REVIEW

Physiological and pathophysiological functions of intestinal mast cells

Stephan C. Bischoff

Abstract The normal gastrointestinal (GI) mucosa is equipped with mast cells that account for 2–3% of lamina propria cells under normal conditions. Mast cells are generally associated with allergic disease, and indeed, food allergy that manifests in the GI tract is usually mast cell dependent. On the other hand, mast cells have a number of physiological functions in the GI tract, namely regulatory functions such as control of blood flow and coagulation, smooth muscle contraction and peristalsis, and secretion of acid, electrolytes, and mucus by epithelial cells. One of the most intriguing functions of intestinal mast cells is their role in host defense against microbes like bacteria, viruses, or parasites. Mast cells recognize microbes by antibody-dependent mechanisms and through pattern-recognition receptors. They direct the subsequent immune response by attracting both granulocytes and lymphocytes to the site of challenge via paracrine cytokine release. Moreover, mast cells initiate, by releasing proinflammatory mediators, innate defense mechanisms such as enhanced epithelial secretion, peristalsis, and alarm programs of the enteric nervous This initiation can occur in response to a primary contact to the microbe or other danger signals, but becomes much more effective if the triggering antigen reappears and antibodies of the IgE or IgG type have been generated in the meantime by the specific immune system. Thus, mast cells operate at the interface between innate and adaptive immune responses to enhance the defense against pathogens and, most likely, the commensal flora. In this respect, it is important to note that mast cells are directly involved in controlling the function of the intestinal barrier that turned out to be a crucial site for the development of infectious and immune-mediated diseases. Hence, intestinal mast cells perform regulatory functions to maintain tissue homeostasis, they are involved in host defense mechanisms against pathogens, and they can induce allergy once they are sensitized against foreign antigens. The broad spectrum of functions makes mast cells a fascinating target for future pharmacological or nutritional interventions.

Keywords Mast cells · Allergy · Food allergy · Histamine · Stem cell factor · IL-4 · Gastrointestinal barrier · Enteric nervous system · Bacteria · Host defense · Innate immunity · Immune tolerance · Hygiene hypothesis · Vitamin A · Inflammatory bowel disease · Irritable bowel syndrome · Mastocytosis

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Mast cells: not only an allergy cell

Mast cells (Fig. 1) are tissue cells typically located at strategically important locations involved in host defense against the environment such as mucosal surfaces [1]. The intestinal mucosa consists of approximately 2–3% of mast cells within the lamina propria in healthy individuals [2]. In the course of intestinal diseases, this amount can augment up to tenfold. Until recently, the function of intestinal mast cells was not clear. It has been generally accepted that mast cells are of relevance in gastrointestinal (GI) diseases such as food allergy or parasitosis, but more recently, it became clear that mast cells regulate multiple tissue functions of central importance for normal gut function [3–5].

Fig. 1 Human mast cells isolated from intestinal tissue

Mast cells have been established as key effector cells of allergic inflammation [6, 7]. They are located in tissues that form the large host barriers such as skin, respiratory and intestinal mucosa, and blood vessels, the classical sites of allergic disease; they express the high-affinity IgE receptor and bind IgE on their surface. Furthermore, they release histamine and other mediators upon crosslinking of surface-bound IgE by allergen. All these events are known to be of central relevance in the pathophysiology of allergic diseases, and therefore, mast cells can be indeed interpreted as directors of allergic responses [7–9]. However, considering the multiple functions of mast cells including regulation of epithelial and endothelial cells, fibroblasts and muscle cells, neurons, and, most recently, T regulatory cells, this cell type must do more than just mediating allergic reactions. Indeed, recent research findings indicate that mast cells are involved in multiple regulatory processes. They maintain tissue homeostasis, they mediate danger signals, and they have been proposed to participate in wound healing processes.

The broad spectrum of functions might explain why mast cells can be involved in so many different GI 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 from their granules such as proteases, histamine, and heparin, or by releasing de novo synthesized mediators upon activation including lipid mediators and cytokines (Fig. 2). These mediators render mast cells to regulate either local tissue functions or host defense by either acting as innate immune cells or by interacting with the specific immune system or by inducing and regulating inflammation. A number of mediators released by mast cells are molecules mediating innate immunity such as tumor necrosing factor a (TNFα) and leukotriene B4 (LTB4; recruitment of neutrophils),

interleukin (IL)-5 (recruitment of eosinophils), and chemokines (endothelial regulation, chemotaxis).

In the following chapter, the versatile functions of intestinal mast cells, both under normal conditions and in allergic as well as nonallergic disease, will be described. As much as possible, the explanations will focus on the human situation that might differ from findings in rodents; however, rodent data will be included if human data are lacking. Indeed, the differences between human and rodent are particularly striking in case of mast cells, as shown before [5].

Biology of human mast cells

Mast cell origin

Human mast cells develop from myeloid-cell progenitors under the influence of particular growth factors such as stem cell factor (SCF) and IL-4, cytokines that also regulate the development of mast-cell subtypes [10–12]. The relationship between human mast cells and other leukocyte lineages is not clear as yet. Human mast cells have been described as the tissue equivalents of basophil granulocytes, because both cells contain basophilic plasma granules, release histamine, and express the high-affinity IgE receptor; however, the definition of a cellular relationship based on growth-factor responsiveness during development or on cellular markers is limited [13–16]. Morphological and functional analyses, which are probably more relevant, have indicated that human mast cells are more closely related to monocytes and macrophages, whereas basophils share properties mainly with eosinophils. Gene expression and mutation studies have shown that mast cells can still have monocytic features [17] and that human mast cells and basophils do not derive from a common bilineage-restricted committed progenitor [18]. This is supported by the observation that although both human mast cells and basophils have functional SCF receptors, the mutation of the gene can be found only in mast cells in mastocytosis patients [19]. By contrast, murine mast cells seem to be closer to human basophils in terms of functional properties, whereas human mast cells obviously form a separate cell type lacking a full equivalent in rodents. This notion is supported by the fact that some murine mast cell populations as well as human basophils respond well to IL-3, whereas human mast cells either lack the IL-3 receptor or hardly respond to it [20–22]. This is true not only for cell development but also for the regulation of mature mast cells by cytokines [23].

The factors regulating the development of particular human mast cell subtypes such as tryptase-positive mast cells (MC_T) or tryptase/chymase-double-positive mast cells
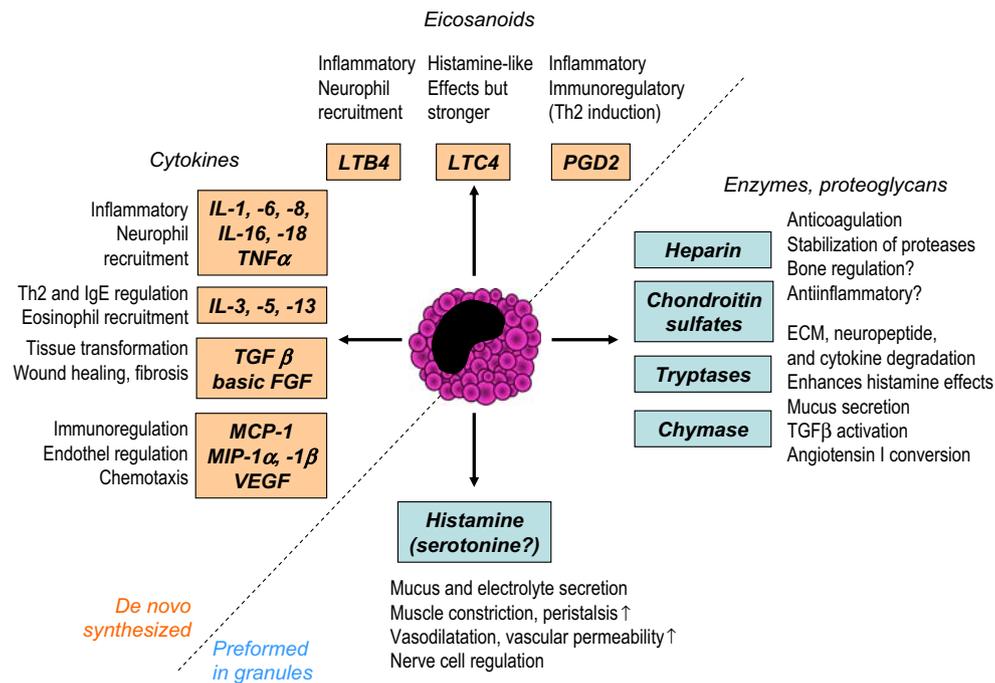
Fig. 2 Human mast cell mediators. Mediators of human mast cells comprise small molecules acting mostly as proinflammatory molecules (histamine, leukotriene B4 and C4, prostaglandin D2), cytokines (*IL* interleukins, *TNFα* tumor necrosis factor alpha, *TGF-β* transforming growth factor beta, *FGF* basic fibroblast growth factor, *MCP-1* monocyte chemotactic protein 1, *MIP* macrophage inflammatory protein, *VEGF* vascular endothelial growth factor), proteases (tryptases, chymase), and proteoglycans (heparin, 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 cytoplasmatic granules. The major biological effects of each mediator are indicated

(MC_{TC}) are poorly defined. Own studies suggest that IL-4 preferentially promotes the development of MC_T found predominantly in lung and intestinal mucosa, whereas coculture of human mast cells with human endothelial cells promotes the MC_{TC} phenotype typical for skin and cardiac mast cells [24, 25].

Effector functions

Mast cells exert their biological functions almost exclusively by humeral functions. There are a few reports about mast cell phagocytosis and other nonhumoral mast cell functions, but typically, mast cell functions are restricted to the release of mediators. The array of mediators released by human mast cells is enormous and further explains how mast cells can be involved in so many different physiological and pathophysiological functions (Fig. 2).

The mast cell mediators can be classified into small molecule mediators (histamine, serotonin), protein mediators (cytokines, proteases), lipid mediators (leukotrienes, prostaglandins), and proteoglycans (heparin, etc.). Some of the mediators are stored in granules (histamine, proteases, proteoglycans, small amounts of TNFα) and therefore can be released within seconds or a few minutes; others are newly synthesized within minutes to hours upon stimula-

tion of the cells (lipid mediators, most cytokines) and often need RNA transcription. On the other hand, the mediators stored in plasma granules are also synthesized de novo once the cell becomes stimulated for mediator release.

Mast cell regulation

The classical and possibly most effective mast cell stimulus is crosslinking of cell surface-bound IgE by allergen in sensitized individuals. This mechanism first described shortly after the discovery of IgE in the late 1960s of last century is central in type I hypersensitivity reactions. It can be simulated by different ways in vitro by using anti-IgE or anti-IgE receptor antibodies, but is likely of no importance in healthy individuals. Our knowledge about human mast cell regulation under normal conditions is poor.

An important group of mast cell regulators are growth factors and cytokines that either promote mast cell development from progenitor states, or act as regulators of mediator release, or do both. The first and still unique mast cell growth factor described in the literature is SCF, the ligand of c-kit, a protease expressed on the surface of all human and rodent mast cells. SCF, either membrane bound or in its soluble form, promotes mast cell development, survival of mature human mast cells, and adhesion to

extracellular matrix (ECM) proteins [24–26]. In addition, SCF can regulate human mast cell mediator release by either enhancing IgE-dependent mediator release or by directly inducing mediator release in mast cells kept in a SCF-deprived milieu [27, 28]. The mechanisms of SCF effects in human mast cells have been identified to a large extent. Binding of SCF induces autophosphorylation of its receptor Kit and subsequently activation of several signaling molecules including PI3K and mitogen-activated protein kinase [26, 29]. In mast cells derived from human CD34+ peripheral blood cells, SCF was found to phosphorylate STAT5 and STAT6 as well as the transmembrane adaptor non-T cell activation linker (NTAL) suggested to link Kit and FcεRI signaling leading to an enhanced IgE-dependent degranulation [30, 31]. More recently, the same group found that of Btk activated via Lyn is another key regulator of a Kit-mediated amplification pathway that augments IgE-mediated mast cell activation [32, 33].

More recently, IL-4 has been described as a human mast cell regulator. In contrast to SCF, IL-4 does not affect mast cells by itself, but acts synergistically with SCF on mast cell survival, proliferation, and IgE-dependent mediator release. IL-4 markedly enhances human mast cell proliferation and IgE-dependent mediator release [24, 34, 35]. Moreover, it changes the cytokine profile released by mast cells by reducing proinflammatory cytokines such as TNFα and IL-6 and in turn enhancing Th2 cytokines such as IL-5 and IL-13 [36, 37]. The IL-4 priming of human mast cells for enhanced proliferation and mediator release is associated with an increased activity of extracellular signal-regulated kinase (ERK) and c-Fos, the downstream target of ERK and component of the transcription factor AP-1 [37]. Interestingly, the enhancing effects of IL-4 were reversible [37] and restricted to mature human mast cells, whereas IL-4 exerts opposite effects in maturating human mast cells [35]. Considering that IL-4 also induces the development of Th2 cells and IgE switch in B cells, this cytokine turns out to be a key cytokine in the pathogenesis of allergic inflammation.

Our knowledge on IgE-independent triggers of human mast cells other than cytokines is poor. Obviously, the list of IgE-independent mast cells agonists varies between human and rodent mast cells and also between human mast cell from different body sites. Human mast cells challenged to interferon (IFN)γ express FcγRI at sufficient quantity to become activated for mediator release upon FcγRI aggregation [38, 39]. This mechanism could be of relevance for the otherwise poorly understood IgE-independent allergic reactions as well as for nonallergic mast cell activation during type III hypersensitivity reactions or infections.

Mediators such as C3a, C5a, substance P and other neuropeptides, IL-8, NGF, SCF, bacterial products, and UV light have been suggested; however, most of these mediators only affect human skin mast cells and not mucosal mast cells [40, 41]. In contrast, human mucosal mast cells do not respond to such triggers; however, if primed by cytokines such as SCF and IL-4, they start to express NK-1 and can respond to substance P with mediator release [41, 42]. Possibly, costimulatory mast cell signals other than IL-4 have to be considered in this respect. Recently, MIP-1α has been identified as amplifier of IgE-dependent mediator release in rodent mast cells [43]. It is yet unclear if this finding holds true also for human mast cells and if such priming agents like IL-4 or MIP1α render mast cells responsive to otherwise inactive IgE-independent triggering agents like neuropeptides or anaphylatoxins. Nevertheless, these reports show that not only T cells but also mast cells require the cooperation of two signals for optimal activation, an antigen-dependent signal such as the T cell receptor or IgE bound to the cell surface and a costimulatory molecule, e.g., CD80 in T cells or SCF/IL-4 in mast cells.

During the last few years, important progress has been made in understanding mast cell regulation by the discovery of several inhibitory mechanisms that might balance the agonistic activities of mediators discussed before. The inhibitors include not only ligands of immunoreceptor tyrosine-based inhibition motif-containing receptors such as FcγRIIB, gp49B1, SIRPα, the human analogs LIR-5, and LILR B4 but also the anti-inflammatory cytokines transforming growth factor (TGF)-β1 and IL-10, CD200, intracellular signal molecules like NTAL or RabGEF1, and several other molecules such as retinol, β2-adrenoceptor agonists, and ECM proteins binding to CD63 [5]. Most of the data derive from in vitro experiments or from animal models. Therefore, the in vivo relevance of such findings for humans in health and disease cannot be judged definitively so far. However, some of the findings could be recently extended to the human system, e.g., CD200R is expressed and functional in human cord blood-derived mast cells [44]. TGF-β1 was found to inhibit the SCF-dependent growth of human intestinal mast cells and to change the mediator profile released upon FcεRI aggregation by reducing histamine, leukotriene, and TNFα release while selectively enhancing prostaglandin D2 generation [45]. Also, mast cell inhibition by IL-10 and β2-adrenoceptor agonists was shown in human mast cells [46].

Physiological functions of intestinal mast cells

Mast cells and the GI barrier

The major function of the intestine is digestion and absorption of nutrients and the absorption of water and electrolytes to provide the body with liquids and fuels

necessary for survival. Large part of this job is done in the small intestine which is therefore equipped with a macro- and microfolded mucosa forming a huge surface of several hundreds of square meters. This mucosal barrier must be permeable to meet the absorptive functions and on the same time must protect the host against invasion of microbes and toxins with pathogenic capacities (Fig. 3). This "dilemma" of opposing functions is even more pronounced in the large intestine hosting in addition 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 so far. 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 [47].

The intestinal barrier consists of multiple defense system such as epithelial functions (mucus production, secretion, defensin release, etc.), innate and adaptive immune functions, and the enteric nervous system (ENS; Fig. 4). 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 defensin is associated with Crohn's disease and ulcerative colitis, respectively [48]. Possibly, such impairments of the intestinal barrier could be of importance not only for inflammatory bowel diseases (IBD) 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.

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
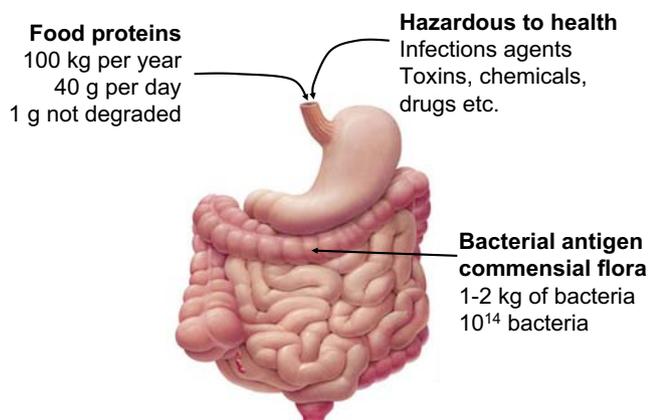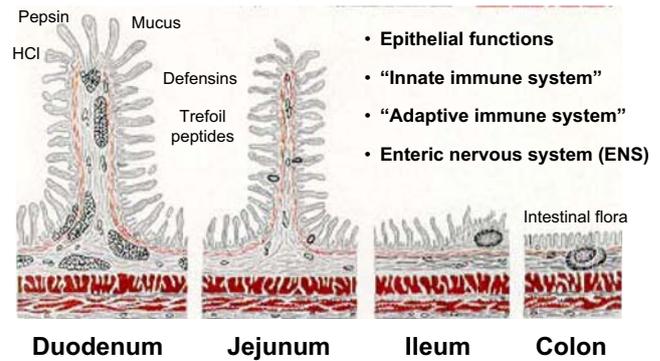

Fig. 4 The intestinal barrier. The intestinal barrier is a functional unit that separates the gut lumen (environment) from the tissue (host). The shape of the barrier varies at different sites of the intestine depending on other functions the intestine has to achieve; however, the basic composition of the barrier remains similar and comprises the epithelial layer and epithelial secretion products, the innate and the adaptive mucosal immune system, and the enteric nervous system

cell-dependent mechanism [49–53]. Using rodent models, it could be demonstrated 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 [51, 52]. Interestingly, stress led to an enhanced release of mast cell mediators (histamine, tryptase) in the proximal small intestine both in healthy controls, but to a larger extent in patients with mast cell-associated diseases such as food allergy [54]. The circumstances that mast cells are in close contact with epithelial cells and nerve endings underline the hypothesis that mast cells are involved in regulating mucosal permeability and intestinal barrier function.

By increasing mucosal permeability, mast cell 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 potentially 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 receptors HR1 and HR2 affects the function of blood vessels (dilatation and increased permeability), smooth muscles (contraction), and epithelial cells (mucus production). A recent human study demonstrated that HR1 and HR2 are upregulated in patients with food allergies within the intestinal tract [55]. Furthermore, histamine acts as an immunomodulator, e.g., in human alveolar macrophages, in which histamine inhibits the release of TNF by triggering the enhanced release of the anti-inflammatory cytokine IL-10 [56]. Histamine also affects epithelial cells, dendritic cells, T lymphocyte, and B lymphocyte. Histamine pro-

Fig. 3 Challenge of the human intestine with food antigen, toxins, and bacteria

motes TH1 cell activation through HR1 and suppresses both TH1 and TH2 cell activation through HR2 [57].

Interaction between mast cells and epithelial cells

It has become clear in recent years that the role of mast cells in the GI mucosa is not only restricted to react to antigens but also involves the active regulation of the barrier and the transport properties of the intestinal epithelium. Mucosal mast cells respond to both IgE/ antigen-dependent and non-IgE-dependent stimulation by releasing bioactive mediators into adjacent tissues where they induce physiological responses. Studies in models of hypersensitivity and stress have provided evidence that changes in mucosal function are due to either direct action of mast cell mediators on epithelial receptors and/or indirect action via nerves/neurotransmitters [58].

Using chamber experiments revealed that histamine at low concentrations (0.1 mM) causes transepithelial ion transport alterations such as an increase in short-circuit current (Isc) that is similar to that induced by antigen derived from *Trichinella spiralis*. Diphenhydramine (0.01 mM) inhibits the epithelial electrical responses to histamine by 100% and to antigen by 60–70%. Indomethacin (0.01 mM), in combination with diphenhydramine, completely blocks the antigen-induced rise in Isc suggesting that histamine and eicosanoids such as PGD2 and LTC4 are mediating the effects on epithelial cells [59]. Interestingly, the same set of mast cell mediators regulates epithelial mucus secretion in the respiratory and intestinal mucosa [60].

As known from mastocytosis studies, enhanced activation of intestinal mast cells causes diarrhea, further emphasizing the regulatory effects of mast cell mediators on intestinal epithelial function [61]. Likely, diarrhea induced by enhanced mast cell activation is part of the mucosal defense system that protects the host against microbes, toxins, and other harmful substances.

Interaction between mast cells and nerves

The ENS, by constantly monitoring the behavior of the intestine, forms a major part of the intestinal mucosal defense system. Information input processed by the ENS is derived from local sensory receptors, the central nervous system, and immune/inflammatory cells including mast cells. Specific IgE or IgG antibodies attach to the mast cells and enable the mast cell to detect sensitizing antigens when they reappear in the gut lumen. Should the sensitizing antigen reappear, mast cells detect it and signal its presence to the ENS. The ENS interprets the mast cell signal as a threat and calls up from its program library secretory and propulsive motor behavior that is organized to eliminate the threat rapidly and effectively. Operation of the alarm program protects the individual, but at the expense of symptoms that include cramping abdominal pain, fecal urgency, and diarrhea [62].

Mast cells use paracrine signaling such as histamine, proteases, and lipid mediators for the transfer of chemical information to the neural networks of the ENS. Apart from such humoral mediators, adhesions molecules such as cell adhesion molecule-1 and SgIGSF/SynCAM seem to be involved in mast cell–nerve interactions [63]. Mast cell signaling to extrinsic nerve fibers can result in visceral pain or extrinsic reflexes contributing to disturbed motor and secretory function of the intestine. Whether mast cells also contribute to the regulation of intestinal peristalsis under normal conditions is not clear as yet.

Morphological and functional studies, especially studies concerning physiological stress, have provided evidence that apart from the interaction between the enteric nervous system and mast cells, there is also a functional communication between the central nervous system and intestinal mast cells. Psychological factors trigger neuronal pathways, which directly or indirectly affect mucosal mast cells [64]. Thus, mucosal mast cells, which are able to detect noxious and antigenic threats and to generate or amplify signals to the other cells, are assigned a rather central position in this complex network of intestinal immune system and the ENS.

Mast cells and host defense against microbes

Human mast cells are capable of recognizing a large number of so-called pathogen-associated molecular patterns and other bacterial products by toll-like receptors (TLRs). The expression of TLRs varies slightly between mast cells of different origin, and in particular, the responsiveness of mast cells to different TLR ligands may differ substantially [4, 65, 66]. For example, mast cells generated from sterile environments such as bone marrow, cord blood, or peripheral blood respond quite well to different TLR ligands such as lipopolysaccharide, peptidogycan, yeast zymosan, whereas mast cells derived from primarily unsterile sites such as intestine and, to some extent lung, respond less efficiently to such stimuli (own unpublished observations). Possibly, this difference 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 to that induced by allergens and other nonbacterial triggers. Whereas allergen induces primarily degranulation and release of proinflammatory mediators such as histamine and eicosanoids, bacterial products hardly induce such mediators but cytokines needed for the initiation of innate and adaptive immune responses [65].

Apart from TLR ligands, other products of infectious agents may serve as mast cell triggers. For example, we could show that *Escherichia coli* alpha hemolysin induces calcium influx in human intestinal mast cells leading to the release of histamine, sulfidoleukotrienes, and proinflammatory cytokines [67]. Furthermore, the type 1 fimbrien protein, FimH, or cholera toxins have been described as mast cell triggers [68, 69]. Most recently, glucopeptides derived from parasites were characterized that are capable of activating mast cells [70, 71].

The role of mast cells in host defense against parasitic infections has been established many years ago. Infections with, e.g., *T. spiralis* or *Nippostrongylus brasiliensis* are accompanied by a substantial mast cell accumulation [52, 72, 73]. It is not clear whether this mast cell accumulation is triggered by the infectious agents or by the subsequent Th2 response [74]. Mast cell proteases (e.g., MCP-1 in mice) were found to be crucial mediators of immune responses against such helminths. A mutation in the MCP-1 gene in a mouse model is associated with a significantly delayed expulsion of *Trichinella* and *Nippostrongylus* [72, 75].

The biological significance of mast cell activation by FcεRI aggregation outside allergy has been repeatedly questioned; however, the definitive answer is still lacking. The most intriguing hypothesis in this respect is possibly the antiparasite hypothesis suggesting that FcεRI aggregation through crosslinking of IgE directed against parasites is a mechanism of parasite recognition initiating an antiparasite immune reaction and that mast cell products including Th2 cytokines are key mediators required for host defense against parasite infection [74]. This hypothesis is confirmed by rodent disease models which revealed that antiparasite IgE is generated following a parasite infection and that blocking mast cell mediators or mast cells itself leads to an impairment of host defense against parasites [76]. Of the mast cell mediators, IL-5 (for eosinophil recruitment) and IL-13 (for B and Th2 cell immunity) seem to be of particular importance [36, 76, 77]. Similar mechanisms have been anticipated in humans albeit direct prove of their existence is lacking. In contrast to findings in rodents, human mast cells are not a source of IL-4, as stated before [24, 36]. The IL-4 expressed in early phases of parasite infections in humans likely derives from basophils (and in later states from Th2 lymphocytes), as suggested by in vitro and rodent in vivo studies [78, 79]. The fact that worm antigens can induce IL-4 production in human basophils and that IL-4 is needed to optimize Th2 cytokine production (namely IL-5 and IL-13) in human mucosal mast cells strongly argues for a role of IL-4 in parasite infection [24, 70]. Recently, in vivo studies using the mouse *T. spiralis* infection model showed that antagonizing the Th2 milieu by IL-18 promotes intestinal parasite survival whereas IL-18 knockout animals are highly resistant to *Trichinella* infection [80]. These findings further argue for a protective role of mast cells and Th2 immune responses against parasites in the intestine. On the other hand, a cytokine milieu shifted too much toward Th2 cytokines could permit otherwise harmless infections that require Th1 immune responses for defense, to initiate severe inflammatory reactions [81].

The protective role of mast cells in bacterial infection arose from studies employing mouse models of *Klebsiella pneumoniae*-dependent lung infections and septic peritonitis using mast cell-deficient and normal mouse strains [82, 83]. In the mast cell-deficient models, lack of mast cell-derived TNFα and leukotrienes impaired neutrophil recruitment, bacterial clearance, and host survival [82–84]. Apart from neutrophil recruitment to the infection side, mast cell-derived TNFα induced hypertrophy of draining lymph nodes and T cell recruitment at sites of infection with *E. coli* [3, 85]. More recently, a novel TNF-independent pathway for mast cell-mediated lymph node hypertrophy and Langerhans cells migration was demonstrated by peptidoglycan derived from *Staphylococcus aureus*. In contrast to the activation of mast cells through TLR and Myd88, this mechanism depended on complement components [86]. Based on such findings, it has been suggested that mast cells provide a link between innate and adaptive immunity.

Most of such data come from rodent mast cells, whereas limited data exist describing the interactions of human mast cells with bacteria [5]. However, mast cell accumulation was observed in patients with *Helicobacter pylori*-associated gastritis and *Shigella* infection, respectively [87, 88]. 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 [87–89]. During the in vitro ingestion of a pathogenic *E. coli* by human mast cells production of TNF-alpha, CC chemokine ligands (CCL-1/I-309, CCL-19/MIP-3beta, and CCL-18/MIP-4), carcinoembryonic antigen-related cell adhesion molecule 1, the integrin CD49d, and CD80 were upregulated. Most interestingly, coincubation of human mast cells with *E. coli* down-regulate FcεR I expression and FcεR I-mediated mast cell degranulation [90].

In recent studies, the role of mast cells as intermediary between innate and adaptive immune system during bacterial infections was further unraveled. For example, mast cells are able to regulate the migration, maturation, and activation of dendritic cells [3, 91] through the release of TNFα, IL-1β, and granulocyte-macrophage colony-stimulating factor after stimulation with TLR ligands [4, 56]. Bacterial antigens are presented to T cells via the major histocompatibility complex (MHC) I or MHC II pathway,

the latter one requiring IFNγ that causes a dose-dependent induction of MHC class II molecules in mast cells. An in vitro study showed that presentation of staphylococcal enterotoxin B through the MHC class II pathway by human mast cells directly activates CD4+ T cell hybridomas [92].

Even more recently, evidence accumulated showing that human mast cells might be involved also in host defense against viruses, particularly against double-stranded RNA viruses recognized by TLR3. Earlier, it has been suggested that mast cells interact with virus through chemokine receptors [93]; more recently, TLR3 came into focus. In rodents, mast cells express TLR3, and stimulation of mast cells through TLR3 using polyI:C leads to the recruitment of CD8+ T cells [94]. Human mast cells also express TLR3, and in vitro studies revealed that TLR3 stimulation causes a decreased adhesion of the cells to ECM proteins and a decreased mediator release in response to IgE/antigen, but an increase in IFNγ production suggesting also a role of human mast cells in host defense against viral infections [95, 96].

Mast cells and regulation of immune tolerance

Contrary to the proinflammatory role of mast cells in allergic disorders, the results obtained in a recent study performed in rodents established that mast cells are essential in peripheral tolerance induction dependent on CD4+ CD25+ Foxp3+ T regulatory cells (Tregs) [97]. In this study, high levels of IL-9, a mast cell growth and activation factor, are produced by activated Tregs, and IL-9 production seems important in mast cell recruitment to and activation in tolerant tissue. Thus, IL-9 represents the functional link through which activated Tregs recruit and activate mast cells to mediate regional immune suppression. Although analogous data in the human system are lacking, these findings opened a new door in understanding the versatile function of mast cells under physiological conditions.

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 sides on the surface of mast cells and basophils [98, 99]. It is tempting to speculate that mast cell mediators are involved in this protection; however, such findings need approval in humans. Moreover, coincubation of human mast cells with E. coli downregulate FcεR I expression and FcεR I-mediated mast cell degranulation [90].

Whether allergen-specific immunotherapy (SIT) is related to such mechanism remains to be determined. The mechanisms by which allergen-SIT has its effects include the modulation of T cell and B cell responses and related antibody isotypes as well as effector cells of allergic

inflammation, such as eosinophils, basophils, and mast cells. The balance between allergen-specific Tregs and Th2 cells appears to be decisive in the development of allergic and healthy immune responses against allergens. The induction of a tolerant state in peripheral T cells represents an essential step in allergen-SIT [100]. Possibly, mast cells can be involved in the induction of allergen-specific Tregs, as shown in the rodent model, provided that particular environmental factors such as bacterial or helminth products are present at appropriate concentrations. A better understanding of mechanisms of mucosal tolerance may enable novel treatment strategies.

## Other physiological functions of intestinal mast cells

Mast cells have been implicated in other physiological functions such as wound healing and regulation of fibrosis, regulation of blood flow and coagulation, protection against neoplasm, and tissue homeostatis [101–103]. However, since most of such data have not been clearly confirmed for the intestinal mucosa, the details will not be discussed in detail here (Fig. 5).

Mast cells and food allergy

Intestinal allergic disease—what is that?

Intestinal allergic disease is defined as an adverse reaction to allergen, in most cases to food, caused by an individually occurring immunologic hypersensitivity against food antigen. This definition clearly separates food allergy from other forms of adverse reactions to food not mediated by immunologic mechanisms such as intolerance reactions caused by enzyme deficiencies or toxic reactions caused by contaminating microbes or chemicals. Since adverse reactions to food are common in the general population—about 20–30% seems to be afflicted—the rather small subgroup of patients suffering from true food allergy needs to be identified by validated diagnostic means. According to recent epidemiologic data, 1/4 of children and 1/10 of adults with adverse reactions to food have true food allergy based on immunologic mechanisms, either IgE-mediated or other forms. Accordingly, the prevalence of food allergy is 3–8% in small children and 1–3% in teenagers and adults [7, 104–106]. The fact that food allergy is preferentially a disease of the early years of life is related to our current understanding of the mechanisms of food allergy closely related to the integrity of the GI barrier. The GI mucosa is the site of sensitization and challenge, but not necessarily the shock organ. Actually, any organ can be involved, but in most cases, symptoms manifest at the level of the skin, the GI or respiratory mucosa, or a combination thereof. About 1/2 of the children and 1/3 of the adults with

Fig. 5 Role of mast cell functions at the gastrointestinal barrier. Intestinal mast cells regulate tissue homeostasis (epithelial secretion and permeability, blood flow and vascular permeability, smooth muscle functions and peristalsis, wound healing and fibrosis), immune functions (recruitment and activation of neutrophils, eosinophils and lymphocytes, induction of Treg cells, defense against microbes), neuronal functions (neuroimmune interactions, peristalsis, and pain), and inflammation (allergy, IBD, IBS, infection, etc.). *FGF* fibroblast growth factor, *IL-5* interleukin 5, *LTC4* leukotriene C4, *PGD2* prostaglandin D2, *TNF* tumor necrosis factor, *TGF* transforming growth factor, *Treg* regulatory T cells, *VLA4* very late antigen 4 (modified from Bischoff [5])
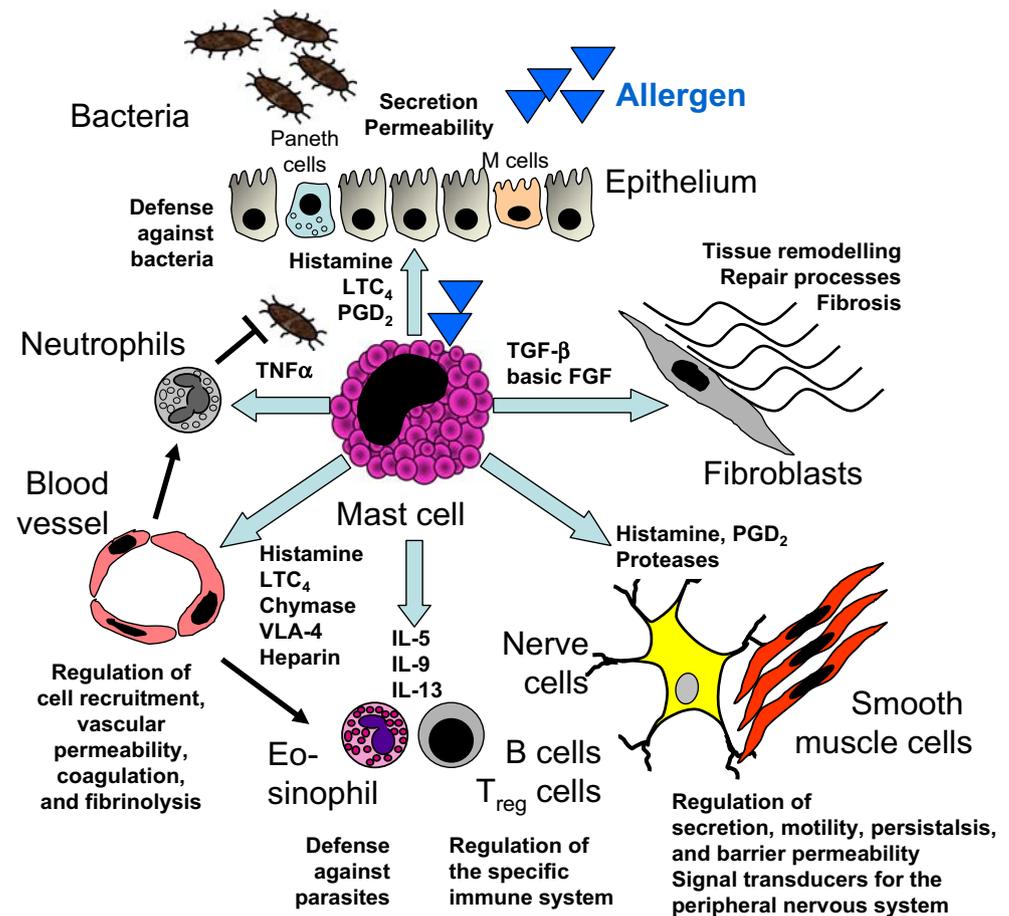
food allergy show with GI symptoms such as nausea and vomiting, diarrhea or blood in stool, or just abdominal pain [7].

Basis of any allergic reaction is an adequate antigen exposure, an abnormal immune response, a genetic predisposition, and an "acquired" predisposition, e.g., an impaired mucosal barrier, which might be of particular relevance for food allergy, but possible also other forms of allergic diseases [7, 107]. Food allergens (mostly proteins) are to a large extent, but by far not totally degraded during passage through the stomach and the intestine. Studies showed that about 2% of the food proteins ingested daily (about 50–100 g/day) reach the intestinal mucosa in intact form. This is necessary to establish a mucosal immune response, which normally leads to the generation of immunologic tolerance provided that the mucosal barrier is intact. Such an immune response is observed in all individuals and can be recognized by the generation of food-antigen-specific T cells (memory cells) and food-antigen-specific IgA and IgG production.

Mast cell functions in allergy

The best characterized hypersensitivity reaction to food is the IgE-mediated type I reaction according to Coombs

[108]. Type I reactions, which are also taken as a basis for many cases of bronchial asthma, seasonal rhinitis, and atopic skin diseases, are divided into an immediate phase and a late phase occurring facultatively some hours after the immediate phase. The immediate phase is characterized by the IgE-dependent activation of mast cells and basophils and the release of proinflammatory mediators from these cells such as histamine, proteases, leukotrienes, and cytokines. This reaction requires a preceding sensitization phase in which the specific immune system is challenged with allergen in a way that leads to the production of sufficient amounts of specific IgE. This IgE is bound to the surface of mast cells and basophils because they express the high-affinity IgE receptor. Once the cell is "loaded" with specific IgE, a second challenge can lead to crosslinking of surface-bound IgE. This is an activation signal for the cells which in response start to degranulate and release mediators like histamine and protease from their granules within a few seconds. At the same time, the cells start to synthesize mediators leading to a more sustained release of mediators such as eicosanoids and cytokines.

The late phase is characterized by the infiltration of the tissue with further inflammatory cells such as neutrophils, eosinophils, and lymphocytes. These cells are attracted by

mediators such as TNFα, IL-5, IL-4, and IL-3 release by mast cells and basophils upon IgE-dependent immediate-type activation. The role of mast cells in this clinically more important late phase reaction, as well as in hypersensitivity reactions other than type I reactions, such as type IV hypersensitivity reactions also occurring during allergic reactions, has been clearly documented (Fig. 6). Especially type IV hypersensitivity reactions to food proteins can be expected, due to the presence of food antigen-specific T helper cells and cytotoxic T cells [7, 107]. Most importantly, human mast cells induce the recruitment and local activation of eosinophils by expressing factors such as IL-5 upon IgE-dependent activation and induce the recruitment of neutrophils by releasing IL-8 and TNFα. The latter one has been shown in vitro for both human and murine mast cells, as well as in murine disease models [109, 110]. In comparison to mouse mast cells, however, the amount of TNF produced by human mast cells on a per cell basis is small, compared with monocytes, and the portion that is preformed and stored in granules is even smaller, although it is consistently detectable [3]. Nevertheless, human mast cells, even by releasing small quantities of preformed TNF, might be responsible for the discrete neutrophil infiltration typically seen at sites of allergic inflammation.

In vitro studies indicate that human mast cells also participate in regulating lymphocyte functions in the course of allergic inflammation. Upon IgE crosslinking, mast cells produce IL-13, a cytokine that supports the production of allergen-specific IgE by B cells. The release of IL-13 can be further increased by the presence of IL-4, which is known to shift the cytokine profile produced by human mast cells away from proinflammatory cytokines such as TNF, IL-1, and IL-6, to TH2 cytokines including IL-13 [36]. Human mast cells can also regulate T cell functions, for example through PGD2, which almost exclusively derives from activated mast cells and is released during allergic reactions [111]. Recently, exciting new functions of PGD2 have been identified that indicate a particular role for PGD2 at the
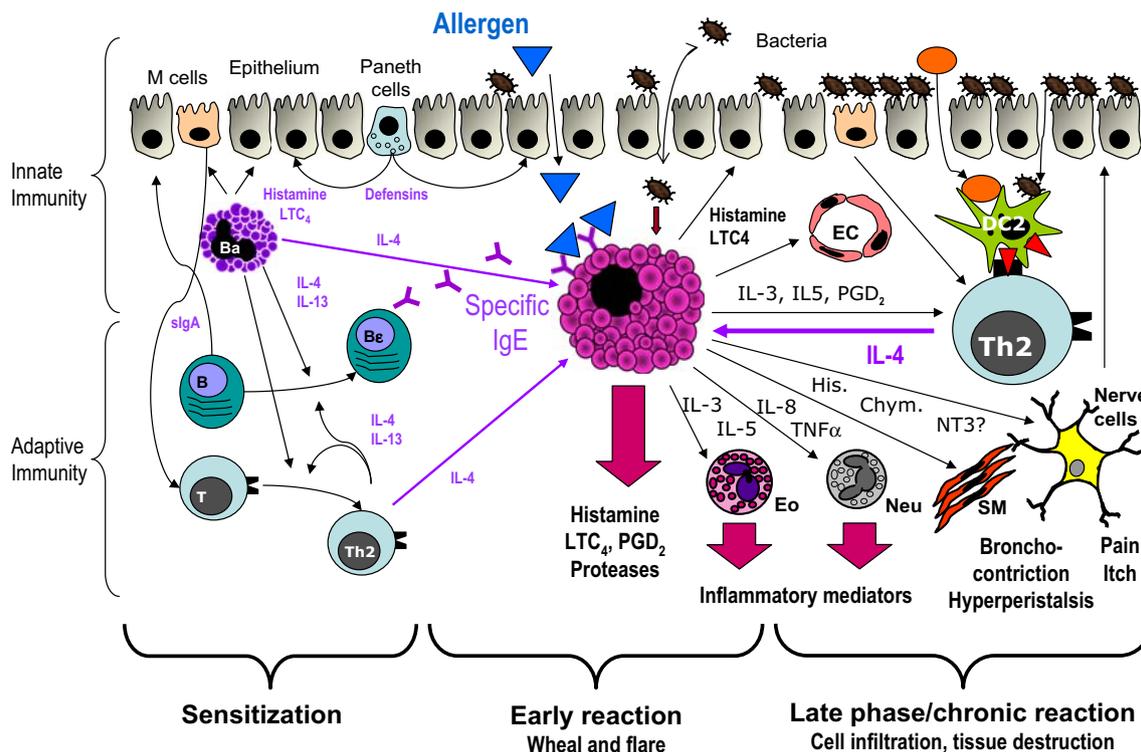

Fig. 6 Role of mast cells in intestinal allergy. Mast-cell activation by IgE crosslinking with allergen requires substantial access of allergen into the intestinal mucosa, e.g., following impairment of the mucosal barrier, and input from the adaptive immune system to become effective. Not only the synthesis of specific IgE by B cells regulated by IL-4 and IL-13 derived from Th2 cells and basophils but also mast cell priming by IL-4 for enhanced mediator release is required for full mast-cell activation. The subsequent release of mast-cell mediators leads to an "early reaction", consisting classically of a "wheal and flare" reaction of the mucosa. Other mast-cell mediators, such as IL-3, IL-5, IL-8, TNF neurotrophin 3 (*NT3*), and proteases contribute to the initiation of a facultative "late-phase" reaction by recruiting and activating eosinophils (*Eo*), neutrophils (*Neu*), and T helper 2 (*Th2*) cells and by interaction with tissue cells such as nerve cells, smooth muscle cells (*SM*), endothelial cells (*EC*), and the epithelium. Ongoing dysregulation of such cell types not only causes symptoms of allergy but also organ dysfunction including loss of barrier function and, subsequently, enhanced bacterial translocation. This enables nonspecific triggers to access mast cells, dendrite cells type 2 (*DC2*), and other cells. Such triggers, such as bacterial products or Ig (fragments) like monomeric IgE and light chains, might perpetuate the inflammatory process, even in the absence of allergen (modified from Bischoff [5])

onset and for the perpetuation of asthma in young adults. The lipid mediator evokes airway hypersensitivity and chemotaxis of T cells, basophils, and eosinophils through interaction with two receptors, the prostanoid DP receptor (PTGDR) on granulocytes and smooth muscle cells, and CRTH2 (chemoattractant receptor-homologous molecule expressed on TH2 cells) on TH2 cells [112, 113]. Furthermore, gene-mutation analyses have identified PTGDR as an asthma-susceptibility gene [113]. Apart from PGD2, other human mast-cell mediators such as LTB4, CCL3 and CCL4, OX40 ligand, and TNF are involved in recruiting T cells and triggering T cell-mediated adaptive immune responses, including memory induction, which enhance and perpetuate allergic reactions [5]. However, mast cells, at least under normal conditions, are not a relevant source of IL-4. It has been repeatedly claimed that mast cells, in addition to TH2 cells, produce IL-4; however, well-performed in vitro studies using mature human mast cells from nonallergic individuals, as well as mouse in vivo studies, could not confirm such findings [24, 36, 79]. Instead, TH2 cells and basophils seem to be the relevant sources of IL-4 in humans, whereas mast cells, if at all, might contribute to local IL-4 production under allergic conditions [114]. This fits with the recent in vivo finding in mice that basophils are crucial for the induction of IgE-mediated chronic allergic inflammation, for which T cells and even mast cells were dispensable [115].

Inflammatory mediators derived from mast cells und eosinophils are primarily responsible for the clinical symptoms of patients with food allergies. These patients have an increased level of histamine (or methyl histamine), tryptase, eosinophilic cationic protein, IL-5, and TNFα in serum, urine, intestinal lavages, and stool samples [7, 116]. Histological examinations show that mast cells and eosinophils degranulate in the intestinal mucosa after localized provocation testing and that they release mediators such as cytokines [117]. Not only is the specific immune system involved in immunological hypersensitivity reactions but also the innate immune system. The characterization of key molecules belonging to the innate immune defense mechanism, such as defensins, mucin, or synactin and their possible mutation in people with allergies, is therefore of the utmost importance for the understanding of the mechanisms and the development of new therapy concepts [61]. Disorders of the innate immune system can also be responsible for deviations of the specific immune system, which lead, for example, to an overproduction of specific IgE.

Clinical studies have shown that IgE is produced locally in the respiratory and GI mucosa. This might explain why serum IgE evaluations and skin tests do not closely correlate with mucosal allergic reactions in the intestines. In atopic patients, the increased IgE levels are closely related to IL-13, whose gene is attributed to a polymorphism, which is associated with atopy. The IgE-induced allergic immune response can therefore be divided into three phases: the clinically silent sensitization phase, usually during infancy or childhood; the symptomatic effector phase, which is composed of an acute and a facultatively delayed reaction; and the chronic organ-destroying phase, which can be the outcome of reoccurring delayed reactions [7].

More recently, it became evident that mast cells stimulated by IgE crosslinking also trigger local nerve responses resulting in pain and diarrhea [52, 118]. It has become apparent in recent years that the ENS plays a role in regulating allergic inflammatory cells such as lymphocytes, mast cells, and eosinophils. The morphologic–functional association between immune cells and nerve cells has mainly been described for mast cells and, in some cases, has been extended to include eosinophils. It should be emphasized that not only is the gut-associated lymphoid tissue (GALT) innervated but conversely that the ENS is also regulated in a crucial manner by mediators derived from mucosal immune cells [52]. Such neuroimmune interactions may explain the frequent psychological and functional accompanying symptoms, which characterize many patients with allergic and other chronic bowel disorders.

A delayed development of the protective IgA system within the GALT in the postnatal phase or a particularly pronounced switch to IgE-producing B lymphocytes is associated with an enhanced risk for the development of allergic diseases. IgA synthesis is induced mainly by TGF-β from Th3 cells and external triggers, while IgE synthesis is dependent on CD40 ligands, as well as the cytokines IL-4 and IL-13, which are produced by the Th2 cells and inflammatory cells (mast cells, basophils) [107]. In contrast, Th1 cytokines such as IFNγ inhibit the activity of Th2 cells, which explains how a controlled Th1-dominant immune response, triggered, for example, by certain bacterial products, can contribute to restricting a primary preexistingTH2 response in the bowels and thus prevent an overproduction of IgE. Such procedures support the "hygiene theory" claiming that high hygiene standard, in particular, during the early years of life may support the development of not only immunologic diseases such as allergy including food allergy but also to other immunological diseases such as rheumatic arthritis, type 1 diabetes mellitus, and chronic inflammatory intestinal disorders [119, 120].

The hygiene hypothesis

Allergic diseases develop on the basis of complex gene–environment interactions. The prevalence of allergies is

steadily increasing and seems to be associated with modern lifestyle. Therefore, it was hypothesized that high living standards and hygienic conditions are correlated with an increased risk for the development of an allergic disease. This so-called hygiene hypothesis states that due to reduced exposure to microbial components, the proposed allergy-preventing potential of these factors is no more present in sufficient qualities and/or quantities, which leads to an imbalance of the immune system with a predisposition to the development of allergic disorders [121].

Meanwhile, several epidemiological studies were conducted supporting this concept and generating novel ideas for the underlying mechanisms that were then followed up by use of well-defined animal models and human studies. The current view of cellular and molecular mechanisms responsible for these phenomena includes changes in the fine balancing of Th1, Th2, and Treg responses which are triggered by altered or missing innate immune cell activation. In fact, proper activation of cells of the innate immune system by bacterial, viral, or parasitic antigens has been demonstrated to play a crucial role in early shaping of the immune system and suppression of the development of Th2-driven allergic immune responses. These processes start already in utero and prenatal as well as early postnatal developmental stages seem to represent a certain "window of opportunity" for allergy-preventing environmental influences [121].

In the meantime, the hygiene hypothesis has been extended to a variety of immunologic disorders including type 1 diabetes, inflammatory bowel disease, multiple sclerosis, and other chronic inflammatory disorders. The use of probiotics, prebiotics, helminths, or microbe-derived immunoregulatory vaccines might therefore become a valuable approach to disease prevention [122]. Based on the Darwinian medicine, which uses knowledge of evolution to cast light on human diseases, some of the organisms that are important for the "Hygiene" or "Old Friends" hypothesis might be identified. Moreover, the Darwinian approach might point to the potential exploitation of these organisms or their components in novel types of prophylaxis with applications in several branches of medicine [123].

The vitamin hypothesis

Spiegl et al. [124] showed that basophils express retinaldehyde dehydrogenase-2 (RALDH2) and thus are a new and unique cellular source of retinoic acid (RA) known to be an important regulator of immune cell functions. In humans, RA derived from vitamin A (retinol and its esters), which is either uptaken from animal food or, as β-carotenes (provitamin A), from plant food. Retinol and its active metabolites, RA and retinal, have major biological effects on cell growth and differentiation, reproduction, vision system, and immune regulation. In particular, RA regulates major immune functions such as immune defense against infections, inflammation, epithelial barrier functions, and lymphocyte function and trafficking to the gut through the nuclear receptors retinoic acid receptor and retinoid X receptor [125–128]. The clinical relevance of these findings is strengthened by the observation that vitamin A deficiency severely compromises host defense and vitamin A supplementation can balance such deficiencies [129].

Metabolism of retinol to retinaldehyde is not tissue-restricted whereas further metabolism of retinaldehyde to RA is the limiting step and tissue-restricted as the most effective enzymes identified are tissue specific [130]. The origin of locally elevated RA levels in postembryonic mammals is basically unknown. Allergen-dependent basophil activation induces low levels of RALDH2, whereas IL-3 not only induces RA receptor activity but also strongly induced the expression of RALDH2 as well as the generation of RA [124]. However, at particular tissue sites, other cells than basophils might contribute to RA formation. Recent studies indicate that dendritic cells from mouse mesenteric lymph nodes constitutively express RALDH2 mRNA and produce RA, which regulates the function and gut-homing properties of T and B cells and may be involved in intestinal tolerance induction [126–128]. Moreover, intestinal mucosa and Peyer's patches dendritic cells express the low efficiency RA-synthesizing enzyme RALDH1 suggesting that RA formation at this site may also depend on high local vitamin A concentrations from food.

Similar suggestions have been made for vitamin D3, the active form of which is generated locally by dendritic dells and T cells and induces CCR10 in naïve T cells, thereby attracting them to the skin [131]. Thus, vitamins might sense the local immune system by directing lymphocytes to different sites, e.g., the skin (vitamin D metabolites) or the GI mucosa (vitamin A metabolites). Locally produced food metabolites program T cell homing and offer a new mechanism explaining why hypersensitivity reactions occur at different body sites.

At present, one can only speculate on the consequences of such findings. Basophil-derived RA polarizes naïve human T cells to produce Th2 cytokines, namely IL-4, and induces the expression of the adhesion receptors CD38 and α4/β7-integrin that may guide them to mucosal sites of inflammation. IL-4 induced by basophil-derived RA in T cells promotes mast cell activation which in turn enhances their production of IL-3 shown to be a major trigger for RA formation in basophils [24]. Therefore, RA generation might be an important missing link in the communication between basophils, mast cells, and T cells, between innate and adaptive immunity that results in Th2 immune

responses (Fig. 7). On the other hand, several important questions need to be addressed in future: Is RALDH2 expression enhanced in allergic patients? What are the local factors regulating RALDH2 expression in basophils or dendritic cells? Is mucosal RA synthesis dependent on the vitamin A status that needs to be measured by accurate means? Additional epidemiologic and basic studies are needed to further support this attractive "vitamin hypothesis", beside the widely accepted "hygiene hypothesis", as a new explanation for the rapid increase in allergy and autoimmune diseases in industrial countries [132].

Other approaches

Any impairment of the GI barrier, either because of immaturity in early life or acquired during later life, promotes the development of food allergy and, possibly, other forms of allergy, because oral tolerance cannot be established or maintained. Common causes for an acquired impairment of the GI mucosa are infections (bacterial, viral), toxins (e.g., bacterial toxins such as *Clostridium difficile*), malperfusion, or disturbances of the GI flora (e.g., caused by treatment with antibiotics). Interestingly, such conditions are known to be associated with the onset of food allergy suggesting a causal link between such events.

This might explain why FA is most common in newborns and small children in whom the GI barrier is not fully maturated yet. Once these children become elder, most of them loose spontaneously their allergy, most likely because of maturation of the GI barrier and this establishment of host defense and tolerance induction. The situation is more complex in adults, but possibly similar mechanisms

could play a role. Interestingly, not only allergy, but also other chronic inflammatory diseases such as IBD and RA increase under such conditions. Therefore, it is tempting to speculate that an impaired GI barrier caused by particular environmental conditions and life style factors may lead to the increased occurrence of immune-mediated chronic diseases including food allergy [7, 107]. Based on such considerations, new intervention tools are envisioned such as immunotherapy, nutrition therapy, and probiotics.

Subcutaneous immunotherapy has been used not only in pollen-allergic individuals but also in individuals with pollen-associated food allergy with variable success [133]. More recently, first data were published on sublingual immunotherapy (SLIT) using hazelnut extract in patients with hazelnut allergy. The trial showed a significant improvement of hazelnut tolerance after verum SLIT compared to control SLIT suggesting a potential of SLIT therapy in FA [134, 135]. However, more studies are needed to confirm these promising results. Alternatively, oral tolerance induction was examined by oral administration of steadily increasing doses of food allergen up to 3–5 g food protein (40–60 steps in 2–3 month). Several reports suggested effectiveness, but not a single randomized controlled trial is available to confirm the results [133]. Therefore, the value of this approach cannot be estimated finally at the moment, and in particular, the long-term effectiveness needs to be confirmed [136]. In summary, immunotherapy could become a valuable additional tool to treat FA by a causal approach; however, more clinical data and data how to perform it are required.

Instead of immunotherapy using classical allergen extracts, the development of new treatments tools such as
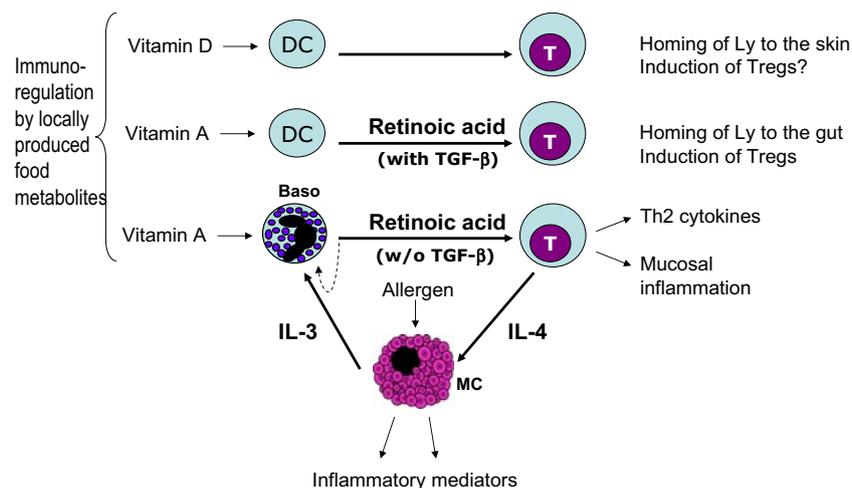

Fig. 7 The "vitamin hypothesis" explanation for allergy increase. High vitamin A uptake might favor the development of allergy, in particular if TGF-β levels are low, by the enhanced generation of retinoic acid in basophils, since RA induces the production of Th2 cytokines and inflammation. Normal vitamin A uptake together with normal TGF-β causes protection against allergy, whereas vitamin A deficiency leads to low numbers of T regulatory cells (*Tregs*) and subsequent inflammation and infection. For more details, see text (modified from Bischoff [132])

tolerogenic peptides, recombinant epitopes for desensitization, and DNA vaccination with allergen DNA might help to improve the effectiveness of future immunotherapy. In addition, methods have been developed for the genetic or chemical modification of antigen structures of food allergens, with the aim of reducing the allergen potential [137]. Finally, anticytokine antibodies or cytokine-receptor antagonists against Th2-cytokines, such as IL-4 and anti-c-kit-antibodies functioning as new antimast cell medicaments [138, 139], are currently examined for their potential in FA treatment.

Studies have been recently published, according to which probiotics, e.g., *Lactobacillus rhamnosus* GG or *Lactobacillus casei* species, are capable of reducing the incidence of allergies in children from high-risk families, or in adolescents with manifest allergy. For example, the prevalence of food-induced atopic dermatitis can be reduced by approximately 50% through treatment with lactobacillus GG, during and immediately after pregnancy, as surveys 2 and/or 4 years after birth of the children have shown [140]. However, these exciting data could not be confirmed in recent follow-up studies from other research groups [141–143].

Mast cells in nonallergic GI diseases

Celiac disease

Celiac disease is a malabsorptive disorder caused by intolerance to gluten and is characterized by a remodeling of the intestinal mucosa including villus atrophy, crypt hyperplasia, and net increase of mucosal volume. Changes of the number of mucosal mast cells in celiac mucosa have been reported since 25 years, suggesting that the mast cell activity could have a pathogenetic role in gluten enteropathy. As compared to controls, the histamine content increased by 80% and MMC numbers by about 60% in the celiac mucosa [144]. The role of mast cells in celiac disease is emphasized by submucosal challenge experiments with gliadin in patients with celiac disease and controls. A significant increase in the number of CD4+ lymphocytes in the lamina propria and a decrease in the number of mast cells (as a result of prior mast cell degranulation) were observed after submucosal challenge with gliadin [145].

IBD

Histological studies revealed that mean mast cell numbers do not differ between patients with IBD and controls. However, a reduced mast cell number was found in toluidine blue-stained sections of actively inflamed tissue areas ($143\pm16/mm^2$, versus $206\pm18/mm^2$ in noninflamed tissue). Immunohistochemical studies using antibodies against the granule proteins tryptase and chymase suggest that this decrease in mast cell numbers is due to mast cell degranulation [2]. Corresponding results were obtained from experiments in dogs with IBD. They had significantly more cells positive for IgE protein and more mast cells in the GI mucosa than healthy dogs [146]. The increased numbers of cells positive for IgE and mast cells in dogs with IBD suggest hypersensitivity, e.g., to bacterial or dietary-derived antigens in the intestinal lumen.

Not only markedly increased numbers of mast cells were observed in the mucosa of the ileum and colon of patients with IBD but also substantial changes in mast cell expression of TNFalpha, IL-16, and substance P. Moreover, elevated histamine and tryptase levels were detected in mucosa of patients with IBD, suggesting that mast cell degranulation is involved in the pathogenesis of IBD [147]. In patients with ulcerative colitis, tryptase-, substance P-, and serotonin-immunopositive mast cells were found in higher amounts than in control specimens in close apposition to the basal lamina of the glands among the epithelial cells and in other layers of the gut wall [148]. However, little is known about the actions of histamine, neurotransmitters, tryptase, chymase, and carboxypeptidase in IBD.

The triggers for mast cell activation in IBD are largely unknown. Possibly, stress factors might play a role, since stress enhances mucosal mast cell degranulation [118]. Recently, it was reported that MC c-kit immunostaining was significantly reduced—at both baseline and post stress samples—in IBD patients compared to controls; however, MC c-kit immunostaining was independent of stress-induced MC degranulation [149].

IBS

Our current understanding of the pathogenesis of irritable bowel syndrome (IBS) is changing fundamentally. In previous times, IBS was defined by a particular set of symptoms and exclusion of any known GI disease such as infection, IBD, celiac disease, food allergy, or malignant disease. Now, there is increasing evidence for the notion that IBS reflects a kind of subclinical inflammatory process of unclear origin [150].

Indeed, histopathologic data demonstrate low-grade mucosal inflammation in a subset of patients with IBS. This inflammatory infiltrate is mainly represented by increased numbers of T lymphocytes and mast cells lying in the lamina propria. The close apposition of immunocytes to gut nerves supplying the mucosa provides a basis for neuroimmune cross-talk, which may explain gut sensorimotor dysfunction and related symptoms in patients with

IBS. A previous gastroenteritis (due to *Campylobacter jejuni*, *Salmonella*, *Shigella*, *E. coli*, and, likely, viruses) is now an established etiologic factor for IBS (hence, post-infectious IBS). Other putative causes, such as undiagnosed food allergies, genetic abnormalities, stress, or bile acid malabsorption, may also promote and maintain a low-grade mucosal inflammation in IBS. The identification of mucosal inflammation in IBS has pathophysiologic implications and paves the way for novel therapeutic options [118, 150].

Possibly, mast cells are responsible for even more GI pathologies of unclear origin accompanied by symptoms such as diarrhea. For example, in chronic intractable diarrhea, colonic or duodenal biopsy specimens may appear unremarkable on routine hematoxylin–eosin staining, but increased mast cells may be demonstrated by immunohistochemistry for mast cell tryptase, with the novel term mastocytic enterocolitis describing this condition [151]. Consequently, a number of mast cells, eosinophils, and intraepithelial lymphocytes in duodenal biopsies have been proposed as novel disease markers in subjects with IBS and functional dyspepsia, since intraepithelial lymphocytes were significantly increased in IBS constipation. Mast cells were significantly increased in IBS, while eosinophils were significantly increased in functional dyspepsia [152].

Thus, duodenal mast cell hyperplasia is linked to IBS. However, the mechanisms that induce mast cell hyperplasia and mast cell mediator release in IBS need to be defined. It is tempting to speculate that changes in GI motility and visceral hypersensitivity that are traditionally thought to play a crucial role in symptom generation might be directly related to the novel additional factors identified by recent studies as the emerging factors of IBS pathogenesis. These factors include GI infections, low-grade infiltration, and activation of mast cells in the intestinal mucosa with consequent release of bioactive substances, altered serotonin metabolism, and modification of small bowel and colonic microflora [153]. However, more studies are required to put all these puzzle pieces together.

Mastocytosis

More than 20 years ago, Cherner et al. [154] prospectively evaluated in 16 consecutive patients with systemic mastocytosis (SM) a variety of GI functions and examined how they relate to the occurrence of GI symptoms. They reported duodenal ulcer or duodenitis (nine patients), hypersecretion of gastric acid (six patients), impaired small intestinal absorption (five patients), and increased plasma histamine concentrations in all patients that correlated with the basal acid output. In contrast, mean fasting plasma concentrations of motilin, substance P, and neurotensin from six patients did not differ significantly from controls, whereas gastrin and vasoactive intestinal peptide were

significantly less than in controls. GI symptoms, consisting of abdominal pain or diarrhea, occurred in 80% of patients. GI transit, however, remains unchanged.

More recently, Jensen [155] reported that as much as 70–80% of patients with SMs are found to have GI symptoms. The most common symptom is diarrhea that occurs in 43% of patients (mean, range 14–100%). A review of gastric acid studies reveals that a proportion of patients develop gastric acid hypersecretion because of the hyperhistaminemia, which can result in ulcer disease that in turn can cause dyspeptic pain, small intestinal mucosal damage, and malabsorption as seen in Zollinger–Ellison syndrome. Hepatomegaly, portal hypertension, splenomegaly, and ascites occur frequently in patients with systemic mastocytosis.

The diagnosis is based on histological and immuno-histological examination of GI tissue specimens using antibodies directed against tryptase, CD117, and CD25. SM is characterized by the accumulation of neoplastic mast cells in bone marrow and other organs such as the GI tract. GI symptoms are common in both SM and cutaneous mastocytosis, also named urticaria pigmentosa, and are usually caused by the release of histamine and other inflammatory mediators. Occasionally, neoplastic mast cells may also directly infiltrate the GI tract [156–158].

Several studies have suggested that enumeration of the mast cells in GI biopsies may help establish the diagnosis of SM. However, mast cells have been reported to be increased in various inflammatory diseases, and mast cell density has not been systematically evaluated in other GI disorders. Recently, expression of CD25 by mast cells in bone marrow has been shown to be specific for SM and can be indeed used to confirm the diagnosis. Also aggregates or sheets of mast cells are only seen in SM. Thus, quantitation of mast cells can be helpful to diagnose SM in GI mucosal biopsies [157–159].

Other diseases

Apart from their role in allergy and host defense against microbes, mast cells have been suggested to be involved in several other pathologies. Some of these pathologies are related to inflammation and immune reactions, whereas in others, such a link is less clear. The experimental evidence for a mast cell involvement in such diseases is mostly based on rodent studies and at best partially confirmed for the human system. Of particular interest are evidences suggesting that mast cells could play a role in *tumor development*. It has been established that cancer is related to inflammation induced by chronic infection, autoimmune reactions, or other forms of tissue irritation [160]. Studies in mast cell-deficient mice revealed that mast cells could promote the development of epithelial tumors in the colon by yet unknown mechanisms [161]. Possibly, this effect is related

to angiogenesis known to be affected by mast cells [162, 163].

The role of mast cells in autoimmune diseases such as inflammatory arthritis is just starting to become unraveled [164–166]. Likely, mast cell accumulation and activation in such processes is related to IgE-independent pathways involving for example interactions with bacteria as discussed before. The role of mast cells could be both supply of inflammatory mediators and recruitment of T cells for adaptive immune responses, and thus, it is not surprising that the anti-c-kit antibody Imatinib has been proposed as new therapy in rheumatoid arthritis [167].

The role of mast cells in vascular diseases is more difficult to understand. Of course, mast cells are of relevance for anticoaglation by releasing tryptase and heparin although the regulation of this process is largely unclear [168]. Of particular interest is the pathophysiological function of mast cells in arterial plaque erosion and rupture that can be induced by the local release of mast cell mediators such as heparin proteoglycans, chymase, and cytokines affecting the function of endothelial cells and smooth muscle cells [169]. Moreover, mast cells can contribute to hypertension further promoting coronary events such as plaque rupture by two ways. First, mast cell chymase acts as an enzyme converting angiotensin I to angiotensin II, analogous to or even more effective than endothelial cell-derived angiotensin-converting enzyme, and secondly, mast cells, beside kidney cells, are a source of renin, which cleaves angiotensinogen to angiotensin I [170, 171]. It is not surprising that mast cell inhibition and, in particular, chymase inhibition have been suggested as new therapeutic strategy in heart disease and heart transplantation [172].

The list of regulatory and pathophysiological functions of mast cells is steadily increasing and involves new areas such as pregnancy, during which mast cells seem to regulate uterus contraction [173], or central nervous system diseases like multiple sclerosis [174], migraine [175], or neuroendocrine disorders and behavioral stress [176]. Some of these issues just start to be discovered by mast cell researchers; they sound exiting but are still preliminary with regard to clinical consequences.

Future directions

Mast cell research increased our understanding of the pathophysiology of allergic and nonallergic GI diseases. Consequently, mast cell research aims to define new therapeutic targets to improve treatment options for mast cell-associated GI diseases. Most anti-allergic drugs currently available do not target mast cells directly but rather receptors of mast cell mediators such as histamine or sulfidoleukotrienes. One exception is sodium cromoglycate thought to act as mast cell stabilizer by modulating cell membrane properties and thereby reducing mast cell releasability. The compound was found to be effective for treatment of allergic diseases like allergic rhinitis, conjunctivitis, and gastroenteritis in about 50% of individuals, when administered for several weeks. This drug is almost free of adverse effects suggesting that it acts rather specifically on mast cells for unknown reasons [177].

More recently, anti-SCF receptor drugs have been developed such as STI571 (Imatinib, Glivec®) that inhibits tyrosine kinases such as c-kit, the SCF receptor, PDGFR activation pathways as well as arginine kinase. Although well established in the treatment of CML, GIST and other neoplastic diseases, and, more recently, hypereosinophilic syndrome, its role for treatment of allergic diseases is unclear. Animal studies suggested that STI571 might ameliorate allergic asthma as well as delayed type hypersensitivity reactions [178, 179]; however, prove of this concept in humans is lacking so far. Possibly, other c-kit tyrosine kinase inhibitors other than STI571 or c-kit independent mast cell inhibitors, e.g., by targeting the IL-4 dependent proliferation and hyperresponsiveness of human mast cells, need to be developed for a more successful antimast cell therapy in allergy. Such treatment strategies as well as the antiprotease therapy suggested for asthma treatment [180] might have implications beyond classical type I hypersensitivity reactions.

Of particular interest is the development of new antimast cell drugs apart from Imatinib and sodium cromoglycate, or receptor antagonists of mast cell mediators. If we could target effectively and selectively human mast cells in a safe manner, this would not only enhance our understanding of human mast cell biology but also provide a new and highly exiting option for the treatment of allergic and nonallergic GI diseases associated with mast cells such as IBD, IBS, etc. Possibly, not only the classical pharmacologic approach should be considered but also, e.g., nutrients such as retinol and many others which might modulate mast cell functions [181, 182].

References

1. Gurish MF, Austen KF (2001) The diverse roles of mast cells. J Exp Med 194:F1–F5
2. Bischoff SC, Wedemeyer J, Herrmann A et al (1996) Quantitative assessment of intestinal eosinophils and mast cells in inflammatory bowel disease. Histopathology 28:1–13
3. Galli SJ, Nakae S, Tsai M (2005) Mast cells in the development of adaptive immune responses. Nat Immunol 6:135–142
4. Marshall JS (2004) Mast-cell responses to pathogens. Nat Rev Immunol 4:787–799
5. Bischoff SC (2007) Role of mast cells in allergic and non-allergic immune responses: comparison of human and murine data. Nat Rev Immunol 7:93–104

6. Costa JJ, Weller PF, Galli SJ (1997) The cells of the allergic response: mast cells, basophils, and eosinophils. JAMA 278:1815–1822

7. Bischoff SC, Crowe SE (2005) Gastrointestinal food allergy: new insights into pathophysiology and clinical perspectives. Gastroenterology 128:1089–1113

8. Brightling CE, Bradding P (2005) The re-emergence of the mast cell as a pivotal cell in asthma pathogenesis. Curr Allergy Asthma Rep 5:130–135

9. Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA (2004) New insights into atopic dermatitis. J Clin Invest 113:651–657

10. Kirshenbaum AS, Kessler SW, Goff JP, Metcalfe DD (1991) Demonstration of the origin of human mast cells from CD34+ bone marrow progenitor cells. J Immunol 146:1410–1415

11. Mitsui H, Furitsu T, Dvorak AM et al (1993) Development of human mast cells from umbilical cord blood cells by recombinant human and murine c-kit ligand. Proc Natl Acad Sci U S A 90:735–739

12. Toru H, Eguchi M, Matsumoto R et al (1998) Interleukin-4 promotes the development of tryptase and chymase double-positive human mast cells accompanied by cell maturation. Blood 91:187–195

13. Denburg JA (1992) Basophil and mast cell lineages in vitro and in vivo. Blood 79:846–860

14. Agis H, Füreder W, Bankl HC et al (1996) Comparative immunophenotypic analysis of human mast cells, blood basophils and monocytes. Immunology 87:535–543

15. Nakajima T, Matsumoto K, Suto H et al (2001) Gene expression screening of human mast cells and eosinophils using high-density oligonucleotide probe arrays: abundant expression of major basic protein in mast cells. Blood 98:1127–1134

16. Foster B, Schwartz LB, Devouassoux G, Metcalfe DD, Prussin C (2002) Characterization of mast cell tryptase-expressing peripheral blood cells as basophils. J Allergy Clin Immunol 109:287–293

17. Ito T, Nishiyama C, Nishiyama M et al (2005) Mast cells acquire monocyte-specific gene expression and monocyte-like morphology by overproduction of PU.1. J Immunol 174:376–383

18. Kempuraj D, Saito H, Kaneko A et al (1999) Characterization of mast cell-committed progenitors present in human umbilical cord blood. Blood 93:3338–3346

19. Kocabas CN, Yavuz AS, Lipsky PE, Metcalfe DD, Akin C (2005) Analysis of the lineage relationship between mast cells and basophils using the c-kit D816V mutation as a biologic signature. J Allergy Clin Immunol 115:1155–1161

20. Razin E, Ihle JN, Seldin D et al (1984) Interleukin 3: a differentiation and growth factor for the mouse mast cell that contains chondroitin sulfate E proteoglycan. J Immunol 132:1479–1486

21. Valent P, Besemer J, Sillaber C, Butterfield JH et al (1990) Failure to detect IL-3-binding sites on human mast cells. J Immunol 145:3432–3437

22. Gebhardt T, Sellge G, Lorentz A et al (2002) Cultured human intestinal mast cells express functional IL-3 receptors and respond to IL-3 by enhancing growth and IgE receptor-dependent mediator release. Eur J Immunol 32:2308–2316

23. Kurimoto Y, De Weck AL, Dahinden CA (1991) The effect of interleukin 3 upon IgE-dependent and IgE-independent basophil degranulation and leukotriene generation. Eur J Immunol 21:361–368

24. Bischoff SC, Sellge G, Lorentz A, Sebald W, Raab R, Manns MP (1999) IL-4 enhances proliferation and mediator release in mature human mast cells. Proc Natl Acad Sci U S A 96:8080–8085

25. Mierke CT, Ballmaier M, Werner U, Manns MP, Welte K, Bischoff SC (2000) Human endothelial cells regulate survival and proliferation of human mast cells. J Exp Med 192:801–811

26. Lorentz A, Schuppan D, Gebert A, Manns MP, Bischoff SC (2002) Regulatory effects of stem cell factor and interleukin-4 on adhesion of human mast cells to extracellular matrix proteins. Blood 99:966–972

27. Bischoff SC, Dahinden CA (1992) c-kit ligand: a unique potentiator of mediator release by human lung mast cells. J Exp Med 175:237–244

28. Undem BJ, Lichtenstein LM, Hubbard WC, Meeker S, Ellis JL (1994) Recombinant stem cell factor-induced mast cell activation and smooth muscle contraction in human bronchi. Am J Respir Cell Mol Biol 11:646–650

29. Taylor ML, Metcalfe DD (2000) Kit signal transduction. Hematol Oncol Clin North Am 14:517–535

30. Tkaczyk C, Horejsi V, Iwaki S (2004) NTAL phosphorylation is a pivotal link between the signaling cascades leading to human mast cell degranulation following Kit activation and Fc epsilon RI aggregation. Blood 104:207–214

31. Hundley TR, Gilfillan AM, Tkaczyk C, Andrade MV, Metcalfe DD, Beaven MA (2004) Kit and FcepsilonRI mediate unique and convergent signals for release of inflammatory mediators from human mast cells. Blood 104:2410–2417

32. Iwaki S, Tkaczyk C, Satterthwaite AB, Halcomb K, Beaven MA, Metcalfe DD, Gilfillan AM (2005) Btk plays a crucial role in the amplification of Fc epsilonRI-mediated mast cell activation by kit. J Biol Chem 280:40261–40270

33. Gilfillan AM, Tkaczyk C (2006) Integrated signalling pathways for mast-cell activation. Nat Rev Immunol 6:218–230

34. Matsuda K, Piliponsky AM, Iikura M et al (2005) Monomeric IgE enhances human mast cell chemokine production: IL-4 augments and dexamethasone suppresses the response. J Allergy Clin Immunol 116:1357–1363

35. Kulka M, Metcalfe DD (2005) High-resolution tracking of cell division demonstrates differential effects of TH1 and TH2 cytokines on SCF-dependent human mast cell production in vitro: correlation with apoptosis and Kit expression. Blood 105:592–599

36. Lorentz A, Schwengberg S, Sellge G, Manns MP, Bischoff SC (2000) Human intestinal mast cells are capable of producing different cytokine profiles: role of IgE receptor cross-linking and IL-4. J Immunol 164:43–48

37. Lorentz A, Wilke M, Sellge G, Worthmann H, Klempnauer J, Manns MP, Bischoff SC (2005) IL-4-induced priming of human intestinal mast cells for enhanced survival and Th2 cytokine generation is reversible and associated with increased activity of ERK1/2 and c-Fos. J Immunol 174:675–676

38. Okayama Y, Hagaman DD, Metcalfe DD (2001) A comparison of mediators released or generated by IFN-gamma-treated human mast cells following aggregation of Fc gamma RI or Fc epsilon RI. J Immunol 166:4705–4712

39. Sellge G, Laffer S, Mierke C, Vrtala S, Hoffmann MW, Klempnauer J, Manns MP, Valenta R, Bischoff SC (2005) Development of an in vitro system for the study of allergens and allergen-specific immunoglobulin E and immunoglobulin G: Fcepsilon receptor I supercross-linking is a possible new mechanism of immunoglobulin G-dependent enhancement of type I allergic reactions. Clin Exp Allergy 35:774–781

40. Guhl S, Lee HH, Babina M, Henz BM, Zuberbier T (2005) Evidence for a restricted rather than generalized stimulatory response of skin-derived human mast cells to substance P. J Neuroimmunol 163:92–101

41. Bischoff SC, Schwengberg S, Lorentz A (2004) Substance P and other neuropeptides do not induce mediator release in isolated

human intestinal mast cells. Neurogastroenterol Motil 16:185–193

42. van der Kleij HP, Ma D, Redegeld FA, Kraneveld AD, Nijkamp FP, Bienenstock J (2003) Functional expression of neurokinin 1 receptors on mast cells induced by IL-4 and stem cell factor. J Immunol 171:2074–2079

43. Miyazaki D, Nakamura T, Toda M, Cheung-Chau KW, Richardson RM, Ono SJ (2005) Macrophage inflammatory protein-1alpha as a costimulatory signal for mast cell-mediated immediate hypersensitivity reactions. J Clin Invest 115:434–442

44. Santos J, Saperas E, Nogueiras C, Mourelle M, Antolin M, Cadahia A, Malagelada JR (1998) Release of mast cell mediators into the jejunum by cold pain stress in humans. Gastroenterology 114:640–648

45. Sander LE, Lorentz A, Sellge G et al (2006) Selective expression of histamine receptors H1R, H2R, and H4R, but not H3R, in the human intestinal tract. Gut 55:498–504

46. Sirois J, Menard G, Moses AS, Bissonnette EY (2000) Importance of histamine in the cytokine network in the lung through H2 and H3 receptors: stimulation of IL-10 production. J Immunol 164:2964–2970

47. Jutel M, Watanabe T, Klunker S (2001) Histamine regulates T-cell and antibody responses by differential expression of H1 and H2 receptors. Nature 413:420–425

48. Yu LC, Perdue MH (2001) Role of mast cells in intestinal mucosal function: studies in models of hypersensitivity and stress. Immunol Rev 179:61–73

49. Russell DA (1986) Mast cells in the regulation of intestinal electrolyte transport. Am J Physiol 251:G253–G262

50. Castells M, Austen KF (2002) Mastocytosis: mediator-related signs and symptoms. Int Arch Allergy Immunol 127:147–152

51. Jeffery P, Zhu J (2002) Mucin-producing elements and inflammatory cells. Novartis Found Symp 248:51–68

52. Wood JD (2004) Enteric neuroimmunophysiology and pathophysiology. Gastroenterology 127:635–657

53. Ito A, Hagiyama M, Oonuma J (2008) Nerve-mast cell and smooth muscle-mast cell interaction mediated by cell adhesion molecule-1, CADM1. J Smooth Muscle Res 44:83–93

54. Van Nassauw L, Adriaensen D, Timmermans JP (2007) The bidirectional communication between neurons and mast cells within the GI tract. Auton Neurosci 133:91–103

55. Okumura S, Kashiwakura J, Tomita H, Matsumoto K, Nakajima T, Saito H, Okayama Y (2003) Identification of specific gene expression profiles in human mast cells mediated by Toll-like receptor 4 and FcepsilonRI. Blood 102:2547–2554

56. Varadaradjalou S, Feger F, Thieblemont N, Hamouda NB, Pleau JM, Dy M, Arock M (2003) Toll-like receptor 2 (TLR2) and TLR4 differentially activate human mast cells. Eur J Immunol 33:899–906

57. Cherwinski HM, Murphy CA, Joyce BL (2005) The CD200 receptor is a novel and potent regulator of murine and human mast cell function. J Immunol 174:1348–1356

58. Gebhardt T, Lorentz A, Detmer F, Trautwein C, Bektas H, Manns MP, Bischoff SC (2005) Growth, phenotype, and function of human intestinal mast cells are tightly regulated by transforming growth factor beta1. Gut 54:928–934

59. Royer B, Varadaradjalou S, Saas P, Guillosson JJ, Kantelip JP, Arock M (2001) Inhibition of IgE-induced activation of human mast cells by IL-10. Clin Exp Allergy 31:694–704

60. Sansonetti PJ (2008) Host–bacteria homeostasis in the healthy and inflamed gut. Curr Opin Gastroenterol 24:435–439

61. Wehkamp J, Fellermann K, Herrlinger KR, Bevins CL, Stange EF (2005) Mechanisms of disease: defensins in gastrointestinal diseases. Nat Clin Pract Gastroenterol Hepatol 2:406–415

62. Demaude J, Salvador-Cartier C, Fioramonti J, Ferrier L, Bueno L (2006) Phenotypic changes in colonocytes following acute stress or activation of mast cells in mice: implications for delayed epithelial barrier dysfunction. Gut 55:655–661

63. Ferrier L, Berard F, Debrauwer L, Chabo C, Langella P, Bueno L, Fioramonti J (2006) Impairment of the intestinal barrier by ethanol involves enteric microflora and mast cell activation in rodents. Am J Pathol 168:1148–1154

64. Jacob C, Yang PC, Darmoul D et al (2005) Mast cell tryptase controls paracellular permeability of the intestine. Role of protease-activated receptor 2 and beta-arrestins. J Biol Chem 280:31936–31948

65. McDermott JR, Bartram RE, Knight PA, Miller HR, Garrod DR, Grencis RK (2003) Mast cells disrupt epithelial barrier function during enteric nematode infection. Proc Natl Acad Sci U S A 100:7761–7766

66. Soderholm JD, Yang PC, Ceponis P, Vohra A, Riddell R, Sherman PM, Perdue MH (2002) Chronic stress induces mast cell-dependent bacterial adherence and initiates mucosal inflammation in rat intestine. Gastroenterology 123:1099–1108

67. Krämer S, Sellge G, Lorentz A, Krueger D, Schemann M, Feilhauer K, Gunzer F, Bischoff SC (2008) Selective activation of human intestinal mast cells by Escherichia coli hemolysin. J Immunol 181:1438–1445

68. Leal-Berumen I, Snider DP, Barajas-Lopez C, Marshall JS (1996) Cholera toxin increases IL-6 synthesis and decreases TNF-alpha production by rat peritoneal mast cells. J Immunol 156:316–321

69. Malaviya R, Gao Z, Thankavel K, van der Merwe PA, Abraham SN (1999) The mast cell tumor necrosis factor alpha response to FimH-expressing Escherichia coli is mediated by the glycosylphosphatidylinositol-anchored molecule CD48. Proc Natl Acad Sci U S A 96:8110–8115

70. Schramm G, Falcone FH, Gronow A et al (2003) Molecular characterization of an interleukin-4-inducing factor from Schistosoma mansoni eggs. J Biol Chem 278:18384–18392

71. Schramm G, Gronow A, Knobloch J et al (2006) IPSE/alpha-1: a major immunogenic component secreted from Schistosoma mansoni eggs. Mol Biochem Parasitol 147:9–19

72. Knight PA, Wright SH, Lawrence CE, Paterson YY, Miller HR (2000) Delayed expulsion of the nematode Trichinella spiralis in mice lacking the mucosal mast cell-specific granule chymase, mouse mast cell protease-1. J Exp Med 192:1849–1856

73. Woodbury RG, Miller HR, Huntley JF, Newlands GF, Palliser AC, Wakelin D (1984) Mucosal mast cells are functionally active during spontaneous expulsion of intestinal nematode infections in rat. Nature 312:450–452

74. Finkelman FD, Urban JF Jr (2001) The other side of the coin: the protective role of the TH2 cytokines. J Allergy Clin Immunol 107:772–780

75. Lawrence CE, Paterson YY, Wright SH, Knight PA, Miller HR (2004) Mouse mast cell protease-1 is required for the enteropathy induced by gastrointestinal helminth infection in the mouse. Gastroenterology 127:155–165

76. Finkelman FD, Shea-Donohue T, Morris SC, Gildea L, Strait R, Madden KB, Schopf L, Urban JF Jr (2004) Interleukin-4- and interleukin-13-mediated host protection against intestinal nematode parasites. Immunol Rev 201:139–155

77. Knight PA, Brown JK, Pemberton AD (2008) Innate immune response mechanisms in the intestinal epithelium: potential roles for mast cells and goblet cells in the expulsion of adult Trichinella spiralis. Parasitology 135:655–670

78. Brunner T, Heusser CH, Dahinden CA (1993) Human peripheral blood basophils primed by interleukin 3 (IL-3) produce IL-4 in response to immunoglobulin E receptor stimulation. J Exp Med 177:605–611

79. Min B, Prout M, Hu-Li J et al (2004) Basophils produce IL-4 and accumulate in tissues after infection with a Th2-inducing parasite. J Exp Med 200:507–517

80. Helmby H, Grencis RK (2002) IL-18 regulates intestinal mastocytosis and Th2 cytokine production independently of IFN-gamma during Trichinella spiralis infection. J Immunol 169:2553–2560

81. Boyce JA (2003) Mast cells: beyond IgE. J Allergy Clin Immunol 111:24–32

82. Echtenacher B, Mannel DN, Hultner L (1996) Critical protective role of mast cells in a model of acute septic peritonitis. Nature 381:75–77

83. Malaviya R, Ikeda T, Ross E, Abraham SN (1996) Mast cell modulation of neutrophil influx and bacterial clearance at sites of infection through TNF-alpha. Nature 381:77–80

84. Malaviya R, Abraham SN (2000) Role of mast cell leukotrienes in neutrophil recruitment and bacterial clearance in infectious peritonitis. J Leukoc Biol 67:841–846

85. McLachlan JB, Hart JP, Pizzo SV, Shelburne CP, Staats HF, Gunn MD, Abraham SN (2003) Mast cell-derived tumor necrosis factor induces hypertrophy of draining lymph nodes during infection. Nat Immunol 4:1199–1205

86. Jawdat DM, Rowden G, Marshall JS (2006) Mast cells have a pivotal role in TNF-independent lymph node hypertrophy and the mobilization of Langerhans cells in response to bacterial peptidoglycan. J Immunol 177:1755–1762

87. Matsuo T, Ikura Y, Ohsawa M et al (2003) Mast cell chymase expression in Helicobacter pylori-associated gastritis. Histopathology 43:538–549

88. Raqib R, Moly PK, Sarker P, Qadri F, Alam NH, Mathan M, Andersson J (2003) Persistence of mucosal mast cells and eosinophils in Shigella-infected children. Infect Immun 71:2684–2692

89. Pulimood AB, Mathan MM, Mathan VI (1998) Quantitative and ultrastructural analysis of rectal mucosal mast cells in acute infectious diarrhea. Dig Dis Sci 43:2111–2116

90. Kulka M, Fukuishi N, Rottem M, Mekori YA, Metcalfe DD (2006) Mast cells, which interact with Escherichia coli, up-regulate genes associated with innate immunity and become less responsive to Fc(epsilon) RI-mediated activation. J Leukoc Biol 79:339–350

91. Cumberbatch M, Dearman RJ, Griffiths CE, Kimber I (2000) Langerhans cell migration. Clin Exp Dermatol 25:413–418

92. Poncet P, Arock M, David B (1999) MHC class II-dependent activation of CD4+ T cell hybridomas by human mast cells through superantigen presentation. J Leukoc Biol 66:105–112

93. Marone G, Florio G, Petraroli A, Triggiani M, de Paulis A (2001) Human mast cells and basophils in HIV-1 infection. Trends Immunol 22:229–232

94. Orinska Z, Bulanova E, Budagian V, Metz M, Maurer M, Bulfone-Paus S (2005) TLR3-induced activation of mast cells modulates CD8+ T-cell recruitment. Blood 106:978–987

95. Kulka M, Metcalfe DD (2006) TLR3 activation inhibits human mast cell attachment to fibronectin and vitronectin. Mol Immunol 43:1579–1586

96. Kulka M, Alexopoulou L, Flavell RA, Metcalfe DD (2004) Activation of mast cells by double-stranded RNA: evidence for activation through Toll-like receptor 3. J Allergy Clin Immunol 114:174–182

97. Lu LF, Lind EF, Gondek DC (2006) Mast cells are essential intermediaries in regulatory T-cell tolerance. Nature 442:997–1002

98. Mitre E, Norwood S, Nutman TB (2005) Saturation of immunoglobulin E (IgE) binding sites by polyclonal IgE does not explain the protective effect of helminth infections against atopy. Infect Immun 73:4106–4111

99. Wills-Karp M, Santeliz J, Karp CL (2001) The germless theory of allergic disease: revisiting the hygiene hypothesis. Nat Rev Immunol 1:69–75

100. Akdis M, Akdis CA (2007) Mechanisms of allergen-specific immunotherapy. J Allergy Clin Immunol 119:780–791

101. Rao KN, Brown MA (2008) Mast cells: multifaceted immune cells with diverse roles in health and disease. Ann N Y Acad Sci 1143:83–104

102. Bachelet I, Levi-Schaffer F, Mekori YA (2006) Mast cells: not only in allergy. Immunol Allergy Clin North Am 26:407–425

103. Maurer M, Theoharides T, Granstein RD, Bischoff SC et al (2003) What is the physiological function of mast cells? Exp Dermatol 12:886–910

104. Bjorksten B (2001) The epidemiology of food allergy. Curr Opin Allergy Clin Immunol 1:225–227

105. Grundy J, Matthews S, Bateman B, Dean T, Arshad SH (2002) Rising prevalence of allergy to peanut in children: data from 2 sequential cohorts. J Allergy Clin Immunol 110:784–789

106. Zuberbier T, Edenharter G, Worm M, Ehlers I, Reimann S, Hantke T, Roehr CC, Bergmann KE, Niggemann B (2004) Prevalence of adverse reactions to food in Germany—a population study. Allergy 59:338–345

107. Brandtzaeg PE (2002) Current understanding of gastrointestinal immunoregulation and its relation to food allergy. Ann N Y Acad Sci 964:13–45

108. Coombs RR (1992) The Jack Pepys Lecture. The hypersensitivity reactions—some personal reflections. Clin Exp Allergy 22:673–680

109. Furuta GT, Schmidt-Choudhury A, Wang MY, Wang ZS, Lu L, Furlano RI, Wershil BK (1997) Mast cell-dependent tumor necrosis factor alpha production participates in allergic gastric inflammation in mice. Gastroenterology 113:1560–1569

110. Malaviya R, Navara C, Uckun FM (2001) Role of Janus kinase 3 in mast cell-mediated innate immunity against gram-negative bacteria. Immunity 15:313–321

111. Dahlen SE, Kumlin M (2004) Monitoring mast cell activation by prostaglandin D2 in vivo. Thoraxm 59:453–455

112. Brightling CE, Bradding P, Symon FA, Holgate ST, Wardlaw AJ, Pavrod ID (2002) Mast cell infiltration of airway smooth muscle in asthma. N Engl J Med 346:1699–1705

113. Oguma T, Palmer LJ, Birben E, Sonna LA, Asano K, Lilly CM (2004) Role of prostanoid DP receptor variants in susceptibility to asthma. N Engl J Med 351:1752–1763

114. Bradding P, Feather IH, Wilson S, Barding PG, Heusser CH, Holgate ST, Howarth PH (1993) Immunolocalization of cytokines in the nasal mucosa of normal and perennial rhinitic subjects. The mast cell as a source of IL-4, IL-5, and IL-6 in human allergic mucosal inflammation. J Immunol 151:3853–3865

115. Mukai K, Matsuoka K, Taya C, Suzuki H, Yokozeki H, Nishioka K, Hirokawa K, Etori M, Yamashita M, Kubota T, Minegishi Y, Yonekawa H, Karasuyama H (2005) Basophils play a critical role in the development of IgE-mediated chronic allergic inflammation independently of T cells and mast cells. Immunity 23:191–202

116. Majamaa H, Laine S, Miettinen A (1999) Eosinophil protein X and eosinophil cationic protein as indicators of intestinal inflammation in infants with atopic eczema and food allergy. Clin Exp Allergy 29:1502–1506

117. Bischoff SC, Mayer J, Wedemeyer J, Meier PN, Zeck-Kapp G, Wedi B, Kapp A, Cetin Y, Gebel M, Manns MP (1997) Colonoscopic allergen provocation (COLAP): a new diagnostic approach for gastrointestinal food allergy. Gut 40:745–753

118. Barbara G, Stanghellini V, De Giorgio R, Cremon C, Cottrell GS, Santini D, Pasquinelli G, Morselli-Labate AM, Grady EF, Bunnett NW, Collins SM, Corinaldesi R (2004) Activated mast cells in proximity to colonic nerves correlate with

abdominal pain in irritable bowel syndrome. Gastroenterology 126:693–702

119. Blumer N, Herz U, Wegmann M, Renz H (2005) Prenatal lipopolysaccharide-exposure prevents allergic sensitization and airway inflammation, but not airway responsiveness in a murine model of experimental asthma. Clin Exp Allergy 35:397–402

120. Rook GA, Brunet LR (2005) Microbes, immunoregulation, and the gut. Gut 54:317–320

121. Garn H, Renz H (2007) Epidemiological and immunological evidence for the hygiene hypothesis. Immunobiology 212:441–452

122. Guarner F, Bourdet-Sicard R, Brandtzaeg P, Gill HS, McGuirk P, van Eden W, Versalovic J, Weinstock JV, Rook GA (2006) Mechanisms of disease: the hygiene hypothesis revisited. Nat Clin Pract Gastroenterol Hepatol 3:275–284

123. Rook GA (2009) Review series on helminths, immune modulation and the hygiene hypothesis: the broader implications of the hygiene hypothesis. Immunology 126:3–11

124. Spiegl N, Didichenko S, McCaffery P, Langen H, Dahinden CA (2008) Human basophils activated by mast cell-derived IL-3 express retinaldehyde dehydrogenase-II and produce the immunoregulatory mediator retinoic acid. Blood 112:3762–3771

125. Stephensen CB (2001) Vitamin A, infection, and immune function. Annu Rev Nutr 21:167–192

126. Iwata M, Hirakiyama A, Eshima Y, Kagechika H, Kato C, Song SY (2004) Retinoic acid imprints gut homing specificity on T cells. Immunity 21:527–538

127. Mora JR, Iwata M, Eksteen B et al (2006) Generation of gut-homing IgA-secreting B cells by intestinal dendritic cells. Science 314:1157–1160

128. von Boehmer H (2007) Oral tolerance: is it all retinoic acid? J Exp Med 204:1737–1739

129. Long KZ, Rosado JL, DuPont HL, Hertzmark E, Santos JI (2007) Supplementation with vitamin A reduces watery diarrhoea and respiratory infections in Mexican children. Br J Nutr 97:337–343

130. Duester G, Mic FA, Molotkov A (2003) Cytosolic retinoid dehydrogenases govern ubiquitous metabolism of retinol to retinaldehyde followed by tissue-specific metabolism to retinoic acid. Chem Biol Interact 143–144:201–210

131. Sigmundsdottir H, Pan J, Debes GF, Alt C, Habtezion A, Soler D, Butcher EC (2007) DCs metabolize sunlight-induced vitamin D3 to 'program' T cell attraction to the epidermal chemokine CCL27. Nat Immunol 8:285–293

132. Bischoff SC (2008) "Vitamin hypothesis": explanation for allergy increase? Blood 112:3535–3536

133. Bischoff SC (2008) Food allergy: Mechanisms and clinical manifestations. In: Pawankar R, Holgate S, Rosenwasser L (eds) Allergy Frontiers: Epigenetics to future perspectives. Springer, Tokyo 2009, p. 411–430

134. Enrique E, Pineda F, Malek T et al (2005) Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. J Allergy Clin Immunol 116:1073–1079

135. Pajno GB (2007) Sublingual immunotherapy: the optimism and the issues. J Allergy Clin Immunol 119:796–801

136. Rolinck-Werninghaus C, Staden U, Mehl A, Hamelmann E, Beyer K, Niggemann B (2005) Specific oral tolerance induction with food in children: transient or persistent effect on food allergy? Allergy 60:1320–1322

137. Valenta R (2002) The future of antigen-specific immunotherapy of allergy. Nat Rev Immunol 2:446–453

138. Wenzel S, Wilbraham D, Fuller R, Getz EB, Longphre M (2007) Effect of an interleukin-4 variant on late phase asthmatic response to allergen challenge in asthmatic patients: results of two phase 2a studies. Lancet 370:1422–1431

139. Jensen BM, Metcalfe DD, Gilfillan AM (2007) Targeting kit activation: a potential therapeutic approach in the treatment of allergic inflammation. Inflamm Allergy Drug Targets 6:57–62

140. Kalliomaki M, Salminen S, Poussa T, Arvilommi H, Isolauri E (2003) Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. Lancet 361:1869–1871

141. Taylor AL, Dunstan JA, Prescott SL (2007) Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: a randomized controlled trial. J Allergy Clin Immunol 119:184–191

142. Brouwer ML, Wolt-Plompen SA, Dubois AE, van der Heide S, Jansen DF, Hoijer MA, Kauffman HF, Duiverman EJ (2006) No effects of probiotics on atopic dermatitis in infancy: a randomized placebo-controlled trial. Clin Exp Allergy 36:899–906

143. Folster-Holst R, Muller F, Schnopp N, Abeck D, Kreiselmaier I, Lenz T, von Ruden U, Schrezenmeir J, Christophers E, Weichenthal M (2006) Prospective, randomized controlled trial on Lactobacillus rhamnosus in infants with moderate to severe atopic dermatitis. Br J Dermatol 155:1256–1261

144. Wingren U, Hallert C, Norrby K, Enerbäck L (1986) Histamine and mucosal mast cells in gluten enteropathy. Agents Actions 18:266–268

145. Lähteenoja H, Mäki M, Viander M, Toivanen A, Syrjänen S (2000) Local challenge of oral mucosa with gliadin in patients with coeliac disease. Clin Exp Immunol 120:38–45

146. Locher C, Tipold A, Welle M, Busato A, Zurbriggen A, Griot-Wenk ME (2001) Quantitative assessment of mast cells and expression of IgE protein and mRNA for IgE and interleukin 4 in the gastrointestinal tract of healthy dogs and dogs with inflammatory bowel disease. Am J Vet Res 62:211–216

147. He SH (2004) Key role of mast cells and their major secretory products in inflammatory bowel disease. World J Gastroenterol 10:309–318

148. Stoyanova II, Gulubova MV (2002) Mast cells and inflammatory mediators in chronic ulcerative colitis. Acta Histochem 104:185–192

149. Farhadi A, Keshavarzian A, Fields JZ, Jakate S, Shaikh M, Banan A (2007) Reduced immunostaining for c-kit receptors in mucosal mast cells in inflammatory bowel disease. J Gastroenterol Hepatol 22:2338–2343

150. De Giorgio R, Barbara G (2008) Is irritable bowel syndrome an inflammatory disorder? Curr Gastroenterol Rep 10:385–390

151. Jakate S, Demeo M, John R, Tobin M, Keshavarzian A (2006) Mastocytic enterocolitis: increased mucosal mast cells in chronic intractable diarrhea. Arch Pathol Lab Med 130:362–367

152. Walker MM, Talley NJ, Prabhakar M, Pennaneac'h CJ, Aro P, Ronkainen J, Storskrubb T, Harmsen WS, Zinsmeister AR, Agreus L (2009) Duodenal mastocytosis, eosinophilia and intraepithelial lymphocytosis as possible disease markers in the irritable bowel syndrome and functional dyspepsia. Aliment Pharmacol Ther 29:765–773

153. Gasbarrini A, Lauritano EC, Garcovich M, Sparano L, Gasbarrini G (2008) New insights into the pathophysiology of IBS: intestinal microflora, gas production and gut motility. Eur Rev Med Pharmacol Sci 12(Suppl 1):111–117

154. Cherner JA, Jensen RT, Dubois A, O'Dorisio TM, Gardner JD, Metcalfe DD (1998) Gastrointestinal dysfunction in systemic mastocytosis. A prospective study. Gastroenterology 95:657–667

155. Jensen RT (2000) Gastrointestinal abnormalities and involvement in systemic mastocytosis. Hematol Oncol Clin North Am 14:579–623

156. Siegert SI, Diebold J, Ludolph-Hauser D, Löhrs U (2004) Are gastrointestinal mucosal mast cells increased in patients with systemic mastocytosis? Am J Clin Pathol 122:560–565

157. Hahn HP, Hornick JL (2007) Immunoreactivity for CD25 in gastrointestinal mucosal mast cells is specific for systemic mastocytosis. Am J Surg Pathol 31:1669–1676

158. Horny HP, Sotlar K, Valent P (2007) Mastocytosis: state of the art. Pathobiology 74:121–132

159. Valent P, Akin C, Escribano L et al (2007) Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. Eur J Clin Invest 37:435–453

160. Coussens LM, Werb Z (2002) Inflammation and cancer. Nature 420:860–867

161. Wedemeyer J, Galli SJ (2005) Decreased susceptibility of mast cell-deficient Kit(W)/Kit(W-v) mice to the development of 1, 2-dimethylhydrazine-induced intestinal tumors. Lab Invest 85:388–396

162. Takanami I, Takeuchi K, Naruke M (2000) Mast cell density is associated with angiogenesis and poor prognosis in pulmonary adenocarcinoma. Cancer 88:2686–2692

163. Ribatti D, Crivellato E, Roccaro AM, Ria R, Vacca A (2004) Mast cell contribution to angiogenesis related to tumour progression. Clin Exp Allergy 34:1660–1664

164. Lee DM, Friend DS, Gurish MF, Benoist C, Mathis D, Brenner MB (2002) Mast cells: a cellular link between autoantibodies and inflammatory arthritis. Science 297:1689–1692

165. Woolley DE (2003) The mast cell in inflammatory arthritis. N Engl J Med 348:1709–1711

166. Nigrovic PA, Lee DM (2005) Mast cells in inflammatory arthritis. Arthritis Res Ther 7:1–11

167. Juurikivi A, Sandler C, Lindstedt KA, Kovanen PT, Juutilainen T, Leskinen MJ, Maki T, Eklund KK (2005) Inhibition of c-kit tyrosine kinase by imatinib mesylate induces apoptosis in mast cells in rheumatoid synovia: a potential approach to the treatment of arthritis. Ann Rheum Dis 64:1126–1131

168. Valent P, Baghestanian M, Bankl HC, Sillaber C, Sperr WR, Wojta J, Binder BR, Lechner K (2002) New aspects in thrombosis research: possible role of mast cells as profibrinolytic and antithrombotic cells. Thromb Haemost 87:786–790

169. Lindstedt KA, Kovanen PT (2004) Mast cells in vulnerable coronary plaques: potential mechanisms linking mast cell activation to plaque erosion and rupture. Curr Opin Lipidol 15:567–573

170. Liao Y, Husain A (1995) The chymase-angiotensin system in humans: biochemistry, molecular biology and potential role in cardiovascular diseases. Can J Cardiol 11(Suppl F):13F–19F

171. Silver RB, Reid AC, Mackins CJ, Askwith T, Schaefer U, Herzlinger D, Levi R (2004) Mast cells: a unique source of renin. Proc Natl Acad Sci U S A 101:13607–13612

172. Fildes JE, Walker AH, Keevil B, Hutchinson IV, Leonard CT, Yonan N (2005) The effects of ACE inhibition on serum angiotensin II concentration following cardiac transplantation. Transplant Proc 37:4525–4527

173. Garfield RE, Irani AM, Schwartz LB, Bytautiene E, Romero R (2006) Structural and functional comparison of mast cells in the pregnant versus nonpregnant human uterus. Am J Obstet Gynecol 194:261–267

174. Zappulla JP, Arock M, Mars LT, Liblau RS (2002) Mast cells: new targets for multiple sclerosis therapy? J Neuroimmunol 131:5–20

175. Theoharides TC, Donelan J, Kandere-Grzybowska K, Konstantinidou A (2005) The role of mast cells in migraine pathophysiology. Brain Res Brain Res Rev 49:65–76

176. Asarian L, Yousefzadeh E, Silverman AJ, Silver R (2002) Stimuli from conspecifics influence brain mast cell population in male rats. Horm Behav 42:1–12

177. Edwards AM (1995) Oral sodium cromoglycate: its use in the management of food allergy. Clin Exp Allergy 25(Suppl 1):31–33

178. Berlin AA, Lukacs NW (2005) Treatment of cockroach allergen asthma model with imatinib attenuates airway responses. Am J Respir Crit Care Med 171:35–39

179. Dietz AB, Souan L, Knutson GJ, Bulur PA, Litzow MR, Vuk-Pavlovic S (2004) Imatinib mesylate inhibits T-cell proliferation in vitro and delayed-type hypersensitivity in vivo. Blood 104:1094–1099

180. Cairns JA (2005) Inhibitors of mast cell tryptase beta as therapeutics for the treatment of asthma and inflammatory disorders. Pulm Pharmacol Ther 18:55–66

181. Ishida S, Kinoshita T, Sugawara N, Yamashita T, Koike K (2003) Serum inhibitors for human mast cell growth: possible role of retinol. Allergy 58:1044–1052

182. Theoharides TC, Bielory L (2004) Mast cells and mast cell mediators as targets of dietary supplements. Ann Allergy Asthma Immunol 93:S24–S34