in rodent tissue in the 1960's on the basis of histochemical and fixation characteristics that reflect, in part, whether heparin proteoglycan was present in secretory granules. Mucosal mast cell (MMC) granules stain blue with copper phthalocyanin dyes, such as Astra blue or Alcian blue, in a staining sequence with safranin, while connective tissue mast cell (MCTC) granules stain red.[10] MC(T) and MC(TC) types of human mast cells (MCs) are distinguished from one another on the basis of the protease compositions of their secretory granules, but their structural, functional differences and developmental relationships have been well characterized by other authors.[11,12] Mast cells are long-lived, surviving for month or even years, in the tissue. Evolutionary, mast cells existed and participated in host defense long before the development of cells of adaptive immune system. Increased numbers of MCT and MCTC mast cells are seen in fibrotic diseases whereas its numbers are relatively unchanged in allergic or parasitic diseases and in HIV infection.[13] The presence of these MCTC cells could help explain why patients with HIV infection continue to have allergic reactions. The MCTC mast cell, however, expresses tryptase, chymase. It tends to predominate in the respiratory tract, gastrointestinal tract as well as in skin, synovium, and subcutaneous tissue.

Mast cell activation and mediator production

The cytoplasm of mast cells contains organelles: lipid bodies where metabolism of arachidonic acid occurs and where the products of this metabolism, including leukotrienes, are stored.[14] Cytokines and histamine are other products found in mast cells organelles (Fig. 1). These organelles are prone to exocytosis and extracellular release of mediators. The release may be induced by: (a) chemical substances, such as toxins, venoms, and proteases; (b) endogenous mediators, including tissue proteases, cationic proteins derived from eosinophils and neutrophils; (c) immune mechanisms that may be IgE-dependent or IgE-independent. IgE-dependent degranulation is a consequence of the preferential production of IgE, in response to certain antigens (allergens). During an allergic response IgE release from B-cells will bind to mast

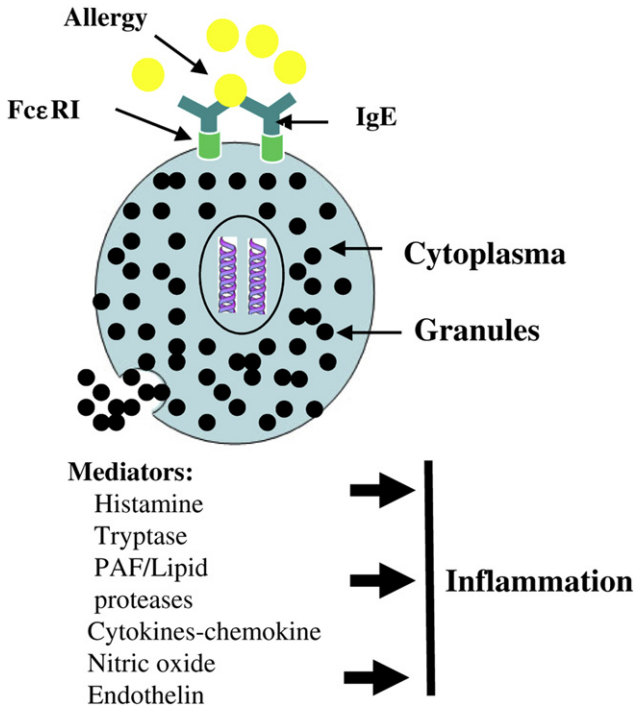

Figure 1 The IgE-primed mast cell releases granules and powerful chemical mediators, such as histamine, cytokines, granulocyte macrophage colony-stimulating factor (GM-CSF), leukotrienes, heparin, and many proteases into the environment. These chemical mediators cause the characteristic symptoms of allergy.

cells, blanketing the plasma membranes of these immune cells. Half a million IgE molecules coat the surface of mast cells, binding to the high-affinity IgE receptors (FcεRI) on membranes with the Fc portion. This leaves their Fab, or antigen binding segment, free to bind the antigen.[9,13,15,16] A subsequent exposure to the same allergen cross-links the cell-bound IgE and triggers the release of preformed prostaglandins, histamines and cytokines (Fig. 2).[9,14,17–19] Mast cell degranulation is preceded by increased Ca^{2+} influx, which is a crucial process; ionophores that increase cytoplasmic Ca^{2+} also promote degranulation, whereas agents which deplete cytoplasmic Ca^{2+} suppress degranulation (Fig. 2).[18,20] Additionally, in some cases, other ligand—receptor interactions, summarized in Fig. 1, can lead to mast cell degranulation.

Newly generated mediators, often absent in the resting mast cells, are as well produced during IgE-mediated activation, and consist of arachidonic acid metabolites, principally leukotriene C_4 (LTC_4), prostaglandin D_2 (PGD_2) and of cytokines.[21–23] Of particular interest in humans is the production of tumor necrosis factor (TNF-α, β), and interleukin (IL)-4, IL-5, IL-6, IL-1β and IL-13.[9,24–26] Those lipid mediators and cytokines and preformed histamine, can have profound effects on vascular endothelium, including the alteration of vascular permeability and adhesiveness. This can allow other circulating inflammatory cells to adhere to the endothelium and to migrate into the surrounding tissue. Cytokines and lipid mediators do as well elicit a direct influence on lymphocytes and macrophages in the murine system.[27] IL-4, IL-5 and IL-6 stimulates the proliferation and differentiation of activated B-cells, and induces class switch.[9,28,29] However, B-cells stimulated with IL-5 become plasma cells secreting IgA. IL-5 is also very important in stimulating growth and differentiation of eosinophils.[30–33] The production of cytokines by human mast cells has not been as extensively studied as in rodents, but several studies suggest that it has a similar pattern. For example, human mast cells have been shown to produce IL-4, IL-5, and IL-6.[30,31] In addition, mast cells produce several neutral proteases including tryptase and chymase that potentially damage and activate the bronchial epithelium, and may contribute to airway wall remodeling. Thus, mast cells are key players in host defense, with a role in immune surveillance, phagocytosis, and immune activation.

Functions of mast cells in physiological and pathological states

The biological function of mast cell neutral proteases remains to be fully clarified. In serum, elevated levels of tryptase are detected in systemic mast cell disorders, such as anaphylaxis and mastocytosis. Ongoing mast cell activation in asthma appears to be a characteristic of the chronic inflammatory nature of the disease. Activation is detected by elevated levels of tryptase and PGD_2 in bronchoalveolar lavage (BAL) and higher spontaneous release of histamine by mast cells obtained from the BAL of asthmatics than those obtained from non asthmatics.[21] Ultrastructural analysis of mast cells in lung tissue also shows that asthmatics have more degranulation than atopic nonasthmatics.[34] The number of the cells increases at sites of inflammation. To reach these areas, mast cell progenitors must migrate from the blood into tissue sites. A crucial step in this process is the adherence of cells to the endothelium. Cell adherence is mediated by several families of adhesion molecules and adhesion receptors on the surface of mast cells that can mediate binding to other cells and to extracellular matrix (ECM) glycoprotein. Upon stimulation, mast cells release cytokines, including TNF-α and IL-4 that can modulate adhesion molecules on endothelial cells. Activated endothelial cells express the intercellular adhesion molecule (ICAM-1), endothelial-leukocyte adhesion molecule-1 (ELAM-1) and vascular cell adhesion molecule (VCAM-1) on their cell surface.[35,36] Human mast cells express integrins as receptors for these molecules. Until recently, the effects of adherence on cell function were believed to result only from changes in cell shape and cytoskeletal organization. However, in addition to cell spreading, aggregated adhesion receptors transduce a variety of intracellular signals that regulate cell function. These signals include protein tyrosine phosphorylation, phosphoinositide hydrolysis and changes in intracellular pH or calcium concentration and the expression of several genes. The adhesion properties of the cells regulate their migration, localization, proliferation and phenotype. Recently, murine mast cells have been implicated in the mediation of inflammatory responses at long distances. TNF alpha containing particles released by the cells were found transported through draining lymphatic system activating cells in the lymph nodes.[37]

Different mechanisms could contribute to the increase in the number of mast cells at the sites of tissue injury: mast

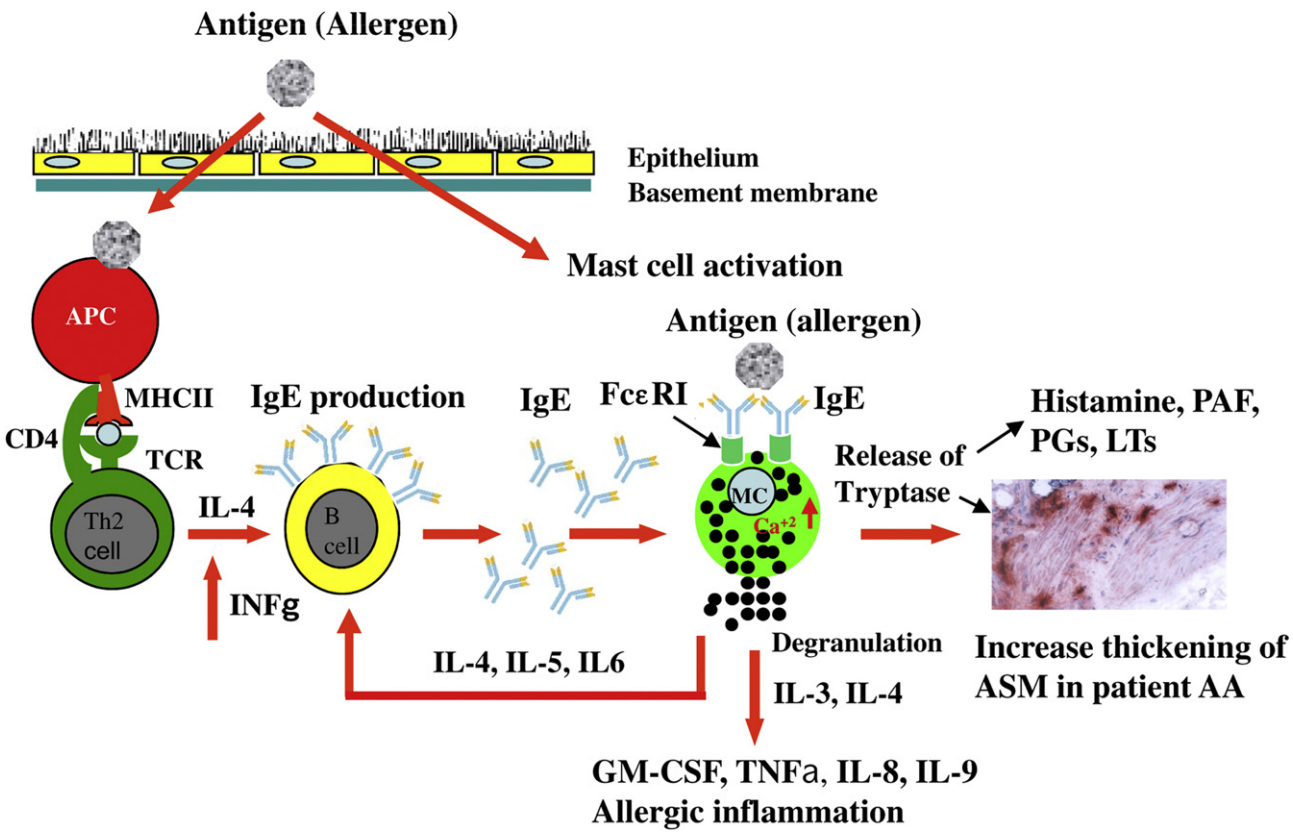

Figure 2 Induction and effector mechanisms in type I hypersensitivity.

cells or their progenitors could migrate to these sites; or resident mast cell precursors could proliferate. Adhesion receptors and their ligands also play a role in the localization and migration of mast cells in normal tissues. ECM proteins that are the ligands for adhesion receptors are chemotactic for mast cells. Adherence of mast cells to fibroblasts, other cells or to ECM proteins can transduce signals that affect cell growth and differentiation. The increase in the number of mast cells,[38,39] and the enhanced secretion at sites of inflammation, can accelerate the elimination of the cause of tissue injury or, paradoxically, may lead to a chronic inflammatory response. Thus, manipulating mast cell adhesion may be an important strategy in controlling the outcome of allergic and inflammatory responses.

In a previous study by us,[1] Mast cell numbers were increased in both allergic and non-allergic asthma. Similar to a more recent study, we found[17] infiltration of mast cells in of the bronchi of both allergic asthmatics and non-allergic asthmatics[40] but the accumulation of mast cells was more pronounced for the allergic asthmatics. We did also find that mast cells in the bronchial mucosa of the allergic asthmatics showed more signs of activation with extracellular deposition of tryptase than mast cells from non-allergic asthmatics.[1] Signs of mast cell activation in allergic asthma have been indicated by others.[40] However, in that study we could not observe any differences between allergic and non-allergic asthmatics.[40] This could be explained by limited number of non-allergic asthmatics included in the study. Specific allergens and their reaction with IgE on the mast cells might provide the mechanisms for activation in the bronchial mucosa in allergic asthma, especially since all those patients were sensitized to perennial allergens such as from pets.[41]

Also, other authors found inflammatory cells in bronchial mucosa in subjects with toluene Diisocyanate (TDI) induced asthma.[42] The mast cell, which is one of the inflammatory cells, plays an important role in TDI activation because the activation of mast cells is associated with TDI-induced early and late asthmatic reaction.[42,43]

Mast cells are increased in number in many fibrotic diseases and may play a crucial role in the development of fibrosis.[44,45] The percentage of human mast cells in BAL fluid from patients with sarcoidosis or interstitial fibrosis is greater than in BAL fluid from healthy individuals,[44,46] and patients with idiopathic interstitial pulmonary fibrosis show evidence of mast cell degranulation and elevated mast cell numbers.[47]

Concluding in a previous study show that Mast cells are located in connective tissue, including the lung, skin, the linings of the stomach and intestine, and other sites. They play an important role in helping defend these tissues from diseases. By releasing chemical such as histamine, mast cells attract other key players of the immune defense system to areas of the body where they are needed.

Mast cells and airway remodeling

Tissue remodeling is characteristic feature of asthma and other lung diseases. The mechanisms behind this relationship between mast cells and fibrosis/tissue remodeling are

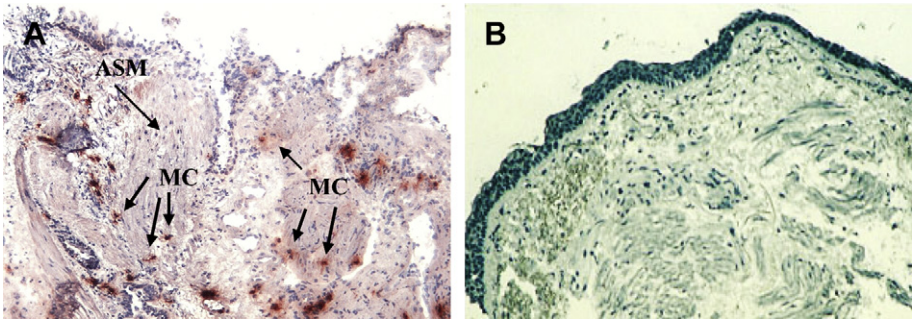

Figure 3 Staining of tissue mast cells with anti-tryptase antibody 1 (AA1) in (A) airway smooth muscle (arrow) of patients with allergic asthma and (B) control subjects, respectively. (Mayer's hematoxylin). Original magnification: ×40. The scale bars 50 μm for A and B are shown in the figures.

unclear. We have shown that mast cells may have a substantial effect on tissue remodeling, especially in the airway, on smooth muscle hypertrophy and on mucus hypersecretion, by releasing proteases such as tryptase, and growth factors.[17] These cells also have an effect on epithelial damage, and on basement membrane thickening in patients with allergic asthma,[1,48] allergic rhinitis,[49] and middle ear infection in allergy patients,[50,51] mast cells related to airway smooth muscle hypertrophy, compared to healthy controls.[17] Fig. 3 shows that mast cells specifically are localized within or close to airway smooth muscle bundles in patients with allergic asthma whereas little or no mast cells are found in the airways of healthy controls (Fig. 3). Tryptase and other proteases such as chymase are abundant in mast cell granules. Therefore, mast cells seem to play a crucial role in airway remodeling by releasing tryptase onto smooth muscle and epithelium, and may play a role in skin tissue remodeling by releasing chymase in an IgE-dependent manner in allergic diseases.

These data suggest multiple mechanisms and multiple levels in different organs in the human body, where mast cells can regulate tissue fibrosis and repair, and provide evidence for the direct involvement of mast cells in fibrosis and human connective tissue remodeling.

Conclusions

Mast cells are fascinating, multifunctional, bone marrow-derived, tissue-dwelling cells. They can be activated to degranulate in minutes, not only by IgE and antigen signaling via the high-affinity receptor for IgE, but also by a diverse group of stimuli. These cells can release a wide variety of immune mediators, including an expanding list of cytokines, chemokines, and growth factors. Mast cells have been shown to play roles in allergic inflammation and, more recently, they have been shown to modulate coagulation cascades, host defense, and tissue remodeling. The role of mast cells in asthma and other diseases is being actively studied.

This review suggests that mast cells may not only contribute to the chronic airway inflammatory response, airway remodeling and symptomatology, but may also have a central role at the initiation of the allergic immune response, that is, providing signals inducing B cell IgE synthesis and Th2 lymphocyte differentiation. Th-targeted therapy would be of considerable interest in controlling allergic asthma. Having more knowledge and resources about mast cells can lead to finding cures to diseases caused by the mast cells.

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