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Evidence for the Role of the Brain–Gut Axis in Inflammatory Bowel Disease: Depression as Cause and Effect?

See "Re-activation of inflammatory bowel disease in a mouse model of depression," by Ghia JE, Blennerhassett P, Deng Y, et al, on page 2280.

As is the case with most chronic illnesses, there is a higher rate of anxiety and depressive disorders in inflammatory bowel disease (IBD) than in the population at large.[1] Past reviews of IBD and co-occurring psychiatric disorders challenged the long-held belief that IBD was primarily a psychosomatic illness, concluding that there was little support for the role of psychological factors in the development of ulcerative colitis or Crohn's disease.[1,2]

In a recent study using the Manitoba IBD Cohort it was shown that patients with IBD compared with a matched control group were significantly more likely to have a lifetime diagnosis of major depression (27.2% vs

12.3%; odds ratio [OR], 2.2; 95% confidence interval [CI], 1.64–2.95).[3] The strength of this study and what distinguished it from other past assessments of depression in IBD was that it used population-based samples of patients with IBD as well as of age-, gender-, and region-matched community controls. It also used a gold standard tool for measuring depression, namely, the Comprehensive International Diagnostic Interview, a structured psychiatric interview. Panic disorder tended to be higher among IBD patients, but agoraphobia without panic was not significantly different between groups and social anxiety actually was significantly lower in the IBD group (6% vs 11%; OR, 0.52; 95% CI, 0.32–0.85). In this study, those with depression versus those without a history of depression had earlier age of onset of their IBD symptoms and earlier age at diagnosis of their IBD. For those with a mood disorder, more than half of mood disorder diagnoses antedated the diagnosis of IBD by >2 years and so depression antedating IBD could not be explained simply by IBD symptoms predisposing to depression. Even if mood disorders are in remission before the onset of IBD, it has been shown that lifetime experience with anxiety or mood disorders can be important, even if not active recently. Previous experience with a mental disorder has been shown to increase the likelihood of a relapse in chronic conditions, particularly during periods of stress.[4] Cumulatively, these data raise the issue as to whether having depression predisposes to IBD, perhaps by enhancing the intestinal immunoinflammatory response. Evidence has emerged about potential common pathways, particularly between depression and inflammatory conditions such as IBD, related to dysfunctioning immunoregulatory circuits.[5–7] Alternatively, perhaps there is a common genetic predisposition shared by both diseases, or perhaps both diseases are triggered by similar environmental factors with variable lead times to overt presentation.

It is less surprising that there might be a higher rate of depression concurrent with or after the diagnosis of IBD.[8–10] Could having depression adversely impact on the course of the bowel disease? One study of IBD patients enrolled after a flare found that those with clinically significant depressive symptoms at baseline were more likely to relapse sooner.[11] In a prospective study of patients with Crohn's disease, major depression was a risk factor for failure to achieve remission with infliximab treatment.[12] Depression is associated with lower adherence to treatment regimens, which may also impact on disease course.[13]

A report in this issue of GASTROENTEROLOGY provides preclinical evidence that depression can adversely affect the course of intestinal inflammation. Using 2 experimental models of colitis, one lymphocyte dependent (oral dextran sulfate sodium [DSS]) and one lymphocyte independent (intracolonic 2,4 dinitrobenzensulfonic acid [DNBS]), Ghia et al[14] explored the impact of depression on the reactivation of quiescent colitis and underlying mechanisms in mice. Induction of depression triggered by 2 independent mechanisms including bulbectomy (to induce maladaptive behavioral patterns similar to the symptoms of patients with depression),[15] resulted in colitis reactivation. Conversely, desmethylimipramine that improved the depression also dampened the colitis. An important control experiment was the demonstration that the tricyclic antidepressant treatment that inhibited depression-induced reactivation of colitis, did not influence gut inflammation in the absence of depression. These studies provide novel experimental evidence of a causal relationship between depression and reactivation of colitis and the relevance of antidepressants in stabilizing the impact of depression on quiescent gut inflammation.

In their study, the authors also pursued mechanistic investigations based on their previous work indicating that depressive-like behaviors increased the severity of acute DSS and DNBS colitis in mice by interfering with the counterinflammatory action of the vagus nerve exerted by nicotine receptors on gut macrophages.[16] They also previously reported that tricyclic antidepressants act by restoring parasympathetic anti-inflammatory function.[16] Using pharmacologic and operative approaches along with genetically modified mice, in the current study Ghia et al[14] similarly implicated impairment of the vagal cholinergic pathway regulating cytokine secretion in depression-induced reactivation of dormant colonic inflammation. Desmethylimipramine treatment normalized these changes.[14] In addition, they identified a critical role of the α-7 subunit of the nicotinic acetylcholine receptor in inhibiting proinflammatory cytokine release from gut macrophages.[14] These studies expand the growing evidence for the "cholinergic anti-inflammatory pathway" coined by Tracey and the involvement of α-7 subunit of the nicotinic acetylcholine receptor.[17,18] Of interest was the demonstration that the colonic barrier function was not altered as monitored 5 days after reactivation of colitis in depressed mice regardless of treatment with desmethylimipramine. However, additional time points would be required to strengthen the conclusion that "the reactivation seen here is not due to the changes in intestinal barrier function."

Gastroenterologists are generally ill equipped to treat depression and perhaps even to diagnose it in its mild form. Inquiry into mood disorders by gastroenterologists might be limited by time constraints, reported as the main barrier to inquiring of patients with irritable bowel syndrome about sexual abuse.[19] Alternatively, they may simply feel they lack the experience to deal with a newly uncovered mental illness. It might just be time for gastroenterologists to become equipped with brief surveys that can screen for depression.[20,21] It would help to have

access to mental health professionals who can consult on their patients expeditiously if depression is diagnosed. Recent European consensus guidelines for Crohn's disease management include recommendations to assess for anxiety and depression and identify appropriate treatment if needed.[22] Both pharmacologic and behavioral therapies commonly used in depression have found some success in managing irritable bowel syndrome.[23] Could these therapies become important adjuncts in IBD treatment? Based on both human and animal model data, it seems warranted to consider clinical trials of antidepressant therapy in IBD both for those who are depressed but possibly also in those without depression. A review of the literature of antidepressant therapy in IBD underscored how limited the data are in this area.[24] Even if antidepressant therapy does not impact on intestinal inflammation, it may impact on quality of life.[25] In view of the clinical evidence of dysregulation of the autonomic nervous system and lower parasympathetic function in IBD patients much like in depressed patients,[26,27] the preclinical findings of Ghia et al[14] highlight the potential relevance in assessing whether antidepressants can improve the autonomic dysfunction in IBD patients and thereby restore the vagal anti-inflammatory pathways.

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Unraveling the Spider Web of Hepatic Stellate Cell Apoptosis

See "Angiotensin II activates IκB kinase phosphorylation of RelA at Ser536 to promote myofibroblast survival and liver fibrosis," by Oakley F, Teoh V, Ching-A-Sue G, et al, on page 2334.

The process of stellate cell trans-differentiation into myofibroblast-like cells, a key event in hepatic and pancreatic fibrogenesis, is associated with the activation of pathways promoting cell survival.[1] This phenomenon has been described also in other cell types that participate in the wound healing response in different organs and, together with the remarkable increase in cell proliferation, leads to hyperplasia of extracellular matrix (ECM)-producing cells, which represent a key factor in chronic wound healing and tissue fibrogenesis. Considering the natural history of chronic liver diseases (CLD), and particularly chronic hepatitis C,[2] it is possible that the acceleration in the rate of fibrosis progression observed in the late phases of the disease occurs when a critical mass of profibrogenic cells is reached and is accompanied by a progressive exhaustion of the molecular mechanisms regulating ECM degradation and remodelling. According to current knowledge, it has been speculated that any feasible treatment able to reduce ECM-producing cell hyperplasia would lead to a reduced rate of fibrosis progression or even to fibrosis regression when associated with a treatment favoring the cessation of tissue damage. In this context, it is likely that hepatic stellate cell (HSC) apoptosis represents a major mechanism. Accordingly, data from animal models indicate that recovery from acute or chronic injury is characterized by apoptosis of HSC and, as a consequence, reduction of tissue inhibitor of metalloproteinases levels and progressive degradation of the fibrotic matrix.[3–6] Along these lines, regression of liver fibrosis and, possibly, cirrhosis has been reported in patients with CLD,[7–9] once achieved with cessation of the causative agent. Although the possibility for regression of complete cirrhosis is unlikely,[10] specific induction of apoptosis in HSC may represent a realistic objective for cell-targeted therapy of liver fibrosis at almost any stage of the disease. From this perspective, it is important to stress that human HSC are characterized by a much higher resistance to apoptosis when compared to rodent HSC and that anti-apoptotic proteins such as Bcl-2 are highly expressed in fibrogenic cells within human liver tissue undergoing active fibrogenesis.[11] This indicates that meaningful indications for therapy of human CLD will be attained only when addressing this issue in human cell models and possibly, in therapeutic clinical trials.

Based on this background, the identification of factors and pathways promoting HSC survival seems to be central, because it may provide the basis for pharmacologic treatments able to induce HSC apoptosis. Candidate survival factors for HSC include transforming growth factor β1, insulin-like growth factor-1, tissue inhibitor of metalloproteinase-1, and type I collagen[3,12,13] together with persistent activation of nuclear factor-κB (NF-κB). Activation of NF-κB is a key event in the activation of HSC in cell culture models[14,15] and is accompanied by a sustained transcriptional repression of IκBα, the inhibitor of NF-κB.[16] NF-κB regulates a number of genes acting as potent inhibitors of the cellular apoptotic machinery and its activation promotes survival of HSC in the presence of apoptotic stimuli.[15,17] IκBα is further inactivated by several agents, including tumor necrosis factor-α and lipo-