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EDITORIAL

Mast Cells in Irritable Bowel Syndrome and Ulcerative Colitis: Function Not Numbers Is What Makes All the Difference

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Background and Significance of Issues and Controversies

Data obtained from animal and human studies support the existence of mast cells (MC) in the gastrointestinal (GI) tract, where they are considered important for the control of luminal parasites and possibly other microorganisms. MC are also implicated in food allergies, GI inflammation, and functional GI diseases, including irritable bowel syndrome (IBS) [1]. MC density may be increased in inflammatory bowel disease (IBD) and IBS, although such studies have yielded variable and sometimes contradictory results, likely due to methodological problems such as sampling issues, poorly characterized MC identification methodology, and lack of adequate documentation of disease correlates. There is no question that MC numbers are likely to be easier to identify and count in lesional areas as they may be present in IBD.

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MC density in the terminal ileum had previously been reported to be significantly increased in patients with IBS, even though MC abundance only correlated weakly with IBS symptoms, and, in some cases, a *decreased* density of colonic c-kit-positive in IgE- or IgG-stained MC, was reported [2], even though IgE- or IgG-staining is *not* an index of MC activation.

In the paper by Choi et al. [3] published in this issue of *Digestive Diseases and Sciences*, the authors analyzed intestinal MC density in: (a) diverse patient cohorts, including diarrhea predominant-IBS (D-IBS), ulcerative colitis (UC) in remission, mild UC, and in healthy controls; (b) random colonic biopsies; (c) different colonic segments; and (d) mucosal MC and lamina propria/intra-epithelial T lymphocytes. The results are important because MC number was significantly increased in 97.6 % of D-IBS patients, intra-epithelial lymphocytes (IEL) were increased in 92.8 %, and lamina propria lymphocytes (LPL) were increased in 81.9 %. Moreover, even though the numbers of immune cells were even higher in some post-infectious (PI)-IBS patients, the remaining D-IBS patients had a significantly higher number of these cells compared with controls. Immunochemically identified were tryptase-positive MC and CD3-positive T cells (and not for *all* lymphocytes, as the authors stated).

All publications to date, including the one by Choi et al. [3], did not report MC *activation*, which, according to some, is more important than actual numbers [4].

For instance, tryptase staining underestimates the number of degranulated MC, since released secretory granule tryptase does not stain. One way to identify degranulated MC is to stain for c-kit (CD117), the surface MC receptor for stem cell factor. Nevertheless, since mediator secretion can also occur *without* degranulation [5], MC activation can best be identified either by ultrastructural appearance

or by qPCR measurement of histidine decarboxylase or tryptase gene expression.

Unfortunately, patients with IBS or UC have not been evaluated for potential triggers, especially their stress status, since stress induces numerous pathological alterations [6], including MC-dependent increased intestinal permeability [7]. A brief period of restraint stress activated mucosal MC and disrupted the gut-blood barrier, as evidenced by breakdown of tight junctions in enteric villi [8]. Corticotropin-releasing hormone (CRH), secreted from the paraventricular nucleus of the hypothalamus in response to stress, activates the hypothalamic-pituitary adrenal (HPA) axis leading to secretion of cortisone that generally has anti-inflammatory effects. Instead, CRH secreted outside the CNS has pro-inflammatory actions [9], apparently through activation of MC [10]. For instance, CRH was reported to increase mucosal barrier permeability, dependent on MC activation [11].

The trigger(s) for MC proliferation and activation may be different in IBS than it is in UC. Stress is important in IBS as discussed above, whereas stress and infections may be more important in UC pathogenesis. For instance, chronic stress disrupted hindgut barrier function, inducing MC-dependent bacterial adhesion and intestinal inflammation [12].

Summary and Future Directions

MC appear to be increased in IBS> (PI)-IBS >UC as compared to controls. This finding alone suggest that there is some common underlying pathogenesis involving MC that may depend on the degree of GI inflammation present. Unfortunately, it is hard to sample the entire gut and use the same preservation and staining techniques to make this approach useful diagnostically. Future studies should focus on GI–MC function by investigating gene expression of unique MC mediators in whole-mount random biopsies or in laser-captured mucosal MC. Given sufficient biopsy tissues, such mediators could also be quantitated using Western blot analysis. Patients should be better characterized and phenotyped for the presence of other related diseases, such as chronic fatigue syndrome, fibromyalgia, mastocytosis, bladder pain syndrome/interstitial cystitis, who share symptoms and other attributes with IBS [13], and may contribute their own pathological characteristics.

Inhibition of mucosal MC may be an effective therapeutic approach since they can also super-stimulate activated T cells [14]. Use of select natural flavonoids, such as luteolin, hold promise for further development since they can inhibit MC and T cell function [14].

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