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Review

Intestinal mast cells in gut inflammation and motility disturbances ☆

Benedicte Y. De Winter [a], Rene M. van den Wijngaard [b], Wouter J. de Jonge [b,*]

[a] Laboratory of Experimental Medicine and Pediatrics, Department of Gastroenterology, University of Antwerp, Antwerp, Belgium
[b] Department of Gastroenterology and Hepatology, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

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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.

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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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* Corresponding author at: Neuro-Immunology Group, Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, S2-180, Meibergdreef 69-71, 1105 BK Amsterdam, The Netherlands.
E-mail address: w.j.dejonge@amc.uva.nl (W.J. de Jonge).

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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

marker lymphocyte function-associated antigen (LFA-1). In a series of elegant bone marrow transfer experiments it was shown that these monocyte derived muscularis APCs contribute to the pathogenesis of POI via release of NO [48]. Furthermore, in a mouse model of genetic depletion of macrophages (due to a spontaneous mutation in the *colony-stimulating factor-1* gene (*csf1*) that is required for early embryonic macrophage development ($Csf1^{op/op}$) mice) [50], it was shown that intestinal manipulation failed to induce inflammatory mediators and subsequent recruitment of leukocytes into the muscularis. These mice had near normal in vitro jejunal circular muscle function and gastrointestinal transit despite surgical manipulation, which may be indicative of the importance of macrophages in POI. With regards to these experiments caution should be taken in interpretation of these data as it should be mentioned that osteoclasts are the prime cell type affected in these mice so the genetic deletion is likely to affect the development of other cell types with APC capacity.

6. Mast cells in pathophysiology in POI in rodent models

Next to a neurogenic component in the early phase of POI [20,21], an inflammatory component is a key pathogenic factor in the late phase of POI and in endotoxin-induced or septic ileus. The importance of mast cells in the inflammatory cascade triggered by intestinal manipulation was demonstrated in experiments using mast cell stabilizers [17]. In addition to the afore-mentioned residential APC population in the intestinal wall, mast cells are proposed as key players in the initiation and maintenance of this inflammatory circuitry. For instance, degranulation of connective tissue mast cells after intestinal manipulation was shown by an increase of mast cell protease in the peritoneal fluid inducing an inflammatory infiltrate in the murine intestine and gastroparesis [17]. Both events could be prevented by mast cell stabilizers such as ketotifen and doxantrazole and could not be elicited in mast cell deficient Kit/Kit^{v} or $KitW^{sh}/W^{sh}$ mice ([17] and unpublished data, 2011). Reconstitution of these mast cells deficient mutant mice with wild-type mast cells restored the capacity to recruit leucocytes in response to intestinal manipulation [17]. Conversely, incubation of intestinal loops in solution containing the mast cell secretagogue compound 48/80 induces an inflammatory response and POI, further indicating the involvement of connective tissue mast cells in this process given the unresponsiveness of mucosal mast cells to Compound 48/80 [6]. A scheme summarizing these experimental data is given in Fig. 1. Also in an endotoxin-induced ileus model there is evidence for an increased number and activity mast cells next to residential macrophages (personal communication) [14]. However more studies on the role of mast cells and their mediators in sepsis-induced ileus are awaited.

Alternative strategies to stabilize mast cells have been explored based on their expression of cholinergic receptors [42,78,79,88]. More recently, additional experimental evidence has been obtained implicating cholinergic receptors expressed on mast cells as anti-inflammatory therapy for POI. It was shown that vagal stimulation reduced the period of intestinal hypomotility. Activation of nicotinic receptors on—presumably—mast cells by vagal input was put forward to attenuate mast cell activation by intestinal manipulation [51,78] and thus promote gastrointestinal postoperative motility. An interesting non-invasive and physiological intervention to activate this neuroimmune pathway is enteral administration of lipid-rich nutrition. Perioperative administration of lipid-rich nutrition reduced manipulation-induced local inflammation of the intestine and accelerated recovery of bowel movement [15,16]. It is likely that the cell types that are targeted by this nutritional activation of CCK-dependent vagal signalling include mast cells, explaining the amelioration of POI pathogenesis by high-lipid nutrition.

7. Evidence for the role of mast cells in human POI

In conjunction to the observed inflammatory response to intestinal manipulation in rodent models, inflammation induced by handling of the intestine is also demonstrated in human tissue. Intestinal tissue removed during surgery shows activation of resident macrophages and time-dependent induction of IL6, IL1β, TNFα, iNOS, COX-2, ICAM-1 and LFA-1 [43–45,80]. In line with this, increased levels of the cytokines TNFα, IL6, IL8 and IL10 have been documented in the peritoneal fluid and blood of patients undergoing abdominal surgery [80,81,85]. In conjunction, influx of leukocytes was clearly demonstrated in intestinal tissue removed at the end of the surgical procedure and in tissue obtained from re-operated patients [80,81]. In addition, in vivo recruitment of radio-labelled leukocytes to the intestine was demonstrated in patients undergoing conventional abdominal surgery, but not in patients undergoing a laparoscopic procedure [80].

The importance of mast cells in the pathogenesis of POI could be verified in human studies as well. Mast cell mediators are detected in peritoneal lavage fluid very early during surgery that involved bowel inspection and handling. Intestinal manipulation during abdominal hysterectomy resulted in an immediate release of tryptase in the peritoneal fluid followed by an increase of IL6 and IL8 [80]. The degree of intestinal handling correlated with the degree of mast cell activation and the subsequent inflammatory response. Even very gentle inspection of the intestines at the beginning of the abdominal procedure increased the level of peritoneal mast cell-derived tryptase in this study [80,81]. Similar data were obtained by others that showed that intestinal handling triggered mast cell activation [80] as well as leukocyte infiltration in large bowel resection material [45].

Stabilization of mast cells has been proven successful in our mouse model of POI [17]. Pre-treatment with the mast cell stabilizers ketotifen and doxantrazole significantly reduced the release of mast cell mediators in the peritoneal cavity, impaired the inflammatory response to intestinal handling and prevented POI. Based on these findings, we conducted a dose-finding pilot study on 60 patients undergoing major abdominal surgery for gynaecological malignancy with standardized anaesthesia, randomized to oral treatment with ketotifen (4 or 12 mg) or placebo [81]. Gastric retention 1 h after liquid intake was significantly reduced by the highest dose compared to placebo. Abdominal cramps improved significantly in patients treated with 12 mg ketotifen, whereas other clinical parameters were unaffected. This study indirectly supports the mast cell-inflammation cascade as key event in postoperative ileus, providing proof-of-concept for further investigation of mast cell stabilizers as a therapeutic approach for postoperative ileus.

8. Mast cells affecting barrier function in POI

Intestinal manipulation induces barrier dysfunction that is likely to perpetuate the inflammatory response, acting via a mechanism that is likely to be dependent on mast cells. In patients, barrier dysfunction frequently occurs during abdominal surgery and has been associated with increased postoperative septic morbidity in surgical patients undergoing laparotomy [52,53,63,66]. In addition to a key role for mast cells in intestinal manipulation (IM) induced inflammation in this model of POI [17], as well as in humans [80,81], mast cell activation has been associated with disturbed intestinal barrier function in several disease entities such as stress-induced hypersensitivity of the bowel [69] and endotoxemia [62]. Hence, mast cell activation may be a contributing factor in the pathogenesis of POI by inducing barrier disturbances after IM. Mast cells degranulate within seconds to a few minutes upon chemical physical and pathogenic stimuli. The quick release of mediators is responsible for a rapid loss of barrier function in in vivo models of helminth infection [56], stress [69] and endotoxemia [23].

The exact mechanistic role mast cells have in POI pathogenesis remains to be demonstrated but in the above mentioned models, the release of serine proteases, including tryptase, following triggering of mast cells is responsible for an increase in epithelial permeability,

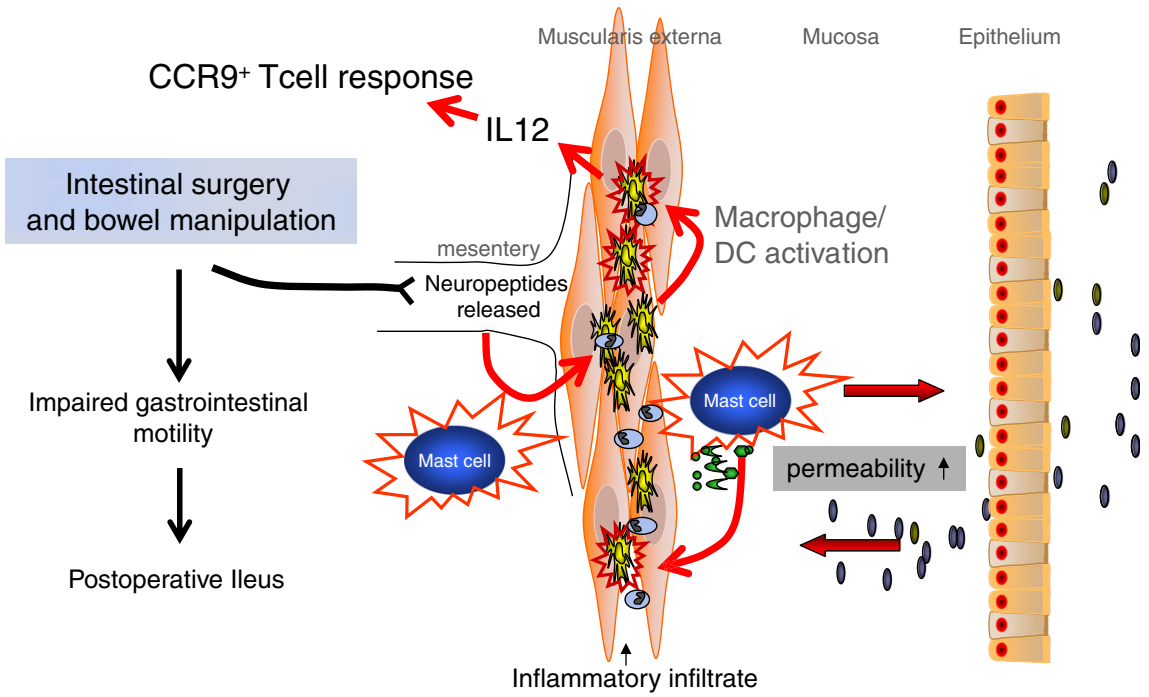

Fig. 1. Neurogenic influences on epithelial barrier function, contributing to the pathogenesis of postoperative ileus. Hypothetical scheme of the pathogenesis of postoperative ileus (POI) based on previous observation in rodent models and human clinical data as mentioned in the text. Intestinal manipulation activates a neurogenic inhibitory pathway that involved sympathetic nerve fibers, leading to an neutrophilic infiltrate in the bowel wall. Alternative mechanisms have recently been described regarding the so-called "field effect" that involves intestinal dendritic cell activation and IL-12 production leading to a systemic Th1 response targeting the gut.

possibly via the activation of protease activated receptor-2 (PAR-2) that is expressed on epithelial cells (see Fig. 2). A purported role for mast cell-related barrier disturbance in POI is not so far-fetched. Within the serosa and mesentery, mast cells are found close to blood vessels before entering the gut wall, often in pairs or threes, and particularly closely associated with afferent nerve fibers (<25 μm) [13]. Mast cells are vital for the recruitment of neutrophils and the elimination of bacteria from the peritoneal cavity, which is exemplified by the fact that mast cell deficient mice show a significantly increased mortality and impaired bacterial clearance in a model of acute septic peritonitis [24].

As indicated, the exact nature of the mast cell mediator that affects barrier function in POI remains to be elucidated, but it likely involves similar rapid mechanisms and neuromediator release. Neuropeptides such as substance P or CGRP released from activated afferent nerves could be involved and once activated, vasoactive and proinflammatory substances such as histamine, and proteases are released by mast cells in the peritoneal cavity. As described above, both in rodents and human, these agents can indeed be detected in the peritoneal fluid immediately after intestinal manipulation. Other mediators, such as IL1β, are presently considered as candidate mast cell-derived cytokines involved in the pathogenesis of POI. Given the anatomical location of mesenteric mast cells, i.e. adjacent to the mesenteric blood vessels where these enter the intestinal wall [13], mast cell mediators will easily diffuse into the mesenteric blood vessels. Despite the involvement of T cell responses in POI [28], mast cell activity could explain the diffuse increase in mucosal permeability observed after intestinal manipulation [84]. When fluorescent LPS and fluorescent microbeads are introduced into the intestine prior to surgery, intestinal handling results in translocation of fluorescent material through the mucosa into the intestinal wall. Once the beads enter the intestinal wall, they are phagocytosed by the resident macrophages or transported to the lymph nodes via the lymphatics and travel back to the gut tissue [71,72,84]. As such, mast cell activation could represent a key event that triggers the next stage of the inflammatory cascade, i.e. activation of muscularis APCs and the subsequent widespread inflammatory response [28]. Mast cells therefore should be considered as sentinels of the peritoneal cavity providing protection against potential threats.

9. The option of mast cells inhibition measured against current treatment of human POI

The preventive techniques and treatment of POI are reviewed elsewhere [46]. Important to stress however is that for new drugs to enter the clinic, they will have to prove their clinical benefit against or in combination with the current new and exciting initiatives in peri-operative patient care. In particular the fast track program, a multimodal approach for patients undergoing colonic surgery, has proven to significantly reduce the rate of peri-operative morbidity, hospital stay and costs [46]. In this program, several peri-operative measures, i.e. restricted fluid management, optimised analgesia, forced patient mobilisation and early oral feeding, are introduced into patient management with impressive results. Most likely fluid restriction and an effective epidural analgesia are the key factors determining the outcome. To what extent a similar improvement is achieved in other types of surgery and whether the fast track program can easily be implemented in a general surgical ward remains to be awaited. Hence, it should be noted that that postsurgical recovery can be significantly improved with relatively simple and cheap measures rather than pharmacological intervention.

10. The role of mast cells in GI disease

10.1. Inflammatory bowel diseases

Inflammatory bowel diseases (IBD) includes ulcerative colitis (UC), Crohn's disease (CD) and indeterminate colitis. It is generally assumed that IBD results from an uncontrolled immune response in genetically predisposed subjects towards a normal microbial gut flora [64,91]. There is substantial evidence for the involvement of mast cells and a mast cell-mediated neuroimmune interaction during IBD as demonstrated both by experimental animal studies and human data a.o.

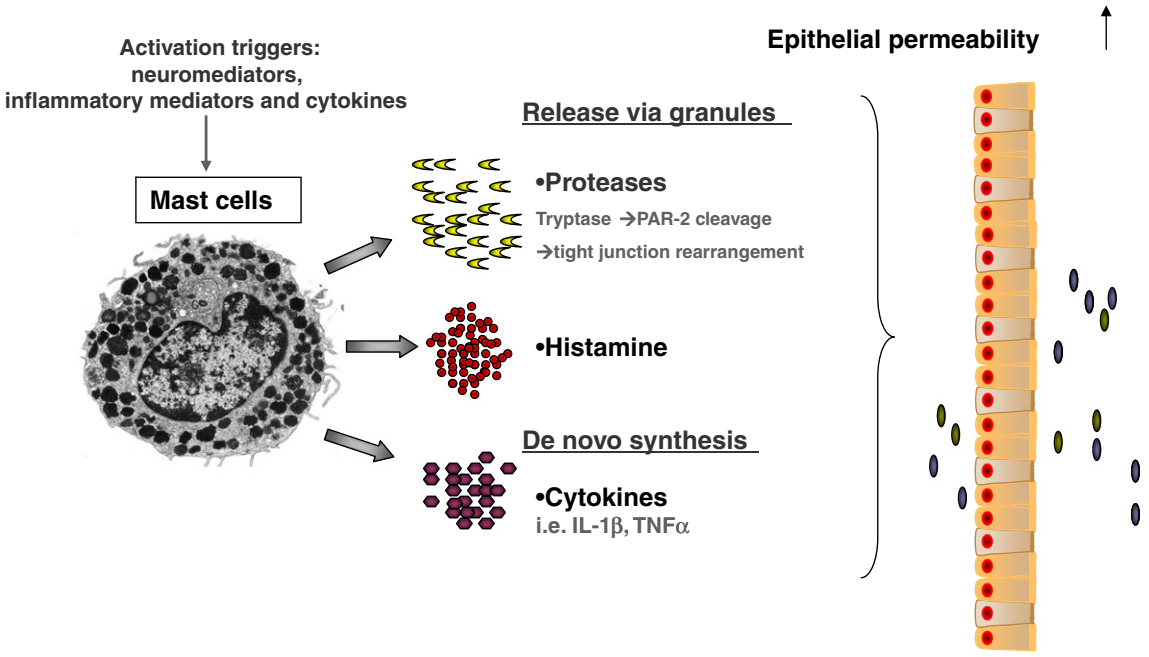

Fig. 2. Mast cells affect intestinal barrier function via the release of pre-stored and de novo synthesized mediators.

reviewed in [49,67]. Coldwell et al. showed an increased number of mast cells close to afferent fibers containing CGRP in the inflamed serosa in a rat model of dextrane sulphate sodium (DSS)-induced colitis, as well as an increased percentage of colonic splanchnic afferent fibers responding to 5-HT during acute inflammation (day 7) and in the recovery period (21 days) [13]. In the trinitrobenzene sulfuric acid (TNBS)-induced rat model of colitis an increase in mast cell number and activation is also shown by others [58,92]. However, Menozzi et al. showed a differential role of mast cells numbers in TNBS colitis in rats with a decrease in the acute period and an increase at day 60 suggesting a role for the mast cells in the late phase in tissue repair [58]. A role for mast cells in fibroblast proliferation, collagen production and contractile activity was also shown by Xu et al. in a rat model of TNBS colitis [92]. Interestingly mast cells seem not be essential in the development of TNBS colitis in rats as TNBS induced similar degrees of colonic inflammation and adhesions in mast cell deficient rats [34]. This conclusion was supported by evidence in an IL10 deficient mice, which are highly susceptible to developing IBD for instance after exposure to the non-steroidal anti-inflammatory drug piroxicam. IL10 deficient mice with mast cell deficiency developed moderate to severe colitis after exposure to piroxicam to the same degree as mast cell-sufficient IL10−/− mice, indicating that the absence of mast cells did not affect the severity of IBD [12]. However, mast cell deficiency predisposed the mice to develop spontaneous colitis (without exposure to piroxicam) associated with increased intestinal permeability indicating a protective role of mast cells probably related by enhancing the efficacy of the intestinal barrier [12].

Another commonly used inflammatory model in rats is the DSS colitis model. Also in this DSS colitis model, there is evidence for mast cell proliferation and increased degranulation [40]. Also in cats with enterocolitis an elevated number of mast cells were identified mainly in the inflamed segments [47]. Eliakim et al. provided evidence for mast cell involvement in an acetic acid-induced and a TNBS-induced colitis model in rats by the use of the mast cell stabilizer ketotifen [25,26,40]. Ketotifen significantly decreased macroscopic damage to the colon accompanied by a decrease in platelet activating factor (PAF), prostaglandin E2, thromboxane B2, leukotriene B4 and C4 generation and nitric oxide synthase activity [25,26]. The effect of ketotifen was also shown in a model of *Trichinella spiralis* infection in the rat by a reduction of mast cell hyperplasia, mast cell protease activity and hypermotility in ketotifen-treated rats [73].

Concerning evidence for mast cells in human IBD, data are reviewed the last years [19,38,67], showing an increased number of mast cells in the colorectal mucosa, in the lamina propria and in the submucosa from patients with CD and UC. Next, not only the mast cell content but also the degranulation of mast cells was markedly altered in the mucosa of IBD patients as evidenced by an increased expression of TNFα, IL6, substance P and elevated histamine, prostaglandins, leukotrienes and tryptase levels [2,65,70]. Together, these studies suggest that mast cells are involved in chronic inflammation of the gut. Also in IBD, the bidirectional communication between mast cells and nerves stands as mediators from both cell types are capable of stimulating or inhibiting each other's function. Mast cell and neuronal mediators can increase vascular permeability, influx of inflammatory cells, gut motility and hyperalgesia [67]. Nevertheless, direct evidence for the interaction between mast cells and nerves is limited in the pathogenesis of IBD as it is the case for ileus. Limitations are the difficulty of studying this interaction directly in human colon and the search for the first trigger for activation of mast cells or nerves also remains a key question.

The therapeutic potential of mast cell stabilizers in the treatment of IBD merits further investigations. This potential is supported by the following evidence. On the one hand some of the drugs currently used in the treatment of IBD possess properties affecting mast cell activities such as 5-aminosalicylic acid, steroid therapy and methotrexate as evidenced by in vitro research [38]. 5-Aminosalicylic acid inhibits histamine and prostaglandin D2 release in stimulated intestinal mast cells in vitro [33]. And it has been known for decades that corticosteroids reduce the number of mast cells in rectal biopsies of IBD patients treated with corticosteroids independent of the degree of inflammation [37], whereas dexamethasone was shown to affect the growth and differentiation of bone marrow derived mucosal mast cells in vitro [57].

On the other hand some preliminary data on ketotifen in the treatment of IBD are available [38]. Marshall and Irvine describe 3 case reports with a benefit from ketotifen in the treatment of respectively a patient with Crohn's disease, colitis ulcerosa and collagenous colitis [55], whereas Jones et al. report the beneficial effect of ketotifen in 5 out of 10 children with mild to moderate ulcerative colitis [41]. Although this evidence is rather anecdotal, a more recent open-label phase II multicentre pilot study in 56 patients with mild to moderate active ulcerative colitis showed a beneficial effect of APC 2059, a

tryptase inhibitor, as evidenced by an improvement or normalization of the disease activity index in more than half of the patients with continuing symptoms despite oral 5-aminosalicylate therapy [82]. The tryptase inhibitor proved to be safe with as most common adverse events reported in more than 10% of the patients headache (19.6%), injection site erythema (12.5%), and injection site burning (10.7%) [82].

11. Concluding remarks

Both the experimental data and the clinical data support 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 or motility disturbances associated with intestinal inflammation. In accepting that the "inflammatory" or "secondary prolonged" phase of POI is clinically most relevant, therapy should preferentially aim to prevent or reduce the inflammatory response to intestinal handling. Needless to stress though that interference with the immune response—or mast cell stabilization—may have devastating effects on the first defence against bacterial infection and perhaps even more importantly on wound healing. The latter is of clinical importance as increased risk on anastomotic leak is the most feared consequence of any immune modulating therapy. Even if drugs prove to be safe, ideally, handling of the intestine should be prevented or minimized, most likely explaining the shortened POI reported after minimal invasive or laparoscopic procedures. Moreover, one would rather like to prevent than to treat inflammation, again provided that treatment does not interfere with the healing process or does not lead to an increased risk of infectious complications. Interference early in the inflammatory cascade may also be more effective compared to drugs administered at a later stage when inflammation is well established and a variety of inflammatory mediators are released. Therefore, given the fact that mast cells and macrophages initiate and to a large extent orchestrate the cascade of events, these immune cells seem to be the most interesting targets for treatment.

It remains an intriguing question whether the main initiators of the inflammatory cascade are residential macrophages or mast cells. The role of residential APCs (dendritic cells or macrophages) is undoubtedly proven [18,28–30,44,48] and some authors support their role as first responders and conductors orchestrating the inflammatory events after surgical manipulation or endotoxin exposure [4]. Recently, a hypothesis was proposed suggesting a first responder role for peritoneal mast cells adjacent to mesenteric blood vessels. According to this hypothesis neuropeptides, such as substance P and calcitonin gene-related peptide (CGRP), released from the adjacent afferent neurons activate mast cells that on their turn release proinflammatory mediators into the peritoneal cavity. Via the blood circulation, these mediators increase mucosal permeability, allowing luminal bacteria and/or bacterial products to enter the gastrointestinal wall and activate the resident macrophages triggering intracellular signalling pathways, leading to transcription of inflammatory molecules, cytokines, chemokines and adhesion molecules. This hypothesis needs to be proven experimentally and meanwhile it remains necessary to further investigate the interplay between these initiating cells and the nervous system as both the mediators released from mast cells and from residential macrophages are able to affect neuronal pathways within the gastrointestinal wall and from the gastrointestinal wall towards higher brain centres.

Also in IBD mast cells might participate in the neuroimmune interactions leading to visceral sensitivity and motility disturbances. Although it is generally believed that mast cells might not be the crucial initiators of pathology in IBD, mast cell stabilizing drugs or drugs interfering with mast cell mediator activity might be a adjunctive therapeutic possibility in the treatment of IBD. These hypotheses support further research in the interplay between mast cells, immunological cells and the neuronal pathways.

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References

[1] A. Artinyan, J.W. Nunoo-Mensah, S. Balasubramaniam, J. Gauderman, R. Essani, C. Gonzalez-Ruiz, A.M. Kaiser, R.W. Beart Jr., Prolonged postoperative ileus—definition, risk factors, and predictors after surgery, World J. Surg. 32 (2008) 1495.
[2] G. Barbara, V. Stanghellini, G.R. De, R. Corinaldesi, Functional gastrointestinal disorders and mast cells: implications for therapy, Neurogastroenterol. Motil. 18 (2006) 6.
[3] G. Barbara, B. Wang, V. Stanghellini, G.R. De, C. Cremon, N.G. Di, M. Trevisani, B. Campi, P. Geppetti, M. Tonini, N.W. Bunnett, D. Grundy, R. Corinaldesi, Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome, Gastroenterology 132 (2007) 26.
[4] A.J. Bauer, Mentation on the immunological modulation of gastrointestinal motility, Neurogastroenterol. Motil. 20 (Suppl 1) (2008) 81.
[5] A.D. Befus, F.L. Pearce, J. Gauldie, P. Horsewood, J. Bienenstock, Mucosal mast cells. I. Isolation and functional characteristics of rat intestinal mast cells, J. Immunol. 128 (1982) 2475.
[6] A.D. Befus, F.L. Pearce, R. Goodacre, J. Bienenstock, Unique functional characteristics of mucosal mast cells, Adv. Exp. Med. Biol. 149 (1982) 521.
[7] S. Ben-Horin, Y. Chowers, Neuroimmunology of the gut: physiology, pathology, and pharmacology, Curr. Opin. Pharmacol. 8 (2008) 490.
[8] J. Bienenstock, G. MacQueen, P. Sestini, J.S. Marshall, R.H. Stead, M.H. Perdue, Mast cell/nerve interactions in vitro and in vivo, Am. Rev. Respir. Dis. 143 (1991) S55–S58.
[9] S.C. Bischoff, Physiological and pathophysiological functions of intestinal mast cells, Semin. Immunopathol. 31 (2009) 185.
[10] S.C. Bischoff, A. Lorentz, S. Schwengberg, G. Weier, R. Raab, M.P. Manns, Mast cells are an important cellular source of tumour necrosis factor alpha in human intestinal tissue, Gut 44 (1999) 643.
[11] G.E. Boeckxstaens, W.J. de Jonge, Neuroimmune mechanisms in postoperative ileus, Gut 58 (2009) 1300.
[12] M. Chichlowski, G.S. Westwood, S.N. Abraham, L.P. Hale, Role of mast cells in inflammatory bowel disease and inflammation-associated colorectal neoplasia in IL-10-deficient mice, PLoS One 5 (2010) e12220.
[13] J.R. Coldwell, B.D. Phillis, K. Sutherland, G.S. Howarth, L.A. Blackshaw, Increased responsiveness of rat colonic splanchnic afferents to 5-HT after inflammation and recovery, J. Physiol. 579 (2007) 203.
[14] D. De Filippis, A. D'Amico, M.P. Cinelli, G. Esposito, V. Di Marzo, T. Iuvone, Adelmidrol, a palmitoylethanolamide analogue, reduces chronic inflammation in a carrageenin-granuloma model in rats, J. Cell. Mol. Med. 13 (2009) 1086.
[15] J.J. de Haan, T. Lubbers, M. Hadfoune, M.D. Luyer, C.H. Dejong, W.A. Buurman, J.W. Greve, Postshock intervention with high-lipid enteral nutrition reduces inflammation and tissue damage, Ann. Surg. 248 (2008) 842.
[16] J.J. de Haan, G. Thuijls, T. Lubbers, M. Hadfoune, K. Reisinger, E. Heineman, J.W. Greve, W.A. Buurman, Protection against early intestinal compromise by lipid-rich enteral nutrition through cholecystokinin receptors, Crit. Care Med. 38 (2010) 1592.
[17] W.J. de Jonge, F.O. The, C.D. van der, R.J. Bennink, P.H. Reitsma, S.J. van Deventer, R.M. van den Wijngaard, G.E. Boeckxstaens, Mast cell degranulation during abdominal surgery initiates postoperative ileus in mice, Gastroenterology 127 (2004) 535.
[18] W.J. de Jonge, R.M. van den Wijngaard, F.O. The, M.L. ter Beek, R.J. Bennink, G.N. Tytgat, R.M. Buijs, P.H. Reitsma, S.J. van Deventer, G.E. Boeckxstaens, Postoperative ileus is maintained by intestinal immune infiltrates that activate inhibitory neural pathways in mice, Gastroenterology 125 (2003) 1137.
[19] H.U. De Schepper, J.G. De Man, T.G. Moreels, P.A. Pelckmans, B.Y. De Winter, Review article: gastrointestinal sensory and motor disturbances in inflammatory bowel disease—clinical relevance and pathophysiological mechanisms, Aliment. Pharmacol. Ther. 27 (2008) 621.
[20] B.Y. De Winter, G.E. Boeckxstaens, J.G. De Man, T.G. Moreels, A.G. Herman, P.A. Pelckmans, Effect of adrenergic and nitrergic blockade on experimental ileus in rats, Br. J. Pharmacol. 120 (1997) 464.
[21] B.Y. De Winter, J.G. De Man, Interplay between inflammation, immune system and neuronal pathways: effect on gastrointestinal motility, World J. Gastroenterol. 16 (2010) 5523.
[22] C.P. Delaney, Clinical perspective on postoperative ileus and the effect of opiates, Neurogastroenterol. Motil. 16 (Suppl 2) (2004) 61.
[23] J.P. Derikx, D.A. van Waardenburg, G. Thuijls, H.M. Willigers, M. Koenraads, A.A. van Bijnen, E. Heineman, M. Poeze, T. Ambergen, O.A. van, L.W. van Rhijn, W.A. Buurman, New insight in loss of gut barrier during major non-abdominal surgery, PLoS One 3 (2008) e3954.
[24] B. Echtenacher, D.N. Mannel, L. Hultner, Critical protective role of mast cells in a model of acute septic peritonitis, Nature 381 (1996) 75.
[25] R. Eliakim, F. Karmeli, E. Okon, D. Rachmilewitz, Ketotifen effectively prevents mucosal damage in experimental colitis, Gut 33 (1992) 1498.
[26] R. Eliakim, D. Rachmilewitz, Inflammatory mediators and the pathogenesis of inflammatory bowel disease, Ital. J. Gastroenterol. 24 (1992) 361.
[27] L. Enerback, P.M. Lundin, Ultrastructure of mucosal mast cells in normal and compound 48-80-treated rats, Cell Tissue Res. 150 (1974) 95.

[28] D.R. Engel, A. Koscielny, S. Wehner, J. Maurer, M. Schiwon, L. Franken, B. Schumak, A. Limmer, T. Sparwasser, A. Hirner, P.A. Knolle, J.C. Kalff, C. Kurts, T helper type 1 memory cells disseminate postoperative ileus over the entire intestinal tract, Nat. Med. 16 (2010) 1407.
[29] M.K. Eskandari, J.C. Kalff, T.R. Billiar, K.K. Lee, A.J. Bauer, Lipopolysaccharide activates the muscularis macrophage network and suppresses circular smooth muscle activity, Am. J. Physiol. 273 (1997) G727–G734.
[30] M.K. Eskandari, J.C. Kalff, T.R. Billiar, K.K. Lee, A.J. Bauer, LPS-induced muscularis macrophage nitric oxide suppresses rat jejunal circular muscle activity, Am. J. Physiol. 277 (1999) G478–G486.
[31] B.O. Fabriek, B.R. van, D.M. Deng, A.J. Ligtenberg, K. Nazmi, K. Schornagel, R.P. Vloet, C.D. Dijkstra, T.K. van den Berg, The macrophage scavenger receptor CD163 functions as an innate immune sensor for bacteria, Blood 113 (2009) 887.
[32] A. Flores-Langarica, S. Meza-Perez, J. Calderon-Amador, T. Estrada-Garcia, G. Macpherson, S. Lebecque, S. Saeland, R.M. Steinman, L. Flores-Romo, Network of dendritic cells within the muscular layer of the mouse intestine, Proc. Natl. Acad. Sci. USA 102 (2005) 19039.
[33] C.C. Fox, W.C. Moore, L.M. Lichtenstein, Modulation of mediator release from human intestinal mast cells by sulfasalazine and 5-aminosalicylic acid, Dig. Dis. Sci. 36 (1991) 179.
[34] Y. Fukumoto, H. Kasai, H. Takahashi, H. Sugiyama, N. Hase, H. Kaneko, I. Hamamura, Y. Aoki, M. Ota, T. Kobayashi, Y. Katsuura, T. Kamimura, K. Komoriya, The role of mast cells in the development of 2, 4, 6-trinitrobenzene sulfonic acid-induced colitis in rats, Scand. J. Gastroenterol. 37 (2002) 555.
[35] S.J. Galli, M. Grimbaldeston, M. Tsai, Immunomodulatory mast cells: negative, as well as positive, regulators of immunity, Nat. Rev. Immunol. 8 (2008) 478.
[36] S.J. Galli, M. Tsai, J.R. Gordon, E.N. Geissler, B.K. Wershil, Analyzing mast cell development and function using mice carrying mutations at W/c-kit or Sl/MGF (SCF) loci, Ann. N.Y. Acad. Sci. 664 (1992) 69.
[37] P. Goldsmith, B. McGarity, A.F. Walls, M.K. Church, G.H. Millward-Sadler, D.A. Robertson, Corticosteroid treatment reduces mast cell numbers in inflammatory bowel disease, Dig. Dis. Sci. 35 (1990) 1409.
[38] S.H. He, Key role of mast cells and their major secretory products in inflammatory bowel disease, World J. Gastroenterol. 10 (2004) 309.
[39] P. Holzer, Role of visceral afferent neurons in mucosal inflammation and defense, Curr. Opin. Pharmacol. 7 (2007) 563.
[40] Y. Iba, Y. Sugimoto, C. Kamei, Participation of mast cells in colitis inflammation induced by dextran sulfate sodium, Methods Find. Exp. Clin. Pharmacol. 24 (2002) 15.
[41] N.L. Jones, C.M. Roifman, A.M. Griffiths, P. Sherman, Ketotifen therapy for acute ulcerative colitis in children: a pilot study, Dig. Dis. Sci. 43 (1998) 609.
[42] N. Kageyama-Yahara, Y. Suehiro, T. Yamamoto, M. Kadowaki, IgE-induced degranulation of mucosal mast cells is negatively regulated via nicotinic acetylcholine receptors, Biochem. Biophys. Res. Commun. 377 (2008) 321.
[43] J.C. Kalff, B.M. Buchholz, M.K. Eskandari, C. Hierholzer, W.H. Schraut, R.L. Simmons, A.J. Bauer, Biphasic response to gut manipulation and temporal correlation of cellular infiltrates and muscle dysfunction in rat, Surgery 126 (1999) 498.
[44] J.C. Kalff, T.M. Carlos, W.H. Schraut, T.R. Billiar, R.L. Simmons, A.J. Bauer, Surgically induced leukocytic infiltrates within the rat intestinal muscularis mediate postoperative ileus, Gastroenterology 117 (1999) 378.
[45] J.C. Kalff, A. Turler, N.T. Schwarz, W.H. Schraut, K.K. Lee, D.J. Tweardy, T.R. Billiar, R.L. Simmons, A.J. Bauer, Intra-abdominal activation of a local inflammatory response within the human muscularis externa during laparotomy, Ann. Surg. 237 (2003) 301.
[46] H. Kehlet, Postoperative ileus—an update on preventive techniques, Nat. Clin. Pract. Gastroenterol. Hepatol. 5 (2008) 552.
[47] S. Kleinschmidt, J. Harder, I. Nolte, S. Marsilio, M. Hewicker-Trautwein, Chronic inflammatory and non-inflammatory diseases of the gastrointestinal tract in cats: diagnostic advantages of full-thickness intestinal and extraintestinal biopsies, J. Feline Med. Surg. 12 (2010) 97.
[48] C. Kreiss, S. Toegel, A.J. Bauer, Alpha2-adrenergic regulation of NO production alters postoperative intestinal smooth muscle dysfunction in rodents, Am. J. Physiol. Gastrointest. Liver Physiol. 287 (2004) G658–G666.
[49] S.E. Lakhan, A. Kirchgessner, Neuroinflammation in inflammatory bowel disease, J. Neuroinflammation 7 (2010) 37.
[50] R.M. Loureiro, K.A. Monaco, J.B. Kearney, C.E. Blickarz-Durand, S.L. Kirby, M.S. Inamdar, V.L. Bautch, csf1 is required for early embryonic macrophage development: characterization of the csf1(op)/csf1(op) mutation in ES cell-derived macrophages, Br. J. Haematol. 141 (2008) 739.
[51] T. Lubbers, M.D. Luyer, J.J. de Haan, M. Hadfoune, W.A. Buurman, J.W. Greve, Lipid-rich enteral nutrition reduces postoperative ileus in rats via activation of cholecystokinin-receptors, Ann. Surg. 249 (2009) 481.
[52] J. MacFie, C. O'Boyle, C.J. Mitchell, P.M. Buckley, D. Johnstone, P. Sudworth, Gut origin of sepsis: a prospective study investigating associations between bacterial translocation, gastric microflora, and septic morbidity, Gut 45 (1999) 223.
[53] J. MacFie, B.S. Reddy, M. Gatt, P.K. Jain, R. Sowdi, C.J. Mitchell, Bacterial translocation studied in 927 patients over 13 years, Br. J. Surg. 93 (2006) 87.
[54] G. MacQueen, J. Marshall, M. Perdue, S. Siegel, J. Bienenstock, Pavlovian conditioning of rat mucosal mast cells to secrete rat mast cell protease II, Science 243 (1989) 83.
[55] J.K. Marshall, E.J. Irvine, Ketotifen treatment of active colitis in patients with 5-aminosalicylate intolerance, Can. J. Gastroenterol. 12 (1998) 273.
[56] J.R. McDermott, R.E. Bartram, P.A. Knight, H.R. Miller, D.R. Garrod, R.K. Grencis, Mast cells disrupt epithelial barrier function during enteric nematode infection, Proc. Natl. Acad. Sci. USA 100 (2003) 7761.
[57] C.C. McMenamin, E.A. Gault, D.M. Haig, The effect of dexamethasone on growth and differentiation of bone-marrow derived mucosal mast cells in vitro, Immunology 62 (1987) 29.
[58] A. Menozzi, C. Pozzoli, E. Poli, M. Lazzaretti, D. Grandi, G. Coruzzi, Long-term study of TNBS-induced colitis in rats: focus on mast cells, Inflamm. Res. 55 (2006) 416.
[59] M. Metz, A.M. Piliponsky, C.C. Chen, V. Lammel, M. Abrink, G. Pejler, M. Tsai, S.J. Galli, Mast cells can enhance resistance to snake and honeybee venoms, Science 313 (2006) 526.
[60] H.B. Mikkelsen, Macrophages in the external muscle layers of mammalian intestines, Histol. Histopathol. 10 (1995) 719.
[61] H.B. Mikkelsen, J.O. Larsen, H. Hadberg, The macrophage system in the intestinal muscularis externa during inflammation: an immunohistochemical and quantitative study of osteopetrotic mice, Histochem. Cell Biol. 130 (2008) 363.
[62] R. Moriez, M. Leveque, C. Salvador-Cartier, F. Barreau, V. Theodorou, J. Fioramonti, L. Bueno, H. Eutamene, Mucosal mast cell proteases are involved in colonic permeability alterations and subsequent bacterial translocation in endotoxemic rats, Shock 28 (2007) 118.
[63] C.J. O'Boyle, J. MacFie, C.J. Mitchell, D. Johnstone, P.M. Sagar, P.C. Sedman, Microbiology of bacterial translocation in humans, Gut 42 (1998) 29.
[64] D.K. Podolsky, The current future understanding of inflammatory bowel disease, Best Pract. Res. Clin. Gastroenterol. 16 (2002) 933.
[65] M. Raithel, S. Winterkamp, A. Pacurar, P. Ulrich, J. Hochberger, E.G. Hahn, Release of mast cell tryptase from human colorectal mucosa in inflammatory bowel disease, Scand. J. Gastroenterol. 36 (2001) 174.
[66] B.S. Reddy, M. Gatt, R. Sowdi, J. MacFie, Surgical manipulation of the large intestine increases bacterial translocation in patients undergoing elective colorectal surgery, Colorectal Dis. 8 (2006) 596.
[67] A. Rijnierse, F.P. Nijkamp, A.D. Kraneveld, Mast cells and nerves tickle in the tummy: implications for inflammatory bowel disease and irritable bowel syndrome, Pharmacol. Ther. 116 (2007) 207.
[68] H.R. Rodewald, M. Dessing, A.M. Dvorak, S.J. Galli, Identification of a committed precursor for the mast cell lineage, Science 271 (1996) 818.
[69] J. Santos, M.H. Perdue, Stress and neuroimmune regulation of gut mucosal function, Gut 47 (Suppl 4) (2000) iv49–iv51.
[70] Y. Sasaki, M. Tanaka, H. Kudo, Differentiation between ulcerative colitis and Crohn's disease by a quantitative immunohistochemical evaluation of T lymphocytes, neutrophils, histiocytes and mast cells, Pathol. Int. 52 (2002) 277.
[71] N.T. Schwarz, D. Beer-Stolz, R.L. Simmons, A.J. Bauer, Pathogenesis of paralytic ileus: intestinal manipulation opens a transient pathway between the intestinal lumen and the leukocytic infiltrate of the jejunal muscularis, Ann. Surg. 235 (2002) 31.
[72] N.T. Schwarz, B. Engel, M.K. Eskandari, J.C. Kalff, J.R. Grandis, A.J. Bauer, Lipopolysaccharide preconditioning and cross-tolerance: the induction of protective mechanisms for rat intestinal ileus, Gastroenterology 123 (2002) 586.
[73] H. Serna, M. Porras, P. Vergara, Mast cell stabilizer ketotifen [4-(1-methyl-4-piperidylidene)-4h-benzo[4,5]cyclohepta[1,2-b]thiophen-10(9H)-one fumarate] prevents mucosal mast cell hyperplasia and intestinal dysmotility in experimental *Trichinella spiralis* inflammation in the rat, J. Pharmacol. Exp. Ther. 319 (2006) 1104.
[74] K.A. Sharkey, A.B. Kroese, Consequences of intestinal inflammation on the enteric nervous system: neuronal activation induced by inflammatory mediators, Anat. Rec. 262 (2001) 79.
[75] K.A. Sharkey, G.M. Mawe, Neuroimmune and epithelial interactions in intestinal inflammation, Curr. Opin. Pharmacol. 2 (2002) 669.
[76] L.E. Smythies, M. Sellers, R.H. Clements, M. Mosteller-Barnum, G. Meng, W.H. Benjamin, J.M. Orenstein, P.D. Smith, Human intestinal macrophages display profound inflammatory anergy despite avid phagocytic and bacteriocidal activity, J. Clin. Invest. 115 (2005) 66.
[77] S.A.Snoek, K.S.Borensztajn, R.M.van den Wijngaard, and W.J.de Jonge, Neuropeptide Receptors in Intestinal Disease: Physiology and Therapeutic Potential, Curr. Pharm. Des (2009).
[78] R.H. Stead, E.C. Colley, B. Wang, E. Partosoedarso, J. Lin, A. Stanisz, K. Hillsley, Vagal influences over mast cells, Auton. Neurosci. 125 (2006) 53.
[79] P.S. Sudheer, J.E. Hall, R. Donev, G. Read, A. Rowbottom, P.E. Williams, Nicotinic acetylcholine receptors on basophils and mast cells, Anaesthesia 61 (2006) 1170.
[80] F.O. The, R.J. Bennink, W.M. Ankum, M.R. Buist, O.R. Busch, D.J. Gouma, H.S. van der, R.M. van den Wijngaard, W.J. de Jonge, G.E. Boeckxstaens, Intestinal handling-induced mast cell activation and inflammation in human postoperative ileus, F.O. The, R.J. Bennink, W.M. Ankum, M.R. Buist, O.R. Busch, D.J. Gouma, H.S. van der, R.M. van den Wijngaard, W.J. de Jonge, and G.E. BoeckxstaensGut 57 (2008) 33.
[81] F.O. The, M.R. Buist, A. Lei, R.J. Bennink, J. Hofland, R.M. van den Wijngaard, W.J. de Jonge, G.E. Boeckxstaens, The role of mast cell stabilization in treatment of postoperative ileus: a pilot study, Am. J. Gastroenterol. 104 (2009) 2257.
[82] W.J. Tremaine, A. Brzezinski, J.A. Katz, D.C. Wolf, T.J. Fleming, J. Mordenti, L.C. Strenkoski-Nix, M.C. Kurth, Treatment of mildly to moderately active ulcerative colitis with a tryptase inhibitor (APC 2059): an open-label pilot study, Aliment. Pharmacol. Ther. 16 (2002) 407.
[83] A. Turler, J.C. Kalff, B.A. Moore, R.A. Hoffman, T.R. Billiar, R.L. Simmons, A.J. Bauer, Leukocyte-derived inducible nitric oxide synthase mediates murine postoperative ileus, Ann. Surg. 244 (2006) 220.
[84] A. Turler, C. Schnurr, A. Nakao, S. Togel, B.A. Moore, N. Murase, J.C. Kalff, A.J. Bauer, Endogenous endotoxin participates in causing a panenteric inflammatory ileus after colonic surgery, Ann. Surg. 245 (2007) 734.
[85] M.I. van Berge Henegouwen, P.T. Test, Peritoneal cytokine release after elective gastrointestinal surgery and postoperative complications, Am. J. Surg. 175 (1998) 311.
[86] L. Van Nassauw, D. Adriaensen, J.P. Timmermans, The bidirectional communication between neurons and mast cells within the gastrointestinal tract, Auton. Neurosci. 133 (2007) 91.

[87] S. Varadaradjalou, F. Feger, N. Thieblemont, N.B. Hamouda, J.M. Pleau, M. Dy, M. Arock, Toll-like receptor 2 (TLR2) and TLR4 differentially activate human mast cells, Eur. J. Immunol. 33 (2003) 899.
[88] I. Wessler, H. Kilbinger, F. Bittinger, R. Unger, C.J. Kirkpatrick, The non-neuronal cholinergic system in humans: expression, function and pathophysiology, Life Sci. 72 (2003) 2055.
[89] J.D. Wood, Histamine, mast cells, and the enteric nervous system in the irritable bowel syndrome, enteritis, and food allergies, Gut 55 (2006) 445.
[90] J.D. Wood, Neuropathophysiology of functional gastrointestinal disorders, World J. Gastroenterol. 13 (2007) 1313.
[91] R.J. Xavier, D.K. Podolsky, Unravelling the pathogenesis of inflammatory bowel disease, Nature 448 (2007) 427.
[92] X. Xu, S. Weksler-Zangen, A. Pikarsky, O. Pappo, D. Wengrower, S.C. Bischoff, M. Pines, A. Rivkind, E. Goldin, F. Levi-Schaffer, Mast cells involvement in the inflammation and fibrosis development of the TNBS-induced rat model of colitis, Scand. J. Gastroenterol. 37 (2002) 330.