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Summary: Mast cells are versatile tissue regulator cells controlling major intestinal functions such as epithelial secretion, epithelial permeability, blood flow, neuroimmune interactions, and peristalsis. Most importantly, mast cells are key regulators of the integrity and function of the gastrointestinal barrier. At the same time, they can act as immunomodulatory cells by reacting to various exogenous signals from bacteria, viruses, and parasites through innate recognition receptors, such as Toll-like receptors (TLRs) or through receptors of the specific immune system, such as immunoglobulins (Igs) bound to their cell surface. This mast cell function is enhanced by an intensive cross talk of mast cells with other cells of the innate or adaptive immune systems. Finally, mast cells act as inflammatory cells mediating diseases such as allergy, once they become dysregulated because of excess of allergen, allergen-specific IgE and cytokines, or invading microbes. The present article focuses on the human mast cell functions in the intestine and compares the data with those derived from animal experiments. In particular, the role of bacteria and TLRs expression by mast cells for allergic reactions are discussed.

Keywords: mast cells, gastrointestinal barrier, bacteria, innate immunity, allergy, inflammation

Intestinal barrier system

The major function of the intestine is digestion and absorption of nutrients, water, and electrolytes to provide the body with liquids and fuels necessary for survival. A large part of this job is done in the small intestine, which is equipped with a macro- and microfolded mucosa forming a surface of several hundred square meters. This mucosal barrier must be permeable to meet the absorptive functions and at the same time must protect the host against invasion of microbes and toxins with pathogenic capacities. This 'dilemma' of opposing functions is even more pronounced in the large intestine, which hosts a remarkable bacterial flora consisting of about 10^{14} bacteria of at least 500 different species, mostly unknown species belonging to anaerobic strains that cannot be cultured. The function of this flora, the composition of which seems to be determined in early life and remains stable like an individual 'fingerprint' during life, is still a matter of debate.

The intestinal flora supports the host, digesting food components, such as particular carbohydrates and fibers, that are not digestible by the small intestine. Moreover, the flora might protect the intestine against more pathogenic bacterial strains, which could colonize the intestine in the absence of a normal intestinal flora. During the first few weeks of life, the flora becomes established, and immune tolerance against such bacterial antigens is initiated by mechanisms far from being understood. Recent data suggest that this tolerance must be acquired after birth but can be impaired during later life. For example, patients with Crohn's disease are characterized by a loss of T-cell tolerance against selected bacterial antigens (1). Development of allergy could be a result of an immature or a disturbed interaction between intestinal bacteria and mucosal immune system in infancy or adulthood, respectively (see below).

The intestinal barrier consists of multiple defense systems, such as epithelial functions (mucus production, secretion, defensin release, etc.), innate and adaptive immune functions, and the enteric nervous system. The impact of intestinal barrier disturbances is emphasized by observations that the breakdown of a single defense system is sufficient to initiate substantial diseases. For example, it was shown recently that an impairment of the production of single defensins is associated with Crohn's disease and ulcerative colitis (2). Possibly, such impairments of the intestinal barrier could be of importance not only for inflammatory bowel diseases but also for other inflammatory reactions such as food allergy, celiac disease, and even irritable bowel syndrome. In addition, the sudden and substantial disturbance of the intestinal barrier can induce more acute diseases such as sepsis and septic shock.

The mast cell at the intestinal barrier

Mast cells are tissue cells typically located at strategically important locations, such as mucosal surfaces, involved in host defense against the environment. The intestinal mucosa consists of approximately 2–3% of mast cells within the lamina propria in healthy individuals (3). In the course of intestinal diseases, this amount can be augmented up to 10-fold (Table 1). Until recently, the function of intestinal mast cells was not clear. It has been generally accepted that mast cells are of relevance in gastrointestinal diseases such as food allergy or parasitosis, but more recently it was shown that mast cells might have several physiological functions in the tissues where they reside. In the intestine, mast cells are now thought to regulate multiple tissue functions of central importance for normal gut function (Table 2). The broad spectrum of functions might explain why

Table 1. Mast cell-associated human intestinal diseases

Type of disease	Examples	References
Proliferative/ malignant	Mastocytosis (localized to the intestine or generalized)	(71)
	Gastrointestinal stroma tumors	(72)
	Gastrointestinal polyps	
	Gastrointestinal cancer	(73, 74)
Benign	Food allergy	(75, 76)
	Celiac disease	(77)
	Inflammatory bowel disease	(3, 78)
	Microscopic colitis	(79)
	Intestinal parasitosis	(80)
	Irritable bowel syndrome	(81)

mast cells can be involved in so many different pathologies beyond allergy. It is further reflected by the fact that mast cells can exert a large array of different effector functions by releasing preformed mediators, such as proteases, histamine, and heparin, from their granules or by releasing *de novo* synthesized mediators on activation including lipid mediators and cytokines (Fig. 1). These mediators allow mast cells to regulate either local tissue functions or host defense by acting as innate immune cells, by interacting with the specific immune system, or by inducing and regulating inflammation. A large portion of mediators released by mast cells is molecules mediating innate immunity, such as tumor necrosis factor (TNF) and leukotriene B4 (recruitment of neutrophils), interleukin (IL)-5 (recruitment of eosinophils), and chemokines (endothelial regulation and chemotaxis) (Fig. 1).

Table 2. Physiological functions of mast cells in the intestine

Physiological function	References
Regulation of epithelial functions	
Water and electrolyte secretion?	(82, 83)
Tight junctions/epithelial barrier integrity	(26–28)
Regulation of endothelial functions	
Blood flow, vessel contraction	
Tight junctions/endothelial permeability/edema	(84, 85)
Coagulation/fibrinolysis	(86)
Regulation of cell influx into tissue and cell function	
Neutrophils	(44, 87, 88)
Eosinophils	(89, 90)
Lymphocytes	(47)
Regulation of neurological functions	
Intestinal peristalsis	(91)
Pain mediation	(92)
Regulation of tissue transformation	
Wound healing	(93, 94)
Fibrosis	(95)
Host defense against microbes	
Bacterial infection	(5, 51)
Viral infection	(4)
Parasitic infection	(34, 35)

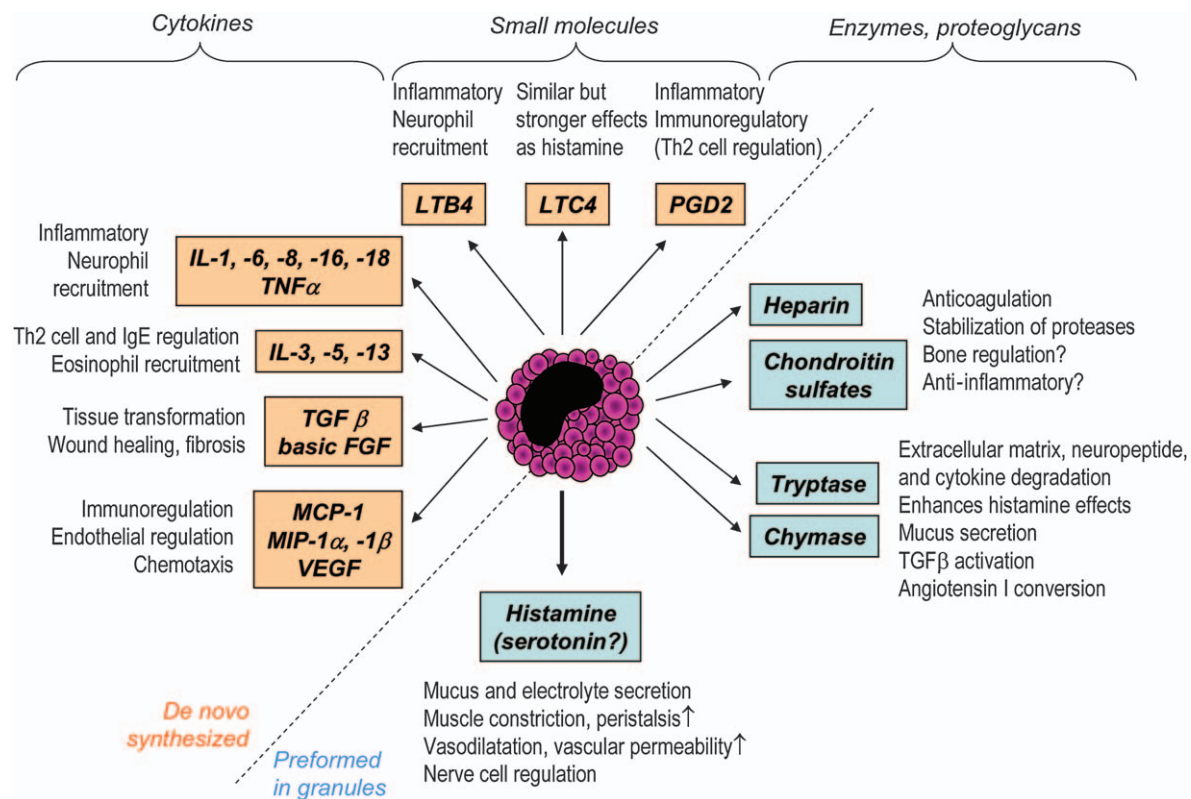


Fig. 1. Human mast cell mediators. Mediators of human mast cells comprise small molecules acting mostly as proinflammatory molecules [histamine, leukotriene (LT) B4 and LTC4, and prostaglandin D2 (PGD2)], cytokines [ILs, TNF α , transforming growth factor β (TGF β), basic fibroblast growth factor (FGF), monocyte chemoattractant protein-1 (MCP-1), MIP, and vascular endothelial growth factor

(VEGF)], proteases (tryptases and chymase), and proteoglycans (heparin and chondroitin sulfate). The mediators placed above the dotted line are mediators synthesized *de novo* upon stimulation of the cells; those below the dotted line exist also preformed in cytoplasmic granules. The major biological effects of each mediator are indicated.

To understand such processes in more detail, we need information not only about the mediators released by mast cells but also about the mechanisms of regulation of this cell type. Loss of mast cell regulation is associated with pain and disease. In the following sections, the regulation of human mast cells by immunoglobulin (Ig) E receptor cross-linking, the major event in type I allergic reactions, and by bacteria-derived molecules, which play a role in host defense against bacteria and in infection, is described. Particular emphasis is put on the possible link between allergy and bacterial challenge because this link might be particular to mast cells.

Recognition of microbes by human mast cells

Human mast cells are capable of recognizing a large number of the so-called pathogen-associated molecular patterns and other bacterial products by Toll-like receptors (TLRs) (Table 3). The expression of TLRs varies slightly between mast cells of different origin, and the responsiveness of mast cells to different TLR ligands may differ substantially (4–7). For example, mast cells

generated from sterile environments such as bone marrow, umbilical cord blood, or peripheral blood respond quite well to different TLR ligands such as lipopolysaccharide (LPS), peptidoglycan, and yeast zymosan, whereas mast cells derived from primarily unsterile sites such as intestine and, to some extent, lung respond less efficiently to such stimuli (unpublished observations). This difference possibly reflects a kind of tolerance mast cells acquire at sites constantly challenged with bacterial products, such as the intestine. Interestingly, the quality of response of mast cells to TLR ligands is different from that of response induced by allergens and other non-bacterial triggers. Whereas an allergen induces primarily degranulation and release of proinflammatory mediators such as histamine and eicosanoids, bacterial products hardly induce such mediators but instead induce cytokines needed for the initiation of innate and adaptive immune responses (6).

Apart from TLR ligands, other products of infectious agents may serve as mast cell triggers. For example, we could show that *Escherichia coli* α hemolysin induces calcium influx in human intestinal mast cells, leading to the release of histamine,

Table 3. Human mast cell surface molecules for recognition of exogenous structures

Receptor	Cell type expressing the receptor	References
Innate immunity		
TLR1	CBMC, PBMC, KU 812, HMC-I, HIMC	(4, 5), UD
TLR2	PBMC, CBMC, HIMC	(4, 5), UD
TLR3	HMC-I, PBMC, HIMC	(4), UD
TLR4*	PBMC, CBMC, HIMC	(4, 7), UD
TLR5	HMC-I, PBMC, CBMC, HIMC	(4), UD
TLR6	HMC-I, PBMC, HIMC	(4, 5), UD
TLR7	HMC-I, PBMC	(4)
TLR8	HMC-I, PBMC, HIMC	(4), UD
TLR9	HMC-I, PBMC, HIMC	(4), UD
FimH R (CD48)	CBMC, HMC-I, HIMC	(9, 96), UD
C3a R	HMC-I	(97)
C5a R	Skin mast cells, cardiac mast cells, HMC-I	(98)
Specific immunity		
FcεRI	All mature mast cells	(6, 21, 99–101)
FcγRI	PBMC, CBMC, HIMC	(100, 102), UD
FcγR 2a	PBMC, skin mast cells, HIMC, CBMC	(12, 13, 103), UD
FcγR 2b†	PBMC, HIMC, CBMC	(13, 103), UD
FcγR 3	PBMC	(13)
MHCI	All mature mast cells	(56, 104)
MHC2†	CBMC, HMC-I	(57, 58)

CBMC, cord blood-derived mast cells; HIMC, human intestinal mast cells; UD, unpublished data; PBMC, peripheral blood-derived mast cells; KU812, human basophil line; HMC-I, human mast cell line.

*After IL-4 priming.

†After exposure to interferon-γ.

sulfidoleukotrienes, and proinflammatory cytokines. Furthermore, type 1 fimbriae and cholera toxins have been described as mast cell triggers (8, 9). Most recently, glucopeptides derived from parasites that are capable of activating mast cells were characterized (10, 11).

Recognition of non-infectious antigens by mast cells

The role of mast cells in allergic reactions is well established. Their number is mostly enhanced at sites of allergic inflammation, and, more importantly, the release of mast cell mediators such as histamine, tryptase, IL-5, and TNF is enhanced. Antigen recognition typically occurs through the allergen-specific Igs bound to the cell surface through Ig receptors (Table 3). The best characterized and likely most relevant mechanism of mast cell activation is cross-linking of surface-bound IgE bound to FcεRI. Apart from IgE, IgG and even IgA might play a role. Human mast cells express receptors for IgA (FcαR) and IgG (stimulatory FcγRI and IIa, inhibitory FcγRIIb), either constitutively (FcγRIIa) or upon induction (FcγRIIb and FcγRIIc), for example by interferon-γ (12, 13). In this way, mast cells form part of the specific immune system,

which is defined by specific antigen recognition through acquired antigen recognition molecules such as Igs or T-cell receptors. Indeed, mast cells are in close cross talk with lymphocytes, both B and T cells. For example, mast cells are regulated by T-cell-derived cytokines such as IL-4 (14, 15) and IL-9 (16, 17), whereby IL-4 enhances mast cell proliferation and effector functions at sites of inflammation and IL-9 mediates interaction with regulatory T cells for induction of peripheral tolerance. In contrast, mast cells can produce cytokines and mediators such as histamine, prostaglandin D₂, and interferons capable of modulating T-cell subsets (18–20). Mast cells are thought to be involved also in the regulation of B-cell functions, namely in the production of IgE by expressing IL-13 (not IL-4, which is found only in human mast cells from allergic individuals but not from healthy individuals) and CD40 ligand (21–23).

The fact that mast cells express not only FcεRI but also other FcRs points to a role for mast cells in immune and inflammatory diseases beyond allergy, for example mediated by IgG complexes or even IgA. This hypothesis is supported by several animal models of immune complex diseases showing mast-cell-dependent mechanisms (24, 25). The role of IgA receptors on human mast cells is not clear.

Abnormal mast cell activation causes impairment of the intestinal barrier

There is now overwhelming evidence that not only infection but also chronic or acute stress, inflammation, and alcohol exposure enhance mucosal permeability by a mast cell-dependent mechanism (26–30). Using rodent models, it was shown that mast cell proteases are directly responsible for the increase of epithelial paracellular permeability and for redistributed expression of tight junctions during parasitic infection and stress (28, 29). Interestingly, stress led to an enhanced release of mast cell mediators (histamine and tryptase) in the proximal small intestine in healthy controls and to a larger extent in patients with mast cell-associated diseases such as food allergy (31). Mast cells are in close contact with epithelial cells and nerve endings, supporting the hypothesis that mast cells are involved in regulating mucosal permeability and intestinal barrier function.

By increasing mucosal permeability, mast cells can contribute to an ongoing inflammatory process, independent of whether the process was initiated by allergen or bacteria. The increased mucosal permeability would lead to an enhanced influx of both potential allergens and harmful microbes into the intestinal tissue.

A major and to a large extent specific mast cell mediator is histamine, which plays an important multifunctional role at the intestinal barrier. Histamine acts through four known histamine receptors. Activation of histamine receptor (HR) 1 and HR2 affects the function of blood vessels (dilatation and increased permeability), smooth muscles (contraction), and epithelial cells (mucus production). A recent human study showed that HR1 and HR2 are upregulated within the intestinal tract in patients with food allergies (32). Furthermore, histamine acts as an immunomodulator, for example in human alveolar macrophages, in which histamine inhibits the release of TNF by triggering the enhanced release of the anti-inflammatory cytokine IL-10 (33). Histamine also affects epithelial cells, dendritic cells, and T and B lymphocytes. Histamine promotes T-helper (Th) 1 cell activation through HR1 and suppresses both Th1 and Th2 cell activation through HR2 (18).

Function of human mast cells in defense against microbes

The role of mast cells in host defense against parasitic infections was established many years ago (29, 34, 35). Infections with *Trichinella spiralis* or *Nippostrongylus brasiliensis* are accompanied by a substantial mast cell accumulation (29, 34, 35). It is not clear whether this mast cell accumulation is triggered by the infectious agents or by the subsequent Th2 response (36). Mast cell protease-1 was found to be a crucial mediator of immune responses against such helminths in mice. A mutation in the mast cell protease-1 gene in a mouse model is associated with a significantly delayed expulsion of *Trichinella* and *Nippostrongylus* (34, 37).

More recently, it was shown in a mast cell knockin mouse model that *Plasmodium* parasites, which are delivered into the host by mosquito bites, activate dermal mast cells and induce a local influx of inflammatory cells. The mast cell-dependent mechanisms were mediated by IL-10 and resulted in down-regulation of the antigen-specific T-cell response (38). Another study indicates that mice pretreated with IL-18 and IL-2 developed a prominent intestinal mastocytosis, which is important for prompt parasite expulsion (39). In mast cell-deficient and wildtype mice, degranulation of mast cells was observed, but the intensity and duration of the *Leishmania* major infection were not altered in mast cell-deficient mice (40). Interestingly, it could be shown that helminth infection protected the host from developing allergic diseases by yet unknown mechanisms, being at least independent of an induction of a Th1 response and of competition with IgE-binding sites on the surface of mast cells and basophils (41, 42). It is tempting to speculate that mast cell mediators are

involved in this protection; however, such findings need confirmation in humans.

The protective role of mast cells in bacterial infection arose from studies using mouse models of *Klebsiella pneumoniae*-dependent lung infections and septic peritonitis using mast cell-deficient and normal mouse strains (43, 44). In the mast cell-deficient models, lack of mast cell-derived TNF α and leukotrienes impaired neutrophil recruitment, bacterial clearance, and host survival (43–45). Apart from neutrophil recruitment into the infection side, mast cell-derived TNF α induced hypertrophy of draining lymph nodes and T-cell recruitment at sites of infection with *E. coli* (46, 47). More recently, a novel TNF-independent pathway for mast cell-mediated lymph node hypertrophy and Langerhans cells migration was shown by peptidoglycan derived from *Staphylococcus aureus*. In contrast to the activation of mast cells through TLR and myeloid differentiation factor 88 (Myd88), this mechanism depended on complement components (48). Based on such findings, it has been suggested that mast cells provide a link between innate and adaptive immunity.

Most data come from rodent mast cells, whereas limited data exist describing the interactions of human mast cells with bacteria (49). However, mast cell accumulation was observed in patients with *Helicobacter pylori*-associated gastritis and *Shigella* infection (50, 51). Mast cell mediators such as lipid mediators or chymase were significantly higher in patients with acute infectious diarrhea (cholera and shigellosis) and in *H. pylori*-associated gastritis (50–52). During the *in vitro* ingestion of a pathogenic *E. coli* by human mast cells, production of TNF α , CC chemokine ligands [CC ligand-1 (CCL-1)/I-309, CCL-19/macrophage inflammatory protein-3 β (MIP-3 β), and CCL-18/MIP-4], carcinoembryonic antigen (CEA)-related cell adhesion molecule 1, the integrin CD49d, and CD80 were upregulated. Most interestingly, coincubation of human mast cells with *E. coli* downregulated Fc ϵ RI expression and Fc ϵ RI-mediated mast cell degranulation (53).

In recent studies, the role of mast cells as intermediaries between innate and adaptive immune systems during bacterial infections was further unraveled. For example, mast cells are able to regulate the migration, maturation, and activation of dendritic cells (46, 54, 55) through the release of TNF α , IL-1 β , and granulocyte-macrophage colony-stimulating factor after stimulation with TLR ligands (5, 7). Bacterial antigens are presented to T cells through the major histocompatibility complex (MHC) class I or MHC class II pathway, the latter requiring interferon- γ , which causes a dose-dependent induction of MHC class II molecules in mast cells (56, 57). An *in vitro* study showed that presentation of staphylococcal enterotoxin B

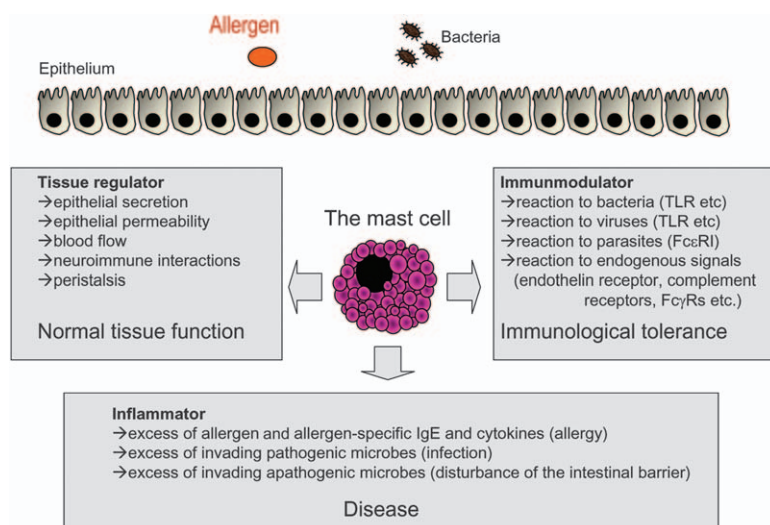


Fig. 2. Role of mast cells at the intestinal barrier.

Putative mast cell functions at the intestinal barrier are shown (for details, see text).

through the MHC class II pathway by human mast cells directly activates CD4⁺ T-cell hybridomas (58).

Role of bacteria and TLR expression by mast cells for allergic reactions

The prevalence of allergic diseases has doubled in the last 2 years. Currently, 10–15% of the Western population is afflicted (59). The ‘hygiene hypothesis’ was the only conclusive explanation for this dramatic development; however, the underlying mechanisms remain to be elucidated (42, 60, 61). In particular, the role of TLR signaling in the context of allergies is far from being clear. In a few *in vitro* and *in vivo* studies, it could be shown that TLR ligands induce a Th1-biased immune responsiveness, which might protect the host from Th2-biased allergic disease (62–65).

The recognition of mast cells as long-living tissue-resident cells producing large amounts of Th1 cytokines in response to TLR ligands could be important in the development of allergic diseases. The study of FcεRI- and TLR4-mediated reactions by gene chip analysis indicates that a unique number of genes are regulated by each of the activation conditions. LPS was able to modulate an exclusive subset of genes encoding for IL-1β, IL-10, IL-15, CCL5, and CCL8 in human mast cells, which were not induced by FcεRI cross-linking (6). Costimulation of human and/or murine mast cells through TLR4 and FcεRI or TLR2 and FcεRI is reported to augment cytokine production (17, 66, 67). TLR2 ligands enhanced the cytokine release induced by suboptimal amounts of antigen in murine bone marrow-derived mast cells. Interestingly, the TLR2 ligand Pam (4) CSK (5) but not MALP-2 suppressed antibody-induced degranulation of murine bone-marrow-derived mast cells (68).

Although most of these data need to be confirmed in human mast cells and in human *in vivo* experiments, they strongly suggest that concurrent stimulation of mast cells with allergen and bacterial products enhances the allergic response in allergic individuals. One could even speculate that the bacterial challenge because of bacterial infection or just because of an impaired gastrointestinal barrier might prime for enhanced mast cell reactions to allergen. Such mechanisms might also explain why bacterial challenge in non-allergic individuals might be protective against allergy (hygiene hypothesis), whereas bacterial challenge in allergic individuals might aggravate allergic responses to allergen, as seen in the course of bacterial superinfection that increases inflammatory reactions in allergic individuals (69, 70).

Conclusion and outlook

Mast cells exert multiple roles in mucosal immunity. They act as versatile tissue regulator cells controlling major intestinal functions such as epithelial secretion, epithelial permeability, blood flow, neuroimmune interactions, and peristalsis. Alternatively, they act as immunomodulatory cells by reacting to various exogenous signals from bacteria, viruses, and parasites through innate recognition receptors, such as TLRs, or through receptors of the specific immune system such as Igs bound to their cell surface. This mast cell function is enhanced by an intensive cross talk of mast cells with other cells of the innate or adaptive immune system. Additionally, mast cells act as inflammatory cells mediating diseases, such as allergy, once they become dysregulated because of excess of allergen, allergen-specific IgE and cytokines, or invading microbes. The causes of such excess are severe genetically

determined dysregulation of the immune system, challenge with highly pathogenic and invasive pathogens, or, perhaps the most common cause, disturbance of the intestinal barrier (Fig. 2).

New treatment options for such diseases (immune disorders, infectious diseases, and allergic diseases) are offered, which

focus not only on immunomodulation and inflammation but also on the restitution and stabilization of the intestinal barrier. In this context, drugs like antibiotics, probiotics, and – most interestingly – mast cell-modulating drugs have a new impact. Based on these data, mast cells and the gastrointestinal barrier should be recognized as new therapeutic targets.

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