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EDITORIAL

Mucosal mast cells are pivotal elements in inflammatory bowel disease that connect the dots: Stress, intestinal hyperpermeability and inflammation

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Abstract

Mast cells (MC) are pivotal elements in several physiological and immunological functions of the gastrointestinal (GI) tract. MC translate the stress signals that has been transmitted through brain gut axis into release of proinflammatory mediators that can cause stimulation of nerve endings that could affect afferent nerve terminals and change their perception, affect intestinal motility, increase intestinal hyperpermeability and, in susceptible individuals, modulate the inflammation. Thus, it is not surprising that MC are an important element in the pathogenesis of inflammatory bowel disease and non inflammatory GI disorders such as IBS and mast cell enterocolitis.

Key words: Mast cells; Intestinal permeability; Stress, Inflammatory bowel disease; Irritable bowel syndrome; Intestinal barrier

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Mast cells (MC) of the intestinal mucosa are key elements in several biological processes. For example, they are an important component in allergic responses to exogenous antigens and they act in concert with IgE to increase the release of MC mediators in allergic reactions. Recently the role of MC in non-allergic phenomena has been getting more attention. In fact, MC are an important component of the mucosal innate immune response[1]. Thus, it is not surprising that these cells are involved in several inflammatory disease processes such as bronchiectasis[2], idiopathic pulmonary fibrosis[3], bronchiolitis obliterans with organizing pneumonia[4], sarcoidosis[5], glomerulonephritis[6] and rheumatoid arthritis[7]. In the gastrointestinal (GI) tract, similar to other mucosal surfaces, Mast cells are part of the allergic response to luminal antigens and of protective innate immune responses.

Mast cells in the GI tract also serve as end effectors of the brain-gut axis (BGA). The BGA is composed of main regulatory cores in the central nervous system that are connected to peripheral (enteric and autonomic) nervous systems through a series of networks of afferent and efferent nerves. One role of the BGA is to transmit information from the brain to the GI tract regarding the perception and/or experience of stressful events.

Upon activation of the BGA by stress, Mast cells release a wide range of neurotransmitters and other proinflammatory molecules. These mediators include histamine, heparin, chondroitin sulfate, chymase, carboxypeptidase, tryptase, platelet activating factor, prostagalanin (PGD2), leukotriene (LTC4) and a variety of interleukins such as IL-1β, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-13, IL-16, IL-18, IL-25, TNF-alpha, 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[8].

The release of these mediators can profoundly affect GI physiology. For example, tryptase can activate PAR-2 receptors on epithelial cells, resulting in modulation of tight junction proteins and increases in permeability through paracellular pathways in the intestinal epithelium[9]. Such increases expose the submucosal immune system to lumen-derived food antigens and bacterial by-products, which will result in immune system activation[10,11]. This is clinically important because an increased mucosal permeability and activation of the mucosal immune system are the two major players in mucosal inflammation in inflammatory bowel disease (IBD). PAR-2 receptors are not limited to epithelial cells and the presence of this receptor on afferent nerve terminals and MC themselves has been shown. Thus, activation of PAR-2, can result in release of proinflammatory mediators from nerve

endings which may cause neurogenic inflammation[12] or even potentiate MC release by creating a positive feedback loop[13,14].

IBD is believed to result from an abnormal responses to normal pro-inflammatory factors in the gut lumen in a susceptible individual with immune dysregulation[15]. The origins of this disease are probably multi-factorial, with interplay between genetic and environmental factors[15,16]. This interplay results in initiation of inflammatory processes and creation of vicious cycles (involving positive feedback loops) that cause sustained, uncontrolled inflammation and tissue damage. However, for luminal factors such as bacterial antigens to initiate an inflammatory cascade, they must be able to bypass the intestinal barrier[17,18]. Indeed, as suggestive above, a decreased intestinal barrier integrity (leaky gut) has been implicated in the pathogenesis of IBD[17-20]. In fact, activation of the BGA by stressful situations and by the associated degranulation of MC in the gut mucosa can result in intestinal hyperpermeability and activation of the mucosal immune function.

Nevertheless, the mechanisms through which MC play a role in the pathogenesis of IBD are not well known. For example, there is a wide variation in the number of MC in IBD in different reports. A few studies have shown a mild to marked increase in the number of MC in subjects with active IBD[21-23]. King *et al*[26] and other researchers reported that MC number was not different between controls and subjects with inactive IBD[24-26]. Surprisingly, in the report by King *et al*[26] the number of MC increased in the area of demarcation between involved and non-involved colon and the number of MC dropped significantly in areas of active inflammation. In our own recent study, we did not find any significant differences in the number of MC in subjects with IBD compared to healthy controls. In addition we showed that there was no increase in the number of MC after stress in human subjects[27]. This contrasts with animal studies in which the number of MC increased after stress[28].

Although there is controversy regarding the number of intestinal MC in IBD, there is consensus that there is a close association among stress, BGA activation, and MC mediated mechanisms in IBD[21,29-35]. For example, studies in animal models of IBD showed that stress results in increased intestinal permeability and worsening of hapten-induced colitis in rats[36]. Stress did not affect gut permeability in MC-deficient rats and failed to cause epithelial mitochondrial damage in a rat model, indicating that stress-induced intestinal hyperpermeability is MC-dependent[28]. In human studies, stress [modeled using cold pressor test (CPT)] in healthy subjects caused activation of mucosal mast cells and release of proinflammatory mediators in the jejunum[37]. This study reaffirmed the finding that was previously showed in animal studies and reaffirmed the BGA activation in humans activates MC in GI mucosa in healthy subjects. Finally, we recently showed that stress (CPT) caused more pronounced MC activation and degranulation in patients with inactive IBD than in healthy controls. The activation of mucosal MC was associated with mucosal oxidative damage[27]. The mechanism for the exaggerated MC response to stress in IBD patients is not known but could be one of the important factors involved in IBD flare up. In fact, it remains to be seen, whether the exaggerated response of mucosal MC to stress in IBD subjects is a primary phenomenon due to an inherently abnormal MC or whether it is a secondary phenomenon due to the inflammatory environment of the MC. After further investigation we recently reported that MC in the intestinal mucosa of patients with IBD have reduced immunostaining of c-kit receptors compared to MC from healthy controls[27,38]. Mucosal MC are identified in intestinal tissues by antibodies against the CD117 (c-kit) antigen[29]. C-kit is a transmembrane, tyrosine kinase containing, growth factor receptor expressed by MC, and its presence on MC membranes represents maturity of the cells[30-32]. In our report, we compared the results of immunostaining with markers of mast cell degranulation (using electron microscopy) and observed that a lack of c-kit immunostaining is not associated with MC activity and degranulation. Whether this MC abnormality underlies MC overactivity in IBD requires further investigation.

Considering MC as the end effector of the BGA, it is not surprising that MC have an important role in the pathogenesis of other stress-related GI disorders such as irritable bowel syndrome (IBS). Barbara showed that the number of MC in ileum of subjects with IBS is increased[39,40]. He also showed that there is a close proximity of the nerve ending and mucosal MC[41]. He noted that MC activation and the close proximity of MC to nerve fibers are correlated with the severity of perceived abdominal painful sensations. The mediators released from MC interact with nerves supplying the gut leading to altered gut physiology and increased sensory perception. This proposes the notion of nerve↔MC activation in stressful situations. In fact, abnormal intestinal permeability has been reported in at least one subgroup of diarrhea -predominant IBS patients[42]. Although, there is a lack of clear histological inflammation in IBS, the apparent presence of a biochemical inflammatory process in IBS is an emerging topic. An abnormal proinflammatory cytokine profile has been reported in subjects with IBS[43,44]. Some researcher have also connected MC and functional bowel disorders such as IBS through allergic responses to food antigens and food intolerance[45]. MC enterocolitis is a new term that was coined by our group and includes a subgroup of IBS with intractable diarrhea who have normal routine histology but an increased number of MC [more than 20 per high power field (HPF)] in special staining for MC. These patients respond well to medicine that curbs the release of proinflammatory MC mediators such as histamine type I and II blockers[46]. Thus, it is not surprising that researchers are now proposing the possibility of using, in management of IBS, drugs that have the potential to control MC[40].

In conclusion, MC is an important component of gastrointestinal tract physiological and immunological functions. As the end effector of the BGA, MC translate the stress signals into release of proinflammatory mediators that can stimulate gastrointestinal nerve endings and affect its perception, change intestinal motility, cause intestinal hyperpermeability and, in susceptible individuals-

those with hyperreactive intestinal immune systems modify the inflammation. Despite the apparent importance of this element in the pathogenesis of several inflammatory and non-inflammatory GI disorders, our knowledge about the role of MC in these disorders is only rudimentary. Further research that more precisely characterizes the role of MC in these diseases could open new doors toward new therapies for IBD and other common GI ailments.

REFERENCES

1 **Dror Y**, Leaker M, Caruana G, Bernstein A, Freedman MH. Mastocytosis cells bearing a c-kit activating point mutation are characterized by hypersensitivity to stem cell factor and increased apoptosis. *Br J Haematol* 2000; **108**: 729-736
2 **Sepper R**, Konttinen YT, Kemppinen P, Sorsa T, Eklund KK. Mast cells in bronchiectasis. *Ann Med* 1998; **30**: 307-315
3 **Hunt LW**, Colby TV, Weiler DA, Sur S, Butterfield JH. Immunofluorescent staining for mast cells in idiopathic pulmonary fibrosis: quantification and evidence for extracellular release of mast cell tryptase. *Mayo Clin Proc* 1992; **67**: 941-948
4 **Pesci A**, Majori M, Piccoli ML, Casalini A, Curti A, Franchini D, Gabrielli M. Mast cells in bronchiolitis obliterans organizing pneumonia. Mast cell hyperplasia and evidence for extracellular release of tryptase. *Chest* 1996; **110**: 383-391
5 **Flint KC**, Leung KB, Hudspith BN, Brostoff J, Pearce FL, Geraint-James D, Johnson NM. Bronchoalveolar mast cells in sarcoidosis: increased numbers and accentuation of mediator release. *Thorax* 1986; **41**: 94-99
6 **Tóth T,** Tóth-Jakatics R, Jimi S, Ihara M, Urata H, Takebayashi S. Mast cells in rapidly progressive glomerulonephritis. *J Am Soc Nephrol* 1999; **10**: 1498-1505
7 **Godfrey HP**, Ilardi C, Engber W, Graziano FM. Quantitation of human synovial mast cells in rheumatoid arthritis and other rheumatic diseases. *Arthritis Rheum* 1984; **27**: 852-856
8 **He SH**. Key role of mast cells and their major secretory products in inflammatory bowel disease. *World J Gastroenterol* 2004; **10**: 309-318
9 **Cenac N**, Chin AC, Garcia-Villar R, Salvador-Cartier C, Ferrier L, Vergnolle N, Buret AG, Fioramonti J, Bueno L. PAR2 activation alters colonic paracellular permeability in mice via IFN-gamma-dependent and -independent pathways. *J Physiol* 2004; **558**: 913-925
10 **Anton PA**. Stress and mind-body impact on the course of inflammatory bowel diseases. *Semin Gastrointest Dis* 1999; **10**: 14-19
11 **Levenstein S**, Prantera C, Varvo V, Scribano ML, Andreoli A, Luzi C, Arcà M, Berto E, Milite G, Marcheggiano A. Stress and exacerbation in ulcerative colitis: a prospective study of patients enrolled in remission. *Am J Gastroenterol* 2000; **95**: 1213-1220
12 **Steinhoff M**, Vergnolle N, Young SH, Tognetto M, Amadesi S, Ennes HS, Trevisani M, Hollenberg MD, Wallace JL, Caughey GH, Mitchell SE, Williams LM, Geppetti P, Mayer EA, Bunnett NW. Agonists of proteinase-activated receptor 2 induce inflammation by a neurogenic mechanism. *Nat Med* 2000; **6**: 151-158
13 **Cenac N**, Coelho AM, Nguyen C, Compton S, Andrade-Gordon P, MacNaughton WK, Wallace JL, Hollenberg MD, Bunnett NW, Garcia-Villar R, Bueno L, Vergnolle N. Induction of intestinal inflammation in mouse by activation of proteinase-activated receptor-2. *Am J Pathol* 2002; **161**: 1903-1915
14 **He SH**, He YS, Xie H. Activation of human colon mast cells through proteinase activated receptor-2. *World J Gastroenterol* 2004; **10**: 327-331
15 **Papadakis KA**, Targan SR. Current theories on the causes of inflammatory bowel disease. *Gastroenterol Clin North Am* 1999; **28**: 283-296
16 **Bjarnason I**, MacPherson A, Hollander D. Intestinal permeability: an overview. *Gastroenterology* 1995; **108**: 1566-1581
17 **Hollander D**. Permeability in Crohn's disease: altered barrier functions in healthy relatives? *Gastroenterology* 1993; **104**: 1848-1851
18 **Hollander D**, Vadheim CM, Brettholz E, Petersen GM, Delahunty T, Rotter JI. Increased intestinal permeability in patients with Crohn's disease and their relatives. A possible etiologic factor. *Ann Intern Med* 1986; **105**: 883-885
19 **Hilsden RJ**, Meddings JB, Sutherland LR. Intestinal permeability changes in response to acetylsalicylic acid in relatives of patients with Crohn's disease. *Gastroenterology* 1996; **110**: 1395-1403
20 **May GR**, Sutherland LR, Meddings JB. Is small intestinal permeability really increased in relatives of patients with Crohn's disease? *Gastroenterology* 1993; **104**: 1627-1632
21 **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
22 **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
23 **Lloyd G**, Green FH, Fox H, Mani V, Turnberg LA. Mast cells and immunoglobulin E in inflammatory bowel disease. *Gut* 1975; **16**: 861-865
24 **Sarin SK**, Malhotra V, Sen Gupta S, Karol A, Gaur SK, Anand BS. Significance of eosinophil and mast cell counts in rectal mucosa in ulcerative colitis. A prospective controlled study. *Dig Dis Sci* 1987; **32**: 363-367
25 **Bischoff SC**, Wedemeyer J, Herrmann A, Meier PN, Trautwein C, Cetin Y, Maschek H, Stolte M, Gebel M, Manns MP. Quantitative assessment of intestinal eosinophils and mast cells in inflammatory bowel disease. *Histopathology* 1996; **28**: 1-13
26 **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
27 **Farhadi A**, Keshavarzian A, Van de Kar LD, Jakate S, Domm A, Zhang L, Shaikh M, Banan A, Fields JZ. Heightened responses to stressors in patients with inflammatory bowel disease. *Am J Gastroenterol* 2005; **100**: 1796-1804
28 **Santos J**, Yang PC, Söderholm JD, Benjamin M, Perdue MH. Role of mast cells in chronic stress induced colonic epithelial barrier dysfunction in the rat. *Gut* 2001; **48**: 630-636
29 **Levenstein S**, Prantera C, Varvo V, Scribano ML, Berto E, Andreoli A, Luzi C. Psychological stress and disease activity in ulcerative colitis: a multidimensional cross-sectional study. *Am J Gastroenterol* 1994; **89**: 1219-1225
30 **Robertson DA**, Ray J, Diamond I, Edwards JG. Personality profile and affective state of patients with inflammatory bowel disease. *Gut* 1989; **30**: 623-626
31 **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
32 **Knutson L**, Ahrenstedt O, Odlind B, Hällgren R. The jejunal secretion of histamine is increased in active Crohn's disease. *Gastroenterology* 1990; **98**: 849-854
33 **Fox CC**, Lazenby AJ, Moore WC, Yardley JH, Bayless TM, Lichtenstein LM. Enhancement of human intestinal mast cell mediator release in active ulcerative colitis. *Gastroenterology* 1990; **99**: 119-124
34 **Björck S,** Dahlström A, Ahlman H. Topical treatment of ulcerative proctitis with lidocaine. *Scand J Gastroenterol* 1989; **24**: 1061-1072
35 **Björck S,** Dahlström A, Ahlman H. Treatment of distal colitis with local anaesthetic agents. *Pharmacol Toxicol* 2002; **90**: 173-180
36 **Qiu BS**, Vallance BA, Blennerhassett PA, Collins SM. The role of CD4+ lymphocytes in the susceptibility of mice to stress-induced reactivation of experimental colitis. *Nat Med* 1999; **5**:

1178-1182
37 **Santos J**, Saperas E, Nogueiras C, Antolín M, Antolin M, Cadahia A, Malagelada JR. Release of mast cell mediators into the jejunum by cold pain stress in humans. *Gastroenterology* 1998; **114**: 640-648
38 **Farhadi A**, Keshavarzian A, Fields JZ, Sheikh M, Banan A. Resolution of common dietary sugars from probe sugars for test of intestinal permeability using capillary column gas chromatography. *J Chromatogr B Analyt Technol Biomed Life Sci* 2006; **836**: 63-68
39 **Barbara G**, De Giorgio R, Stanghellini V, Cremon C, Salvioli B, Corinaldesi R. New pathophysiological mechanisms in irritable bowel syndrome. *Aliment Pharmacol Ther* 2004; **20** Suppl 2: 1-9
40 **Barbara G**, Stanghellini V, De Giorgio R, Corinaldesi R. Functional gastrointestinal disorders and mast cells: implications for therapy. *Neurogastroenterol Motil* 2006; **18**: 6-17
41 **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. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. *Gastroenterology* 2004; **126**: 693-702
42 **Dunlop SP**, Hebden J, Campbell E, Naesdal J, Olbe L, Perkins AC, Spiller RC. Abnormal intestinal permeability in subgroups of diarrhea-predominant irritable bowel syndromes. *Am J Gastroenterol* 2006; **101**: 1288-1294
43 **O'Mahony L**, McCarthy J, Kelly P, Hurley G, Luo F, Chen K, O'Sullivan GC, Kiely B, Collins JK, Shanahan F, Quigley EM. Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology* 2005; **128**: 541-551
44 **van der Veek PP**, van den Berg M, de Kroon YE, Verspaget HW, Masclee AA. Role of tumor necrosis factor-alpha and interleukin-10 gene polymorphisms in irritable bowel syndrome. *Am J Gastroenterol* 2005; **100**: 2510-2516
45 **Zar S**, Kumar D, Kumar D. Role of food hypersensitivity in irritable bowel syndrome. *Minerva Med* 2002; **93**: 403-412
46 **Jakate S**, Demeo M, John R, Tobin M, Keshavarzian A. Mastocytic enterocolitis: increased mucosal mast cells in chronic intractable diarrhea. *Arch Pathol Lab Med* 2006; **130**: 362-367

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