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EDITORIAL

ASTHMA AND MAST CELL BIOLOGY

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Asthma is a chronic inflammatory disease of the lung and its pathophysiology is initiated by mast cell activation in response to the antigen binding to IgE receptor as well as by TH2 cell activation. Mast cells are well established effector cells in asthma where they exacerbate the inflammatory response, playing a key role in early phase, degranulating and increasing histamine. Human mast cells possess high affinity IgE receptors and are ubiquitous but predominantly localized in mucosal and connective tissue and are distributed along blood vessels. There are two types of mast cells: connective tissue mast cells (TC) and mucosal mast cells (T mast cells). TC mast cells contain more heparin, whereas T mast cells contain more chondroitin sulfate. In asthma, mast cell activation can trigger degranulation, releasing secretory granule complex and preformed mediators, such as histamine and proteases, along with the synthesis of leukotrines and prostaglandins, and induction of cytokines and chemokines. Leukotrine inhibitors and omalizumab, which inhibits IgE, both relieve the asthma exacerbation when administered to humans and permit to reduce the use of other drugs. The release of cytokines by mast cells, such as TNF-alpha, IL-1, IL-6 and IL-33, participate in the pathogenesis of asthma. Stress worsens asthma, and this effect is also mediated by mast cell activation through the release of cytokines. Administration of IL-33 in experimental animals provokes pathological effects in the mucosal tissues and augments antibody IgE and IgA in blood vessels. Here, we report the impact of mast cell biology in asthma pathogenesis.

Von Recklinghausen described the presence of granular cells in connective tissue in 1863, the first definition of mast cells (MCs) was later, 1877, attributed to Ehrlich. In addition Ehrlich also associated mast cells with blood vessels, nerves and inflammation. In 1943, Goffman discovered heparin, histamine and serotonin in rodent mast cells. MCs participate in both innate and adaptive immunity and play an important role in maintaining a healthy physiology, in wound healing and in angiogenesis (1). Human mast cells, released from bone marrow, like other myeloid cells, are derived from a common

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myeloid progenitor (2). They possess high-affinity IgE receptors (FcεRI) and are ubiquitous, predominantly localized in mucosal and connective tissues and distributed along blood vessels (3). Substantial evidence indicates that mast cells play a key role in inflammation and their products modulate inflammatory mediator production. Mast cells can be activated by bacterial or viral antigens, cytokines, growth factors, and hormones, leading to differential release of distinct mediators without degranulation (4). Moreover, mast cells accumulate in the stroma of a number of inflamed tissues in response to locally produced chemotactic factors for monocytes/mast cells, such as RANTES and MCP-1 (5).

At least two easily identifiable types of human mast cells have been reported: connective tissue mast cells that contain tryptase and chymase (TC mast cells), and mucosal mast cells that contain only tryptase (T mast cells) (6). These two cell types differ in the number and type of secretory granules they contain, as well as in their responsiveness to stimuli. For instance, TC mast cells contain more heparin, whereas T mast cells contain more chondroitin sulfate; in addition, TC mast cells respond to neuropeptides, whereas T mast cells do not (6).

Mast cells play an important role in inflammatory diseases and have been implicated in the pathophysiology of several diseases, including asthma and allergy (7). Mast cells are known to be a rich source of prostaglandins, and they are crucial effector cells evoking immune responses against bacterial pathogens (8). In addition, innate MC activation can be part of a protective immunity to pathogens, and it also expands several signals that can elicit pathologic airway inflammation in asthma. The ability of mast cells to generate or release the vasoactive/spasmogenic mediator histamine, PGD2, sulfidopeptide leukotrienes, platelet-activating factor, cytokines/chemokines and other factors is thought to be relevant to immediate inflammatory responses (9). In asthma, mast cell activation can trigger degranulation, defined by the release of the preformed secretory granule complex and preformed mediators such as histamine and proteases along with the rapid synthesis of lipid mediators such as cys-LTs, dihydroxy leukotrienes, and prostaglandin D2, and the induction of cytokines and chemokines (10). Some studies have suggested important new applications of LT blockers, such as montelukast, zafirlukast, pranlukast, etc., in several diseases, including asthma, in which leukotrienes play a pathogenic role (11).

Mast cells also secrete primarily pro-inflammatory cytokines such as TNF-α , IL-1, IL-6, and IL-8, which are important factors for innate immunity and they are the only cells that secrete preformed TNF-α (12). TNF-α is a well recognized pro-inflammatory cytokine and when it is inhaled in healthy subjects induces sputum neutrophilia and bronchial hyperresponsiveness, and also in patients with asthma, exacerbates inflammatory responses. IL-1β also participates in the pathogenesis of asthma and induces the generation of TNF-α and IL-6 *in vivo* and *in vitro* (13).

IL-1β, TNF-α, and other stimulants are potent activators of human cord blood- or peripheral blood-derived MCs to generate IL-5, IL-13, IL-6, GM-CSF, IL-10, IL-33, CXCL8, and CCL1(14-15). In addition, mast cells can also produce cytokines that are released from T helper 2 (Th2) cells, such as IL-4, IL-9 and IL-13 which can directly induce airway hyper- responsiveness and play an important role in initiating and generating the physiological abnormalities in the asthmatic subjects (16). Corticotropin-releasing hormone (CRH) is also released by mast cell activation and acts synergistically with NT to increase vascular permeability (17). CRH stimulates selective release of VEGF, which is also pro-inflammatory and vasodilatory and is secreted in stress (18). Stress induces local release of CRH and stimulates CNS mast cells, leading to increased vascular permeability. Human mast cells can release large amounts of CRH and express mRNA and functional CRH receptor-1 (19).

It has been reported that stress worsens asthma and these effects are mediated through activation of mast cells which infiltrate bronchial smooth muscle in asthmatic subjects and release cytokines (20). These cytokines are also present in increased levels in several other diseases. As reported above, an increased Th2 immune response is evidently associated with asthma. In fact, mucus hyper-production in asthma results from a Th2-induced airway inflammation and allergic asthma is associated with a substantial increase in the mucus

content of the airway epithelium (21-22). One of the main targets of IL-9 is the mast cell and, as mentioned earlier, initial studies described a role for IL-9 in promoting the expansion of mast cell populations (23). IL-18 directly stimulates mast cells to produce Th2 cytokines and histamine independently of IgE (24). Moreover, IL-18-activated mast cells and/or basophils release IL-13 and/or IL-4 (25).

Many cytokines are believed to be involved in Th2-mediated inflammatory responses and in allergic diseases such as asthma, anaphylaxis, and atopic dermatitis, and also in host defense against parasites (26). Allergic cells also stimulate superoxide production and undergo degranulation.

MCs are well-established effectors in asthma and its exacerbations. Activated mast cells appear to be the primary effector cell in the pathogenesis of atopic asthma. It has been previously reported that cellular infiltrate in bronchial biopsies and bronchoalveolar lavage of asthmatic patients contains several inflammatory cells, including mast cells (27), eosinophils, and T helper 2 (Th2) lymphocytes generating interleukin-3 (IL-3), IL-4, IL-5, IL-9, IL-13, and granulocyte macrophage colony-stimulating factor (GM-CSF) (28-29).

Some studies highlight that in response to a wide variety of innate signals via TLR2 and 1, TLR2 and 6, TLR3, TLR4, TLR7, and TLR9, mast cells synthesize IL-17 and are also involved in Treg suppression and promote the development of T17 cells which participate in autoimmune diseases and asthma (30).

IL-33

IL-33 is a member of the IL-1 family that signals through the toll/interleukin-1 (TIR) domain-containing receptor ST2 (31) and has been found to be a potent inducer of T helper 2 (Th2) responses and Th2-associated cytokines IL-4, IL-5, and IL-13, but not Th1, in contrast to other closely related family members. ST2 (encoded by *Il1rl*) receptor is involved in Th2 cell pulmonary inflammation (32). The increasing of Th2 plays a relevant role in the adaptive immunity and this novel cytokine seems to act more as an immunoregulatory than as a pro-inflammatory cytokine like other IL-1 family members (33). However, IL-33 may plays an important role in asthma and other allergic-type diseases (34). IL-33 is localized in the nucleus, associates with heterochromatin and mitotic chromosomes, and exhibits potent transcriptional effect. MCs release IL-33 from peripheral blood or cord blood-derived $CD34^+$ MC progenitors to generate IL-5, IL-13, GM-CSF, TNF-α, IL-10, IL-6, CXCL8, and CCL1, without degranulation or the production of PGD_2 and LTC_4 (35). Authors have reported that activated MCs by IL-33 in asthmatic subjects have a baseline increase in serum IL-33 receptor levels as compared to normal controls, and these levels increase during asthma exacerbations (36). Moreover, IL-33, through its receptor ST2, can activate NFκB and transcription of pro-inflammatory cytokines (37) such as interleukins IL-1β, IL-6, IL-8, IL-13, TNF, chemokines, and arachidonic acid products. IL-33 enhances experimental allergic inflammation by directly stimulating mast cells to produce inflammatory cytokines (38) and it is abundantly expressed by high endothelial venules in humans. We previously demonstrated that IL-33 augments human mast cell release of vascular endothelial growth factor (VEGF) in response to substance P (39). Administration of IL-33 in experimental animals causes several pathological effects in the mucosal tissues, such as eosinophilia in the lung, esophagus, intestines and spleen, and augments antibody IgA and IgE in blood levels (40).

Asthma

Asthma is a chronic inflammatory disease of the lungs (17) which affects about 10 million people in the United States and has increased significantly in recent years. It is well known that mast cells are involved in asthma; in fact, the pathophysiology of atopic asthma is initiated by mast cell activation in response to allergen binding to IgE receptor as well as by TH2 cells activating to antigens. Many triggers may participate in asthma, including neuropeptides secreted locally that stimulate mast cells. Therefore, mast cells participate in the development of allergic reactions through cross-linking of their surface high affinity receptors for IgE (FcεRI) leading to degranulation and the release of vasoactive, pro-inflammatory compounds, such as metabolites, histamine, cytokines, proteolytic enzymes and arachidonic acid compounds. Human mast cell proteases increase C-C chemokine (CCL8) and

fibronectin in cultured airway smooth muscle cells (41).

It is evident that mast cells play a role in human asthma which in the early phase is associated with mast cell degranulation and an increase in plasma histamine and urinary LTE_4. These processes are inhibited by pretreatment by chromoglycate, or 5-lipoxygenase inhibitor, or anti-histamines. The inhibitory effect of omalizumab, an anti-IgE monoclonal antibody which blocks IgE binding receptor to FcεRI, also inhibits asthma exacerbation. This last treatment permits to reduce the use of corticosteroids. It has been also reported that there is a selective increase in tryptase and chymase positive mast cells in the smooth muscle layer of subjects with asthma, suggesting that MCs in bronchial smooth muscle are important for airway hyperresponsiveness.

However, the interaction of mast cells with other asthma immune cells, including macrophages, dendritic cells and T cells, to induce protective immunity in allergic diseases is very important.

Therefore, the involvement of mast cells and their products in asthma is interesting, but very complex, and the exact role of these cells still remain to be determined. The issue needs more study in order to understand the physiopathology of these chronic diseases.

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