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• REVIEW •

# Key role of mast cells and their major secretory products in inflammatory bowel disease

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## Abstract

Historically, mast cells were known as a key cell type involved in type I hypersensitivity. Until last two decades, this cell type was recognized to be widely involved in a number of non-allergic diseases including inflammatory bowel disease (IBD). Markedly increased numbers of mast cells were observed in the mucosa of the ileum and colon of patients with IBD, which was accompanied by great changes of the content in mast cells such as dramatically increased expression of TNFα, IL-16 and substance P. The evidence of mast cell degranulation was found in the wall of intestine from patients with IBD with immunohistochemistry technique. The highly elevated histamine and tryptase levels were detected in mucosa of patients with IBD, strongly suggesting that mast cell degranulation is involved in the pathogenesis of IBD. However, little is known of the actions of histamine, tryptase, chymase and carboxypeptidase in IBD. Over the last decade, heparin has been used to treat IBD in clinical practice. The low molecular weight heparin (LMWH) was effective as adjuvant therapy, and the patients showed good clinical and laboratory response with no serious adverse effects. The roles of PGD2, LTC4, PAF and mast cell cytokines in IBD were also discussed. Recently, a series of experiments with dispersed colon mast cells suggested there should be at least two pathways in man for mast cells to amplify their own activation-degranulation signals in an autocrine or paracrine manner. The hypothesis is that mast cell secretogogues induce mast cell degranulation, release histamine, then stimulate the adjacent mast cells or positively feedback to further stimulate its host mast cells through $H_1$ receptor. Whereas released tryptase acts similarly to histamine, but activates mast cells through its receptor PAR-2. The connections between current anti-IBD therapies or potential therapies for IBD with mast cells were discussed, implicating further that mast cell is a key cell type that is involved in the pathogenesis of IBD. In conclusion, while pathogenesis of IBD remains unclear, the key role of mast cells in this group of diseases demonstrated in the current review implicates strongly that IBD is a mast cell associated disease. Therefore, close attentions should be paid to the role of mast cells in IBD.

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## INTRODUCTION

Historically, mast cells were known as a key cell type involved in type I hypersensitivity[1]. Until last two decades, this cell type was recognized to be widely involved in a number of non-allergic diseases in internal medicine including chronic obstructive pulmonary disease (COPD), Crohn's disease, ulcerative colitis, liver cirrhosis, cardiomyopathy, multiple sclerosis and rheumatoid arthritis, *etc*. (Table 1). This article will focus solely on the relationships between mast cells and inflammatory bowel disease, give evidence for a hypothesis of self-amplification mechanism of mast cell degranulation in gut and discuss the potential therapies for the treatment of inflammatory bowel disease (IBD).

**Table 1** Mast cells involved in non-allergic diseases in internal medicine

| Disease | Evidence |
|---|---|
| Chronic obstructive pulmonary disease (COPD) | Mast cell hyperplasia in epithelia and bronchial glands[2,3], tryptase and histamine release in BALF[4] |
| Cor pulmonale | Mast cell hyperplasia in bronchial and vascular tissues[5] |
| Bronchiectasis | Increased numbers of degranulated mast cells in lung tissue, and higher tryptase concentrations in BALF[6] |
| Acute respiratory distress syndrome (ARDS) | Mast cell hyperplasia[7] and degranulation[8] |
| Bronchiolitis obliterans-organizing pneumonia | Mast cell hyperplasia[9] and degranulation[10] |
| Cystic fibrosis | Mast cell hyperplasia[11] and degranulation[12] in lung |
| Interstitial lung diseases | Mast cell hyperplasia[13] and degranulation[14] |
| Silicosis | Mast cell hyperplasia[15] |
| Sarcoidosis | Mast cell hyperplasia[16], and degranulation[17] in lung |
| Lung cancer | Mast cell hyperplasia[18] |
| Tuberculosis | Mast cell degranulation[19] |
| Gastritis | Mast cell hyperplasia[20] and degranulation[21] |
| Peptic ulcer | Mast cell hyperplasia[22] and degranulation[23] |
| Hepatocellular carcinoma | Mast cell hyperplasia[24] |
| Ulcerative colitis | Mast cell hyperplasia[25,26] and degranulation[27] |
| Crohn's disease | Mast cell hyperplasia[28] and degranulation[29] |
| Liver cirrhosis | Mast cell hyperplasia[30] |
| Hepatitis | Mast cell hyperplasia[31,32] |
| Pancreatitis | Mast cell hyperplasia and degranulation[33] |
| Atherosclerosis | Mast cell hyperplasia[34] |
| Myocardial infarction | Mast cell hyperplasia and degranulation[35,36] |
| Congenital heart disease | Mast cell hyperplasia and subtype change[37] |
| Myocarditis | Mast cell hyperplasia[38] |
| Cardiomyopathy | Mast cell hyperplasia[39] and degranulation[40] |
| Diabetes | Mast cell hyperplasia[41] |
| Thyroiditis | Mast cell hyperplasia[42] |
| Osteoporosis | Mast cell hyperplasia[43] |
| Glomerulonephritis | Mast cell hyperplasia[44] |
| Nephropathy | Mast cell hyperplasia[45] |
| Multiple sclerosis | Mast cell hyperplasia[46] |
| Rheumatoid arthritis | Mast cell degranulation[47] |
| Osteoarthritis | Mast cell hyperplasia[48] |
| Rheumatic arthritis | Mast cell hyperplasia[49] |

## MAST CELLS

### Morphology

Mast cell is the cell that contains numerous metachromatically stained basophilic granules in its cytoplasm. It has various sizes between species with diameters of up to 30 μm reported in humans, and from 3.5 μm to 22 μm in rodents[28,50]. In human lung, for example, the range of mast cell diameters has been reported to be between 9.9 μm and 18.4 μm[51] and in human skin between 4 μm and 18 μm[52]. The shape of mast cell varies as well, it has been described as polyhedral, fusiform, ovoid, and rectangular, and appears dependent on tissue locations. Mast cell nuclei are usually round or oval and have peripherally dispersed heterochromatin[53].

Up to 40% of the volume of mast cell is occupied by membrane-enclosed secretory granules[54]. There are 50 to 500 secretory granules in one mature human mast cell, each with a diameter ranging from 0.2 to 0.5 μm. Within a given mast cell, these granules are usually of a uniform size, but there is variability from cell to cell[55]. Mast cell granules originate from the Golgi apparatus, which is responsible for the synthesis and organization of the preformed mediators contained therein[56].

### Mediators

Upon activation mast cell can release its mediators to fulfill its biological functions. Among preformed mediators, histamine is a primary amine synthesized from histidine in the Golgi apparatus, from where it is transported to the granule for storage in ionic association with the acidic residues of glycosaminoglycans side chains of heparin and proteinases[57,58]. The histamine content of mast cells dispersed from human lung and skin is similar at 2 to 5 pg/cell, and the stored histamine ranges from 10 to 12 μg/g in both tissues[53]. As only mast cell and basophil contain histamine in man, and few basophils in human tissue histamine can be used as a marker of mast cell degranulation.

Proteoglycans in human mast cells include heparin and chondroitin sulphate, which contains several highly sulphated glycosaminoglycan side chains attached to a single chain protein core. They comprise the major supporting matrix of the mast cell granule with the sulphate groups binding to histamine, proteinases and acid hydrolases.

Neutral proteases of mast cells are also preformed mediators. Three mast cell unique neutral proteinases (tryptase, chymase and carboxypeptidase) have been isolated in man and there is evidence also for a proteinase with antigenic and enzymatic properties similar to those of neutrophil cathepsin G in mast cells[59,60]. Mast cell tryptase, chymase and carboxypeptidase are reliable markers of mast cell degranulation. Based on their content of proteinases, mast cells can be classified into two types in man, with $MC_T$ cells defined as those containing tryptase but not chymase, and $MC_{TC}$ cells as those containing both tryptase and chymase[61]. Subsequently both carboxypeptidase[62] and cathepsin G like proteases[63,64] have been found to be localised exclusively in the $MC_{TC}$ population.

Newly generated mediators include eicosanoids and platelet activating factor (PAF). Eicosanoids are a group of newly generated mediators of mast cells. Immunological activation of mast cells results in the liberation of arachidonic acid from phospholipids in the cell membrane. This 20-carbon fatty acid is then rapidly oxidized along either of two independent pathways, namely the cyclooxygenase pathway to form $PGD_2$ and the lipoxygenase pathway to form $LTC_4$. These are the only two eicosanoids produced by human mast cells[65]. PAF is also a product of phospholipid metabolism in mast cells.

Mast cell cytokines may constitute a third category in that they may be both preformed and newly synthesized. For instance, it has been reported that approximately 75%, 10%, 35%, and 35% of mast cells contain IL-4, IL-5, IL-6 and TNFα, respectively in the nasal mucosa and bronchus[66]. Mast cell contains also IL-1β, IL-3, IL-8, IL-9, IL-10, IL-13, IL-16, IL-18, IL-25, granulocyte-macrophage colony-stimulating factor (GM-CSF), stem cell factor macrophage chemotactic peptide (MCP)-1, 3, 4, regulated on activation of normal T cell-expressed and secreted protein (RANTES) and eotaxin[67].

### Mast cell activation

Mast cell activation is a crucial step in mast cell involved events because it seems that only activated mast cells are able to cause pathophysiological changes. There are a number of compounds that can activate mast cells. They are antigens, anti-IgE and ionophores. Skin mast cells but not those of lung, tonsil or gut can be activated by other diverse compounds including substance P, VIP, C5a and C3a, somatostatin, compound 48/80, morphine, pepstatin, MBP, PAF, platelet factor 4 and very-low-density lipoproteins[68,53]. Stem cell factor[69], eosinophil cationic protein[70] and tryptase[71] have also been found to be able to activate human mast cells.

The mechanisms of mast cell activation differ with different classes of triggers. Human skin mast cells are able to respond to non-crosslinking stimuli, such as neuropeptides, morphine, and complement fragments[68]. IgE-dependent mast cell activation is a complicated process. It involves a specific IgE bound to its high affinity receptor (FcεR1) on the surface of mast cells, a multivalent antigen (Ag) crosslinking specific IgEs bound to FceR1 and a signal transduction and translation process in mast cells.

### Models for mast cell degranulation

While normal human mast cell line is not available, dispersed and purified mast cells are essential for investigating mast cell functions. Human mast cells have been dispersed from skin, lung, tonsil, synovium heart and intestine tissues by incubation with collagenase and hyaluronidase. These dispersed cells have appreciable morphological and functional properties of mast cells. Since dispersed cells can be evenly distributed in experiment, it is the most popular method at present. However, the purity of mast cells with this system is only 0.5-10% depending on tissues.

Chopped tissue fragments were also used for mast cell degranulation study. We found that it was difficult to evenly distribute cells in tissue fragments, therefore causing large experimental errors.

Laboratory animal tissues or mast cells are widely used in mast cell degranulation study. Thus, rat and mouse peritoneum, guinea pig lung and cultured mouse bone marrow derived mast cells are the most popular models. However, it is always adequate to use human mast cells to investigate the pathophysiological process of human disease.

## INCREASED NUMBERS OF MAST CELLS IN IBD

As early as in 1980, Dvorak and colleagues[28] reported that the number of mast cells was markedly increased in the involved area of the ileum of patients with Crohn' s disease. In 1990, Nolte *et al*.[72] found that the mast cell count in patients with ulcerative colitis was increased compared with that in control subjects and patients with Crohn' s disease. In an individual patient, the mast cell count obtained from inflamed tissue was greater than that of normal tissue. This finding was taken further by King *et al*.[26] in 1992 that the number of mast cells in active ulcerative colitis was 6.3 in active inflammation, 19.5 at the line of demarcation and 15.8 in 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. Recently, a report[73] provided us an even more convincing evidence and clear picture on the elevated number

of mast cells in inflammatory bowel disease. Nishida and colleagues found that there were greater numbers of mast cells than macrophages in the lamina propria of patients with inflammatory bowel disease though this was not found in patients with collagenous colitis. 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 inflammatory bowel disease. This could result from that accumulated mast cells released their proinflammatory mediators, and these mediators, at least tryptase[74] and chymase[75], induced macrophage accumulation in the lower part of lamina propria. Dramatically increased numbers of mast cells were also observed in the hypertrophied and fibrotic muscularis propria of strictures in Crohn' s disease compared with normal bowel ($81.3/mm^2$ *vs* $1.5/mm^2$)[76].

Not only the number of mast cells was elevated[77], but also the contents of mast cells were greatly changed in inflammatory bowel disease in comparison with normal subjects. Laminin, a multi-functional non-collagenous glycoprotein, which is normally found in extracellular matrix was detected in mast cells in muscularis propria (but not those in submucosa), indicating that mast cells may be actively involved in the tissue remodeling in Crohn' s disease[76]. Similarly, the number of TNF-α positive mast cells was greater in the muscularis propria of patients with Crohn' s disease than that in normal controls[78]. In the submucosa of involved ileal wall of Crohn' s disease, more TNF-α positive mast cells were found in inflamed area than uninflamed area. Since those TNF-α positive mast cells were mail cell type that expressed TNF-α in ileal wall, the successful treatment of Crohn' s disease with anti-TNF-α antibody could well be the consequence that the antibody neutralized the excessively secreted TNF-α from mast cells. This indirectly proved the important contribution of mast cells to the development of Crohn' s disease. Increased number of IL-16 positive mast cells, which was correlated well with increased number of $CD4^+$ lymphocytes, was also observed in active Crohn' s disease[79], indicating that this chemokine may selectively attract $CD4^+$ lymphocytes to the involved inflammatory area[80,81]. In chronic ulcerative colitis, increased number of substance P positive mast cells was observed in gut wall, particularly in mucosa[82], indicating the possibility of neuronal elements being involved in the pathogenesis of the disease.

Increased number of mast cells was also seen in a number of diseases closely related to inflammatory bowel disease. Primary sclerosing cholangitis and chronic sclerosing sialadenitis showed similar marked mast cell infiltration pattern with inflammatory bowel disease[83]. Focal active gastritis is a typical pathological change in Crohn' s disease[84], in which large number of mast cells accumulate at the border of the lesions[20]. In the animal models, increased number of mast cells in gastrointestinal tract was observed in dogs with inflammatory bowel disease in comparison with healthy dogs[85]. When given 3% dextran sulphate sodium for 10 days[86] or water avoidance stress for 5 days[87], pathological changes such as mucosal damage and edema were developed in rats, and these were accompanied by mast cell hyperplasia and activation. However, the same treatment had little effect on mast cell deficient Ws/Ws rats, implying the importance of mast cells in the development of inflammatory bowel disease.

## EVIDENCE OF MAST CELL DEGRANULATION IN IBD

As early as in 1975, Lloyd and colleagues observed that there were marked degranulation of mast cells and IgE-containing cells in the bowel wall of patients with Crohn' s disease[29], and this observation later became an important investigation area for understanding the pathogenesis of Crohn' s disease. In 1980, Dvorak *et al*. described in more detail the degranulation of mast cells in the ileum of patients with Crohn' s disease[28] with transmission electron microscopy technique. Similarly, with electron microscopy technique, degranulation of mast cells was seen in the intestinal biopsies of patients with ulcerative colitis[88]. Using immunohistochemistry technique with antibodies specific to human tryptase or chymase, both of which are exclusive antigens of human mast cells, mast cell degranulation was found in the mucosa of bowel walls of patients with Crohn' s disease, ulcerative colitis[89] and chronic inflammatory duodenal bowel disorders[90].

## INVOLVEMENT OF HISTAMINE IN PATHOGENESIS OF IBD

Using segmental jejunal perfusion system with a two-balloon, six channel small tube, Knutson and colleagues found that the histamine secretion rate was increased in patients with Crohn' s disease compared with normal controls, and the secretion of histamine was related to the disease activity, indicating strongly that degranulation of mast cells was involved in active Crohn' s disease[91]. The highly elevated mucosal histamine levels were also observed in patients with allergic enteropathy and ulcerative colitis[27]. Moreover, enhanced histamine metabolism was found in patients with collagenous colitis and food allergy[92], and increased level of N-methylhistamine, a stable metabolite of the mast cell mediator histamine, was detected in the urine of patients with active Crohn' s disease or ulcerative colitis[93,94]. Since increased level of N-methylhistamine was significantly correlated to clinical disease activity, the above finding further strongly suggested the active involvement of histamine in the pathogenesis of these diseases.

Interestingly, mast cells originated from the resected colon of patients with active Crohn' s disease or ulcerative colitis were able to release more histamine than those from normal colon when being stimulated with an antigen, colon derived murine epithelial cell associated compounds[95]. Similarly, cultured colonrectal endoscopic samples from patients with IBD secreted more histamine towards substance P alone or substance P with anti-IgE than the samples from normal control subjects under the same stimulation[96]. In a guinea pig model of intestinal inflammation induced by cow' s milk proteins and trinitrobenzenesulfonic acid, both IgE titers and histamine levels were higher than normal control animals[97].

As a proinflammatory mediator, histamine is selectively located in the granules of human mast cells and basophils and released from these cells upon degranulation. To date, a total of four histamine receptors $H_1$, $H_2$, $H_3$ and $H_4$ have been discovered[98] and the first three of them have been located in human gut[99,100], proving that there are some specific targets on which histamine can work in intestinal tract. Histamine was found to cause a transient concentration-dependent increase in short-circuit current, a measure of total ion transport across the epithelial tissue in gut[101]. This could be due to the interaction of histamine with $H_1$-receptors that increased Na and Cl ions secretion from epithelium[102]. The finding that $H_1$-receptor antagonist pyrilamine was able to inhibit anti-IgE induced histamine release and ion transport[103] suggests further that histamine is a crucial mediator responsible for diarrhea in IBD and food allergy. The ability of SR140333, a potent NK1 antagonist in reducing mucosal ion transport was most likely due to its inhibitory actions on histamine release from colon mast cells[104].

## INVOLVEMENT OF MAST CELL PROTEASES IN PATHOGENESIS OF IBD

Tryptase is a tetrameric serine proteinase that constitutes some

20% of the total protein within human mast cells and is stored almost exclusively in the secretory granules of mast cells[105] in a catalytically active form[106]. The ability of tryptase to induce microvascular leakage in the skin of guinea pig[107], to accumulate inflammatory cells in the peritoneum of mouse[74] and to stimulate release of IL-8 from epithelial cells[108], and the evidence that relatively higher secretion of tryptase has been detected in ulcerative colitis[109] implicated that this mediator is involved in the pathogenesis of intestinal diseases. However, little is known about its actions in IBD. Recently, proteinase activated receptor (PAR)-2, a highly expressed receptor in human intestine[110] was recognized as a receptor of human mast cell tryptase[111]. Colonic administration of PAR-2 agonists up-regulated PAR-2 expression, induced granulocyte infiltration, colon wall edema and damage and stimulated an increased paracellular permeability of colon mucosa[112]. PAR-2 agonists were also able to stimulate intestinal electrolyte secretion[113]. Interestingly, some 60% and 46% of mast cells in ulcerative colitis tissues expressed PAR-2 or TNF-α, respectively. PAR-2 agonists were able to stimulate TNF-α secretion from mast cells[114] and secreted TNF-α could then enhance PAR-2 expression in a positive feedback manner[113]. These findings indicated further the importance of TNF-α and mast cells in the pathogenesis of IBD.

Chymase is a serine proteinase exclusively located in the same granules as tryptase and could be released from granules together with other preformed mediators. Large quantity of active form chymase (10 pg per mast cell) in mast cells[115] implicates that this mast cell unique mediator may play a role in mast cell related diseases. Indeed, chymase has been found to be able to induce microvascular leakage in the skin of guinea pig[116], stimulate inflammatory cell accumulation in peritoneum of mouse[75], and alter epithelial cell monolayer permeability *in vitro*[117]. However, little is known about its actions in IBD. Mast cell carboxypeptidase is a unique product of $MC_{TC}$ subtype mast cells. There is some 10 pg in each mast cells. No information about the relationship between mast cell carboxypeptidase and IBD is available, but the successful coloning of mast cell carboxypeptidase from human gut tissue and obtaining of recombinant human mast cell carboxypeptidase [chen 2004] will certainly help to initiate the investigation of the role of mast cell carboxypeptidase in IBD. It is astonished to learn the fact that the potential roles of mast cell neutral proteinases in IBD have been almost completely ignored till today. Since they are the most abundant granule products of mast cells and have been demonstrated to possess important actions in inflammation, they should certainly contribute to the occurrence and development of IBD.

## INVOLVEMENT OF HEPARIN IN PATHOGENESIS OF IBD

Over the last decade, heparin, a unique product of human mast cells and basophils, has been used to treat IBD in clinical practice. Using combined heparin and sulfasalazine therapy, Gaffney and colleagues successfully treated 10 patients with ulcerative colitis poorly controlled on sulfasalazine and prednisolone[119]. Similarly, Evans *et al*. found that heparin was effective in treating corticosteroid-resistant ulcerative colitis[120], and Yoshikane *et al*. reported that heparin was very effective in the treatment of disseminated intravascular coagulation (DIC) caused by ulcerative colitis[121]. Recently, heparin was even suggested as a first line therapy in the treatment of severe colonic inflammatory bowel disease[122], but should be administered in hospitalized patients only because of the risk of possible serious bleeding[123]. To overcome bleeding side effect, low molecular weight heparin (LMWH) was employed as adjuvant therapy[124], and the patients showed good clinical and laboratory response with no severe adverse effects[125,126].

Apart from anticoagulation activity, the mechanisms by which heparin was able to treat IBD were considered to include its ability to inhibit the recruitment of neutrophils, reduce production of pro-inflammatory cytokines[127] and restore the high-affinity receptor binding of antiulcerogenic growth factor[128,129]. The ability of heparin to inhibit neutrophil activation, adhesion, and chemotaxis was also found in a mouse model of inflammatory bowel disorder[130,131], suggesting that balanced interactions between mast cells and neutrophils might be important for the development of IBD. In rat models of IBD, heparin revealed its ability to attenuate TNFα induced leucocyte rolling and CD11b dependent adhesion[132], reduce serum IL-6 level and improve microcirculatory disturbance in rectal walls[133,134]. Thus, preformed mast cell mediators seemed to have dual actions on the pathogenesis of IBD. On the one hand, tryptase, histamine, and TNF-α can cause damage in the intestinal wall, and on the other hand, heparin can protect the intestinal wall from damage.

## INVOLVEMENT OF PGD2, LTC4 AND PAF IN PATHOGENESIS OF IBD

It was reported that mast cells in the actively involved areas of ulcerative colitis released greater amount of PGD2, in parallel to histamine and LTC4[135]. In a rat experimental colitis model, the time for stimulating PGD2 release was initiated within 1 h and increased 4 fold within 3 h[136]. This was accompanied by a significant granulocyte infiltration, indicating the likelihood of involvement of PGD2 in IBD. The basal release of LTC4 was enhanced in the gut of Crohn' s disease patients[137], but the meaning of this enhancement still remains uninvestigated.

It was found that mast cell activators, calcium ionophore A23187 and anti-IgE, were able to stimulate more PAF release from colon with ulcerative colitis than from normal colon, and this increased PAF release could be inhibited by steroids and 5-aminosalicylic acid[138,139]. The increased secretion of PAF was detected in the stool of patients with active Crohn' s disease, but not in that of patients with irritable bowel syndrome[140]. The level of PAF was also higher in colonic mucosa of patients with Crohn' s disease than in colonic mucosa of healthy controls[141]. These indicated that PAF might be involved in the pathogenesis of Crohn' s disease[142]. The elevated level of PAF in colon was likely to be the result of increased production by colonic epithelial cells[143], lamina propria mononuclear cells[144] and mast cells, and decreased PAF acetylhydrolase (the major PAF degradation enzyme activity)[145]. In patients with ulcerative colitis, colonic production of PAF was increased in comparison with control patients[146], and the level of PAF in the stool of patients with ulcerative colitis was much higher than that in the stool of healthy volunteers[147]. Since increased colonic production of PAF was correlated to local injury and inflammation[146], it implicats strongly that PAF is involved in the pathogenesis of ulcerative colitis. However, a randomized controlled trial with a specific PAF antagonist SR27417A showed that this compound had no significant effect on patients with active ulcerative colitis though it was safe in humans[148].

## INVOLVEMENT OF CYTOKINES IN PATHOGENESIS OF IBD

Dozens of proinflammatory cytokines were reported to be involved in the pathogenesis of IBD, but only several of them have been considered to be therapeutic targets. TNFα was considered being secreted mainly from intestinal mast cells in IBD[78], and bacteria and anti-IgE were able to substantially enhance their release from mast cells[149]. The released mast cell products TNFα and histamine could then synergistically stimulate ion secretion from intestinal epithelium[150]. The anti-

TNFα therapy will be described below. In IBD, most intestinal mast cells produce IL-3, and this increased expression of IL-3 could be inhibited by administration of steroid[151]. IL-10, a cytokine which can be produced by human mast cells[152], was reported to have some anti-inflammatory role in IBD[153]. However, the results from clinical trials were heterogeneous[154]. IL-1 was found to be excessively released from patients with ulcerative colitis and could stimulate the short-circuit current response to IL-1[155]. As for IL-3, steroid could significantly inhibit IL-1 release in IBD[156]. Mast cells from healthy controls did not produce IL-5, but mast cells from patients with intestinal inflammatory disease could release a relatively large amount of IL-5[157]. However, the effect of IL-5 on IBD needs to be investigated. It is still in early days to understand the role of cytokines in IBD, therefore it is difficult to draw a conclusive line on the issue whether cytokine related therapy is beneficial for IBD.

## HYPOTHESIS OF SELF-AMPLIFICATION MECHANISM OF MAST CELL DEGRANULATION IN GUT

Tryptase has been proved to be a unique marker of mast cell degranulation *in vitro* as it is more selective than histamine to mast cells. Inhibitors of tryptase[71,158] and chymase[159] have been discovered to possess the ability to inhibit histamine or tryptase release from human skin, tonsil, synovial[160] and colon mast cells[161,162], suggesting that they are likely to be developed as a novel class of mast cell stabilizers. Recently, a series of experiments with dispersed colon mast cells suggested there should be at least two pathways in man for mast cells to amplify their own activation-degranulation signals in an autocrine or paracrine manner, which may partially explain the phenomena that when a sensitized individual contacts allergen only once the local allergic response in the involved tissue or organ may last for days or weeks. These findings included both anti-IgE and calcium ionophore were able to induce significant release of tryptase and histamine from colon mast cells[163], histamine was a potent activator of human colon mast cells[164] and the agonists of PAR-2 and trypsin were potent secretagogues of human colon mast cells[165]. Since tryptase was reported to be able to activate human mast cells[71] and $H_1$ receptor antagonists terfenadine and cetirizine[166] were capable of inhibiting mast cell activation, the hypothesis of mast cell degranulation self-amplification mechanisms is that mast cell secretogogues induce mast cell degranulation, release histamine, then stimulate the adjacent mast cells or positively feedback to further stimulate its host mast cells through $H_1$ receptor, whereas released tryptase acts similarly to histamine through its receptor PAR-2 on mast cells (Figure 1).

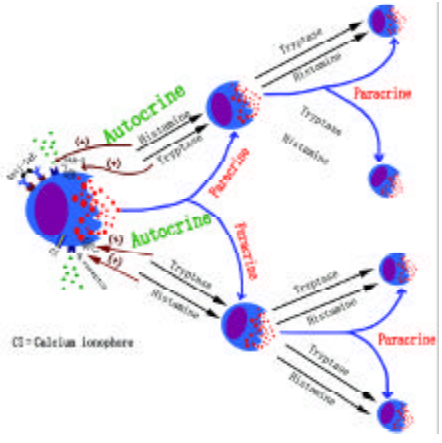


**Figure 1** Hypothesis of self-amplification mechanism of mast cell degranulation in gut.

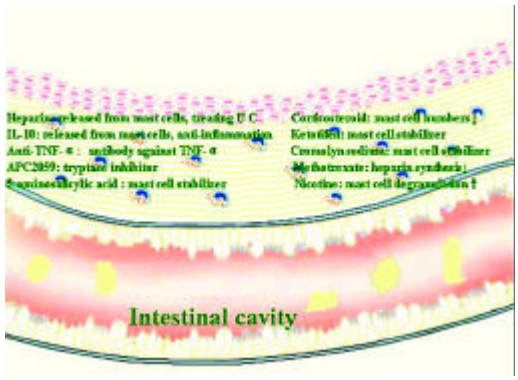


**Figure 2** Association of mast cells with IBD therapies.

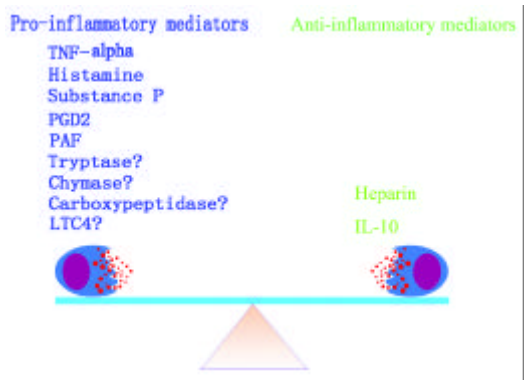


**Figure 3** Balance between "pro-inflammatory" and "anti-inflammatory" mast cell mediators in IBD.

## RELATIONSHIP BETWEEN THERAPIES FOR IBD AND MAST CELLS

Although aminosalicylates and corticosteroids remain the mainstream therapeutic drugs for the treatment of IBD[167], the mast cell related therapy should be given some close attentions. Besides heparin therapy mentioned above, anti-TNFα monoclonal antibody[168,169], infliximab in particular[170] showed promising results in treating Crohn' s disease. Thalidomide, an agent with antiangiogenic and immunomodulatory properties[171], possessed inhibitory activity towards TNFα[172] and was therapeutically effective in IBD[173]. Mast cell tryptase inhibitor APC2059 was also effective and safe in treating ulcerative colitis[174]. Even 5-aminosalicylic acid, an aminosalicylate drug was an effective inhibitor of anti-IgE induced histamine and PGD2 release from human intestinal mast cells[175]. Thus the beneficial effects of 5-aminosalicylic acid on IBD were at least partially due to its mast cell stabilizing activity. Similarly, the effective treatment of IBD by corticosteroids might also be partially associated with its action on mast cells as significantly reduced numbers of mast cells were observed in the colon throughout steroid therapy[176].

The ineffective treatment of ulcerative colitis by mast cell stabilizer, cromolyn sodium[177] was most likely due to the drug that did not affect release of histamine from colon mast cells[178]. However, it was recently found to be effective in treating chronic or recurrent enterocolitis in patients with Hirschsprung' s disease[179]. In 1992, Eliakim and colleagues found that ketotifen, a mast cell stabilizer, was able to significantly decrease mucosal damage of ulcerative colitis in an experimental colitis model[180] and inhibit accumulation of PGE2, ITB4 and LTC4 in ulcerative colitis colon mucosa organ-culture[181], suggesting that this anti-asthma drug may be useful for the treatment of IBD. Indeed, ketotifen was revealed to be effective in treating IBD with 5-aminosalicylate intolerance[182], and acute ulcerative colitis in

children[183], most likely through inhibition of mast cell and neutrophil degranulation[184].

It was surprising to learn that even immunomodulatory drug methotrexate, which showed promise in Crohn' s disease therapy[185] was able to inhibit heparin synthesis in mast cells[186], suggesting that the beneficial action of methotrexate on Crohn' s disease might be due to the reduction of heparin secretion from mast cells. Nicotine, an addictive component of tobacco, had a dual effect on IBD. It could ameliorate disease activity of ulcerative colitis but deteriorate disease process of Crohn' s disease[187]. Since nicotine was reported to be able to induce degranulation of mast cells[188], its dual action on IBD could be related to the locally imbalanced quantities of mast cell products, such as histamine and heparin. The association of these therapies with mast cells strongly indicates that mast cells are key cells in the development of IBD (Figure 2).

## CONCLUSION

Mast cells are a key cell type, which is actively involved in the pathogenesis of IBD. The different actions of mast cell mediators in IBD suggest that there must be a balance between ' pro-IBD' and ' anti-IBD' mast cell mediators (Figure 3). Breaking this balance may cause diseases. There are at least two pathways, histamine pathway and tryptase pathway, for mast cells to amplify their degranulation signals. Each of them is likely to act in either autocrine or paracrine manner. These mast cell degranulation signal amplification mechanisms may be the key event in the pathophysiological process of long-lasting local response of mast cell associated diseases such as IBD, asthma and rhinitis.

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