gastroenterology insights

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Review

Insights into the Characteristics and Functions of Mast Cells in the Gut

Yuexin Guo [1,†], Boya Wang [2,†], Han Gao [3,4], Chengwei He [3], Shuzi Xin [3], Rongxuan Hua [3], Xiaohui Liu [3], Sitian Zhang [3] and Jingdong Xu [3,*]

1 Department of Oral Medicine, Beijing Stomatological Hospital, Capital Medical University, Beijing 100050, China; gyxin2014@163.com
2 Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing 100142, China; wbysonnig@163.com
3 Department of Physiology and Pathophysiology, School of Basic Medical Sciences, Capital Medical University, Beijing 100069, China; gaohan703851@163.com (H.G.); hcw_1043@foxmail.com (C.H.); xinshuzi@gmail.com (S.X.); andrewhdd@126.com (R.H.); m13484363443@163.com (X.L.); sitianccmu@163.com (S.Z.)
4 Department of Clinical Laboratory, Aerospace Center Hospital, Peking University, Beijing 100049, China
* Correspondence: xujingdong@163.com; Tel.: +86-10-83911486
† These authors contributed equally to this work.

Abstract: Mast cells have vital functions in allergic responses and parasite ejection, while the underlying mechanisms remain unclear. Meanwhile, MCs are essential for the maintenance of GI barrier function, and their interactions with neurons, immune cells, and epithelial cells have been related to various gastrointestinal (GI) disorders. An increasing number of investigations are being disclosed, with a lack of inner connections among them. This review aims to highlight their properties and categorization and further delve into their participation in GI diseases via interplay with neurons and immune cells. We also discuss their roles in diseases like inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS). Based on the evidence, we advocated for their potential application in clinical practices and advocated future research prospects.

Keywords: gastrointestinal; mast cell; neuron; diseases; immune

Citation: Guo, Y.; Wang, B.; Gao, H.; He, C.; Xin, S.; Hua, R.; Liu, X.; Zhang, S.; Xu, J. Insights into the Characteristics and Functions of Mast Cells in the Gut. *Gastroenterol. Insights* **2023**, *14*, 637–652. https://doi.org/10.3390/gastroent14040043

Academic Editor: Gaetano Luglio

Received: 21 August 2023
Revised: 1 November 2023
Accepted: 14 November 2023
Published: 5 December 2023

1. Introduction

Mast cells have caught scientists' curiosity since their discovery in 1878 as essential subsets of immune cells present in a variety of organs and tissues [1]. Its distribution in vascular tissues as well as the connective tissues of the organ mucosa is of particular concern [2]. Unlike other hematopoietic-derived cells, MCs bear more resemblance to macrophages and differentiate from yolk sac and bone marrow precursors [3]. Further differentiation occurs in adjacent tissues under stimulation, where they secrete granules and initiate immunological responses and cell proliferation [4]. In the meantime, they could phagocytose bacteria and particles in response to Toll-like receptors (TLRs) [5,6]. Monoclonal antibody Ki-MC1 is recognized as one marker of mast cells, and more detailed classifications are also put forward to distinguish different functional subgroups of them [7,8]. Two common subgroups of mast cells include mucosal mast cells (MMCs) and connective tissue mast cells (CTMCs), which possess high immune similarity but differ in growth rate [9] as well as mast cell proteases (MCP) expression profiles [10].

The gastrointestinal (GI) system is the largest immune organ in the human body and a crucial location for food digestion [11]. GI diseases differ from one another and have substantial impacts on patient life quality. However, most current therapies are symptomatic, with patients waiting for more comprehensive and complete healing [12]. Meanwhile, most GI diseases exhibit alterations in GI neurons [13,14]. As a significant

hub between the nervous system and the immune system, mast cells are of particular importance in the interaction between pathological inflammation and clinical discomfort. IBD and IBS are typical diseases in the GI system, and the involvement of mast cells and the production of numerous bioactivators are reported in these diseases [15]. Considering the intimate connections of mast cells with the GI microorganism and the nervous system, improved understandings of them would be extremely beneficial in promoting optimal therapy for gastrointestinal diseases [15,16].

After analyzing the biological properties of mast cells in the gastrointestinal tract, we clarified essential roles of mast cells in maintaining the GI epithelial barrier. Furthermore, we summarized the roles of mast cells in the immune system and neuroinflammation. Specifically, we provide in-depth descriptions of the mast cells involvement in complications.

2. Biological Characteristics of Mast Cells in the Gastrointestinal Tract

Mast cells are distributed throughout the body and are abundant in the GI [17]. With a mean diameter of 12.6–13.5 μm, they can vary in morphology between organs [18]. Agents like compound 48/80 have the potential to degranulate 50–55% of the cytoplasm [19]. Considering the complex maturation states and classifications of mast cells, immunostaining is utilized as an index for mast cell tryptase and c-Kit, and ultrasonic examinations are also under evaluation [20]. Based on MC-specific proteases of chymase, tryptase, or carboxypeptidase A(MC-CPA) type, mast cells can be classified into MC_T and MC_{TC} in human beings [21,22] and MMC as well as CTMC in mice [23,24]. MC_T is responsible for tryptases α and β(I, II, III) and MC_{TC} is also responsible for chymases CMA1 and MC-PCA. In mice, MMC is related to mMCP-1 and mMCP-2, and CTMC is responsible for mPCP-4, mPCP-5, mPCP-6, mPCP-7, and mPCP-9. Moreover, both MC_T and MC_{TC} are found in the mucosa of the GI and lung, whereas MCs are also identified in the skin and lymph nodes [25].

3. Mast Cells in IBD: Initiating Immunity and Maintaining Epithelial Barrier

3.1. Interactions between MCs and Cytokines: Initiating Immunity

MCs interact with nearly all immune cells and play vital roles in pathphysiology [26,27]. In times of inflammation, stem-cell factor (SCF), also known as the ligand for the receptor c-Kit (CD117), is considered the paramount survival and developmental factor for MCs [28], and other ligands, such as CXC chemokine receptor 2 (CXCR2) and cytokines, are also involved in MC maturation [29]. The chemokine (C-C motif) receptor 2 (CCR2)/chemokine (C-C motif) ligand 2 (CCL2) axis is implicated in MC recruitment in several models, including abdominal aortic aneurysm lesions [30] and increased in the gastric cancer cell line BGC-823 via the SCF/c-Kit signaling pathway activated by PI3K-Akt [31]. Exogenous intraperitoneal injection of IL-3 into human MCs during development could also result in mastocytosis [32].

MC and MC-derived granules remain at a low level to regulate the balance of water and electrolytes in healthy settings but are elevated in tissue inflammation, resulting in a cascade of immunological responses both in the gut and throughout the body [33,34]. Mas-related GPCR-X2 (MRGPRX2, mouse ortholog, MrgprB2), a novel human G protein-coupled receptor (GPCR) specifically expressed after IgE-mediated mast cell activation, promotes bacterial clearance and mucosal healing [35].

Elevated numbers of MCs are associated with diarrhea in the IBD [36], and in the SAMP1/YitFcs (SAMP1) mice model of spontaneous ileitis, an increased number of MC and elevated levels of the degranulation marker, β-hexosaminidase enzyme, were associated with inhibition of an essential Cl^-/HCO^{3-} exchanger (SLC26A3, also known as "down-regulated in adenoma (DRA)) [37]. As mentioned above, MCs also contribute to intestinal barrier dysfunction in ischemia reperfusion damage by activating the LR4-NF-κB/TNF-α pathway [38], and ATP-P2X7 purinoceptor-mediated activation in MC activation is involved in GI inflammation [39].

Granules secreted from MCs play an essential role in regulating gut homeostasis. Tryptase proteins stimulate the differentiation of human colon fibroblasts (CCD-18Co fibroblasts) into myofibroblasts via the Protease-Activated Receptors-2 (PAR-2)/Akt/mTOR pathway, allowing them to release more ECM proteins [40].

3.2. Roles of MCs in Maintaining Epithelial Barrier

Derived from monocytes, mast cells are capable of phagocytosis and protect the GI against infection [6]. In the meantime, MCs are also responsible for the maintenance of tight junctions and cytoskeletal proteins, which are essential for the GI epithelial barrier. MiR-223, an exosome-mediated functional miRNA, is abundant in MC-derived exosomes [23,24] and inhibits claudin-8 (CLDN8) expression in intestinal epithelial cells (IECs) [41]. Apart from directly down-regulating the epithelial barrier proteins, MCs also facilitated antigen transportation across the epithelium via upregulation of CD23 [42]. In physiological conditions, MCs promote migration and morphology-shifting of IECs and contribute to epithelial barrier permeability via mcpt4 and normal crypt expression of CLDN3 [43]. Similar effects are witnessed in the duodenum and ileocecal, and the one in the duodenum coincides with its involvement in functional dyspepsia (FD) [44], while clear mechanisms in the ileocecal remain unknown [45].

In allergic responses, tryptase secreted by mast cells can suppress the production of ubiquitin E3 ligase A20 (A20) in the intestinal epithelial cell lines, disturb the fusion of antigen-carrying endosomes and lysosomes, and promote antigen transport across the epithelial barrier, all of which contribute to intestinal epithelial barrier dysfunction [46]. And IL-9-deficient mice fail to develop oral-originated intestinal allergy via IL-9-mediated anaphylaxis [47].

Induction of enterotoxigenic Escherichia coli K88 also elevated the concentration of MC proteases (MCPs) and carboxypeptidase A3 (CPA3) mRNA levels, both of which are known as MC activators, and resulted in intestinal epithelial dysfunction [48]. Bacteria and other allergens are known as MC activators via Toll-like receptors (TLRs) and the nucleotide-binding and oligomerization domain (NOD) [49,50]. Naïve MC line human MC-1(HMC-1) cells or monocyte cell line THP-1 cells are used as standard models for investigations, and studies have corroborated their roles in pro-inflammatory cytokine secretion via NF-κB [51]. In allergic diseases, MC activation via the adenosine A3 receptor in response to myenteric neurons is accompanied by vagal afferent and 5-HT signaling [52,53].

4. Roles of MCs in Defending against Infection

Interactions between MCs and gut bacteria and their metabolites are also worth mentioning, as bacterial peptidoglycan could result in the breakdown of intestinal tolerance via TLR and NOD-mediated MC activation [49]. And bacteria overgrowth is related to increased MCP-2 in mice's small intestines [54]. These investigations establish the basis for drug development and treatment for both neuronal and immune diseases [55,56]. Bacteria, as well as their metabolites, could regulate MC activation and over-proliferation [57]. Meanwhile, MC activation by other immune cells initiated by bacteria via cytokines like IL-33 and Fc receptors is also a significant protective measure in the GI [58]. These controls are also mediated by IL-3, IL-5, and GM-CSF [59]. These interactions, on the other hand, provide prospective targets for clinical therapy and medication research, such as the utilization of metabolites by beneficial bacteria such as *Lactobacillus paracasei* [60]. MC activation plays protective roles in pathological conditions, providing crucial mucosal defense against Strongyloides venezuelensis [61] and facilitating worm expulsion [62]. And reduced MC responses to bacterial antigen stimulation in C57BL/6 mice were confirmed in recent studies [63]. Diabetic mice showed reduced IL-3 and MC number levels, which could be induced by insulin, are associated with decreased immunity [64]. Other mediators, such as IL-4, stem cell factor, and nerve growth factor, have proven to suppress MC apoptosis in the human intestine in times of infection [65]. These findings lay the foundation for the pathological involvement of MCs in the gut and provide directions for future

investigations. IL-33, associated with IL-3, is responsible for parasitic helminth expulsion via ILC2-mediated IL-9 secretion, resulting in MC-driven intestinal anti-helminth immunity [66]. It could also attenuate MC apoptosis via B-cell lymphoma-X large (BCLXL) [67]. Similar effects were seen in response to allergens and inflammation, with the involvement of CXCL1 [68,69].

However, higher levels of MC also facilitate small bowel cancer in mice [70], accompanied by improved epithelial permeability in IL-9 transgenic mice [71]. The double-edged role of IL-9 indicates the significance of homeostatic balance in GI related to MCs, and a better understanding of the underlying mechanisms might lead to more effective therapy. Meanwhile, other potential pathways for MC differentiation in other organs are summarized in previous reviews and have an indicative meaning for their uses in the GI [72,73] (refer to Figure 1 for the roles of MCs in the GI).

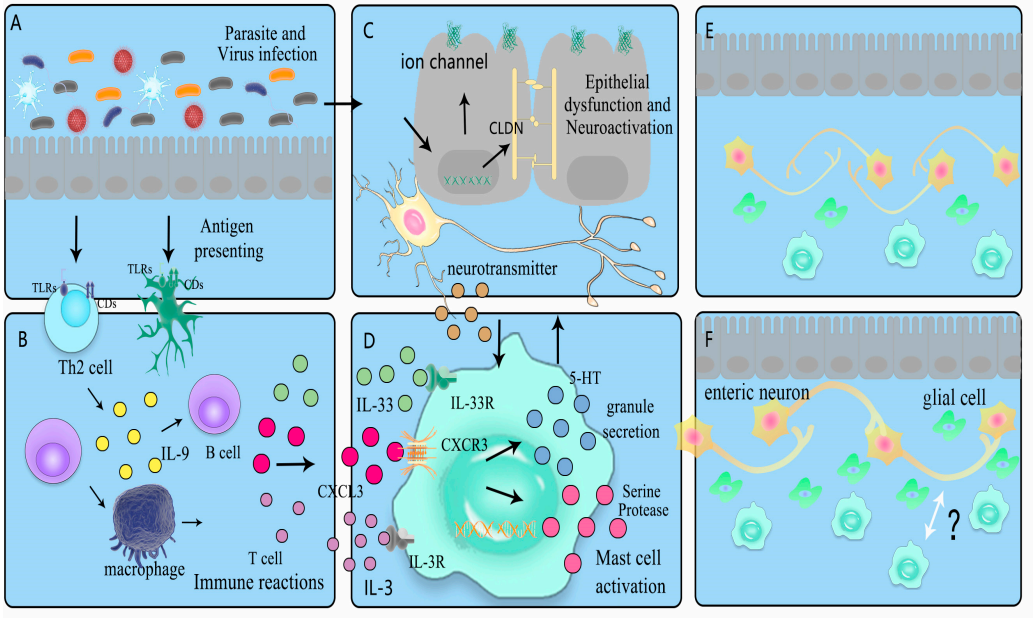

Figure 1. Underlying mechanisms of MC in the GI tract. MCs are pivotal regulators of GI via interactions with immunological and neurological system cells. Triggers could be signals from both parasites (**A**) and antigens presented in other immune cells by recognizing factors like TLRs and CDs (**C**). Both epithelial cells and enteric neurons are involved in this regulation, primarily achieved by granule secretion (**B**) via key molecules including CXCL3, IL-3, and IL-33, which further stimulates MC proliferation, culminating in cascades of host reactions (**D**). In both physiological (**E**) and IBS (**F**), MCs are significant regulators of the enteric nervous system, and their number increased in IBS. However, detailed understandings of them remain elusive.

5. Roles of Mast Cells in IBS via Neurotransmitters and Molecules

Apart from secreting cytokines [74], MCs can release neurotransmitters and interact with the gastrointestinal nervous system [75]. MCs have intimate connections with GI neurons, as the number of MCs rises in response to stress along with increased macromolecular flux and epithelial mitochondrial swelling [76]. The enhanced corticotropin-releasing hormone (CRH) produced by eosinophils via substance P (SP) interacting with neurokinin receptors 1 and 2 on subepithelial mast cells could account for typical neurological diseases in IBS [77]. CRH signaling is also responsible for MC initiation of the GI nervous system [78]. MC stimulation improved the excitability of isolectin B4 (IB4)-positive colonic neurons while suppressing A-type K^+ current (I(A)) density and shifting the inactivation curves of $I_{(A)}$ and $I_{(K)}$ in the hyperpolarizing direction in neuron cells [79]. Apart from neuron activation, MCs could also reduce enteric neuron survival in culture [80].

Histamine derives from histidine decarboxylation during MC maturation and serves as the initiator for angiectasis and tissue edema in response to pro-inflammatory factors [81]. Furthermore, it is involved in inflammation-associated colon carcinogenesis, in part by allowing *L. reuteri*-mediated suppression of keratinocyte chemoattractant (KC), *IL-22*, *IL-6*, *Tnf*, and *IL-1α* gene expression in the colonic mucosa [82] (refer to Box 1 for current understandings of mast cells and GI cancer). Meanwhile, histamine down-regulates IL-12p70 and CXCL10 production in mDCs after TLR2 and TLR4 stimulation via the small Rho GTPase CdC42 and PAK1 pathway [83]. Histamine could be secreted from mast cells and GI bacteria, and targeting bacterial histamine could be used to treat visceral hyperalgesia in IBS patients with chronic abdominal pain [84]. Apart from roles in inflammation and anti-infection, histamine from mast cells is also a significant mediator in food allergies, as shown in precision-cut intestinal slices (PCIS) [85,86], and leads to visceral hypersensitivity (VHS) in IBS [87]. Botschuijver et al. reported that fungal-induced release of mast cell-derived histamine could activate histamine-1 receptors on sensory afferents and induce sensitization of the nociceptive transient reporter potential channel V1 (TRPV1)-ion channel, and drugs targeting TRPV1 can be potential drugs for alleviating abdorminal pain [88]. However, there are also researchers who consider the influences of histamine on GI inflammation to be mediated via histamine receptor 4(H_4R) but the concrete pathways underlying them remain unclear [84].

Box 1 Controversial roles in colon cancer

Mast cell proliferation in colorectal cancer (CRC) is related to angiogenesis, the number of malignant lymph nodes spreading, and the prognosis. Both angiogenic factors, including VEGF-A, CXCL 8, and MMP-9, and lymphangiogenic factors, including VEGF-C and VEGF-D, can be stored in granules and secreted [89]. On the one hand, a lack of MC showed enhanced CD8+T cell infiltration related to tumor proliferation [90]. On the other hand, a higher density of perivascular mast cells was observed in adenomas [91]. Further investigations put forward different expression patterns of MCs in different phases and areas of colorectal carcinoma [91]. Based on these findings, we suggest that more investigations are required to control the number and activation of MCs in colorectal cancer. Their interactions with other cells and underlying mechanisms should also be evaluated to clarify the comprehensive roles of MCs in colorectal cancer [90].

Serotonin (5-HT) is also detected in MC granules, with an increase in patients with mastocytosis [92], and dopamine storage is corroborated in rodent MCs and increased throughout maturation from bone marrow precursors [93]. These discoveries have provided major ramifications for the understanding of the complexities underlying the mechanisms of MC function processes. 5-HT spontaneous release is markedly enhanced, which coincides with the number of MCs and the severity of abdominal pain [94]. Gao et al. reported that mucosal serotonin reuptake transporter expression in IBS is modulated by the gut microbiota via mast cell-Prostaglandin E2(PGE2) [95]. This is also accompanied by the activation of enteric neurons and is higher in cases of intestinal inflammation [47]. The amount of muscularis tryptase-positive MC is also positively associated with GI transit time (GITT) throughout the healing process [96]. Therefore, the roles of MCs in the immune and nervous systems should be taken together in evaluating their roles in disease progression and treatment development.

Chymotrypsin-like (chymase) is another kind of granule serine proteinase released by MCs and is analogous to trypsin-like (tryptase). However, their expression patterns differ from each other and vary among the species, disease models, and phases [97,98]. Mucosal MCs of the rat express predominantly chymases, in particular rat mast cell proteinase (rMCP-2, -3, -4), and the three members of the rMCP-8 subfamily (rMCP-8, -9, and -10). Rat connective tissue MCs, on the other hand, express two chymases, rMCP-1 and -5, and two tryptases, rMCP-6 and -7 [99]. Tryptase could cleave the bronchodilator VIP and decrease the nonadrenergic neural inhibitory influence mediated by VIP [100], whereas ancestral chymase reconstructed with the use of phylogenetic inference, total gene synthesis, and protein expression are responsible for converting angiotensin I to angiotensin II [101].

However, both chymase and tryptase are known as mast cell proteinases and regulate GI tight junctions and gut permeability [99]. Increased cleavage specificity of mouse mast cell proteinase-1 (mMCP-1), the major mucosal MC protease, is found in several parasite mouse models [102,103] and indicates the high substrate selectivity they have. MCs are also activated via the TLR4-NF-κB/TNF-α pathway in 3- and 7-day-old rats with small intestinal ischemia-reperfusion(I/R) injury [104], resulting in increased mast cell carboxypeptidase A (MC-CPA), which could degrade toxins and endothelin 1 (ET-1) [105]. Despite the research, more detailed and comprehensive investigations of these granules would provide novel insights into GI pathology and effective treatment for patients.

Previous research confirmed the intimate interactions between MCs and the nervous system, which are primarily accomplished through granules secreted by MCs and receptors on neurons (Table 1). This establishes the anatomical foundation for the involvement of MCs in GI diseases and clinical symptoms in the nervous system. IBS is characterized by neuroinflammation and irregular and recurring digestive problems resulting from non-pharmacological or pathological stimuli as well as emotional feelings. Biopsies from IBS patients revealed elevated CXCL11 levels in the duodenum along with enhanced mast cell infiltration, suggesting relations between MC and micro-inflammation in IBS while more concrete interactions remain unknown [106]. Meanwhile, research confirmed that the amount of MC is associated with morphological changes in neuron densities during nematode *Nippostrongylus brasiliensis* (Nb) infection in mice and could be one of the underlying mechanisms for MC and inflammation [107]. These effects are also corroborated by MC inhibition via antinociception of oxytocin through the Ca^{2+}-NOS pathway [108], accompanied by down-regulation of CXCL8, CCL2, CCL3, and CCL4 in human intestinal MCs by Cinnamaldehyde (CA) [109]. Polydatin also attenuated food allergy in MC by lowering the Ca^{2+} channel [110], and IFN-α/β showed similar effects, inhibiting intestinal hypersensitivity through MC stabilization [111]. More investigations on roles of MCs on GI diseases are summarized in Table 2 and detailed information on the mechanisms remains to be elucidate.

Table 1. Summary of the functions and mechanisms of mast cells.

Model	Findings	Conclusions	Possible Sense	Refs
Mice with lactose or FOS	Increased MCs in colonic mucosa	Lactose or FOS could increase MCs in colonic mucosa and affect the GI barrier functions	Regulators of MCs	[112]
Functional dyspepsia (FD)	Increased MCs in colonic mucosa	Eosinophils and MCs are relative to FD	Effective regulators of FD MCs remain unclear	[95]
Exosomes isolated from HMCs-1or CaCO2 of IECs	Inhibited expression of CLDN8, CD23, mcpt4, CLDN3, and A20 in IECs	MC regulated GI barrier functions via regulating CLDN8, CD23, mcpt4, CLDN3 and A20	Potential drugs targeting gut permeability	[41]
HT29	Upregulated CD23 expression	MCs modulate transport of CD23/IgE/antigen complex across intestinal epithelial barrier	Promoting antigen transportation	[42]
Adult male SD rats	MCs activated by substance P (SP)	Improved the excitability of $IB4^+$ colonic neurons but pressing I_A and shifting the inactivation of I_A and I_K in the hyperpolarizing direction in neuron cells	Regulation of ion transportation by MCs remains unclear	[79]
Preclinical or IBS patients	MCs and bacteria secrete histamine	visceral hypersensitivity (VHS)	Histamine is a marker and target for regulating VHS	[113]
Polyposis-prone mice	MCs secrete histamine during maturation	Involved in Inflammation-associated colon carcinogenesis	/	

Table 1. *Cont.*

Model	Findings	Conclusions	Possible Sense	Refs
C57Bl/6 mice	MCs secrete serotonin with mastocytosis	Associated with abdominal pain	Serotonin is a target for the treatment of abdominal pain and diarrhea	[114]
Male rabbits with intragastric inoculation of *Eimeria magna oocytes*	B0AT1 and SN2 in crypts are regulated by MCs	MCs regulated gut permeability	B0AT1 and SN2 as potential targets in MCs related to IBS	[115]
WKY and IBS rat model by balloon catheter insertion	MCs could secrete NGF but are probably not directly associated with IBS	Expression of NGF is not in the same area of MCs	A more precise relationship between MC and enteric neurons is required	[116]
SD rats	CPA is secreted by MCs in I/R injury	MC limit toxins and ET-1 in I/R injury	IPC protected against I/R injury via the MC degranulation-mediated release of MC-CPA	[104]
Specimens from patients	Enhanced level of CXCL11 in IBS	Positive correlation between the MCs number of duodenal and ileal IELs in diarrhea	CXCL11 as potential target and marker for IBS	[106]
IEC lines	Lowering A20 production	Tryptase suppressed A20 in the IEC lines and lowered barrier dysfunction	Treatment targeting allergens	[46]

Table 2. Key molecules related to MCs and their roles in typical diseases.

Diseases	Key Molecules	Mast Cell Alterations	Typical Symptoms	Refs
IBS	Advanced glycation end products (AGEs)	Number increased	Colonic mucus barrier dysregulation in mice	
	5-HT and SERT	Main sources	Diarrhea and visceral hypersensitivity	
	5-HT signaling	Number increased	Stress parameters	[55]
	Histamine and HR4	MC activation	Visceral hyperalgesia	[84]
	Serine Protease	MC infiltration	Functional dyspepsia (FD)	[117]
	Estrogen	MC infiltration	Stress-worsened intestinal alterations	[118, 119]
	Nr4a3	Promoted MC activity	Stress-induced visceral hyperalgesia in mice	[120]
	Active VIP and VIP receptors (VPAC1/VPAC2)	Increased MC and VPAC1$^+$ MC numbers and decreased VIP$^+$ MC	Detrimental consequences to colonic permeability	[121]
	Acetylcholine	Mast cell overactivation	Visceral hypersensitivity (VH)	[122]
	Hereditary α-tryptasemia (HαT)	Increased MC number	IEC pyroptosis	[123]
	5-HT	Increased MC activation	Intestinal dysfunction and depression-like behaviors	[124]
	IL-1β, IL-6, PAR-2, and mast cell tryptase		Visceral hypersensitivity	[125]
	TLR4	Enhanced MCs activation	Visceral hypersensitivity and barrier loss	[126, 127]
GI cancer	Tryptase release after c-Kit receptor activation	Mast cell activation	Increased number of metastatic lymph nodes	[128]
	Inflammatory responses	MC density	Benign cancer	[129]
	Angiogenesis and carcinoma progression	MC density	Patient malignancy	[130]
	c-Kit receptor-related pathway	MC number	Early time intestinal tumor	[131]
Colitis	Ki-67 and β-catenin protein	MC activation	Gastrointestinal tumorigenesis	[132]
	MRGPRX2-mediated	MC degranulation	MC degranulation and activation modules	[34, 133]
	Not mentioned	MC counts and degranulation	Gastrointestinal motility	[134]

Table 2. *Cont.*

Diseases	Key Molecules	Mast Cell Alterations	Typical Symptoms	Refs
	Mannose receptor (MR)	Mφs/MC distribution	Mφs/MC distribution	[96]
	Kit-mediated	MC activation	Experimental colitis	[135]
	P2X7 purinoceptors	MC activation	Intestinal inflammation	[39]
	free-Ca^{2+} and GTPγS	MC activation	Secretory responses	[136]
AD	Mast cell-glia axis and a Fyn kinase	MCs activation	Aggravated AD pathology	[137]

Based on the studies above, we infer that typical symptoms, including visceral hypersensitivity, are prevalent in IBS and are associated with mast cell overactivity and over-proliferation. Signals from neurons and immune cells both stimulate aberrant activities and provide novel avenues for treatment techniques and drug development via neurotransmitters and cytokines. Moreover, the majority of these factors could initiate various inflammatory pathways and lead to broader immune responses that are difficult to manage, and more precise regulation of molecules in key pathways is required.

Box 2 Interactions between MCs and viruses

Apart from bacterial infection, GI is also exposed to virus proliferation [138]. Some viruses can directly infect MCs and activate them [139]. Research found that MCs might enhance NK cell activities and upregulate the CD69 molecule and cytotoxicity-related genes in response to virus-infected mast cells, demonstrating increased cytotoxic activity in response to virus-infected mast cells. Also, mast cells express numerous pattern recognition receptors (PRRs) and secrete inflammatory mediators that have historically been engaged in the antiviral response in the gut. MC interactions with viruses and pathogen products, on the other hand, are complicated and can have adverse and beneficial consequences. MCs can limit viral infection by releasing antiviral mediators and interacting with γδ T cells [140]. However, the detailed mechanisms between MCs and viruses in the gut are not yet completely clarified.

In IBS and GI infection, the number of MCs increased [141] in accordance with the number of neurons [142]. Morphological alterations in IBS [143] and their interactions with the brain have also been put forward as part of the gut–brain axis [144]. However, despite the higher level of mast cells in the gut–brain axis observed in IBS [145], no evidence supports their roles in the gut–brain axis [116]. Mast cells could secrete nerve growth factor (NGF) and contribute to IBS [146]. However, in the rat IBS model, NGF is localized more in the mucosal enteric glial cells (EGCs) but not in the mucosa mast cells. And glial processes in the submucosa of the colon showed bulbous swelling of terminals that overlapped with neurons, known as glial hyperplasia [116]. An increased number of MCs is also seen in several psychological diseases, including neonatal maternal deprivation and stress, and indicates the similarities underlying them [147,148]. In IBS patients, enhancing mesenteric nerve firing and mobilization of Ca^{2+} in dorsal root ganglia neurons are related to the activation of MC accompanied by histamine release and higher neuronal sensitivity to capsaicin [149]. Moreover, B0AT1, Na^{+}-dependent glutamine co-transporters, in villus cells, and SN2 in crypt cells are also regulated by MCs, decreasing co-transporter numbers in villus and enhancing affinity for glutamine in crypt cells [116]. SHIP, a hematopoietic-specific lipid phosphatase, can dephosphorylate PI3K-generated PI(3,4,5)-trisphosphate and suppress the activation of MC, alleviating Crohn's disease in the GI [150]. And substance P and other eicosanoids secreted by MCs could lead to neuron activation [151]. Based on the summaries above, addressing an increased number of MCs might provide a novel aspect in the prevention and treatment of Crohn's disease in future research.

6. Conclusions and Future Perspectives

MCs encompass different kinds of bioactive molecules that are generated upon activation and participate in various biological functions. They could interact with cells of both

immunological and nervous system cells, as well as microbes in the GI. These processes are critical for GI homeostasis, and MC malfunction can result in severe disorders impairing life quality (refer to Figure 2 for detailed information).

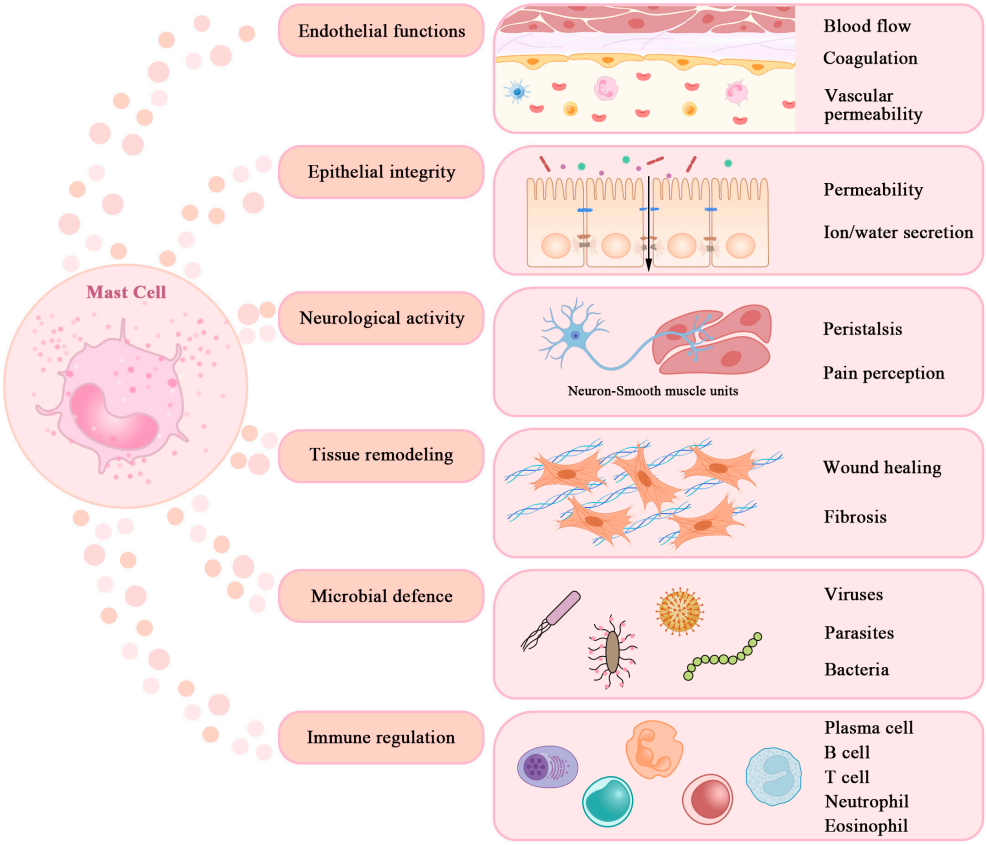

Figure 2. Schematic summary of the MC function. MCs are multifunctional immune cells that release multi-potent active molecules to regulate many physiological functions and immunological responses. They have been found to impact vasodilation, vascular homeostasis, and angiogenesis and possess close interactions with dendritic cells, macrophages, T cells, B cells, fibroblasts, eosinophils, endothelial cells, and epithelial cells.

In this review, we provided a detailed illustration of MC properties and classifications, as well as their involvement in maintaining GI barrier functions. We further analyzed their interactions with immune cells and neurons and especially highlighted MCs' prospective applications in therapeutic development. These provide directions for future investigations and have crucial roles in both clinical and pathological research.

Author Contributions: Y.G. and B.W. analyzed the reference and wrote the manuscript. Y.G., B.W. and R.H. polished the images. C.H., S.Z., X.L. and S.X. analyzed the data. H.G., S.Z. and J.X. revised the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the National Natural Science Foundation of China Grant (No. 82174056 JD Xu).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: All data available.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

BCLXL	B-cell lymphoma-X large
CA	cinnamaldehyde
CP	carboxypeptidase
C-C motif	chemokine
CCL2	chemokine ligand 2
CCR2	chemokine receptor 2
CD117	c-Kit
chymase	Chymotrypsin-like
CLDN8	claudin-8
COX	cyclooxygenase
CPA3	carboxypeptidase A3
CRC	colorectal cancer
CRH	corticotrophin-releasing hormone
CTMC	connective tissue mast cells
CXCR2	CXC chemokine receptor 2
ET-1	endothelin 1
FD	functional dyspepsia
FOS	fructo-oligosaccharides
FD	functional dyspHmm
GI	gastrointestinal
GPCR	G protein-coupled receptor
H4R	histamine receptor 4
HMC-1	human mast cell-1
HMCs-1	human mast cells-1
I/R	ischemia-reperfusion
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IECs	intestinal epithelial cells
IECs	intestinal epithelial cells
IPC	ischemic preconditioning
IB4	isolectin B4
KC	keratinocyte chemoattractant
Mφ	macrophage
MCP	mast cell proteases
MMC	mucosal mast cells
MRGPRX2	mMas-related GPCR-X2
Nb	nippostrongylus brasiliensis
NGF	nerve growth factor
NOD	nucleotide-binding and oligomerization domain
NSAIDs	non-steroidal anti-inflammatory drugs
PAR-2	protease-activated receptors-2
PCIS	precision cut intestinal slices
PGs	prostaglandins
SCF	stem-cell factor
TLR	Toll-like receptors
TRPV1	transient reporter. potential channel V1
VHS	visceral hypersensitivity
VIP	vasoactive intestinal peptide

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