Comorbidity between depression and inflammatory bowel disease explained by immune-inflammatory, oxidative, and nitrosative stress; tryptophan catabolite; and gut–brain pathways

Marta Martin-Subero,1,2 George Anderson,3 Buranee Kanchanatawan,4 Michael Berk,5,6,7,8 and Michael Maes4,6,9†

1 Department of Psychiatry, Hospital Universitari Germans Trias I Pujol, Badalona, Spain
2 Department of Psychiatry, Faculty of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain
3 Department of Psychiatry, CRC, Glasgow, UK
4 Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
5 Department of Psychiatry, University of Melbourne, Parkville, Victoria, Australia
6 School of Medicine, Deakin University, Geelong, Victoria, Australia
7 Orygen Youth Health Research Centre, Centre for Youth Mental Health, University of Melbourne, Parkville, Australia
8 Barwon Health and the Geelong Clinic, Swanston Centre, Geelong, Victoria, Australia
9 Department of Psychiatry, Health Sciences Center, Londrina State University, University Hospital, Londrina, Paraná, Brazil

The nature of depression has recently been reconceptualized, being conceived as the clinical expression of activated immune-inflammatory, oxidative, and nitrosative stress (IO&NS) pathways, including tryptophan catabolite (TRYCAT), autoimmune, and gut–brain pathways. IO&NS pathways are similarly integral to the pathogenesis of inflammatory bowel disease (IBD). The increased depression prevalence in IBD associates with a lower quality of life and increased morbidity in IBD, highlighting the role of depression in modulating the pathophysiology of IBD.

This review covers data within such a wider conceptualization that better explains the heightened co-occurrence of IBD and depression. Common IO&NS underpinning between both disorders is evidenced by increased pro-inflammatory cytokine levels, e.g., interleukin-1 (IL-1) and tumor necrosis factor-α, IL-6 trans-signalling; Th-1 and Th-17-like responses; neopterin and soluble IL-2 receptor levels; positive acute phase reactants (haptoglobin and C-reactive protein); lowered levels of negative acute phase reactants (albumin, transferrin, zinc) and anti-inflammatory cytokines (IL-10 and transforming growth factor-β); increased O&NS with damage to lipids, proteinsm and DNA; increased production of nitric oxide (NO) and inducible NO synthase; lowered plasma tryptophan but increased TRYCAT levels; autoimmune responses; and increased bacterial translocation. As such, heightened IO&NS processes in depression overlap with the biological underpinnings of IBD, potentially explaining their increased co-occurrence. This supports the perspective that there is a spectrum of IO&NS disorders that includes depression, both as an emergent comorbidity and as a contributor to IO&NS processes. Such a frame of reference has treatment implications for IBD when “comorbid” with depression.

Introduction: The Co-Association Between Depression and Inflammatory Bowel Disease

Inflammatory bowel disease (IBD), including both ulcerative colitis (UC) and Crohn’s disease (CD), is a chronic disorder with that peaks around 20 years of age, is thought to be multifactorial in nature, and is characterized by alternating exacerbations and remissions.1 The estimated prevalence of IBD is 200 per 100,000 people.2 The interactions between genetic susceptibility and environmental factors lead to dysregulation of the mucosal immune mechanisms.3 A psychosomatic component has classically been associated with IBD,4,5 while recent work suggests that psychosomatic symptoms may be a consequence of emerging biological processes.

Key words: Comorbidity, haptoglobin, immunology, inflammatory bowel disease, major depression, oxidative stress.
involving immune-inflammatory, oxidative, and nitrosoative stress (IO&NS) pathways and various tryptophan catabolites (TRYCATs), with psychosomatic symptoms being reframed as physio-somatic symptoms. While this view is the subject of ongoing research, the prevalence of classical psychiatric disorders is significantly higher in IBD patients than in healthy people.

Numerous studies have compared IBD with other chronic illnesses or healthy controls in regard to the presence of psychiatric disorders, especially depression, invariably showing increased rates in IBD patients. However, the findings are limited by inadequate study design. To date, only a few studies have used structured psychiatric interviews to determine psychiatric diagnoses and assess their prevalence in IBD patients.

As with IBD, depression has a waxing and waning pattern, with recent work suggesting that the course of repetitive episodes leads to changes in the IO&NS underpinnings driving depression. As relatively few patients have only one depressive episode, the majority will show a changing course in the IO&NS underpinnings associated with their depression, with consequences for how depression interacts levels of cognitive and functional decline.

Overall, the rates of mood disorders, including depression and anxiety, are higher in patients with IBD than in controls, both in hospital and population cohorts, with a frequency of approximately 24%-27% during remission, which is 2 to 3 times higher than in the normal population. During relapse rates, the prevalence of depression and anxiety can reach 60%-64. Of the wide body of data reviewed, there are no gender differences in the prevalence of depression in IBD patients, although it should be noted that prevalence rates are variable across countries, being higher in Canada, Scandinavia, and New Zealand than in other countries. As to whether this is linked to the distance of these countries from the equator, and therefore with sunlight-driven vitamin D, a known modulator of IBD and likely also depression, remains to be determined.

Another controversy has been as to whether depression emerges at different phases of the course of IBD. In a nested case-control study with a sample of 12,500 individuals, Kurina et al observed that both depression and anxiety preceded the onset of UC significantly more often than would be expected, but not in CD. These authors also found increased depression and anxiety in UC and CD during the first year after diagnosis. Depression scores at baseline correlate with the time to IBD recurrence, suggesting that depression is a susceptibility factor for IBD relapse, while other work shows that the appearance of affective symptoms in IBD is related to lower physical recovery rates. The high prevalence of depression in these patients suggests that it plays a role in the pathophysiology and/or course of IBD, with relevance for its clinical management. Such data suggest that depression may arise from processes underpinning IBD. However, it should be noted that the directionality of depression and IBD has still to be experimentally determined.

The aim of this review is to overview the data on the biological associations of depression with IBD, and on the basis of this to propose a role for common biological underpinnings based on IO&NS processes. Given that a systematic review on the co-occurrence of depression and IBD has recently been published, this is a more selective narrative review on the nature of the IO&NS interactions of these 2 common conditions. As such, this article focuses on IO&NS pathways including the microbiome-gut-brain axis.

The Microbiome–Gut–Brain Axis

The gut-brain axis is the bidirectional communication system that integrates hormonal, neural, and immune signals between the brain and the gut, including gut microbiota influence on the development and function of the brain. The human lower gastrointestinal tract contains almost 100 trillion microorganisms, most of which are bacteria. Although several gut-derived bacterial products can induce behavioral changes, such as short chain fatty acids and hydrogen, we focus here on lipopolysaccharide (LPS) given its proven importance to the microbiota-gut-brain axis. LPS is a structural portion of the external membrane of Gram-negative bacteria. The intestinal barrier normally prevents Gram-negative bacteria and LPS from reaching the systemic circulation. However, the slackening of epithelial tight junctions can increase the translocation of commensal bacteria, including Gram-negative bacteria, from the gut to the lamina propria and the mesenteric lymph nodes (MLN). From the MLN, bacteria and thus LPS may spread to the systemic circulation, especially when there are alterations in immune responses. Once in the blood, LPS may increase the production of pro-inflammatory cytokines by binding to the CD14-Toll-like receptor-4 (TLR4) complex. Mononuclear cells, endothelial cells, microglia, astrocytes, and neurons can express TLRs, which when activated by LPS produce an innate immune response involving activation of nuclear factor-κB (NF-κB) and the mitogen-activated protein kinases pathways. This drives increases in peripheral and central pro-inflammatory cytokines, consequently altering neuronal functions.

Methods

This is a narrative review. Data for this article were sourced from the electronic databases PUBMED, Google
Scholar, and Scopus, and were not limited by publication date or language. Key words were as follows: depression, mood disorders, IBD, CD, UC, immune, inflammation, oxidative stress, nitrosative stress, antioxidants, tryptophan and tryptophan catabolites, leaky gut, bacterial translocation, gut permeability, tight junctions, gut commensals, LPS, Gram-negative bacteria.

Inflammation and Oxidative and Nitrosative stress (IO&NS) Pathways in Depression

Inflammation and cell-mediated immune activation in depression

Since 1990, accumulating evidence has indicated that activation of immune-inflammatory pathways and neural-immune interactions are intimately involved in the pathophysiology of unipolar and bipolar depression. The first article on the topic reported increased serum levels of soluble IL-2 receptors (sIL-2Rs) in depression, indicating T cell activation. There are 3 major findings that signify immune-inflammatory processes in depression and which have consistently emerged in reviews on the condition.

The first finding is elevated levels of pro-inflammatory cytokines (PICs), including IL-1, IL-6, IL-8, IL-12, and tumor necrosis factor-alpha (TNFα) coupled to decreased levels of anti-inflammatory cytokines, such as transforming growth factor-beta (TGF-β) and IL-10. The serum levels of sIL-6R are significantly increased in unipolar depression and bipolar disorder, suggesting that these diseases are accompanied by increased IL-6 trans-signaling. Increased IL-6 trans-signaling is considered to be a key phenomenon underpinning the pathophysiology of depression.

Second, there are signs of T-cell activation in depression, characterized by elevated serum levels of neopterin, serum sIL-2Rs and sCD8, and T cell activation markers such as CD25+ and HLA-DR+, as well as activation of peripheral T helper (Th1)-like and Th-17-like cells, including increased production of IL-2, interferon (IFN)γ, and IL-17. Given its role in both mucosal defense and autoimmune responses, IL-17 may be of particular salience.

Third, increased plasma acute phase protein (APP) concentrations, such as α-1-antitrypsin, haptoglobin, fibrinogen, and C-reactive protein (CRP) have been consistently reported. An acute phase response is also indicated by decreased plasma levels of negative acute phase proteins, such as transferrin and albumin. Polymorphisms in haptoglobin modulate susceptibility to depression. There are also diminished levels of serum zinc, which is another negative acute phase reactant and biomarker of the inflammatory response in depression. Complement activation is evident as indicated by increased levels of the complement factors C3 and C4.

Oxidative and nitrosative stress (O&NS) in depression

Activation of immune-inflammatory pathways is accompanied by elevated O&NS. This is accompanied by the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) that may react with proteins, DNA, and fatty acids, including mitochondrial DNA, thus causing damage in cell membrane construction and adhesiveness, which in turn can lead to aberrations in function and expression of multiple proteins and receptors.

Evidence shows that unipolar and bipolar depression are accompanied by O&NS processes, as indicated by increased plasma levels of malondialdehyde (MDA), a by-product of polyunsaturated fatty acid peroxidation; increased levels of 4-hydroxynonenal, which is also generated by lipid peroxidation, in brain regions, such as the anterior cingulate cortex; and increased levels of xanthine oxidase activity in post-mortem brain tissue. Damage to DNA in depression is indicated by increased levels of 8-hydroxy-2-deoxyguanosine, a mutagenic DNA lesion, in the serum of patients. DNA damage increases the DNA repair response, including increased poly(ADP-ribose) polymerase, which decreases nicotinamide, further contributing to mitochondrial dysfunction and ROS production.

Depressed patients also show disorders in iron metabolism and the erythron, including decreased hemoglobin and iron, in association with inflammation and increased blood levels of MDA, hydrogen peroxide, and DNA damage. Moreover, telomere shortening has also been observed in patients with mood disorders. There is also evidence for chromosomal aberrations in cell nuclei and telomere dysfunction.

Such increases in IO&NS and their consequences are coupled to increased levels of endogenous antioxidants in depressed patients, including zinc, glutathione, coenzyme Q10, and vitamin E, as well as decreased intake of anti-oxidant-rich foods. Overall, IO&NS are significantly increased in depressed patients, with wider cellular and system consequences, including decreased mitochondrial functioning, which further contribute to increased IO&NS, as well as energetic regulation.

Autoimmune responses in depression

Depression is accompanied by autoimmune responses, including increased levels of anti-nuclear factor, and antiphospholipid and anti-serotonin antibodies.
These autoimmune responses are significantly correlated with activated immune-inflammatory pathways. For example, significant correlations were found between antinuclear antibodies and serum sIL-2R levels and between anti-serotonin autoantibodies and levels of pro-inflammatory cytokines, including IL-1 and TNFα.55,59 Also, in other medical disorders, autoimmune markers may be associated with depression. For example, in patients with systemic lupus erythematosus, depression is associated with serum antibodies directed against N-methyl-D-aspartate receptor and anti-ribosomal P antibodies.60,61

By altering the chemical structure of functional proteins, O&NS can create a variety of modified epitopes (neoepitopes), such as oxidative-specific epitopes (OSEs) and nitroso-specific epitopes (NSEs), which can become immunogenic by inducing an autoimmune response against them.12 Increased IgM- and IgG-mediated immune responses against OSEs, such as oxidized low density lipoproteins and anchorage molecules, including phosphatidyl inositol and palmitic acid, and NSEs, including NO-cysteiny1, are evident in depressed patients.62,63

The TRYCAT pathway in depression

The serotoninergic system is closely related to the pathophysiology of depression, with decreases in the plasma levels of the serotonin precursor, L-tryptophan, being one of the most significant markers of depression. Tryptophan is also catabolized by indoleamine 2,3-dioxygenase (IDO), leading to the synthesis of TRYCATs such as kynurenine, kynurenic acid, quinolinic acid, and xanthurenic acid.62 Some TRYCATs, such as kynurenic and quinolinic acid, have depressogenic, neuroregulatory, and neurotoxic effects, driving changes in behavioral responses, including the induction of anxiety and depression.64,65 Quinolinic acid is excitatory and neurotoxic, and is proposed to play a role in driving central changes that occur in depression patients.6 Other TRYCATs, like kynurenic acid, have shown neuroprotective properties. As such, the pattern of TRYCATs locally expressed in the CNS can significantly determine the nature of neuronal and behavioral responses.

Cytokines such as IFN-γ, TNFα, IL-2, IL-6, IL-18, and IL-1β can induce IDO, driving tryptophan down to TRYCATs production and away from serotonin synthesis.66 For instance, INFα-based immunotherapy in hepatitis C patients can induce depressive symptoms that are strongly associated with increased IDO activity, thereby leading to the production of neuroregulatory TRYCATs.67,69

As such, immune-inflammation related cytokines, by increasing IDO and driving tryptophan to TRYCATs production, not only deplete serotonin levels but locally induce changes in the levels of central and peripheral neuroregulatory TRYCATs that contribute to the changes evident in depressed patients. Moreover, the immune-inflammatory processes that increase IDO and deplete tryptophan will also decrease levels of N-acetylseryotonin (NAS) and melatonin.6 Depression is also accompanied by increased levels of cortisol, which may activate tryptophan 2,3-dioxygenase, which, like IDO activation, decreases serotonin and melatonin, as well as increasing neuroregulatory TRYCATs.6

Activation of the TRYCAT pathway is part of the compensatory anti-inflammatory reflex system (CIRS), which is induced by IO&NS responses and subsequently attenuates the primary immune-inflammatory response.38 Lowered tryptophan and increased TRYCAT levels (except quinolinic acid) have negative immunoregulatory effects, while a chronic increase of TRYCATs, such as kynurenine, kynurenic acid, and quinolinic acid, may have depressogenic, neuroregulatory, and neurotoxic effects.

Bacterial translocation in depression

Increased levels of IgM and IgA antibodies against LPS of different Gram-negative enterobacteria are also a common finding in depression, especially chronic depression.70 This indicates a slackening of the tight junction barrier with increased translocation of commensal bacteria from the gut into the MLN and the blood.70 In depression, the increased IgM/IgA levels directed against LPS are significantly correlated to different IO&NS markers, suggesting that increased bacterial translocation drives gut-derived immune-inflammation.53

LPS can induce depression- and anxiety-like behaviors, fatigue, and mild cognitive impairment through activated IO&NS pathways. For instance, several studies have shown that LPS administration can diminish appetite, body weight, social interaction, and activity, as well as produce anhedonia.71,72 The psychosocial environment can also modulate the effects of LPS, with social stress arousing higher expression of LPS-specific binding receptors, the TLR4, on the surface of splenic macrophages.73 As such, the systemic effects of increased LPS in combination with the upregulation of TLRs due to psychological stress are common features in depression.

Recently, a systematic review indicated that melatonin may benefit in inflammatory bowel disease.74 Melatonin is a hormone that is highly expressed in the gut and a significant inhibitor of gut permeability,75,76 which suggests that the depletion of melatonin will have consequences for gut permeability, bacterial translocation, and the increased LPS evident in depressed patients.70,73
Inflammation and Oxidative and Nitrosative Stress (IO&NS) Pathways in IBD

**Inflammation and cell-mediated immune activation in IBD**

Being an important interface with the environment, the gut is under high immune system surveillance, including a large system of dendritic cells and macrophages that play a role in adaptive immune responses, but that can also become dysregulated, leading to immune system-driven pathology.\(^{77}\) Increases in these immune cell populations have been observed in experimental models of IBD and colitis, with associated increases in their secretion of pro-inflammatory cytokines, including TNF-\(\alpha\) and IL-6, IL-13, IL-17, IL-22, and IL-23.\(^{76}\) TNF-\(\alpha\) is a major target for IBD’s treatment following the clinical utility of the anti-TNF-\(\alpha\) antibody, first shown in 1998.\(^{79}\) IL-6 is elevated in the intestinal mucosa and contributes to the changes occurring in IBD, with most pro-inflammatory effects being mediated by increased IL-6 trans-signaling.\(^{80,81}\) IL-6 also upregulates IL-17, while IL-23 activates a set of tissue-homing memory cells, increasing the production of the pro-inflammatory mediators IL-6 and IL-17.\(^{82}\) The production of IL-1 as well as the sIL-1RA is increased in patients with active UC and CD.\(^{83,84}\) Not only TNF\(\alpha\) and IL-6, but IL-1 is also involved in the onset and amplification of IBD-related intestinal injury.\(^{84}\)

IL-13 may have a role in producing natural killer T cells in UC\(^{85}\) and is a significant treatment target in IBD.\(^{86}\) IL-22 expression is increased in CD\(^{87}\) and can have both protective and damaging effects in IBD, depending on the disease phase.\(^{88}\) Studies in several mouse models of IBD have observed an association between IL-23 and intestinal inflammation.\(^{89}\) with increased IL-23 receptors being evident in UC and CD patients.\(^{90}\) Increases in levels of such Th-17-inducing cytokines, such as IL-6 and IL-23 in the inflamed gut, have raised interest in the role of Th-17 cells in the pathogenesis of IBD,\(^{91,92}\) with the suppression of Th-17 cell activity ameliorating colitis in murine models.\(^{93,94}\) This is concordant with the shared role of the Th-17 system in both mucosal defense and the development of autoimmunity.

Plasma levels of pro-inflammatory and Th-1 cytokines, including IFN\(\gamma\) and TNF\(\alpha\), are increased in adults and children with CD when compared with controls,\(^{95}\) indicative of wider peripheral pro-inflammatory processes. Beltrán et al\(^{96}\) found increased expression of IFN-\(\gamma\), IL-17, IL-5, and IL-13 in peripheral blood of UC and CD patients when compared to healthy controls. In patients with UC and CD, significantly increased levels of serum and fecal neopterin are observed, suggesting local and peripheral T cell-mediated processes.\(^{97,98}\) sIL-2R levels are not only increased in peripheral blood of CD and UD patients, but also their intestinal cells produce more sIL-2R than peripheral cells.\(^{99}\) In CD, elevations in sIL-2R levels also are observed during remission, with increased sIL-2R levels being associated with the number of CD relapses.\(^{100}\) UC is also accompanied by increased sIL-2R levels in association with different autoimmune markers.\(^{101,102}\) In CD, but not UC, spontaneous production of IL-2R by mucosal cells is significantly increased as compared with surgical controls.\(^{99}\) While serum sIL-2R levels are significantly elevated in CD patients, serum sCD8 levels are only mildly elevated in those patients.\(^{103}\)

Some acute phase proteins are also increased in IBD, including serum CRP levels, which have been used as a marker of disease activity and remission.\(^{104,105}\) Plasma haptoglobin levels are also increased in the active phase of the disease,\(^ {106}\) with increased frequency of the haptoglobin allele being higher in CD.\(^{13}\) Increased concentrations of haptoglobin, \(\alpha\)(1)-antitrypsin, \(\alpha\)(1)-antichymotrypsin, orosomucoid, and hemopexin in the serum of IBD patients were shown decades ago, while the concentrations of albumin, prealbumin, \(\alpha\)(2)-HS glycoprotein, ceruloplasmin, \(\alpha\)(2)-macro-globulin, and transferrin were decreased.\(^{106}\) Finally, lower serum levels of zinc, a micronutrient involved in the systemic immune response, have been found in IBD patients, as in depressed patients.\(^{107,108}\)

In addition to increased immune-inflammatory processes, the activity of the immune-suppressive cytokines TGF-\(\beta\) and IL-10 appear to be diminished in IBD.\(^{109,110}\) High concentrations of TGF-\(\beta\) are found in the intestinal tract, where they modulate the local immune response.\(^{111}\) IL-10 has anti-inflammatory and negative immunoregulatory effects,\(^ {112}\) with deletion of IL-10 production in mice leading to the development of colitis.\(^{112,113}\) IL-10 receptor gene mutations are also associated with severe early-onset IBD.\(^ {114}\)

**Oxidative and nitrosative stress (O&NS) in IBD**

Substantial evidence shows that chronic intestinal inflammation is intimately related to O&NS formation,\(^ {115}\) with increased O&NS and wider biomarkers of oxidative injury, such as lipid peroxidation products and protein modifications, evident in UC and CD patients.\(^ {116}\) The cellular sources of O&NS have been identified in experimental models of IBD,\(^ {115}\) which include inflammatory cells, such as neutrophils and macrophages that can produce large quantities of superoxide and nitric oxide. These two species interact to form the potent oxidant peroxynitrite, which can induce IBD-like inflammation and pathological changes in animal models when intrarectally administered.\(^ {117}\) Moreover, pro-inflammatory cytokines promote intestinal epithelial cells’ production of NADPH-oxidase (NOX) and iNOS, thereby driving increases in O&NS. Myeloperoxidase (MPO) is another
indicant of gut inflammation and increased O&NS in experimental IBD models,118 where it is used as an IBD biomarker.115 Other ROS pathways are also involved in the pathology of IBD, including xanthine oxidase, 5-lypoxigenase, and cytochrome P450 enzymes.115 Nitrosothiols are significantly increased in UC and CD in children.119

Decreased endogenous antioxidants are evident in IBD patients, especially in periods of remission,120 which suggests that increased O&NS and decreased antioxidants contribute to recurrent disease activity. For example, Alzoghaibi121 reported lower blood levels of vitamins C and E and lowered intestinal mucosa concentrations of glutathione, β-carotene, and vitamin A, C, and E in CD patients.

Autoimmune responses in IBD

The presence of several anticarbohydrate antibodies has been consistently shown in IBD,122 where they have been used as disease biomarkers. Increased levels of antiphospholipid antibodies in the blood of patients with severe forms of CD and UC have also been found,123 while antibodies against luminal antigens are found in CD. Antineutrophil cytoplasmic (auto)antibodies (ANCA) and anti-glycan antibodies are other serologic markers of IBD.124 The finding of antibodies against these glycans suggests an interaction between the adaptive and innate arms of the immune response in CD patients.122,125

The TRYCAT pathway in IBD

Plasma levels of kynurenine and kynurenic acid, but not tryptophan, 3-hydroxykynurenine, or xanthurenic acid, are higher in IBD patients.126 Patients with active CD show lowered levels of serum tryptophan and an increased serum kynurenine/tryptophan ratio as compared with controls and patients in remission.127 The kynurenine/tryptophan ratio was significantly correlated with disease activity and with inflammatory markers, while clinical improvement was associated with normalization of tryptophan and kynurenine levels.127 In a mouse CD model, increased TRYCAT levels, including xanthurenic acid, are associated with inflammatory processes in the gastro-intestinal tract.128 In supernatants from colonic explant cultures of CD patients, increased kynurenine levels and an increased kynurenine/tryptophan ratio were found, while these indicators of IDO activation improved after treatment with infliximab.129 These authors conclude that elevated IDO activity may represent a CIRS response attenuating the damaging effects of inflammatory infiltrations in the colon mucosa. All in all, the results suggest increased IDO activity in IBD in peripheral blood and colon cells (lamina propria and epithelium).130

Bacterial translocation in IBD

Accumulating evidence suggests a fine balance between the intestinal microbiota and the host immune system at the mucosal frontier, which is core to the initiation and pathogenesis of IBD.131 The epithelial barrier and mucosal homeostasis display anatomical features that physically impede the penetration of macromolecules, bacteria, food antigens, and environmental toxins. Tight junctions are pivotal to barrier formation and are regulated by cytokines. Gut biopsies show a downregulation of tight junctional complexes in IBD patients.132 Such increased intestinal permeability is present not only in IBD patients, but also in their healthy relatives.133-135 Increased intestinal permeability is also often accompanied by changes in the composition of gut microbiota, a process designated as dysbiosis.21 IBD patients showed a reduction in bacterial diversity. This is exemplified in a recent study of mucosal biopsy samples, where UC patients showed increases in Actinobacteria and Proteobacteria, coupled to a decrease in Bacteroidetes, versus their healthy siblings.136 Moreover, a striking difference in microbial diversity between CD patients and healthy controls is observed primarily due to a reduced complexity of the phylum Firmicutes in CD and UC patients.137 Overall, decreased bacterial diversity in IBD patients is coupled to increased gut permeability and enhanced intestinal bacteria infiltration that drives the immune response, which ultimately leads to progressive systemic inflammation.131 Activation of different epithelial and endothelial sphingosine-1-phosphate (S1P) receptors plays a significant role in determining intestinal permeability.138,139

Shared Pathways in Depression and IBD

Common immune-inflammatory pathways

As reviewed above, immune-inflammatory reactions occur in depression as well as in IBD, with evidence of common markers across both conditions, including increased levels of IL-1, IL-1RA, sIL-2R, IL-6, sIL-6R, IL-17, IL-22, IL-23, TNF-α, and IFN-γ. Given the increase in Th-17-inducing cytokines, recent work has looked for changes in Th-17 cells in IBD and depressed patients. The suppression of Th-17 cell activity ameliorates colitis in murine models,93,94 with increased Th-17 cell numbers being evident in depressed patients.140 Th-17 cells and increased IL-17 production may also have a role in the etiology and course of depression as suggested by animal models.10 Given such heightened immune-inflammatory activity, it is not surprising that the activity of immune-suppressive cytokines, such as TGF-β and IL-10, is decreased in IBD,112 as well as in depressed patients.33,35,36
In addition, some APP that are increased in depression seem also to be associated with the pathophysiology of IBD. CRP serum levels have been used as a marker of disease activity and remission in CD and UC,\textsuperscript{104,106} with CRP concentrations also being higher in depressed patients.\textsuperscript{141} Higher CRP appears to be a risk biomarker for depression, with higher levels predicting a higher risk of de-novo depression.\textsuperscript{142} CRP increases blood-brain barrier permeability,\textsuperscript{143} suggesting that increased serum CRP in IBD, and other conditions, will contribute to changes centrally. Haptoglobin is another acute phase protein that is consistently elevated in depression,\textsuperscript{42} with levels also being significantly higher in the active phase of IBD.\textsuperscript{106} An increased frequency of the haptoglobin 1 allele is associated with depression and CD.\textsuperscript{13} α1-Antitrypsin is a positive APP that is increased in IBD\textsuperscript{106} and depression.\textsuperscript{42} As such, several wider inflammation-associated proteins are increased in both IBD and depression.

**Common O\&NS pathways**

Both IBD and depression accompanied by increased O\&NS and ROS/RNS, and also damage to proteins, DNA, and lipids, increased nitrosylation and lowered levels of some antioxidants. Common biomarkers are increased MDA, MPO, iNOS, and xanthine oxidase and lowered glutathione and zinc levels. Systemic inflammation and LPS-induced inflammatory cytokines can enhance peripheral and central O\&NS processes, including microglia and astrocyte activation, with chronic glia activation contributing to a cascade of IO\&NS that can compromise neural functioning thus causing depression.\textsuperscript{144,145}

Chronic intestinal inflammation is closely related to increased ROS/RNS, including superoxide, hydrogen peroxide, and NO, which drive increased O\&NS.\textsuperscript{115,116} The importance of ROS/RNS is emphasized by the utilization of MPO as a biomarker for gut inflammation.\textsuperscript{115,118} Likewise, increased O\&NS also accompanies inflammation in depression,\textsuperscript{38} with increased NADPH oxidase driving depression by stress-induction in animal models.\textsuperscript{146} Some of the efficacy of classical antidepressants may be mediated via the inhibition of ROS/RNS.\textsuperscript{147} The decrease in endogenous antioxidants in IBD patients in remission\textsuperscript{120} suggests an important role for ROS/RNS in the course of IBD recurrence. The efficacy of some antidepressant drugs is linked to induction of endogenous antioxidants, with many novel antidepressants being powerful antioxidants.\textsuperscript{6} Lower serum zinc levels are evident in IBD patients, although it is unclear as to whether this is a risk factor for, or a consequence of, the disease.\textsuperscript{148} Decreased blood zinc levels and lower zinc intake are also evident in depressed patients,\textsuperscript{46,49,149} and are another commonality between these conditions. Hypozincemia in humans is associated with other conditions, including dysphoria, anorexia, cognitive impairment, and wider psychiatric disorders, as well as taste and smell deterioration.\textsuperscript{149,150} The clinical efficacy of melatonin, a powerful anti-oxidant and anti-inflammatory, in IBD highlights the significant role of ROS/RNS in the course of the disorder.\textsuperscript{74} As with IBD, targeting melatonergic receptor activation has proved useful in the treatment of depression.

Such commonalities in increased ROS/RNS/O\&NS in IBD and depressed patients may be driven by mitochondrial dysfunction in both conditions,\textsuperscript{151,152} with mitochondria being a major source of ROS, both centrally and peripherally. As such, factors impinging on mitochondrial functioning are likely to contribute to the commonalities between IBD and depression, including variations in local melatonin production, which may well occur in the mitochondria.\textsuperscript{153}

**Common auto-immune responses**

Increased levels of antiphospholipid antibodies have been found in the blood of individuals with severe forms of CD and UC,\textsuperscript{123} paralleling similar data in depressed patients.\textsuperscript{58,59} A number of other characteristics are evident across autoimmune disorders, with similar changes being evident in IBD and depressed patients, including the following: (i) These disorders show a recurrent course of alternations characterized by remissions and exacerbations\textsuperscript{154}; (ii) there are high levels of wider neural and psychiatric manifestations in autoimmune disorders; (iii) they have a similar immune cell profile, with IL-6 trans-signaling and Th-17 cells commonly being increased. The pathophysiology of autoimmune disorders is associated with dysfunctions in the interaction network between dendritic cells and adaptive immune cell types.\textsuperscript{155}

**Common TRYCAT pathway activation**

As reviewed above, both depression and IBD are accompanied by activation of the TRYCAT pathway with decreased concentrations of plasma tryptophan but increased kynurenine levels. Activation of IDO in both disorders may be part of the CIRS response, which downregulates the primary immune-inflammatory response. Thus, increased levels of pro-inflammatory cytokines in both IBD and depression, including IFNγ, IL-1, and IL-6, may induce the TRYCAT pathway, thereby lowering plasma tryptophan and increasing TRYCAT levels. Chronically decreased levels of plasma tryptophan and increased TRYCAT levels are involved in the onset of the physio-somatic symptoms of depression and neurotoxic processes, including lowered neuroplasticity and neurogenesis.\textsuperscript{38}
Common gut–brain axis dysfunction

We have highlighted the role of LPS in the gut-microbiota-brain axis above. Acute LPS administration can induce depressive-like behaviors, while chronic-intermittent administration of LPS to mice for 4 months causes a depressive state. Experimental investigations show increased immune responses against LPS in depressed patients, with animal studies showing that both peripheral and centrally administered LPS induces depressive-like behaviors via the induction of different central TRYP CATs. Normally the intestinal barrier prevents bacterial translocation, but when this barrier is suboptimal, as in IBD and depressed patients, LPS translocation generates an O&NS process, with peripheral and central cytokine elevations that can alter central processing, at least in part via altered glia activity and TRYP CAT induction. It is these overlapping processes that drive the association of IBD with depression.

Endotoxemia can drive alterations in serotonergic functioning. Generally, increased gut serotonin is evident in IBD where it contributes to the course of the disorder, whereas serotonin is decreased centrally and peripherally in depressed patients. Given that melatonin is protective of IBD, it requires investigation as to whether there are any variations in the conversion of serotonin to NAS and melatonin in gut-associated cells of IBD patients.

Changes occurring centrally also have consequences for gut regulation, allowing the microbiota-gut-brain axis to be a bidirectional system. The brain may also influence the composition of commensal gut bacteria, with some studies demonstrating that exposure to stress can result in substantial changes to the microbial composition of the gut. As such, the central changes, classically most often associated with depression, have impacts on gut functioning, in turn impacting on the course of depression and IBD, as well as in their interaction.

Discussion and Perspectives

Conclusions

In conclusion, shared IO&NS, including TRYP CAT, autoimmune, and gut-brain pathways, underpin both the pathophysiology of IBD and depression. These shared pathways include increased pro-inflammatory cytokines (such as IL-1, IL-6, IL-17, IL-22, IL-23, TNF-α, IFN-γ); increases in the levels of APPs; activated T cells; autoimmunity; lowered tryptophan and increased TRYP CATs; intestinal permeability with bacterial translocation; O&NS with damage to DNA; lipid peroxidation; and increased NO and iNOS production. These pathways are involved in the pathogenesis of IBD and depression as well. These pathways may also explain that depression could worsen the outcome of IBD. In animal (C57BL/6 mice) models of induced colitis, injections of reserpine or olfactory bulbectomy, which both induce depression, are accompanied by inflammatory flare-ups and elevated levels of pro-inflammatory cytokines. These findings suggest that depression, when present, may reactivate dormant colitis.

Two different models highlighting the commonalities that drive the co-occurrence of IBD and depression are shown in Figures 1 and 2 shows that IBD may be primed by IO&NS, including autoimmune, TRYP CAT, and gut-brain pathways, for an increased prevalence

<table>
<thead>
<tr>
<th>Inflammatory bowel disease</th>
<th>Central Neuroinflammation Neurotransmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gut inflammation</td>
<td>Peripheral</td>
</tr>
<tr>
<td>Peripheral</td>
<td>↑TNFα, IL-1</td>
</tr>
<tr>
<td>↑IL-6 trans-signalling</td>
<td>↑IL-22, IL-2, IFNγ, Th17, TGFβ, IL-10</td>
</tr>
<tr>
<td>Acute Phase Response</td>
<td>↑CRP, Hp</td>
</tr>
<tr>
<td>↑Alb, Tf, Zinc</td>
<td>↑Lipid peroxidation</td>
</tr>
<tr>
<td>↑DNA damage</td>
<td>↑Nitrosylation</td>
</tr>
<tr>
<td>↑Autoantibodies</td>
<td>↑Tryptophan</td>
</tr>
<tr>
<td>↑Kynurenine</td>
<td>↑Leaky gut</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Depression secondary to IBD in vulnerable subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral</td>
</tr>
<tr>
<td>↑Immune activation</td>
</tr>
<tr>
<td>↑Inflammation</td>
</tr>
<tr>
<td>↑O&amp;NS</td>
</tr>
<tr>
<td>↑Anti-ox defences</td>
</tr>
<tr>
<td>↑Autoimmunity</td>
</tr>
<tr>
<td>↑IDO activation</td>
</tr>
<tr>
<td>↑Bacterial translocation</td>
</tr>
</tbody>
</table>
of depression. Figure 2 shows that the comorbidity between inflammatory bowel disease (IBD) and depression may be explained by shared pathways, including peripheral activation of cell-mediated immune (CMI), inflammatory, oxidative and nitrosative stress (O&NS), autoimmune, and tryptophan catabolite (TRYCAT) pathways. These peripheral pathways are associated with (a) central neuroinflammation and disorders in neurotransmission, thereby causing the symptoms of depression; and (b) mucosal and transmural inflammatory lesions, thereby causing the symptoms of IBD. An increased frequency of the haptoglobin (Hp) 1 allele is associated with depression and Crohn’s disease. The above-mentioned pathways in depression are triggered by interactions between a wide variety of immune-inflammatory hits, genes, and environmental factors, whereas in IBD the inflammatory lesions are induced by interactions between luminal antigens, genes, and environmental factors. CVD: cardio-vascular disorder, COPD: chronic obstructive pulmonary disease, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, IFN: interferon.

Finally, Raison et al tested the effect of a monoclonal antibody directed at TNFα (infliximab) in patients with resistant depression. They observed that TNF antagonist may improve depressive symptoms in patients with high baseline inflammation biomarkers.169

As such, cytokine-blocking agents have potential as future antidepressant treatments, with a mechanism of action that is driven by a reconceptualization of processes underlying depression and its association with other disorders, including IBD. Since anti-TNFα agents are already in use for several immunologic pathologies, such as psoriasis, ankylosing spondylitis, or IBD, they have a known safety profile, further increasing their appeal in the treatment of depression. This will be important to determine, especially when depression is not associated with concurrent medical conditions such as IBD. N-Acetyl cysteine, which has robust effects on O&NS pathways, has shown some promise in the treatment of depression, and there is preclinical evidence that it reduces gut permeability.172,173

Some recent data show that antidepressants may also improve IBD. There is now evidence that antidepressants have negative immunoregulatory effects by decreasing the IFN/IL-10 production ratio, and anti-inflammatory...
effects by attenuating the production of pro-inflammatory cytokines, including IL-1 and TNFα.\textsuperscript{174} When antidepressant drugs were employed to treat depression in IBD patients, it was observed that antidepressants also reduced relapse rates, use of steroids, and number of endoscopies.\textsuperscript{175} In another small-sample-size study (n = 15), all IBD patients treated with antidepressants reported improved quality of life and 33% reported that antidepressants improved the course of their IBD.\textsuperscript{176} These results were replicated in another study that showed that antidepressants improved psychological well-being in 87% of 98 IBD patients, while 25% reported that their IBD had improved.\textsuperscript{177} In 81 patients with IBD, 49.4% of the patients showed improvements in IBD symptoms following treatments with tricyclic antidepressants, while patients with UC improved significantly more than those with CD.\textsuperscript{178} In mice models, desmethylimipramine, an antidepressant, reduces the increased depression-induced vulnerability to develop colitis. It additionally reduces intestinal inflammation (including increased levels of CRP, IL-1, IL-6, and TNFα) and restores normal intestinal function.\textsuperscript{177} Therefore it will be important to determine, especially when IBD is not associated with concurrent depression, whether antidepressants may improve IBD through effects on the I&ONS pathways, including the TRYCAT pathways and bacterial translocation. It is also noteworthy that 2 forms of psychotherapy for young people with depression and IBD have proven some utility.\textsuperscript{179} As to whether such psychotherapies modulate the pathophysiological processes linking depression and IBD, as highlighted above, will be important to determine.

**Disclosures**

Marta Martin-Subero, Buranee Kanchanatawan, George Anderson, and Michael Maes do not have anything to disclose. Michael Berk has the following disclosures: Stanley Medical Research Foundation: researcher, research support; MBF: researcher, research support; NHMRC: researcher, research support; Cooperative Research Centre: researcher, research support; Simons Autism Foundation: researcher, research support; Cancer Council of Victoria: researcher, research support; Rotary Health: researcher, research support; Meat and Livestock Board: researcher; research support; Woolworths: researcher, research support; BeyondBlue: researcher, research support; Geelong Medical Research Foundation: researcher, research support; Bristol-Myers Squibb: consultant, advisor, speaker, researcher, honoraria and research support; Eli Lilly: consultant, advisor, speaker, researcher, honoraria and research support; Servier: consultant, advisor, speaker, researcher, honoraria and research support; Glaxo SmithKline: consultant, advisor, speaker, researcher, honoraria and research support; Organon: researcher, research support; Novartis: researcher, research support; Mayne Pharma: researcher, research support; AstraZeneca: consultant, advisor, speaker, honoraria; Biodvantage: consultant and advisor, honoraria; Merek: consultant and advisor, honoraria; Lundbeck: consultant, advisor, speaker, honoraria; Janssen Cilag: consultant, advisor, speaker, honoraria; Solvay: speaker, honoraria; Wyeth: speaker; honoraria; Pfizer: speaker, honoraria.

**REFERENCES:**


