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Review

Intestinal mast cells in gut inflammation and motility disturbances ☆

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ABSTRACT

Mast cells may be regarded as prototypes of innate immune cells that can be controlled by neuronal mediators. Their activation has been implicated in many types of neuro-inflammatory responses, and related disturbances of gut motility, via direct or indirect mechanisms that involve several mechanisms relevant to disease pathogenesis such as changes in epithelial barrier function or activation of adaptive or innate immune responses. Here we review the evidence for the involvement of mast cells in the inflammation of the bowel wall caused by bowel manipulation that leads to motility disturbances such as postoperative gastroparesis and ileus. Also in IBD there is substantial evidence for the involvement of mast cells and a mast cell-mediated neuroimmune interaction showing an increased number and an increased degranulation of mast cells. We discuss the potential of mast cell inhibition as a bona fide drug target to relief postoperative ileus. Further research on mast cell-related therapy either by stabilizing the mast cells or by blocking specific mast cell mediators as adjunctive therapy in IBD is encouraged, bearing in mind that several drugs currently used in the treatment of IBD possess properties affecting mast cell activities. This article is part of a Special Issue entitled: Mast cells in inflammation.

1. Mast cells and gut functions: scope of this review

Inflammation of the gut wall as observed in postoperative ileus (POI) or in inflammatory bowel diseases (IBD) can involve a complex interplay between neurons, smooth muscle cells, interstitial cells of Cajal, enteric glial cells, vascular tissue, mucosal epithelial cells, mast cells, enteroendocrine cells and immunocytes [11,21,77,86]. In this process mast cells are proposed to act as sentinels at the host–environment interface, responding to allergens, bacteria, toxins, parasites, neuropeptides and stress by initiating enhanced epithelial secretion, peristalsis and alarm programs by releasing proinflammatory mediators [3,8,9,60]. Mast cells in the gut can be sensitized against foreign antigens but also play an important role in the innate and adaptive immune responses that are very relevant to human disease, such as in oral vaccination strategies, or snake and honeybee responses [59]. Other more specific examples thereof are POI and IBD, which are described in the current review. Elsewhere in this special issue a critical role for mast cell activation in for instance the pathogenesis of functional GI disorders such as IBS and eosinophilic esophagitis is highlighted.

2. Mast cells in the gastrointestinal tract

Progenitor mast cells are derived from myeloid pluripotent hematopoietic progenitor cells in bone marrow; they circulate in the blood flow and migrate into peripheral tissues where they further differentiate towards different subtypes of mature mast cells depending on the local microenvironment [67,86]. Mast cells are derived from hematopoietic $Thy1^{+}cKit^{high}$ mast cell-committed precursors [68], and their growth and proliferation is regulated by growth factors such as the cKit ligand stem cell factor (SCF), nerve growth factor (NGF) and interleukins (IL3, IL4, IL9, and IL10) [36]. There are large species differences in mast cell distribution as well as density, where especially the mouse GI tract is generally low in intestinal mast cells. In other rodents, mast cells can be found in the lamina propria of the intestine, but also associated with the epithelium, the submucosa and the serosa, where subsets of mast cells exist divided in different classes such as connective tissue mast cells, located mainly in connective tissue around blood vessels and in the peritoneal cavity and mucosal mast cells found in the intestinal mucosa. Important differences exist in these subpopulations of mast cells for instance regarding their activation and responses to basic secretagogues, such as compound 48/80 and bee venom peptide 401 [5,6,27]. Specific differences in mast cell subpopulations are highlighted more extensively in this review series and elsewhere, i.e. see [36] and for recent reviews [35] and [9] amongst others.

In humans, mast cell contents are used to describe different classes: tryptase and chymase containing mast cells (closely resemble

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connective tissue mast cells) and only tryptase containing mast cells (closely resembling the rodent mucosal mast cells) [9,10,67]. Mast cell regulators such as SCF and IL4 promote mast cell development and/or regulate mediator release [9]. Mast cells can be activated via the classical IgE-mediated pathway but can also be activated by a variety of substances such as cytokines, hormones, immunoglobulins, neuropeptides, and complement components. TLR triggering also activates mast cells and activates cytokine production most likely via mechanisms that require new protein synthesis [87]. Hence, functional activation of mast cells leads to degranulation of their mediators preformed and stored in secretory granules or to de novo synthesis of mediators. Piecemeal degranulation is an alternative form of secretion involving the selective secretion of certain mediators (and therefore not the whole content) of the secretory granules. The preformed mediators include tryptase, histamine, serotonin (5-hydroxytryptamine), serine proteases, proteoglycans and cytokines such as tumor necrosis factor α (TNFα). Arachidonic acid metabolites (prostaglandins and leukotrienes), platelet activating factor and several chemokines and cytokines (Il-1β and IL-6) can be synthesized de novo. Cytokines also change the cytokine profile released by mast cells: IL4 decreases the amount of proinflammatory cytokines and increases the release of Th2 cytokines [35,89].

3. Neurogenic control of mast cells in the GI tract

Mast cells function as intermediaries between the inflammatory cells and their mediators and the neuroenteric system. Both cell types are affected by the inflammatory environment and upon activation release mediators which affect the gastrointestinal neuromuscular and secretory functions [7,8,19,75,78]. These mediators can stimulate epithelial cells, residential macrophages and intrinsic and extrinsic neurons amongst others. The close morphological relationship between mast cells and afferent nerve endings both in human and animal studies supports the latter notion [78]. There is early evidence for bidirectional communication between mast cells and neurons in the gastrointestinal tract and the mast cell may be regarded as the classical immune cell that is activated by neuronal factors and neurotransmitters. MacQueen et al. demonstrated in 1989 that rats sensitized to a protein antigen in combination to an audiovisual cue, and then re-exposed to an audiovisual cue alone released a quantity of protease that was not significantly different from animals re-exposed to both the cue and the antigen [54]. These results support a role for the central nervous system as a functional effector of mast cell function [7,19,75,78]. In conjunction, a positive feedback loop is described during which mast cell mediators activate nerves that on their turn release neurotransmitters able to enhance mast cell activity [74]. These effects might influence the secretory response for instance in allergic or inflammatory conditions. However mast cell activation and the subsequent activation of afferent nerves might also influence motility or blood flow via mediators such as substance P, calcitonin gene related peptide (CGRP), proteases (PAR2) [75]. These protective mechanisms affecting blood flow and motility, triggered by sensory neurons, also orchestrate modifications of the immune function [39]. Therefore, the mast cell induced secretion, increased blood flow and increased propulsive motor activity actually fit within a gastrointestinal defence program aiming at flushing and eliminating the luminal antigens, microbes, toxins or harmful substances, as put forward by Wood [90].

4. The clinical features of postoperative ileus

Postoperative ileus (POI) is an almost inevitable phenomenon occurring after each abdominal surgical procedure that includes bowel manipulation, although POI may sometimes also be associated with extra-abdominal operations. It clinically presents as the inability to tolerate food with abdominal distension, absence of bowel sounds and lack of flatus and defecation. Nausea and vomiting, pain and postoperative fatigue further contribute to the morbidity and prolonged hospitalization of patients. On average, this period lasts 2–4 days for conventional abdominal procedures, but decreases to as little as 2 days or less in case of laparoscopic surgery [22]. Some surgeons consider the inability to tolerate food and absence of bowel sounds during the first few postoperative days as a normal phenomenon, and only consider "prolonged" or "pathologic paralytic ileus," which lasts more than 3 days after surgery, as clinically relevant. Others propose to prolong this period to more than 6 days [1]. Transient inhibition of gastrointestinal motility is well documented as underlying mechanism and involves the entire gastrointestinal tract. It is established that not all segments are equally affected; small intestinal motility is on average disturbed for approximately 24 h, gastric motility between 24 and 48 h, whereas colonic motility is impaired between 48 and 72 h (reviewed for instance in [21,22,46]). It should be emphasized though that normalization of motility, for example the return of the migrating motor complex in the small intestine, does not necessarily imply that normal function and transit have returned. Nevertheless, these studies underscore that colonic motility is the main determinant of clinical recovery.

5. The pathophysiology of POI

Over the past decade, our insight in the pathophysiology has increased exponentially. The general paralysis of the entire GI tract, including the un-manipulated segments, is a commonly seen characteristic of POI. This clinically important aspect of POI involves the activation of an inhibitory neural reflex arch by local inflammatory infiltrates [18], and was recently also shown to involve the production of IFNγ by CCR9+ T-cells that are activated at the site of manipulation [28]. Although a role of gut-homing inflammatory cells triggered by handling of the intestine is now put forward as the key event in the widespread inflammatory response seen after local intestinal manipulation in POI, see for instance [28], insight in the bidirectional interaction between the immune system (mast cells, macrophages and other leukocytes) and the autonomic nervous system (afferents and efferents) has significantly contributed to a better understanding of its pathophysiology [4,11]. Moreover, it has become clear that inflammatory mediators released by leukocytes within the gut wall also directly impair smooth muscle contractility [4,48,83].

The intestinal mucosa, submucosa, and muscularis externa are densely populated with several subsets of resident phagocytes and antigen presenting cells (APCs) of haematopoietic origin [32]. Under healthy conditions, such resident macrophages are organized into a network of intramuscular antigen presenting macrophage-like cells, that reside at the level of the myenteric plexus (between the longitudinal and circular muscle layer) and in the intestinal serosa [60,61]. Most of these cells possess phagocytic properties, express LPS binding receptor CD14 [32], express TLRs and are activated by LPS [11,21,29,32,61]. The latter distinguishes these muscularis phagocytes from those found in the lamina propria that are—at least in human—generally negative for CD14 and most TLRs and display a surprising tolerance towards TLR ligation [76]. Moreover, muscularis macrophages stain for macrophage scavenger receptor CD163, that has been shown to possess bacteria binding and sensing capacities [31]. Thus, this phagocyte population in the muscularis externa has an interesting nature and most likely consists of different subsets of APCs, including macrophage-like cells expressing F4/80 and dendritic cell-like cells expressing most common DC markers such as CD11c and DEC205 [32]. However in mouse bowel wall, MHCII-positive cells outnumber $F4/80^{+}$ cells indicating that the majority of these resident muscularis macrophages function as APC. Hence, the exact cellular constituent of the phagocyte population is yet to be defined but their importance in the development of the intestinal inflammation following intestinal manipulation was first demonstrated in earlier studies done by Kalff et al. [43,44]. In a rodent model, surgical manipulation caused an increased expression of intergrins on muscularis macrophages, as well as an increase in resident phagocytes that stained for the activation