Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

Allergy

REVIEW ARTICLE

Histamine and gut mucosal immune regulation

S. Smolinska[1,2], M. Jutel[1,2], R. Crameri[3] & L. O'Mahony[3]

[1]Department of Clinical Immunology, Wroclaw Medical University, Wroclaw; [2]'ALL-MED' Medical Research Institute, Wroclaw, Poland; [3]Swiss Institute of Allergy and Asthma Research, University of Zurich, Davos, Switzerland

To cite this article: Smolinska S, Jutel M, Crameri R, O'Mahony L. Histamine and gut mucosal immune regulation. *Allergy* 2013; DOI: 10.1111/all.12330.

Keywords
allergy; histamine; inflammation; microbial metabolites; mucosal immunology.

Correspondence
Dr. Liam O'Mahony, SIAF, Obere Strasse 22, 7270 Davos Platz, Switzerland.
Tel.: +41-81-4100853
Fax: +41-81-4100840
E-mail: liam.omahony@siaf.uzh.ch

Accepted for publication 21 October 2013

DOI:10.1111/all.12330

Edited by: Hans-Uwe Simon

Abstract

Histamine is a biogenic amine with extensive effects on many cell types, mediated by the activation of its four receptors (H1R–H4R). Distinct effects are dependent on receptor subtypes and their differential expression. Within the gastrointestinal tract, histamine is present at relatively high concentrations, particularly during inflammatory responses. In this review, we discuss the immunoregulatory influence of histamine on a number of gastrointestinal disorders, including food allergy, scombroid food poisoning, histamine intolerance, irritable bowel syndrome, and inflammatory bowel disease. It is clear that the effects of histamine on mucosal immune homeostasis are dependent on expression and activity of the four currently known histamine receptors; however, the relative protective or pathogenic effects of histamine on inflammatory processes within the gut are still poorly defined and require further investigation.

Histamine [2-(4-imidazolyl)-ethylamine] is a short-acting endogenous amine, which is widely distributed throughout the body (1, 2). Histamine is synthesized by the enzyme histidine decarboxylase (HDC), which decarboxylates the semi-essential amino acid L-histidine. Originally discovered more than 100 years ago, histamine was first chemically synthesized by Windaus and Vogt in 1907. Soon afterward in 1910, Dale and Laidlaw reported the first biological functions of histamine, whereby they recognized that histamine had the ability to mimic smooth muscle-stimulating and vasodepressor action previously observed during anaphylaxis (3, 4). Subsequently, histamine was isolated from many different tissues, and thus, its name was based on the Greek word 'histos', which means tissue. Studies utilizing HDC-knockout animals have revealed the multiple effects of histamine on allergic, peptic, and neurologic functions, while more recent studies demonstrate the influence of histamine on wound healing, circulatory disease, immunology, oncology, and infectious disease (5).

Histamine can be produced by a wide variety of different cell types (6–10). Mast cells, basophils, gastric enterochromaffin-like cells, and histaminergic neurons are the best described cellular sources of histamine, but other cell types, for example platelets, dendritic cells (DCs), and T cells, can also express HDC following stimulation. In addition, certain microbes can express HDC, and these will be discussed further below. HDC expression and histamine release is influenced by cytokines including IL-1, IL-3, IL-12, IL-18, GM-CSF, macrophage colony-stimulating factor, and tumor necrosis factor (TNF)-α (1, 11, 12). Mast cells and basophils store large quantities of histamine, which is released upon degranulation in response to immunological and nonimmunological stimuli. However, other cell types such as DCs and lymphocytes do not store histamine intracellularly, but secrete it following synthesis (13–15).

An important aspect of histamine biology are the enzymes that degrade histamine. Histamine can be metabolized by oxidative deamination (diamine oxidase – DAO) or by ring methylation (histamine-N-methyltransferase – HNMT) (16). Diamine oxidase is stored in plasma membrane-associated vesicular structures in epithelial cells and is secreted into the circulation following stimulation. Histamine-N-methyltransferase is a cytosolic enzyme, which can convert histamine

Abbreviations
CD, Crohn's disease; DAO, diamine oxidase; DC, dendritic cells; GM-CSF, granulocyte–macrophage colony-stimulating factor; GPCR, G-protein-coupled receptors; HDC, histidine decarboxylase; HNMT, histamine-N-methyltransferase; HR, histamine receptor; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IL, interleukin; iNKT, invariant natural killer T cell; OVA, ovalbumin; RAST, radioallergosorbent test; SNPs, single-nucleotide polymorphisms; T_H, T helper cell; TNF, tumor necrosis factor; UC, ulcerative colitis.

only in the intracellular space of cells. Thus, it has been proposed that DAO may be responsible for scavenging extracellular histamine, while HNMT metabolizes intracellular histamine. Histamine-N-methyltransferase has a slightly higher affinity for histamine [Michaelis–Menten constant (kM): 6–13 μM] compared to DAO (kM: 20 μM). In mammals, DAO expression is restricted to specific tissues; the highest activities are in the small bowel, colon, placenta, and kidney (17). Histamine-N-methyltransferase is widely expressed in human tissues; the greatest expression is in kidney and liver, followed by spleen, colon, prostate, ovary, spinal cord cells, bronchi, and trachea. Histamine-N-methyltransferase is regarded as the key enzyme for histamine degradation in the bronchial epithelium (18).

While histamine is well recognized for its effects in the immediate-type hypersensitivity response (i.e., increased vascular permeability, smooth muscle contraction, activation of nociceptive nerves, wheal and flare reaction and itch response), the pathological relevance of increased histamine levels at diseased sites is less well understood in other disorders such as inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) (19, 20). Indeed, histamine may negatively or positively influence parasitic and bacterial infections (21, 22). Within the gastrointestinal tract, histamine levels can be influenced by host allergic and inflammatory responses, altered activity of degradative enzymes, dietary intake, and microbial processes (Fig. 1). In this review, we will discuss the potential pathological and potential

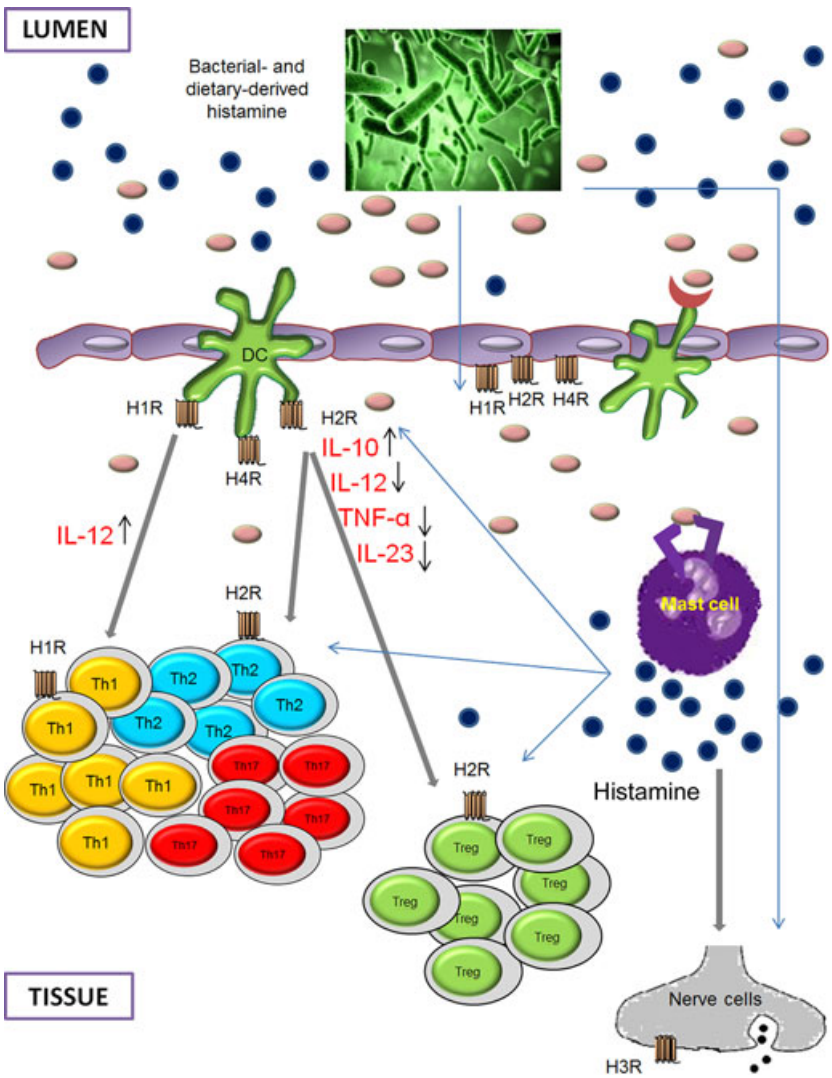

Figure 1 Histamine within the mucosa. The major cellular sources of histamine within the gastrointestinal tract are illustrated. Histamine alters the dendritic cell response to microbes by enhancing IL-12 secretion via H1R, while H2R activation promotes IL-10 secretion and inhibits IL-12, TNF-α, and IL-23 secretion. In addition, the activation of H1R on lymphocytes promotes TH1 polarization, while the activation of H2R suppresses TH1 and TH2 polarization, favoring polarization to TREGs. H4R may aid TH2 polarization, and H4R displays chemotactic properties. Activation of epithelial cells with histamine influences barrier function. Enteric neurons are activated via H3R.

protective roles of histamine in gastrointestinal disorders. In addition, we will highlight some of the limitations regarding the diagnosis of and treatment for these ailments.

Immunomodulatory effects of histamine

The immune response is strictly controlled by effector and regulatory processes, which normally result in protection from infection and tolerance of innocuous environmental antigens. However, in inflammatory diseases, the activated immune response results in a chronic pro-inflammatory state characterized by activated innate pathways with aberrant expansion and polarization of T_H1, T_H2, T_H9, T_H17, T_H22, or T_{REG} lymphocyte populations. Thus, the ongoing identification of appropriate controlling factors that augment protective immune responses while limiting tissue damage is being intensively investigated. Many host-derived and environment metabolites can influence immune reactivity, for example microbiota and dietary factors significantly influence mucosal immune homeostasis (23).

Cells of both the innate and adaptive immune system can be regulated by histamine (24–26). The regulatory nature of histamine in immunology is dependent on its binding to four subtypes of histamine receptors, which are named chronologically in order of their discovery – H1R–H4R. These four receptors belong to the rhodopsin-like family of G-protein-coupled receptors, which are differentially expressed in numerous cell types and contain seven transmembrane domains (27). The different receptor molecular responses to histamine are primarily due to the activation of specific Gα subunits, as each Gα subunit activates distinct molecular signaling cascades. H1R binding leads to the activation of Gαq and H2R is coupled to Gαs, while H3R and H4R are both activators of Gαi/0. Simultaneous activation of more than one receptor on a specific cell can lead to altered effects, for example H1R signaling can antagonize or amplify H2R-mediated responses depending on the time and context of receptor activation (28).

H1R is expressed by a broad range of cell types including neurons, airway and vascular smooth muscle cells, epithelial cells, hepatocytes, chondrocytes, endothelial cells, DCs, monocytes, neutrophils, T cells, and B cells (29, 30). H1R gene expression can be upregulated by IL-3, IL-4, and histamine, while H1R activation is responsible for many of the features associated with the allergic immediate-type hypersensitivity response, such as redness, itching, and swelling. Peripheral H1R-mediated effects include rhinorrhea, bronchoconstriction, anaphylaxis, conjunctivitis, and urticaria, while central-associated H1R effects include the regulation of food and water intake, convulsion, attention, and sleep regulation. H1R antagonists have been shown to have multiple effects on the allergic inflammatory response, and murine H1R-knockout models have revealed significant immunological (impairment of T- and B-cell responses), metabolic, and behavioral abnormalities (31–33).

Similar to H1R, expression of H2R is found in a variety of tissues and cells including brain, gastric parietal cell, smooth muscle cells, T and B cells, DCs, and cardiac tissue. H2R can modulate a range of immune system activities such as mast cell degranulation, antibody synthesis, cytokine production, and T-cell polarization. In particular, DC responses to microbial ligands were significantly altered by histamine in a H2R-dependent manner (34). Other effects, such as the suppression of IL-27 secretion, were mediated via H2R and H4R (35). Murine H2R-knockout mice display defects in gastric and immune regulatory functions as well as selective cognitive defects and abnormalities in nociception (36, 37).

H3R is a presynaptical autoreceptor in the peripheral and central nervous system and has been shown to be involved in the sleep–wake cycle, cognition, homeostatic regulation of energy levels, and inflammation. H3R-knockout mice display a metabolic syndrome characterized by hyperphagia, late-onset obesity, increased insulin and leptin levels (38). In addition, H3R knockouts had an increased severity of neuroinflammatory diseases associated with enhanced expression of MIP-2, IP-10, and CXCR3 by peripheral T cells (39).

The H4R is the most recent receptor to be discovered, and it shares some molecular and pharmacological properties with the H3R. However, in contrast to H3R, H4R is expressed by a wide range of cells including keratinocytes, Langerhans cells, DCs, neutrophils, and lymphocytes (40–42). Invariant NK T (iNKT) cells are numerically and functionally impaired in HDC-knockout mice with diminished secretion of IL-4 and IFN-α following stimulation. H4R signaling was essential for the histamine effect on iNKT cytokine secretion (43). An exciting new development suggests that the combined treatment with H1R and H4R antagonists may have a significant therapeutic effect on chronic dermatitis through the synergistic inhibition of pruritus and skin inflammation (44).

The role of histamine in inflammatory disorders of the gut

Histamine intolerance

Histamine intolerance is thought to result from an incorrect balance between accumulated histamine and the capacity for histamine degradation. The increased availability of histamine may be caused by endogenous histamine overproduction (e.g., allergies or mastocytosis) or increased exogenous ingestion of histidine or histamine (in food, alcohol, or from bacteria), but the main cause is currently thought to be due to impaired enzymatic degradation of histamine, possibly due to genetic or acquired impairment of the enzymatic functions of DAO or HNMT. Diamine oxidase is the primary enzyme required for the degradation of ingested histamine (45). Histamine intolerance is associated with a range of symptoms that mimic an allergic reaction, such as diarrhea, headache, rhinoconjunctival symptoms, asthma, hypotension, arrhythmia, urticaria, pruritus, and flushing (46, 47). Some estimates suggest that approximately 1% of the population is histamine intolerant, and 80% of those patients are middle-aged (45). However, these estimates are controversial and the exact proportion of individuals exhibiting histamine intolerance is still unknown.

Due to the various symptoms observed in multiple organs, the diagnosis of histamine intolerance is difficult. Diagnosis of histamine intolerance requires the presentation of ≥2 typical symptoms of histamine intolerance and improvement following the introduction of a histamine-free diet and the use of antihistamines. Potential food allergies should be excluded by skin prick test or by the determination of specific IgE for food allergens. Occult systemic mastocytosis should be also excluded, for example by measuring serum tryptase levels. The accurate diagnosis of histamine intolerance should be based on the well-documented association between food consumption and symptoms, identification of food causing symptoms, determination of histamine content of the food causing the symptoms, exclusion of other causes (e.g., allergy, toxins, metabolites), oral histamine provocation (if possible), determination of DAO and HNMT contents and activity in intestinal mucosa (not in peripheral blood), and the analysis of DAO and HNMT genetic polymorphisms (48).

For histamine-intolerant patients, alcohol and long-ripened or fermented (and therefore histamine-rich) foods, for example aged cheese, cured meat, yeast products, spinach, tomatoes, and histamine liberators, such as citrus fruit, should be avoided (49). A histamine-free diet can be complemented with adjuvant administration of antihistamine receptor drugs. In addition, histamine degradation can be supported by the administration of vitamin C and B-6, which may increase DAO activity (50, 51). The use of drugs that interfere with histamine metabolism should be avoided. Recently, capsules containing DAO isolated from pig kidneys have been generated to supplement the proposed deficit of endogenous human DAO in patients with histamine intolerance (45).

Scombroid poisoning

Scombroid poisoning (the term 'scombroid' is derived from the type of fish *Scombridae*, which were first implicated), or histamine fish poisoning, is a type of food poisoning with symptoms and treatment similar to those associated with seafood allergies (52). Scombroid poisoning results from the consumption of mishandled fish. Histamine and other decomposition products are generated in fish tissues by bacterial conversion of free histidine (53). Scombrid fish have high levels of free histidine in their muscle tissues, compared to nonscombroid species, which have lower levels. However, nonscombroid fish species have also been implicated in scombroid poisoning. Histamine is produced by a wide range of bacteria, but the major histamine-producing bacteria in fish are Gram-negative mesophilic enteric and marine bacteria (54, 55). Examples include strains of *Morganella morganii*, *Enterobacter aerogenes*, *Raoultella planticola*, *Raoultella ornithinolytica*, and *Photobacterium damselae*, some of which can secrete ≥1000 ppm histamine during optimal *in vitro* culture conditions. Strains of other species, including *Hafnia alvei*, *Citrobacter freundi*, *Vibrio alginolyticus*, and *Escherichia coli*, are weak histamine producers (or nonproducers), yielding concentrations <500 ppm under similar *in vitro* culture conditions (56, 57). The symptoms of scombroid poisoning are variable and can include a peppery or metallic taste, oral numbness, headache, dizziness, palpitations, rapid and weak pulse, low blood pressure, difficulty in swallowing, thirst, hives, rash, flushing, and facial swelling. Sometimes nausea, vomiting, and diarrhea are also observed. The symptoms of scombroid poisoning typically are rapid in onset following the consumption of fish and recovery is usually complete within 24 h, but in rare cases can last for days. Treatment for scombroid poisoning includes the administration of antihistamines, while corticosteroids are ineffective (52). The proper handling and storage of fish is the most effective preventive measure as cooking contaminated fish does not prevent histamine poisoning because the toxins are heat stable.

In addition to the presence of histamine, other mechanisms have also been proposed that contribute to scombroid poisoning. Firstly, histamine toxicity could be potentiated by toxins, which inhibit histamine-metabolizing enzymes. Histamine toxicity is potentiated by the action of DAO and HNMT inhibitors that are also present together with dietary histamine in the ingested fish. Inhibition of HNMT and DAO, which usually degrade histamine, leads to increased histamine levels within the gut, and subsequently, increased amounts of histamine are available for absorption to extraintestinal tissues (58). Secondly, the induction of mast cell degranulation will release endogenous histamine. The second hypothesis is based on 'scombrotoxins' that are mast cell degranulators associated with the spoiled fish. This hypothesis is significantly different from the first in that dietary histamine in the implicated fish is not solely required. Rather, the observed toxicity may be due to the endogenous release of histamine (59). Finally, currently unknown histamine receptor agonists may be present within the decomposed fish. For example, gizzerosine is a small peptide found in poor-quality feed produced by overheating decomposed fish material (60). It is a potent H2R agonist, approximately 200 times more potent than histamine itself, and gizzerosine kills poultry by causing excessive excretion of digestive acids (60). Although certainly not implicated in scombroid poisoning, gizzerosine provides an excellent example of a previously unknown and histidine-derived agonist active at a histamine receptor. Based on this precedent, there may be other histidine-derived compounds in scombroid poisoning-implicated fish that could bind to histaminergic receptors, and thus, it is not possible to rule out the existence of other agonists without comparing the total histamine receptor bioactivity with the predicted activity based on known histamine concentrations in outbreak-implicated sample extracts. If there were other histaminergic receptor agonists for the various histaminergic receptors with activity comparable to that shown by gizzerosine for H2 receptors, low levels of bioactive compounds could be enough to cause illness.

Food allergy

The gut immune system is exposed daily to a large number and variety of foreign proteins, and the ability to avoid allergic reactions to food is significantly influenced by the way these potential allergens are transported, presented, and responded to (61). The influence of histamine on altering the

gut immune response to food antigens has not been definitively examined; however given the immunoregulatory functions of histamine described above, it is tempting to speculate that histamine and its receptors could be involved either directly or indirectly in food antigen tolerance and sensitization mechanisms. In addition to eliciting the major symptoms of IgE-mediated food allergy, the ingestion of histamine-rich food, alcohol, or drugs that release histamine or block DAO may induce diarrhea, hypotension, arrhythmia, bronchial constriction, rhinoconjunctivitis, urticaria, or headache, which can confuse the diagnosis of food allergy.

In food-allergic subjects, enhanced secretion of histamine and increased numbers of mast cells in the intestines have been demonstrated (62–64). From the duodenal mast cells of food-allergic patients, the anti-IgE-mediated mast cell histamine release was increased compared with nonallergics. Histamine release from basophils was positively correlated with the test scores of the RAST analysis, skin prick test, and food challenge (65). This result was confirmed in other studies, whereby incubation of biopsies from food-allergic patients with anti-human IgE antibodies or allergens induced a ninefold increase in histamine release. Stimulation of biopsies *ex vivo* with histamine itself induced a concentration-dependent NO response only in food-allergic subjects (66). It has been postulated that this method can also be utilized diagnostically to quantify allergen-induced histamine secretion in live human colorectal biopsy tissue and has been suggested to correlate with alterations in transepithelial resistance (67).

It is important to note that not only mast cells or basophiles are cellular sources of histamine. Other host cells and an altered microbiome may also contribute to increased histamine levels and the associated response to food allergens. However, this has not been studied in detail for food-allergic patients.

The relative contribution of the different histamine receptors to the induction of food allergy has also not been adequately studied. In mice, intraperitoneal administration of cimetidine (H2R antagonist) together with ovalbumin (OVA) resulted in enhanced T_H2 cytokine secretion by spleen cells stimulated with OVA *in vitro* and increased IgE levels in the sera (68). In humans, treatment with H2R antagonists results in enhanced IgE production against food antigens (69, 70). These results indicate that H2R antagonists may contribute to the development of IgE-mediated food allergies; however, the use of other non-H2R targeting antacids is also a risk factor for the development of food allergies.

Current therapy for food allergy is not curative. The effectiveness of antihistamines and mast cell stabilizers in ameliorating food allergy symptoms is very limited. Single-nucleotide polymorphisms in the DAO gene have been detected in patients with food allergy symptoms; however, the IgE status of these patients was not described and this group could potentially include histamine-intolerant, rather than food-allergic, individuals (71). Current DAO preparations did not reduce mast cell degranulation in response to allergens; however, porcine kidney DAO shows antihistaminic activity *in vivo* and protects against pig anaphylactic shock in an experimental model, which is directly related to the inactivation of histamine (72). A new concept for the treatment of food allergy is based on the oral administration of DAO associated with catalase. An oral bi-enzymatic therapy with DAO and catalase was suggested to reduce the levels of intestinal histamine via degradation by DAO, with the production of H_2O_2, NH_3, and imidazole acetaldehyde. As H_2O_2, a by-product of degradation, is toxic due to its pro-oxidant effects on intestinal cells, catalase has been included to decompose H_2O_2.

Irritable bowel syndrome

Irritable bowel syndrome is a chronic condition that affects 10–20% of the population. Patients experience recurrent abdominal discomfort or pain, in combination with altered bowel habits. The etiology and the pathophysiology are only partly understood, with some evidence suggesting that disrupted mucosal immune responses play a role (73, 74). In addition, the composition of the gastrointestinal microbiota is altered and the administration of specific microbes has therapeutic effects (75–77). Frequently patients with IBS experience postprandial worsening of their symptoms, and patients typically avoid certain foods to reduce symptoms. Thus, the majority of patients with IBS feel that specific foods are important triggers of their symptoms. In a recent study, 58% of the patients with IBS studied experienced gastrointestinal symptoms from histamine-releasing food items and foods rich in biogenic amines (78). Interesting, the use of spherical carbon absorbent (which adsorbs molecules such as histamine from the gut lumen) has been beneficial for some patients (79).

Endogenous histamine has been implicated as an important mediator associated with symptom severity in IBS. Activated mast cells, which were spontaneously secreting higher amounts of histamine, in proximity to colonic nerves were correlated with abdominal pain in patients with IBS (80). Mucosal biopsy supernatants from patients with IBS contained higher levels of histamine compared to biopsy supernatants from healthy volunteers, while the mast cell stabilizer and H1R antagonist ketotifen reduces some IBS symptoms (20, 81).

Inflammatory bowel diseases

Crohn's disease (CD) and ulcerative colitis (UC) are the two major forms of IBD, and both diseases are associated with high morbidity and healthcare costs. The two disorders have distinct features (82). Ulcerative colitis is characterized by inflammation with superficial ulcerations limited to the mucosa of the colon. Inflammation usually starts in the rectum and continuously spreads throughout the colon. Crohn's disease, however, is characterized by a discontinuous pattern, potentially affecting the entire gastrointestinal tract. In contrast to ulcerative colitis, inflammation in patients with CD is transmural with large ulcerations, and occasionally, granulomas are observed. The precise mechanisms causing these diseases remain unknown but complex interactions between the immune system, enteric microbiota, and host genotype underlie the development of IBD. Some studies have demonstrated

that components of the intestinal microbiota can drive protective or pathological responses in IBD models, highlighting the importance of host–microbe communication in the development of these diseases.

The importance of mast cells has been well documented in patients with IBD. In 1980, Dvorak and colleagues reported that the number of mast cells was markedly increased in the involved area of the ileum of patients with CD (83). In 1990, Nolte et al. found that the mast cell count in patients with ulcerative colitis was increased compared with that in control subjects and patients with CD. In addition, more mast cells were present in inflamed tissue compared to adjacent noninflamed tissue (84). Additional studies confirmed the finding that mast cell number was significantly increased in inflamed tissue from patients with ulcerative colitis, particularly at the line of demarcation between inflamed and normal mucosa. The accumulation of mast cells at the visible line of demarcation between normal and abnormal mucosa suggested that mast cells played a crucial role in the pathogenesis of the disease, either causing further damage or limiting the expansion of damage (85). Nishida and colleagues found that there were greater numbers of mast cells than macrophages in the lamina propria of patients with IBD, although this was not found in patients with collagenous colitis (86). Interestingly, increased numbers of mast cells were observed throughout the lamina propria, particularly in the upper part of lamina propria, whereas increased numbers of macrophages were only seen in the lower part of lamina propria in patients with IBD. This suggests that the release of pro-inflammatory mediators from accumulated mast cells could have led to the recruitment of macrophages to the lamina propria. Dramatically increased numbers of mast cells were also observed in the hypertrophied and fibrotic muscularis propria of strictures in CD compared with normal bowel (87).

The rate of histamine secretion from the jejunum was increased in patients with CD compared with normal controls, and the secretion of histamine was related to disease activity, indicating that degranulation of mast cells may be important in active CD (88). Highly increased mucosal histamine levels were also observed in allergic enteropathy and ulcerative colitis (63). Increased levels of N-methylhistamine, a stable histamine metabolite, were detected in the urine of patients with active CD or ulcerative colitis (89). Because an increased level of N-methylhistamine was significantly correlated with clinical disease activity, the above findings further suggest that histamine plays an important role in the pathogenesis of these diseases. Mast cells isolated from the resected colon of active CD or ulcerative colitis patients were able to release more histamine than those from normal colon when being stimulated with epithelial proteins (90). Similarly, cultured colorectal biopsies from patients with IBD secreted more histamine toward substance P alone or substance P with anti-IgE compared to the samples from control subjects cultured under the same conditions (91). Histamine-N-methyltransferase gene expression is reduced in inflamed mucosa and DAO polymorphisms have been identified for patients with IBD, suggesting that there could be dysregulated metabolism of histamine within the inflamed gut (71, 92).

While it is clear that histamine is present at higher levels within the mucosa of patients with IBD, the potential protective or pathological role for histamine signaling through its different receptors has not been determined in patients with IBD. Recently, the use of H2R antagonists, but not proton pump inhibitors, significantly increased the risk of hospitalization or surgery in patients with CD (93). Although these results should be interpreted with caution, one could hypothesize that histamine signaling through the H2R may have some protective effects within the mucosa of patients with IBD. In contrast, inhibition of the H1R may have some protective effects in a subset of patients with IBD, but these studies need to be repeated in larger cohorts (94, 95).

The role for microbial-derived histamine

There are many new examples, appearing regularly in the literature, which describe novel microbe–host interactions that impact the immunological health of the host. Specific microbes within the microbiota have been described to release the biogenic amine histamine. In bacteria, the expression and activity of amino acid decarboxylases is enhanced in acidic environments, such as in the stomach. This leads to a local increase in pH around the bacteria and protects it from the acidic, chloride-rich environment. Furthermore, expression and activity of decarboxylases in bacteria is regulated by the presence of fermentable carbohydrates and oxygen, the redox potential of the medium, the temperature, and the sodium chloride concentration. The biological consequences of biogenic amine secretion *in vivo* by the resident microbiota are largely unknown. Histamine can have both pro-inflammatory and anti-inflammatory effects on immunoregulatory processes, depending on which histamine receptor is activated. With the exception of scombroid poisoning, it is currently unknown whether histamine secretion by the microbiota is altered during, or contributes to, mucosal inflammatory disorders. Maintenance of mucosal homeostasis is heavily dependent on appropriate sampling and processing of microbial ligands by the innate immune system, in particular DCs. We have demonstrated that histamine significantly alters the DC response to microbial ligands via the H2R and administration of a histamine-secreting *Lactobacillus rhamnosus* strain to H2R-knockout mice results in a loss of the microbe's immunoregulatory activities (32). Other *in vitro* studies have also confirmed this finding, for example histamine secretion by a *Lactobacillus reuteri* strain modulates TLR-2-induced TNF-α secretion *in vitro* (96). These observations suggest that histamine from the enteric microbes might exert immunoregulatory effects *in vivo*; however, it remains to be determined whether these effects are protective or pathological.

Future perspectives and conclusions

It is clear that histamine is present within the gastrointestinal mucosa and increased levels are associated with a range of mucosal inflammatory disorders. Due to the obvious overlap in symptoms, great care needs to be exercised in the differential diagnosis of these disorders. Treatment strategies that promote H2R expression and activity, with decreased H1R or

H4R activity, may improve mucosal immunoregulatory activity and protect against allergic sensitization and inflammatory disorders. The contribution of the microbiota to the histamine content of the gut and histamine receptor activation is currently unknown. Even though histamine was first discovered more than 100 years ago, there remain substantial gaps in our knowledge concerning the immunoregulatory activity of histamine, particularly within the gastrointestinal tract.

Funding

The authors are supported by Swiss National Foundation grants (project numbers: 310030-127356 and 310030-144219), Allergiestiftung Ulrich Müller-Gierok, European Union research grants, EU Marie Curie grants, and Polish National Science Centre grants No. 2011/01/B/NZ6/01872, 2012/04/M/NZ6/00355 and 2012/04/A/NZ6/00407.

Conflicts of interest

Liam O'Mahony is a consultant to Alimentary Health Ltd and has received research funding from GSK. Marek Jutel is a consultant to Allergopharma, GER, Anergis, CH, Biomay, and received lecture fees from GSK, Allergopharma, Stallergens, ALK. Sylwia Smolinska and Reto Crameri have no conflict of interests to declare.

References

1. Jutel M, Akdis M, Akdis CA. Histamine, histamine receptors and their role in immune pathology. *Clin Exp Allergy* 2009;**39**:1786–1800.
2. Westly E. Nothing to sneeze at. *Nat Med* 2010;**16**:1063–1065.
3. Barger G, Dale HH. Chemical structure and sympathomimetic action of amines. *J Physiol* 1910;**41**:19–59.
4. Dale HH, Laidlaw PP. The physiological action of beta-iminazolylethylamine. *J Physiol* 1910;**41**:318–344.
5. Ohtsu H. Pathophysiologic role of histamine: evidence clarified by histidine decarboxylase gene knockout mice. *Int Arch Allergy Immunol* 2012;**158**(Suppl 1):2–6.
6. Akdis CA, Blaser K. Histamine in the immune regulation of allergic inflammation. *J Allergy Clin Immunol* 2003;**112**:15–22.
7. Jutel M, Watanabe T, Akdis M, Blaser K, Akdis CA. Immune regulation by histamine. *Curr Opin Immunol* 2002;**14**:735–740.
8. Dy M, Schneider E. Histamine-cytokine connection in immunity and hematopoiesis. *Cytokine Growth Factor Rev* 2004;**15**:393–410.
9. Schneider E, Rolli-Derkinderen M, Arock M, Dy M. Trends in histamine research: new functions during immune responses and hematopoiesis. *Trends Immunol* 2002;**23**:255–263.
10. MacGlashan D Jr. Histamine: a mediator of inflammation. *J Allergy Clin Immunol* 2003;**112**(4 Suppl):S53–S59.
11. Yoshimoto T, Tsutsui H, Tominaga K, Hoshino K, Okamura H, Akira S et al. IL-18, although antiallergic when administered with IL-12, stimulates IL-4 and histamine release by basophils. *Proc Natl Acad Sci U S A* 1999;**96**:13962–13966.
12. Miadonna A, Salmaso C, Marco MP, Pugni L, Milazzo N, Tedeschi A et al. Priming and inducing effects of interleukin-3 on histamine release from cord-blood basophils. *Allergy* 1997;**52**:992–998.
13. Saxena SP, McNicol A, Brandes LJ, Becker AB, Gerrard JM. Histamine formed in stimulated human platelets is cytoplasmic. *Biochem Biophys Res Commun* 1989;**164**:164–168.
14. Kubo Y, Nakano K. Regulation of histamine synthesis in mouse CD4+ and CD8+ T lymphocytes. *Inflamm Res* 1999;**48**:149–153.
15. Radvany Z, Darvas Z, Kerekes K, Prechl J, Szalai C, Pallinger E et al. H1 histamine receptor antagonist inhibits constitutive growth of Jurkat T cells and antigen-specific proliferation of ovalbumin-specific murine T cells. *Semin Cancer Biol* 2000;**10**:41–45.
16. Klocker J, Matzler SA, Huetz GN, Drasche A, Kolbitsch C, Schwelberger HG. Expression of histamine degrading enzymes in porcine tissues. *Inflamm Res* 2005;**54**(Suppl 1):S54–S57.
17. Schwelberger HG, Hittmair A, Kohlwein SD. Analysis of tissue and subcellular localization of mammalian diamine oxidase by confocal laser scanning fluorescence microscopy. *Inflamm Res* 1998;**47**(Suppl 1):S60–S61.
18. Yamauchi K, Sekizawa K, Suzuki H, Nakazawa H, Ohkawara Y, Katayose D et al. Structure and function of human histamine N-methyltransferase: critical enzyme in histamine metabolism in airway. *Am J Physiol* 1994;**267**(3 Pt 1):L342–L349.
19. He SH. Key role of mast cells and their major secretory products in inflammatory bowel disease. *World J Gastroenterol* 2004;**10**:309–318.
20. Buhner S, Li Q, Vignali S, Barbara G, De Giorgio R, Stanghellini V et al. Activation of human enteric neurons by supernatants of colonic biopsy specimens from patients with irritable bowel syndrome. *Gastroenterology* 2009;**137**:1425–1434.
21. Beghdadi W, Porcherie A, Schneider BS, Dubayle D, Peronet R, Huerre M et al. Inhibition of histamine-mediated signaling confers significant protection against severe malaria in mouse models of disease. *J Exp Med* 2008;**205**:395–408.
22. Metz M, Doyle E, Bindslev-Jensen C, Watanabe T, Zuberbier T, Maurer M. Effects of antihistamines on innate immune responses to severe bacterial infection in mice. *Int Arch Allergy Immunol* 2011;**155**:355–360.
23. Frei R, Lauener RP, Crameri R, O'Mahony L. Microbiota and dietary interactions: an update to the hygiene hypothesis? *Allergy* 2012;**67**:451–461.
24. O'Mahony L, Akdis M, Akdis CA. Regulation of the immune response and inflammation by histamine and histamine receptors. *J Allergy Clin Immunol* 2011;**128**:1153–1162.
25. Ferstl R, Akdis CA, O'Mahony L. Histamine regulation of innate and adaptive immunity. *Front Biosci* 2012;**17**:40–53.
26. Bachert C. The role of histamine in allergic disease: re-appraisal of its inflammatory potential. *Allergy* 2002;**57**:287–296.
27. Akdis CA, Simons FE. Histamine receptors are hot in immunopharmacology. *Eur J Pharmacol* 2006;**533**:69–76.
28. Garbarg MSJ. Synergism between histamine H1- and H2-receptors in the cAMP response in guinea pig brain slices: effects of phorbol esters and calcium. *Mol Pharmacol* 1988;**33**:38–43.
29. Gschwandtner M, Mildner M, Mlitz V, Gruber F, Eckhart L, Werfel T et al. Histamine suppresses epidermal keratinocyte differentiation and impairs skin barrier function in a human skin model. *Allergy* 2013;**68**:37–47.
30. Togias A. H1-receptors: localization and role in airway physiology and in immune functions. *J Allergy Clin Immunol* 2003;**112**(Suppl 4):S60–S68.
31. Baroody FM, Naclerio RM. Antiallergic effects of H1-receptor antagonists. *Allergy* 2000;**55**(Suppl 64):17–27.
32. Masaki T, Yoshimatsu H. The hypothalamic H1 receptor: a novel therapeutic target for

disrupting diurnal feeding rhythm and obesity. *Trends Pharmacol Sci* 2006;**27**:279–284.
33. Jutel M, Watanabe T, Klunker S, Akdis M, Thomet OA, Malolepszy J et al. Histamine regulates T-cell and antibody responses by differential expression of H1 and H2 receptors. *Nature* 2001;**413**:420–425.
34. Frei R, Ferstl R, Konieczna P, Ziegler M, Simon T, Rugeles TM et al. Histamine receptor 2 modifies dendritic cell responses to microbial ligands. *J Allergy Clin Immunol* 2013;**132**:194–204.
35. Gschwandtner M, Bunk H, Kother B, Thurmond RL, Kietzmann M, Werfel T et al. Histamine down-regulates IL-27 production in antigen-presenting cells. *J Leukoc Biol* 2012;**92**:21–29.
36. Teuscher C, Poynter ME, Offner H, Zamora A, Watanabe T, Fillmore PD et al. Attenuation of Th1 effector cell responses and susceptibility to experimental allergic encephalomyelitis in histamine H2 receptor knockout mice is due to dysregulation of cytokine production by antigen-presenting cells. *Am J Pathol* 2004;**164**:883–892.
37. Dai H, Kaneko K, Kato H, Fujii S, Jing Y, Xu A et al. Selective cognitive dysfunction in mice lacking histamine H1 and H2 receptors. *Neurosci Res* 2007;**57**:306–313.
38. Yoshimoto R, Miyamoto Y, Shimamura K, Ishihara A, Takahashi K, Kotani H et al. Therapeutic potential of histamine H3 receptor agonist for the treatment of obesity and diabetes mellitus. *Proc Natl Acad Sci U S A* 2006;**103**:13866–13871.
39. Teuscher C, Subramanian M, Noubade R, Gao JF, Offner H, Zachary JF et al. Central histamine H3 receptor signaling negatively regulates susceptibility to autoimmune inflammatory disease of the CNS. *Proc Natl Acad Sci U S A* 2007;**104**:10146–10151.
40. Glatzer F, Gschwandtner M, Ehling S, Rossbach K, Janik K, Klos A et al. Histamine induces proliferation in keratinocytes from patients with atopic dermatitis through the histamine 4 receptor. *J Allergy Clin Immunol* 2013; doi: 10.1016/j.jaci.2013.06.023. [Epub ahead of print]
41. Gschwandtner M, Rossbach K, Dijkstra D, Baumer W, Kietzmann M, Stark H et al. Murine and human Langerhans cells express a functional histamine H4 receptor: modulation of cell migration and function. *Allergy* 2010;**65**:840–849.
42. Baumer W, Wendorff S, Gutzmer R, Werfel T, Dijkstra D, Chazot P et al. Histamine H4 receptors modulate dendritic cell migration through skin–immunomodulatory role of histamine. *Allergy* 2008;**63**:1387–1394.
43. Leite-de-Moraes MC, Diem S, Michel ML, Ohtsu H, Thurmond RL, Schneider E et al. Cutting edge: histamine receptor H4 activation positively regulates in vivo IL-4 and IFN-gamma production by invariant NKT cells. *J Immunol* 2009;**182**:1233–1236.
44. Ohsawa Y, Hirasawa N. The antagonism of histamine H1 and H4 receptors ameliorates chronic allergic dermatitis via anti-pruritic and anti-inflammatory effects in NC/Nga mice. *Allergy* 2012;**67**:1014–1022.
45. Maintz L, Novak N. Histamine and histamine intolerance. *Am J Clin Nutr* 2007;**85**:1185–1196.
46. Lessof MH, Gant V, Hinuma K, Murphy GM, Dowling RH. Recurrent urticaria and reduced diamine oxidase activity. *Clin Exp Allergy* 1990;**20**:373–376.
47. Wantke F, Hemmer W, Haglmuller T, Gotz M, Jarisch R. Histamine in wine. Bronchoconstriction after a double-blind placebo-controlled red wine provocation test. *Int Arch Allergy Immunol* 1996;**110**:397–400.
48. Schwelberger HG. Histamine intolerance: a metabolic disease? *Inflamm Res* 2010;**59**:S219–S221.
49. Wantke F, Gotz M, Jarisch R. Histamine-free diet: treatment of choice for histamine-induced food intolerance and supporting treatment for chronic headaches. *Clin Exp Allergy* 1993;**23**:982–985.
50. Johnston CS. The antihistamine action of ascorbic acid. *Subcell Biochem* 1996;**25**:189–213.
51. Martner-Hewes PM, Hunt IF, Murphy NJ, Swendseid ME, Settlage RH. Vitamin B-6 nutriture and plasma diamine oxidase activity in pregnant Hispanic teenagers. *Am J Clin Nutr* 1986;**44**:907–913.
52. Hungerford JM. Scombroid poisoning: a review. *Toxicon* 2010;**56**:231–243.
53. Rawles DD, Flick GJ, Martin RE. Biogenic amines in fish and shellfish. *Adv Food Nutr Res* 1996;**39**:329–365.
54. Kim SH, Barros-Velazquez J, Ben-Gigrey B, Eun JB, Jun SH, Wie CI et al. Identification of the main bacteria contributing to histamine formation in seafood to ensure product safety. *Food Sci Biotechnol* 2003;**12**:451–460.
55. Bjornsdottir-Butler K, Bolton GE, Jaykus LA, McClellan-Green PD, Green DP. Development of molecular-based methods for determination of high histamine producing bacteria in fish. *Intl J Food Microbiol* 2010;**139**:161–167.
56. Kim SH, Field KG, Chang DS, Wei CI, An HJ. Identification of bacteria crucial to histamine accumulation in Pacific mackerel during storage. *J Food Protect* 2001;**64**:1556–1564.
57. Takahashi H, Kimura B, Yoshikawa M, Fujii T. Cloning and sequencing of the histidine decarboxylase genes of gram-negative, histamine-producing bacteria and their application in detection and identification of these organisms in fish. *Appl Environ Microbiol* 2003;**69**:2568–2579.
58. Hui JY, Taylor SL. Inhibition of in vivo histamine-metabolism in rats by foodborne and pharmacologic inhibitors of diamine oxidase, histamine N-methyltransferase, and monoamine-oxidase. *Toxicol Appl Pharm* 1985;**81**:241–249.
59. Ijomah P, Clifford MN, Walker R, Wright J, Hardy R, Murray CK. The importance of endogenous histamine relative to dietary histamine in the etiology of scombrotoxicosis. *Food Addit Contam* 1991;**8**:531–542.
60. Okazaki T, Noguchi T, Igarashi K, Sakagami Y, Seto H, Mori K et al. Gizzerosine, a new toxic-substance in fish-meal, causes severe gizzard erosion in chicks. *J Agric Food Chem* 1983;**47**:2949–2952.
61. Cochrane S, Beyer K, Clausen M, Wjst M, Hiller R, Nicoletti C et al. Factors influencing the incidence and prevalence of food allergy. *Allergy* 2009;**64**:1246–1255.
62. Raithel M, Weidenhiller M, Abel R, Baenkler HW, Hahn EG. Colorectal mucosal histamine release by mucosa oxygenation in comparison with other established clinical tests in patients with gastrointestinally mediated allergy. *World J Gastroenterol* 2006;**12**:4699–4705.
63. Raithel M, Matek M, Baenkler HW, Jorde W, Hahn EG. Mucosal histamine content and histamine secretion in Crohn's disease, ulcerative colitis and allergic enteropathy. *Int Arch Allergy Immunol* 1995;**108**:127–133.
64. Bijlsma PB, Backhaus B, Weidenhiller M, Donhauser N, Hahn EG, Raithel M. Food allergy diagnosis by detection of antigen-induced electrophysiological changes and histamine release in human intestinal biopsies during mucosa-oxygenation. *Inflamm Res* 2004;**53**(Suppl 1):S29–S30.
65. Nolte H, Schiotz PO, Kruse A, Skov PS. Comparison of intestinal mast-cell and basophil histamine-release in children with food allergic reactions. *Allergy* 1989;**44**:554–565.
66. Raithel M, Hagel AF, Zopf Y, Bijlsma PB, De Rossi TM, Gabriel S et al. Analysis of immediate ex vivo release of nitric oxide from human colonic mucosa in gastrointestinally mediated allergy, inflammatory bowel disease and controls. *J Physiol Pharmacol* 2012;**63**:317–325.
67. Bijlsma PB, Backhaus B, Weidenhiller M, Donhauser N, Hahn EG, Raithel M. Food allergy diagnosis by detection of antigen-induced electrophysiological changes and histamine release in human intestinal biopsies during mucosa-oxygenation. *Inflamm Res* 2004;**53**:S29–S30.
68. Arae K, Oboki K, Ohno T, Hirata M, Nakae S, Taguchi H et al. Cimetidine enhances antigen-specific IgE and Th2 cytokine production. *Allergol Int* 2011;**60**:339–344.
69. Untersmayr E, Bakos N, Scholl I, Kundi M, Roth-Walter F, Szalai K et al. Anti-ulcer

drugs promote IgE formation toward dietary antigens in adult patients. *FASEB J* 2005;**19**:656–658.
70. Scholl I, Untersmayr E, Bakos N, Roth-Walter F, Gleiss A, Boltz-Nitulescu G et al. Antiulcer drugs promote oral sensitization and hypersensitivity to hazelnut allergens in BALB/c mice and humans. *Am J Clin Nutr* 2005;**81**:154–160.
71. Petersen J, Raithel M, Schwelberger HG. Characterisation of functional polymorphisms of the human diamine oxidase gene. *Inflamm Res* 2005;**54**(Suppl 1):S58–S59.
72. Masini E, Vannacci A, Marzocca C, Mannaioni PF, Befani O, Federico R et al. A plant histaminase modulates cardiac anaphylactic response in guinea pig. *Biochem Biophys Res Commun* 2002;**296**:840–846.
73. Macsharry J, O'Mahony L, Fanning A, Bairead E, Sherlock G, Tiesman J et al. Mucosal cytokine imbalance in irritable bowel syndrome. *Scand J Gastroenterol* 2008;**43**:1467–1476.
74. Dinan TG, Quigley EM, Ahmed SM, Scully P, O'Brien S, O'Mahony L et al. Hypothalamic-pituitary-gut axis dysregulation in irritable bowel syndrome: plasma cytokines as a potential biomarker? *Gastroenterology* 2006;**130**:304–311.
75. Codling C, O'Mahony L, Shanahan F, Quigley EM, Marchesi JR. A molecular analysis of fecal and mucosal bacterial communities in irritable bowel syndrome. *Dig Dis Sci* 2010;**55**:392–397.
76. O'Mahony L, McCarthy J, Kelly P, Hurley G, Luo F, Chen K et al. *Lactobacillus* and *bifidobacterium* in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology* 2005;**128**:541–551.
77. Whorwell PJ, Altringer L, Morel J, Bond Y, Charbonneau D, O'Mahony L et al. Efficacy of an encapsulated probiotic *Bifidobacterium infantis* 35624 in women with irritable bowel syndrome. *Am J Gastroenterol* 2006;**101**:1581–1590.
78. Bohn L, Storsrud S, Tornblom H, Bengtsson U, Simren M. Self-reported food-related gastrointestinal symptoms in IBS are common and associated with more severe symptoms and reduced quality of life. *Am J Gastroenterol* 2013;**108**:634–641.
79. Tack JF, Miner PB Jr, Fischer L, Harris MS. Randomised clinical trial: the safety and efficacy of AST-120 in non-constipating irritable bowel syndrome – a double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2011;**34**:868–877.
80. Barbara G, Stanghellini V, De Giorgio R, Cremon C, Cottrell GS, Santini D et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. *Gastroenterology* 2004;**126**:693–702.
81. Klooker TK, Braak B, Koopman KE, Welting O, Wouters MM, van der Heide S et al. The mast cell stabiliser ketotifen decreases visceral hypersensitivity and improves intestinal symptoms in patients with irritable bowel syndrome. *Gut* 2010;**59**:1213–1221.
82. Sheil B, Shanahan F, O'Mahony L. Probiotic effects on inflammatory bowel disease. *J Nutr* 2007;**137**(3 Suppl 2):819S–824S.
83. Dvorak AM, Monahan RA, Osage JE, Dickersin GR. Crohn's disease: transmission electron microscopic studies. II. Immunologic inflammatory response. Alterations of mast cells, basophils, eosinophils, and the microvasculature. *Hum Pathol* 1980;**11**:606–619.
84. Nolte H, Spjeldnaes N, Kruse A, Windelborg B. Histamine release from gut mast cells from patients with inflammatory bowel diseases. *Gut* 1990;**31**:791–794.
85. King T, Biddle W, Bhatia P, Moore J, Miner PB Jr. Colonic mucosal mast cell distribution at line of demarcation of active ulcerative colitis. *Dig Dis Sci* 1992;**37**:490–495.
86. Nishida Y, Murase K, Isomoto H, Furusu H, Mizuta Y, Riddell RH et al. Different distribution of mast cells and macrophages in colonic mucosa of patients with collagenous colitis and inflammatory bowel disease. *Hepatogastroenterology* 2002;**49**:678–682.
87. Gelbmann CM, Mestermann S, Gross V, Kollinger M, Scholmerich J, Falk W. Strictures in Crohn's disease are characterised by an accumulation of mast cells colocalised with laminin but not with fibronectin or vitronectin. *Gut* 1999;**45**:210–217.
88. Knutson L, Ahrenstedt O, Odlind B, Hallgren R. The jejunal secretion of histamine is increased in active Crohn's disease. *Gastroenterology* 1990;**98**:849–854.
89. Winterkamp S, Weidenhiller M, Otte P, Stolper J, Schwab D, Hahn EG et al. Urinary excretion of N-methylhistamine as a marker of disease activity in inflammatory bowel disease. *Am J Gastroenterol* 2002;**97**:3071–3077.
90. Fox CC, Lichtenstein LM, Roche JK. Intestinal mast cell responses in idiopathic inflammatory bowel disease. Histamine release from human intestinal mast cells in response to gut epithelial proteins. *Dig Dis Sci* 1993;**38**:1105–1112.
91. Raithel M, Schneider HT, Hahn EG. Effect of substance P on histamine secretion from gut mucosa in inflammatory bowel disease. *Scand J Gastroenterol* 1999;**34**:496–503.
92. Schulze HA, Hasler R, Mah N, Lu T, Nikolaus S, Costello CM et al. From model cell line to in vivo gene expression: disease-related intestinal gene expression in IBD. *Genes Immun* 2008;**9**:240–248.
93. Juillerat P, Schneeweiss S, Cook EF, Ananthakrishnan AN, Mogun H, Korzenik JR. Drugs that inhibit gastric acid secretion may alter the course of inflammatory bowel disease. *Aliment Pharmacol Ther* 2012;**36**:239–247.
94. Raithel M, Nagel A, Zopf Y, deRossi T, Stengel C, Hagel A et al. Plasma histamine levels (H) during adjunctive H1-receptor antagonist treatment with loratadine in patients with active inflammatory bowel disease (IBD). *Inflamm Res* 2010;**59**(Suppl 2):S257–S258.
95. Jones NL, Roifman CM, Griffiths AM, Sherman P. Ketotifen therapy for acute ulcerative colitis in children: a pilot study. *Dig Dis Sci* 1998;**43**:609–615.
96. Thomas CM, Hong T, van Pijkeren JP, Hemarajata P, Trinh DV, Hu W et al. Histamine derived from probiotic *Lactobacillus reuteri* suppresses TNF via modulation of PKA and ERK signaling. *PLoS One* 2012;**7**:e31951.