Mast Cells in Allergy/Inflammation Regulation

Subjects: Immunology

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It is well known that mast cells (MCs) initiate type I allergic reactions and inflammation in a quick response to the various stimulants, including—but not limited to—allergens, pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs). MCs highly express receptors of these ligands and proteases (e.g., tryptase, chymase) and cytokines (TNF), and other granular components (e.g., histamine and serotonin) and aggravate the allergic reaction and inflammation. On the other hand, accumulated evidence has revealed that MCs also possess immune-regulatory functions, suppressing chronic inflammation and allergic reactions on some occasions. IL-2 and IL-10 released from MCs inhibit excessive immune responses.

Keywords: mast cells ; allergy ; inflammatory bowel disease ; immunotherapy

1. Introduction

Mast cells (MCs) are a type of innate immune cell that belongs to the myeloid lineage. It is generally believed that MCs from both humans and rodents are derived from hematopoietic stem cells (HSCs). Mast cell progenitors (MCPs) leave the bone marrow as immature cells and enter the blood circulation, with the help of surface molecules, such as α4β7 integrin, MAdCAM-1 and VCAM1, to migrate to various target tissues [1][2]. MCs have high plasticity and heterogeneity due to their unique process of maturation.

MCs are also regulators of inflammatory disorders and fibrosis occurred in various organs. Associations between MCs recruitment/infiltration and fibrosis have been found in various tissues [3]. Current studies have found that many MCs products, including—but not limited to—tryptase, chymase, histamine, TGF- β1, IL-13, IL-9, CCL2, platelet-derived growth factor (PDGF), glycosaminoglycan and fibroblast growth factor-2 (FGF-2) can promote fibrosis [3]. MCs have long been regarded as the initiators of allergy and inflammation, as well as the promoters of fibrotic diseases, which are pathogenic. However, as every coin has two sides, in addition to some harmful effects, MCs possess anti-allergic and inflammatory effects. MCs appear to play an immunomodulatory role in allergic, acute, and chronic inflammation (e.g., fibrosis [4][5]). There is growing evidence that MCs play an enormous role in allergic responses, inflammatory responses, and wound healing [4][6][7].

2. Origin and Heterogeneity of MCs

It is generally believed that MCs from both humans and rodents are derived from HSCs. In the bone marrow, HSCs first grow into myeloid progenitors and then differentiate into MCPs [8]. Next, MCPs transfer from the bone marrow as immature cells into the bloodstream. Eventually, with the help of surface molecules (e.g., α4β7 integrin, MAdCAM-1, and VCAM1) [2], MCPs migrate to various target tissues, such as the serous cavity, in close contact with the micro-environment (e.g., the skin, gastrointestinal tract, upper airways and lungs [9]) and some vascularized organs (e.g., the liver and kidneys) [10][11]. These tissues contain various tissue-specific factors (e.g., cytokines, growth factors and extracellular matrix [ECM]), which help MCPs finally become phenotypically mature and perform different functions [12].

However, the exact origin of MCs remains a matter of debate. It is generally believed that MCPs in mice are derived from bone marrow. It has also been reported that MCs are developed from the common myeloid progenitor cells (CMPs) [13]. However, Dahlin et al., who demonstrated that MCPs were derived from multipotential progenitor cells (MMPs) rather than CMPs, disagreed [14]. Recent studies have found that mouse MCs have dual developmental origins. A portion of the MCs have a primitive origin. They are derived from the yolk sac during embryogenesis. MCPs derived from the yolk sac migrate to different connective tissues, such as the skin. Another part of adult definitive MCs comes from the HSCs of the aortic-gonad-mesonephros vascular endothelium [15]. Studies have also shown that MCs in adult tissues are supplemented by the proliferation/differentiation of resident precursors in long-lived tissues [16]. Thus, in mouse-based studies, MCs have at least two maturation pathways; however, whether these pathways apply to other mammals, such as humans, has not been fully clarified.

MCs also have high plasticity and heterogeneity due to their unique process of maturation. They show subtype-dependent differences in cell morphology, histochemical characteristics, granular protease expression, function, and survival according to the microenvironment, activating factors and the cytokine milieu [17].

According to the traditional classification system, MCs are divided into two subsets in mice: MMCs and CTMCs. The two subsets have different anatomical localization and protease expression patterns [8]. CTMCs, as the name suggests, are mainly located in the connective tissue of the intestinal submucosa and muscularis propria, the peritoneal cavity, and skin. This subset expresses both chymase and tryptase [14]. Their cytoplasm also contains heparin proteoglycan and a high level of histamine [18]. In contrast, MMCs are a chymase-expressing type [14]. They are usually present in the mucosal tissues of the lung and gastrointestinal tract, with little or no heparin proteoglycans in their granules, and have lower amounts of histamine [18].

Similarly, in humans, the MCs subtypes are classified according to whether they secrete both tryptase and chymase (MCTC) or tryptase alone (MCT). The former is comparable with mouse MMCs, while the latter corresponds to CTMCs [17] [18]. The MCTCs are mainly distributed in the skin, the gastrointestinal tract, and conjunctiva and the MCTs can be found in the lungs, nose and sinuses [19].

3. Pro-Allergic and Inflammatory Actions of MCs

3.1. Regulation of Receptor-Mediated MCs Activation

As one of the most common immune cells, the main characteristics of MCs are their pro-allergy and pro-inflammatory effects. MCs can express a variety of receptors, which, when combined with corresponding ligands, can induce the activation of MCs, thereby triggering various pathways. MCs activation mainly occurs by IgE-dependent and IgE-independent pathways [20].

MCs degranulation mediated by the IgE high-affinity receptor (FcεRI) is the most classical mechanism of MCs activation. Immunoglobulin E (IgE) is a class of antibodies produced by plasma cells that shows high affinity to MCs, and which can mediate Type I hypersensitivity reactions, such as food allergy and asthma. The first pathogenic step of IgE-mediated type I hypersensitivity reactions is sensitization (**Figure 1**A). When the body's first contact with allergens, antigen-presenting cells like monocytes-macrophages and dendritic cells (DCs) present antigen information to T helper lymphocytes, causing them to secrete cytokines. B lymphocytes then transform into plasma cells and secrete various allergen-specific IgE in response to the cytokines derived from T helper lymphocytes [21]. Specific IgE can bind to FcεRI on the surface of MCs. FcεRI is a type of high-affinity receptor of IgE that exists in the form of a trimer or tetramer. FcεRI contains one α chain, two identical γ chains and one β chain which is sometimes missing. In humans, FcεRI can be expressed as both αβγ2 and αγ2. In rodents, however, FcεRI is only expressed in the form of αβγ2 [21][22]. The extracellular domain of the α chain can bind to the Fc segment of IgE, which is a critical site for triggering allergic reactions. The primary role of the β subunit is to enhance the tyrosine kinase activity and calcium influx and then to amplify the expression of FcεRI on the surface of MCs [14]. When the allergens enter again, FcεRI/IgE complexes are cross-linked with high-affinity antigens on the surface of sensitive MCs, the FcεRI receptor will be activated, causing signal transduction in MCs and promoting the degranulation of MCs and the subsequent release of inflammatory mediators, like histamine, serotonin and leukotriene, which are involved allergic reactions or inflammation [21].

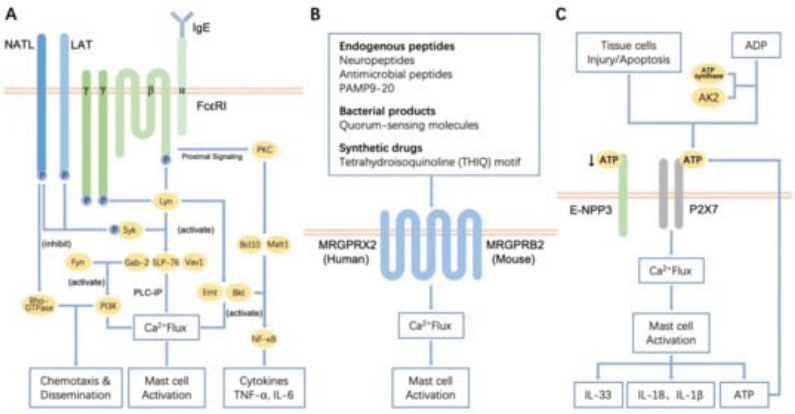

Figure 1. Regulation of receptor-mediated MCs activation. (**A**) IgE-FcεRI is the most classical mechanism of MCs activation, which mainly relies on the Lyn-Syk and Fyn pathways to activate MCs. (**B**) MRGPRX2/B2 is a novel class of G-protein-coupled receptors that can bind to various secretory proteins (mostly cationic peptides) to activate MCs. (**C**) P2X7

is an ATP-gated ion channel that is highly expressed in colonic MCs. P2X7 can also be activated by autocrine released ATP, and extracellular ATP can be degraded by E-NPP3 on the membrane.

The degranulation of MCs, which is mediated by IgE-FcεRI, mainly depends on the Lyn-Syk pathway (**Figure 1**A). In this pathway, the Lyn and Syk kinases are activated at first, and then phosphorylated Lyn and Syk activate some junction proteins (e.g., SLP-76, Gab2 and Vav1) with the help of the linker for activation of T cell (LAT), causing the downstream effector protein PLCγ1/2 to participate in the reaction [23].

Furthermore, Fyn also plays a pivotal part in the degranulation of MCs (**Figure 1**A). Fyn is another non-receptor tyrosine-protein kinase of the Src family, which is located on the cell membrane. When FcεRI is activated, Fyn activates phosphatidylinositol-3-kinase (PI3K) through interaction with Gab2, thereby affecting calcium mobilization and regulating the degranulation of MCs [24].

MCs can also be activated through IgE-independent pathways. Cytokines, some complement fragments, neuropeptide substance P, inflammatory mediators, β-defensins and exogenous molecules (e.g., artemisinin, PAMP9-20, etc.) are able to activate MCs through specific G-protein-coupled receptors (GPCR).

Many cytokines can mediate the activation of MCs. Results show that IL-3 can recruit and tend to the expression of MCs in the nasal mucosa and reflect the severity of allergic rhinitis. IL-6 can regulate the expression of protease activated receptors (PARs) on the MCs membrane; thus, participating in allergic inflammation. IL-9 can promote the release of IL-2 by MCs, leading to the expansion of $CD25^+$ type 2 innate lymphoid cells (ILC2), thus activating Th9 cells, and promoting lung inflammation in cystic fibrosis [25].

The complement system is involved in specific and non-specific immunity of the body and can regulate immunity and mediate the antimicrobial response. Some of the complement fragments can regulate the activity of MCs. C3a is an allergic toxin molecule produced after the activation of the complement system. It can activate MCs to release inflammatory mediators and is a crucial chemokine of MCs [26]. C5a is another complement fragment that affects MCs. Likewise, C5a was found to induce the degranulation of MCs through PLC [27].

Mas-related G-protein-coupled receptors (MRGPRs) are a new class of G-protein- coupled receptors, that are specifically distributed on the surface of peripheral sensory neurons and MCs (**Figure 1**B). According to a preliminary analysis, MRGPRX2 binds to basal secretin (mostly cationic peptides), activates MCs through the non-IgE transduction pathway, which induces the degranulation of MCs and plays a pivotal role in host defense, pseudo-allergy, pruritus, neurogenic inflammation and pain [28][29][30].

Last but not least, P2X7 is also an important receptor that activates MCs (**Figure 1**C) [31]. There is no expression of P2X7 in the skin, but it is highly expressed on colonic MCs, leading to the initiation and exacerbation of intestinal inflammation [32][33]. P2X7 is a type of P2 purinoceptor, an ATP-gated ion channel that can specifically recognize ATP and which then participates in inflammation by mediating the release of IL-1β and IL-18 (**Figure 1**C) [33].

3.2. Fibrogenic Actions of MCs

Although the exact relationship between inflammation and fibrosis is not clear at present, the relationship between MCs recruitment/infiltration and fibrosis has been reported in the intestines, lungs, kidneys, liver, heart and other organs [12][34][35][36][37][38]. In addition, toluidine blue staining showed that MCs was mostly adjacent to fibroblasts in animal skin simulating trauma and it has been found that a variety of cell surface proteins on fibroblasts can connect to the interaction between fibroblasts and MCs, such as membrane-bound stem cell factor, hyaluronic acid receptors, fibrinogen and gap-junctional intercellular communication (GJIC) [39][40]. Consequently, it is reasonable to assume that MCs are regulators of fibrosis in different organ systems. Current studies have found that many MCs products, including—but not limited to—tryptase, chymase, histamine, TGF- β1, IL-13, IL-9, CCL2, PDGF, glycosaminoglycan and FGF-2 can promote fibrosis [3]. These secretory components of MCs can not only promote fibroblasts to produce collagen but also participate in the extracellular stage of fiber formation [39].

Chymase is produced by the degranulation of MCs and is closely related to fibrosis. Chymase promotes fibroblast mitosis and promotes the synthesis and secretion of type I and III collagen in the ECM [41]. Tryptase is another typical protease secreted by MCs, which can also promote fibrosis [34]. Histamine, another substance secreted by MCs, also induces fibrosis. It is reported that histamine stimulates fibroblast proliferation and collagen synthesis [42][43]. TGF-β1 is widely known to be one of the main driving factors of fibrosis. Its expression is significantly upregulated in fibrotic tissues [12].

Glycosaminoglycans secreted by MCs assist fiber formation in the extracellular stage [39]. As mentioned above, in the ECM, the polymerization of tropocollagen macromolecules can be polymerized into microfibers, fibrils and fibers. Glycosaminoglycan can absorb water before that, which helps to increase the concentration at the time of the polymerization, thus facilitating the polymerization of the tropocollagen. Along with this, there is an electrostatic interaction between glycosaminoglycan and collagen. A recent study showed that heparin forms a bridge between two collagen molecules, which makes it possible to regulate the distance between them, thus determining the thickness of the fibrils [44]. Accordingly, MCs, as the only source of heparin and other glycosaminoglycan in tissues, have a great contribution to the formation of fibers. What's more, granules released by MCs can also act as nucleators, which can be used as the starting molecular loci of collagen molecular polymerization [39].

Some studies have found that the enzyme released by MCs can digest the membrane-bound form of SCF to produce soluble SCF, which helps the maturation of MCs by stimulating KIT. It also promotes fibrosis [12]. Moreover, it has recently been found that chymase may have an inhibitory effect on fibrosis at the same time. Chymase can degrade two alarmins, IL-33 and HMGB1 [45], which have been shown to promote the progression of fibrosis. In addition, MCs can secrete matrix metalloproteinases (MMPs), an enzyme required for collagen fiber degradation [39]. Thus, MCs protease may have more than one role and needs to be treated rationally according to the development of the disease.

4. Regulatory-Type Actions of MCs in Allergy and Inflammation

MCs have long been regarded as the initiators of immunity and inflammation, which is pathogenic. For example, specific MCs proteases can promote inflammation, such as tryptase, chymase and carboxypeptidase A3 [46][47][48][49]. However, there are two sides to every coin. In addition to some harmful effects, the benefits of MCs to the human body cannot be ignored. MCs appear to play an immunomodulatory role in inflammation, allergy and fibrosis.

4.1. Regulation of Chronic Inflammation/Fibrosis/Wound Healing

Many results show that while the depletion of MCs cannot prevent tissue repair and remodeling, it can delay wound healing [7][50]. Hence, MCs can promote wound healing. It has been pointed out that MCs are involved in wound healing at several stages [7]. Under the influence of SCF released by keratinocytes as well as CCL2 (MCP-1) and IL-33, MCs gather at the edge of the wound in the first few days [51]. The TNF secreted by them can enhance the expression of XIIIa factor in dermal dendritic cells and then promote hemostasis and clot formation, which help reduce injury [52]. Through the secretion of histamine, lipid mediators, and VEGF, they increase vascular permeability and recruit other cells, such as neutrophils, to help heal the wound (**Figure 2**) [3]. In the proliferation stage of wound healing, the migration and proliferation of fibroblasts and the formation of collagen fibers are the key steps of wound healing [3]. MCs can release a variety of substances that interact with fibroblasts to promote wound healing (**Figure 2**). As mentioned before, proteases released by MCs can chemotaxis fibroblasts and promote their mitosis [39][53]. In addition, VEGF, IL-4 and basic fibroblast growth factor (bFGF) derived from MCs can stimulate the proliferation of fibroblasts [54].

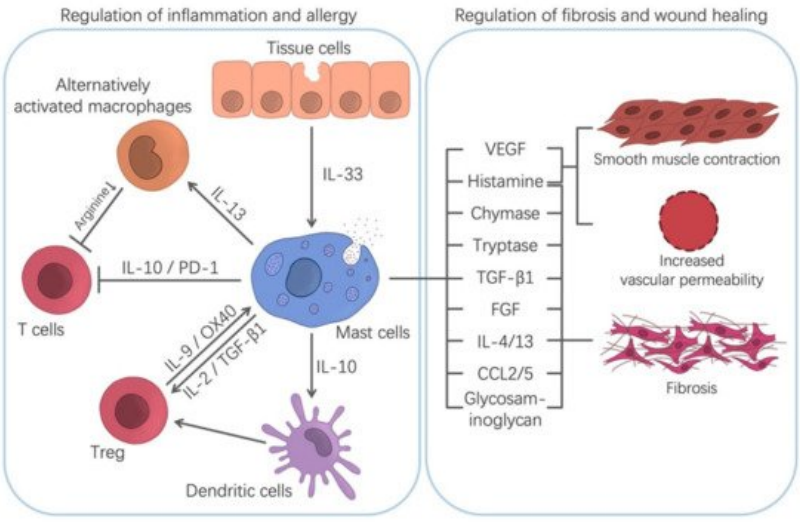

Figure 2. MCs in allergic reactions and inflammation. By releasing various cytokines and mediators, MCs can interact with other immune cells (e.g., they can promote the growth of Tregs and inhibit the generation of common T cells). Furthermore, MCs promotes smooth muscle contraction, increasing vascular permeability and promoting fibrosis. These processes suggest that MCs play an important role in wound healing, immune tolerance, and the suppression of allergies and inflammation.

The regulation of chronic inflammation by MCs has also been reported [4][5]. It is generally believed that $CD4^+CD25^+Foxp3^+$ regulatory T cells (Tregs) are a crucial cell in graft-versus-host disease (GVHD), which can mediate immunosuppression, thereby inhibiting disease progression and significantly reducing the incidence and mortality of the disease [4]. Remarkably, MCs are also involved in this process. It was reportedly difficult for MCs-deficient mice to develop graft tolerance [4]; however, immune tolerance can be re-established after the infusion of bone marrow-derived MCs [55]. Further studies have shown that activated Tregs can release IL-9, a factor associated with the growth and activation of MCs, to induce the recruitment and activation of MCs, which mediates local immunosuppression and immune tolerance [4]. Moreover, activated MCs can release TGF-β, which further activates Tregs and regulate the release of IL-9 [56]. Besides, Tregs can stabilize the cell membrane of MCs through the OX40-OX40L receptor, thus inhibiting the degranulation of MCs mediated by FcεRI and reducing rejection (**Figure 2**) [57].

4.2. Regulation of Allergic and Inflammatory Diseases

There is growing evidence that MCs play an important role in inhibiting allergic reactions and inflammation. It has been found that oral immunotherapy (OIT)-induced desensitized MCs have a robust regulatory function and can cooperate with Tregs to form a regulatory network, which helps control food allergy [6]. It has been reported that the anti-allergic part of MCs is mainly realized through the production of regulatory cytokines, such as IL-2 and IL-10 [6]. Several studies have found that the inhibition of the immune responses in the skin, intestines and bladder by MCs depends on IL-10 [19]. MCs-derived IL-10 can induce the production of Tregs by DCs (**Figure 2**). However, how the immunosuppressive effect of IL-10 is regulated at the molecular level remains to be determined. Thymic-derived Tregs are a type of suppressive T cell, which accounts for 5–10% of circulating $CD4^+$T cells [58]. Studies have shown that Tregs can reduce the production of allergen-specific IgE and pathogenic Th2 and inhibit the degranulation of MCs and basophils, which push forward an immense influence on the control of allergic symptoms [6][59]. Tregs impairment is related to a loss of tolerance, autoimmunity and allergy [59]. In a similar manner, IL-2 is also involved in MCs-mediated immunosuppression and is critical for the development, amplification, activity and survival of Tregs [60]. IL-2 secreted by MCs can effectively expand Tregs populations and then inhibit the immune response. Another cytokine, IL-33, can indirectly participate in the immunosuppressive response by stimulating MCs to secrete IL-2, promoting ST2-independent immunosuppression in Tregs (**Figure 2**) [61][62]. Meanwhile, some studies have shown that IL-33 can promote the secretion of IL-13 by MCs, which inhibits the production of IL-12 by DCs in the skin. This can hinder the Th1 cell response to cutaneous antigen exposure [63].

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