Emerging concepts: mast cell involvement in allergic diseases

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In a process known as overt degranulation, mast cells can release all at once a diverse array of products that are preformed and present within cytoplasmic granules. This occurs typically within seconds of stimulation by environmental factors and allergens. These potent, preformed mediators (ie, histamine, heparin, serotonin, and serine proteases) are responsible for the acute symptoms experienced in allergic conditions such as allergic conjunctivitis, allergic rhinitis, allergy-induced asthma, urticaria, and anaphylaxis. Yet, there is reason to believe that the actions of mast cells are important when they are not degranulating. Mast cells release preformed mediators and inflammatory cytokines for periods after degranulation and even without degranulating at all. Mast cells are consistently seen at sites of chronic inflammation, including nonallergic inflammation, where they have the ability to temper inflammatory processes and shape tissue morphology. Mast cells can trigger actions and chemotaxis in other important immune cells (eg, eosinophils and the newly discovered type 2 innate lymphocytes) that then make their own contributions to inflammation and disease. In this review, we will discuss the many known and theorized contributions of mast cells to allergic diseases, focusing on several prototypical allergic respiratory and skin conditions: asthma, chronic rhinosinusitis, aspirin-exacerbated respiratory disease, allergic conjunctivitis, atopic dermatitis, and some of the more common medication hypersensitivity reactions. We discuss traditionally accepted roles that mast cells play in the pathogenesis of each of these conditions, but we also delve into new areas of discovery and research that challenge traditionally accepted paradigms. (Translational Research 2016;174:98–121)

Abbreviations: AA = arachidonic acid; AERD = aspirin exacerbated respiratory disease; BAL = bronchoalveolar lavage; CF = cystic fibrosis; CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; ILC2 = type 2 innate lymphocytes; MCAD = mast cell activation disease; MCAS = mast cell activation syndrome; MC_{TC}s = tryptase- and chymase-positive mast cells; MC_Ts = tryptase-only-positive mast cells; PAMP = pathogen-associated molecular pattern

INTRODUCTION

Mast cells are derived from hematopoietic stem cells that exit the bone marrow as undifferentiated CD117+, CD34 + progenitor cells. They develop in resident tissues where they become long living, highly specialized granulocytes.[1,2] Mast cell differentiation and survival in the peripheral tissue is largely determined by the local tissue and cytokine milieu.[3-20] Although mast cells reside in all vascularized tissue, they are most predominant at sites

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exposed to the external environment: skin, pulmonary epithelia, and gastrointestinal tracts. Mast cells surround blood vessels and monitor the local environment by extending membranous projections into the vessel lumens.[21,22] In this way, mast cells are well positioned to sample and respond to changes in the local environment.

Mast cells are most well known for their roles in fighting human parasitic infections and orchestrating IgE-mediated allergic responses. As we explain in this review, mast cells are important in ways that go beyond these two conditions. Mast cells are important to the defense against bacterial and parasitic infections.[2] Specifically, mast cells are known to recognize molecular patterns that are unique to microbial pathogens (ie, pattern-associated molecular patterns)[23-27] and activate the innate system.[28,29] Mast cells help tissues heal and repair from damage.[21,24,30-33] They temper inflammation by producing an immune-inhibitory cytokine (ie, interleukin [IL] 10) and by degrading proinflammatory cytokines with granule proteases.[34-36] As mature granulocytes, mast cells release cytokines (eg, transforming growth factor-β [TGF-β]) and other factors that act as pleiotropic mediators and shape tissue morphology.[21] Thus, it makes sense that while mast cells are increased at mucosal sites of allergic inflammation such as allergic conjunctivitis,[37] allergic rhinitis,[38] food allergy,[39,40] and asthma,[41-43] they are also consistently observed in the mucosal sites of nonallergic inflammation such as inflammatory bowel disease,[44,45] parasitic infections,[46,47] lung fibrosis,[48-52] and chronic kidney rejection.[53]

The fact that mast cells are involved in such a wide range of functions likely results from a unique adaptability of these cells in response to changes in the local environment. As mast cells take on different characteristics and functions in response to the local tissue and inflammatory milieu, they become more specialized cells known as subtypes or subphenotypes. The idea that mast cells reside and act in the body as different subtypes began when researchers discovered two distinct mast cell subtypes in mice.[54,55] An equivalent model was subsequently discovered in humans. The human mast cell subtypes were named according to contents of their secretory granules: tryptase- and chymase-positive mast cells (MC_{TC}s) and tryptase-only-positive mast cells (MC_Ts). The MC_{TC} subtype, which is comparable to the "connective tissue" mast cell in rodents,[56] contains tryptase, chymase, carboxypeptidase A3, and cathepsin G[56] in their secretory granules. The MC_T subtype, which is comparable to the rodent "mucosal" mast cell subtype,[56] is comparably smaller, less developed, and contain only tryptase in their secretory granules.[57-63]

MC_{TC}s are the predominant mast cell in the gastrointestinal tract, skin, and conjunctiva. All together they comprise most mast cells in the body. Alternatively, MC_Ts are more prevalent at mucosal sites, something that may depend on the concomitant presence of T cells because studies show that patients with congenital or acquired T cell deficiencies lack MC_Ts in the intestinal mucosa.[38,52] MC_Ts are also the majority of mast cells found in the lungs.[52,64] They are found in the alveolar septae, airway epithelium, and submucosa.[58,65] MC_{TC}s are still present within the lung but are typically located beneath the epithelium in the lamina propria and submucosa. They are often found surrounding blood vessels, or in close proximity to the submucosal glands,[52] or within and around airway smooth muscle of major bronchi.[52,58,64,66] Although these were some of the first studies to introduce the idea of distinct mast cell subtypes, more recent ones indicate that human mast cell subtypes are likely more numerous and diverse than this biphenotypic model.[67] In fact, evidence suggests that mast cells demonstrate differences in cellular functions and surface markers even in relation to microlocalizations within the same tissue.[67]

In the traditionally accepted model, cross-linking of IgE immunoglobulins bound to high-affinity FcεR1 surface receptors on mast cells by an allergenic protein triggers immediate, overt mast cell degranulation with the release of a diverse array of preformed mediators. This process can occur within seconds and is responsible for the acute symptoms experienced in most allergic conditions. Although we discuss this immediate, IgE-mediated reaction in relation to many allergic diseases, this review focuses a great deal on the functions and actions of mast cells when they are not degranulating. For example, after degranulation, mast cells begin secreting proinflammatory leukotrienes and prostanoids derived from cellular phospholipid membranes (ie, arachidonic acid [AA]) and proinflammatory cytokines. These potent signaling molecules act together to amplify inflammation by activating nearby cells and recruit important immune cells such as eosinophils, neutrophils, and type 2 innate lymphoid cells (ILC2s).

Although mast cells play an important role in almost all allergic disease, a thorough review of all diseases is beyond the means of a single review article. We focus this review on what are considered the prototypical allergic respiratory and skin conditions: asthma, chronic rhinosinusitis (CRS), aspirin-exacerbated respiratory disease (AERD), allergic conjunctivitis, atopic dermatitis, and some of the more common medication hypersensitivity reactions. We discuss traditionally accepted roles that mast cells play in the pathogenesis of each