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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* 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* 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[38,39]. 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[40,41]. He also showed that there is a close proximity of the nerve ending and mucosal MC[42]. 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[43]. 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[44,45]. Some researcher have also connected MC and functional bowel disorders such as IBS through allergic responses to food antigens and food intolerance[46]. 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[47]. 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[41].

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.

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