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Mast cells are at the interface between the external environment and the inner organism

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Mast cells localized at the level of the mucosal barrier in the skin, lung, and gastrointestinal tract, intervene in the modulation of the function of the epithelial cells and are involved in innate and adaptive defensive responses. In this context, mast cells intervene in the recognition and clearance of microbial pathogens. This mini-review article discusses the role of mast cells in these barrier systems.

KEYWORDS

mast cells, gastrointestinal tract, lung, skin, barrier system

Introduction

In rodents, mast cells are classified into mucosal mast cells (MMCs) or connective tissue mast cells (CTMCs) (1). MMCs are localized between epithelial cells in the mucosa of the lung and gastrointestinal tract. In their cytoplasmatic granules, chondroitin sulfate and a few amounts of histamine and carboxypeptidase, are present (2), whereas CTMCs are localized in the intestinal submucosa, skin, peritoneal cavity, and generally occupy a perivascular position surrounding blood vessels. In their granules heparin and large amounts of histamine and carboxypeptidase are present (3).

Another possibility to classify mast cells in humans is founded on the presence in their granules of high levels of tryptase but little or no chymase (MC_T) in intestinal and pulmonary mucosa, predominantly found at mucosal sites, resembling rodent MMCs, or mast cells containing chymase, and little or no tryptase (MC_C), and finally, mast cells containing tryptase, chymase, and carboxypeptidase (MC_{TC}), resembling rodent CTMCs, predominantly found in the skin, lymph nodes, and lung and gut submucosa (4, 5). In the human small intestine, MC_T constitutes ~98% of all mast cells in the mucosa, while ~13% of MCs in the submucosa are MC_T (6). The protease content of mast cells is strictly correlated with heterogeneous cytokines and receptor expression.

More recently, Tauber et al. (7) using *in silico* investigation, have analyzed single-cell profiles of mast cells from different organs in mice and humans. In these latter, they identified seven mast cell subsets distributed in 12 organs with different transcriptomic core signatures. MC1 is preferentially localized in the bladder, MC2 in the lung, and MC4, MC6, and MC7 in the skin. MC3 and MC5 are localized in different organs, but not in the skin.

The contribution of mast cells to mucosal barrier control is mediated through the modulation of epithelial function and innate and adaptive immunological responses. The skin, lung, and gastrointestinal tract are potential portals of entry for foreign agents and are involved in the recognition and clearance of microbial pathogens (8), through the modulation of defense functions in these strategically important sites (9, 10). Activation of mast cells in the skin, gastrointestinal tract, and airways mediates the release of several mediators, responsible for different symptoms (Table 1).

TABLE 1 Different symptoms induced by the release of mast cell mediators in the skin, gastrointestinal tract, and airways.

Skin
Flushing
Pruritus
Urticaria
Angioedema
Gastrointestinal tract
Abdominal pain
Diarrhea
Esophageal reflux
Nausea
Vomiting
Airways
Nasal congestion
Nasal pruritus
Bronchospasm
Swelling
Wheezing

Mast cells in the skin

The most important skin function is to protect the host from invasion, using physical barriers and a complex network of resident immune cells, including macrophages, T and B lymphocytes, mast cells, neutrophils, eosinophils, and Langerhans cells, and non-immune cells. Skin mast cells are regulated by the skin microbiota extending from the surface to the dermis and dermal adipose tissue. In germ-free mice, few mast cells are recognizable in the dermis, and the intradermal injection in these mice of staphylococcal-derived lipoteichoic acid is responsible for the induction of the expression of stem cell factor (SCF) in keratinocytes, which induces the rescue of the dermal mast cells (11).

Skin mast cells are formed by three distinct cell populations, derived from the yolk sac and the aorta–gonad–mesonephros–derived hematopoietic stem cells in pre-natal life, and bone marrow in post-natal life (12, 13). SCF is secreted by different cells in the skin, and promotes skin mast cell differentiation (11, 14–16).

The number of skin mast cells involved in immune response and host defense (17) varies between 5,120 and 9,472 per mm^3 in physiological conditions, to 260,000/380,000 per mm^3 in pathological conditions, such as mastocytosis (18). Moreover, their number is greatest in the skin's superficial layers as compared with the deep layers (19), and are localized around hair follicles (20), sebaceous and sweat glands, near small blood vessels, and near nerve fibers positive to vasoactive intestinal peptide (VIP), which suppresses mast cell degranulation (21). Small mast cells are found in the subepithelial layer of the skin, and their size and granule content gradually increase in the deep layers.

Skin mast cells are a source of cytokines, chemokines, and growth factors (22, 23). Mast cells induce skin fibroblast proliferation via interleukin (IL)-4 (24, 25), IL-13 (26), vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (bFGF) (27–29). Moreover, mast cells contribute and interact with keratinocytes (30, 31), which, in turn, produce SCF (11, 32). Mast cells synthesize and release keratinocyte growth factor (KGF) (33) and platelet-activating factor (PAF) (31, 34) that activate keratinocytes, and in the meantime, they release histamine, heparin, which inhibit keratinocyte proliferation, controlling epidermal regeneration (35, 36). Finally, tryptase and chymase stimulate fibroblast, inhibit keratinocyte proliferation (37), and regulate epidermal differentiation complex genes, modulating epidermal barrier integrity (38).

Mast cells are involved in many different pathological conditions, including acute and chronic contact hypersensitivity, psoriasis, wound healing, and fibrosis. In acute contact hypersensitivity, mast cell-derived tumor necrosis factor-alpha (TNFα) enhances skin dendritic cell migration to draining lymph nodes, inducing Th-cell expansion in the sensitization phase of contact hypersensitivity (39). In chronic contact hypersensitivity, crosslinked hapten/hapten-specific IgG complexes stimulate mast cells to synthesize IL-10, which, in turn, suppresses the inflammatory reaction (40). In psoriasis, mast cells synthesize TNFα, which promotes dendritic cell migration from the skin to draining lymph nodes (41). In wound healing and fibrosis, mast cells degranulate and release mediators enhances vascular permeability, and recruit inflammatory cells in injured sites. Moreover, mast cell mediators activate fibroblasts to release collagen-promoting fibrosis (42, 43).

Mast cells in the gastrointestinal tract

The intestinal mucosa is lined with enterocytes, separating the lumen from the internal milieu, avoiding the passage of harmful substances, and allowing nutrient and electrolyte absorption. The gut may be considered as a barrier with a defensive function exerted through immune responses, and the acquisition of tolerance against food antigens and the microbiota. The intestinal leakage allows the bacteria to enter the bloodstream, activate pattern recognition receptors, and trigger an immune response (44).

Mast cells are present in all layers of the gastrointestinal tract; their number is higher in the mucosa's lamina propria of the duodenum and colon, as compared to the submucosa (5, 45). Mast cells are preferentially localized next to nerve terminals of the lamina propria, and are activated by substance P, which stimulates mast cells to release inflammatory mediators, including serotonin and proteases, and pro-inflammatory cytokines.

Intestinal mast cells perform intervene in the regulation of ion and water secretion and permeability, blood flow, coagulation, vascular permeability, wound healing, fibrosis, neuro-immune interactions, peristalsis, pain perception, bacterial, viral, and parasitic infections, and innate and adaptive immunity reactions (4, 46–48). All these activities are exerted by intestinal mast cells in physiological conditions and explain their involvement in many pathological conditions including allergic disorders, gastrointestinal infections, chronic inflammatory diseases, and colon cancer (49).

An increased number of mast cells in inflamed segments of the bowel compared with the non-inflamed segments has been demonstrated in patients with chronic inflammatory bowel disease, including ulcerative colitis and Crohn's disease. An impaired balance between pro- and anti-inflammatory mediators released by mast cells causes excessive inflammatory reactions and subsequently symptoms

such as abdominal cramps, diarrhea, and rectal bleeding (50). Mast cells are involved in the inflammatory process in celiac disease. Intestinal bioptic specimens of patients with celiac disease show a correlation between mast cell density and disease severity (51). Gastrointestinal mastocytosis is characterized by an accumulation of mast cells in the gastrointestinal tissue, which may occur during systemic mastocytosis involving other organs such as bone marrow, liver, and skin. Mast-cell infiltration can result in organ dysfunction in aggressive systemic mastocytosis, and gastrointestinal symptoms, including abdominal pain and diarrhea, are present in 60–80% of cases (52). The term mastocytic enterocolitis was coined to describe an increase in mucosal mast cells in patients with chronic diarrhea (53).

Mast cells in the airways

Each of the MC_T and MC_{TC} populations can be further differentiated based on their size, shape, and molecular expression profiles in different lung compartments (54, 55). More than 90% of the mast cells located in bronchi, bronchioles, and alveolar walls are MC_T, whereas MC_{TC} is localized in the subepithelial regions and the connective tissue (56). The higher number of mast cells are localized in the alveoli, where they are involved in the homeostatic regulation of blood flow and act as immune modulators and pro-fibrotic cells.

Bronchial MC_T expresses more histidine decarboxylase than alveolar MC_T. In contrast, in both MC_{TC} and MC_T, the high-affinity receptor for IgE (FcεRI) is expressed in conducting airways but absent in alveolar parenchyma (54). IgE-mediated mast cell degranulation is an established hallmark of allergic respiratory conditions, and none of the mast cell effector functions executed in allergy and asthma take place in the alveolar parenchyma.

In addition to the evidence presented for the role of mast cells in the pathophysiology of asthma (57), there is growing evidence that mast cells may also play roles in other diseases of the airways, such as chronic obstructive pulmonary disease (COPD) (58). Mast cell numbers in the lungs of patients with fibrotic disease are increased compared to control subjects and correlate with the severity of fibrosis (59). Patients with idiopathic pulmonary arterial hypertension have marked infiltration of Kit^+ mast cells near remodeled pulmonary arteries with a predominant perivascular distribution (60). Initial stages of viral rhinitis are characterized by the high presence of mast cells which, together with other immune cells such as T and B lymphocytes, start the inflammatory cascade in the upper airways (61). Histological examination of the lungs of patients who died from SARS-CoV-2 infection revealed extensive infiltration of mast cells in the interstitium and alveoli (62).

Concluding remarks

Mast cells are involved in the first line of defense against foreign pathogens, producing antimicrobial peptides and releasing different pre-formed and newly synthesized mediators. Mast cells exert protection against systemic or localized bacterial infections in the skin, gastrointestinal tract, and airways by facilitating the clearance of enterobacteria from these tissues.

Mast cells exert this action by engulfing bacteria and secrete inflammatory mediators that, in turn, recruit and activate phagocytes, such as neutrophils through the secretion of TNFα, leukotrienes B4 and C4, and are implicated in the protective response (63). The local increase in mast cell number at the site of infection mediated by the c-kit ligand SCF amplifies mast cell-mediated immune response (64). Mast cells themselves are involved in phagocytosis and the production of nitric oxide, superoxide radicals, and antimicrobial peptides. As concerns viral infection, mast cell number increases during pulmonary viral infections in humans (65), and toll-like receptor 3 expression by human mast cells is implicated in the production of interferon-alpha in response to viral exposure (66).

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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