Immunology Letters 177 (2016) 16–21

Contents lists available at ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Review

Mast cells in human digestive tube in normal and pathological conditions

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ARTICLE INFO

Article history:
Received 20 May 2016
Received in revised form 20 June 2016
Accepted 4 July 2016
Available online 5 July 2016

Keywords:
Digestive tube
Ileum
Inflammation
Mast cells
Tumors

ABSTRACT

Mast cells (MCs) are localized in connective tissues and are more numerous near the boundaries between the external environment and the internal milieu including the skin, the respiratory tract, the gastrointestinal tract and the conjunctiva. In the gastrointestinal tract, MCs represent 1–5% of mononuclear cells in the lamina propria of the mucosa and in the submucosa, and they are also found inside the epithelium and deep in the muscle and serosal layers. The gastrointestinal MCs perform their biological functions, releasing mediators, as amines (histamine, serotonin), cytokines, proteases, lipid mediators (leukotrienes, prostaglandins), and heparin. MCs are involved in the pathogenesis of different inflammatory conditions and tumors of the gastrointestinal tract. The use of MCs' tryptase inhibitors or c-KitR tyrosine kinase inhibitors could represent a potential anti-MC therapeutic approach in all the inflammatory and tumor pathological conditions of the digestive tube in which MCs are involved.

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1. Introduction

Mast cells (MCs) originate from progenitor cells in the bone marrow, which move through the circulation and become mature MCs after homing to different organs under the influence of the local microenvironment [1]. MC progenitors enter the blood and exit into tissues by transendothelial migration and are undetectable in the blood. Indeed, MCs are found in human mucosal and epithelial tissues throughout the body, in all vascularized tissues except for the central nervous system and the retina [2].

MCs are localized in connective tissues and are more numerous near the boundaries between the external environment and the internal milieu [3] including the skin [4], the respiratory tract [5], the gastrointestinal tract [6] and the conjunctiva [7].

Human MCsT, containing tryptase alone, correspond to the rodent mucosal mast cells (MMCs) while human MCsTC, containing both tryptase and chymase along with other proteases (carboxypeptidase A and cathepsin G), correspond to the rodent connective tissue mast cells (CTMCs). MCsT are prevalent in the alveolar septa of the lung and in the small intestinal mucosa. In human intestinal mucosa, MCs consist of approximately 2–3% of the inflammatory cell infiltrate localized in healthy subjects [8]. MCsTC predominate in the connective tissue areas, such as

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http://dx.doi.org/10.1016/j.imlet.2016.07.002
0165-2478/

skin, submucosa of the stomach and intestine, breast parenchyma, myocardium, thymus, lymph nodes, conjunctiva, and synovium [9,10].

MCs contain inside their secretory granules powerful biologically active molecules including cytokines, histamine, proteases and proteoglycans, which are released when MCs are activated, and which exert sometimes opposing biological effects [4].

Indeed, it is believed that the role of MCs to physiologic and pathological processes extends far beyond the allergic disease; they are involved in wound healing, in chronic inflammation, tumor growth, and angiogenesis, and may be considered as a component of the immune system [11].

2. Mast cells in the human digestive tube

In physiological conditions, MCs are distributed near to blood vessels and nerves in oral mucosa and dental pulp, and their number increases in several pathological conditions. MCs count range from 25 mm^2 to 42/mm^2 in normal oral mucosa [12]. Kathuriya et al. [13] counted in oral mucosa 32/mm^2 MCs positive to toluidine blue and Batista et al. [14] counted 71/mm^2 in normal healthy gingival. Aminova and Grigorenko [15] estimated the number of MCs in human oesophagus in different ages. In young age, the number of MCs increase from the upper to the lower portion. In old and senile age, they observed delamination and formation of microerosions of the oesophageal epithelium, thickening of the bundles of collagen fibers in the lamina propria and in the submucosa, and increase in the number of MCs. In advanced age, MCs decrease from the mucosa towards the adventitia.

In the gastrointestinal tract, MCs represent 1–5% of mononuclear cells in the lamina propria of the mucosa and in the submucosa, and they are also found inside the epithelium and deep in the muscle and serosal layers [16]. The gastrointestinal MCs perform their biological functions, releasing mediators, as amines (histamine, serotonin), cytokines, proteases, lipid mediators (leukotrienes, prostaglandins), and heparin [17–20].

In the stomach, MCs are distributed mainly in the upper third of the fundic glands portion and in the upper half of the pyloric glands [21]. The intestinal mucosa is coated with a monolayer of epithelial cells, including M cells, goblet cells, Paneth cells, and columnar epithelial cells and is exposed to various stimuli including food materials, commensal and pathogenic microorganisms. In the intestinal lumen there are more than 10^{14} microorganisms [22], which supply nutrients from food materials.

MCs are located in the lamina propria of the healthy intestinal mucosa, where they account for 3% of the cells. MCs regulate these barrier functions, acting on blood flow, smooth-muscle contraction, peristalsis, and immune responses [8,23,24].

MCs in the intestinal mucosa have their own characteristics, different from those of MCs in other sites, as it has been demonstrated by morphological [25,26], and immunohistochemical [25,27] investigations. In humans, most mucosal MCs are tryptase-positive and chymase-negative, alike the rodent mucosal MC subtype, while MC submucosal are tryptase-positive and chymase-positive, alike the rodent connective tissue MC subtype [8,24]. In the human small intestine tryptase-positive MCs amount to ~ 98% of all mucosal MCs and 13% of all MCs in the submucosa [28].The density of mucosal MCs is higher in the terminal ileum due to its immunological role than in the colon, while significant differences within the colon are not recognizable [29,30].

Mucosal MCs are in close spatial relationship with nerve terminals suggesting a their role in neural transmission [31–33] as it has been demonstrated in the rat intestinal mucosa nerve terminals in direct contact with the plasma membrane of mucosal MCs [34] and enteric nerves apposed to intestinal MCs through substance P (SP) and calcitonin gene-related peptide (CGRP)-immunoreactive varicosities [35]. By combined histochemical and immunocytochemical techniques, an association between mucosal MCs and nerve fibers has been demonstrated [36]. In this context, parasympathetic nerve fibers stimulate MCs to release their mediators, which, in turn, may stimulate or inhibit neuronal activity [37]. MCs may affect villous architecture by exerting neurotrophic and neurogenic effects via nerve growth factor (NGF) secretion [38]. Electrical stimulation of nerve fibers causes degranulation of tissue MCs and that these effects are inhibited by atropine or prior treatment with capsaicin [39]. For instance, electrical vagal stimulation was observed to induce gastric mucosal MC degranulation.

2.1. The role of mast cells in inflammation of digestive tube: experimental evidence

MCs contribute to the maintenance of intestinal architecture, regulating turnover, and permeability of intestinal epithelium [40]. The presence and activation of MCs is essential to maintain homeostasis of intestinal mucosa, as an abnormal activation or an excessive activation causes a state of inflammation.MCs intervene in the mechanisms controlling intestinal permeability. Corticotropin-releasing hormone (CRH) acts on intestinal MCs causing an increase of mucosal permeability to horseradish peroxidase [41]. The increased permeability to horseradish peroxidase was abolished by the MC stabilizer, lodoxamide. In this study, electron microscopy showed transcellular passage of horseradish peroxidase through colonocytes. CRH receptor subtypes R1 and R2 were detected in the HMC-1 cell line and in lamina propria MCs in human colon, suggesting that CRH mediates transcellular uptake of horseradish peroxidase in human colonic mucosa via CRH receptor subtypes R1 and R2 on subepithelial MCs. CRH-induced macromolecular uptake in human colon mucosa may have implications for stress-related intestinal disorders.

MCs eliminate pathogens directly by producing proteases and indirectly employing neutrophils and eosinophils to the intestine by increasing vascular permeability [42]. The epithelial layer is influenced by bacterial components and bacteria-derived food metabolites, such as short-chain fatty acids, promoting the production of both antimicrobial peptides [43], and MCs preserve the bacterial homeostasis, stimulating IgA production by B cells/plasma cells [44], favouring epithelial turnover [40], and secreting proteases which regulate epithelial permeability.

MCs are able to recognize and kill the bacterium *Salmonella typhimurium* coated with the C3b fragment of complement and other IgG-coated bacteria [45,46]. These bacteria are then endocytosed via an endosome lysosome pathway. MCs may exert bactericidal activity by an extracellular phagocytosis-independent mechanism, which consists in the production of extracellular structures similar to the neutrophil extracellular traps (NETs). The major components of these MC extracellular traps are DNA, histones, and granule proteins such as tryptase and the cathelicidin antimicrobial peptide LL-37 [47]. Besides their potential capacity to clear bacteria through endocytotic pathway, MCs initiate the immune and inflammatory responses of the host to the invading pathogens. MCs, indeed, are a rich source of early-response cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-4 (IL-4), that can rapidly recruit inflammatory cells at the site of pathogen entry [3]. In mutant W/W^v mice, the absence of MCs leads to a defective innate immune response against bacteria [24].

2.2. The role of mast cells in inflammation of digestive tube: human evidence

MCs exert detrimental effects to the host during bacterial infections by excessive or inappropriate release of inflammatory