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REVIEW

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Immune Activation in Irritable Bowel Syndrome: Can Neuroimmune Interactions Explain Symptoms?

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Irritable bowel syndrome (IBS) is a functional disorder of the gastrointestinal (GI) tract characterized by pain or discomfort from the lower abdominal region, which is associated with altered bowel habit. Despite its prevalence, there is currently a lack of effective treatment options for patients. IBS has long been considered as a neurological condition resulting from alterations in the brain gut axis, but immunological alterations are increasingly reported in IBS patients, consistent with the hypothesis that there is a chronic, but low-grade, immune activation. Mediators released by immune cells act to either dampen or amplify the activity of GI nerves. Release of a number of these mediators correlates with symptoms of IBS, highlighting the importance of interactions between the immune and the nervous systems. Investigation of the role of microbiota in these interactions is in its early stages, but may provide many answers regarding the mechanisms underlying activation of the immune system in IBS. Identifying what the key changes in the GI immune system are in IBS and how these changes modulate viscerosensory nervous function is essential for the development of novel therapies for the underlying disorder.

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INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic debilitating functional illness affecting more than 10% of the population (1). Patients are diagnosed if they have recurring pain or discomfort in the lower abdomen, accompanied by altered stool form or frequency. Importantly, these symptoms occur in the absence of gross structural abnormalities. As biomarkers are lacking, IBS patients are grouped according to symptom-based criteria, with the current ROME classification system subcategorizing patients as diarrhea predominant (IBS-D), constipation predominant (IBS-C), alternating (IBS-A), or unspecified (IBS-U) (1). The sensory symptoms of pain/discomfort are the most debilitating aspects to patients, yet are the least responsive to pharmacological treatment. IBS is currently considered as a neurological motility disorder resulting from alterations in the brain gut axis; however, the underlying mechanisms are unclear. The gastrointestinal (GI) tract contains extensive immune and nervous systems (outlined in **Figure 1**), and alterations in the immune system are increasingly implicated in the pathogenesis of IBS (2). This was first observed in patients that attributed their symptoms to prior exposure to a GI pathogen, termed post-infectious IBS, but more recently has also been shown in other IBS cohorts (2,3). Surprisingly, little is known of how changes in the immune function affect the nerve function in IBS. This is despite the substantial body of work showing that luminal contents and inflammatory mediators modulate intestinal nerve function in animal models, demonstrating that the function of these nerves remains altered long after resolution of the inflammatory insult (4,5). This review focuses on how alterations in the immune system of IBS patients modulate GI nerve activity and symptoms. Understanding this is essential for the development of novel therapies against the underlying etiology of the disease.

ROLE OF MICROBIOTA IN IBS

The GI tract contains a dense society of commensal bacteria, estimated to number in trillions. The relationship between the host and the microbe is immunologically complex, as commensals comprise a balance between beneficial and harmful strains in health. Any disruptions in this homeostasis leads to dominance by pathogenic species rather than normal intestinal flora and, thus, decreased variation in bacterial strains in patients with IBS (6–9). Microbiota are most abundant in the colon where a striking switch in strain predominance from

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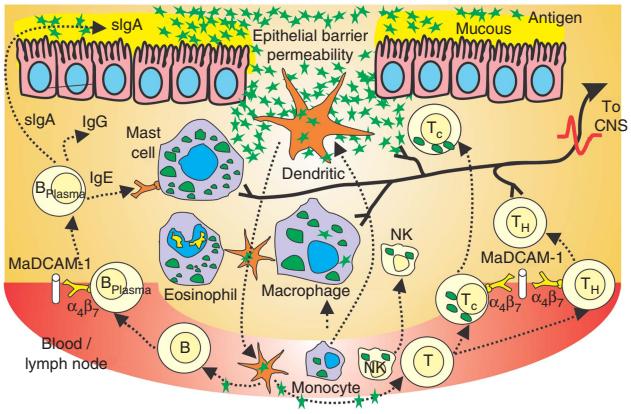

Figure 1. Alterations in the gastrointestinal (GI) immune system in irritable bowel syndrome. Nonspecific defenses are provided by mucous, the epithelial barrier, and innate immune cells, including macrophages, dendritic cells, natural killer (NK) cells, mast cells, and eosinophils. Specific defenses are cell mediated (T-cell dominant) or humoral (B-cell dominant) responses directed against repeated exposure to specific antigen. Dendritic cells are antigen-presenting cells that phagocytose antigenic material at the site of infection and travel to lymph nodes where they present antigen to T cells, and are therefore key mediators between the innate and adaptive immune response. Repeated exposure to antigen activates adaptive B and T cells in lymph nodes, which are selectively home to the GI tract via expression of $\alpha_4\beta_7$. Intestinal nerves are modulated by antigen and also immune mediators secreted by a number of different immune cell types. CNS, central nervous system; Ig, immunoglobulin; MadCAM-1, mucosal addressin cell adhesion molecule-1.

Gram-positive aerobes to Gram-negative anaerobes occur, and the colon is therefore the major site of fermentation and subsequent production of organic acids and gases (10). Bacteria, their shed proteins, and/or fermentation products, such as hydrogen sulfide and methane, modulate the activity of sensory nerves innervating the lower GI tract (**Figure 2**) (11–15). Rectal infusion of fecal supernatants from IBS patients sensitizes mice to colorectal distension, which is suggested to occur via microbe-secreted serine proteases, which activate protease-activated receptor-2 on nerve endings (16–18). The direct effects on sensory nerves may also be compounded by activation of the innate and adaptive immune responses, as suggested by the elevated levels of antibodies against bacterial flagella in IBS patients (19,20). Oral probiotic preparations aimed at restoring the "healthy commensal biota balance" have been met with much enthusiasm by IBS patients, and studies have shown *Lactobacilli* and *Bifidobacteria* preparations both modulate immune function and improve IBS symptoms (21–23). Furthermore, rectal infusion of bacteria, particularly the *Lactobacillus* strains, also induces analgesic effects, possibly due to upregulation of μ-opioid receptors on epithelial cells rather than direct actions on GI nerves (24,25). Recent studies indicate that treatment with a nonabsorbable broad spectrum antibiotic provided relief for IBS-D patients (26,27). However, much remains to be understood regarding how changes in microbiota contribute to IBS symptoms, including details of the immunological aspects underpinning the homeostasis of the symbiotic relationship between the host and the bacteria, which bacterial strains are the most pathogenic in IBS, and how they interact with nerve endings to cause altered sensations. As such, considerable contention surrounds the mechanistic role of probiotics and antibiotics in the treatment of IBS (3,28–30).

ARE BARRIER DEFENSES ALTERED IN IBS?

Intestinal barrier defenses provide the first line of protection in the GI tract. The lumen is lined with a thick layer of mucus, which comprises a complex mixture of glycoproteins, including mucins and bacteriocidal enzymes, and also large amounts of secretary immunoglobulin A (IgA) in most individuals (**Figure 1**). The mucus coats a monolayer of polarized epithelial cells that regulate permeability through the formation of tight junctions, termed the epithelial barrier. The epithelial barrier has a prominent role in the exchange of nutrients and fluids in the intestine, but is relatively impervious to larger molecules and organisms in health. Several studies now indicate barrier defenses are altered in IBS patients, with increased intestinal permeability, increased fecal concentrations of the bacteriocide β-defensin-2, and increased expression of mucosal proteins MUC20 and PARM1 (31–39). Single-nucleotide polymorphisms in *CDH1*, which encodes the tight junction protein E-cadherin, are associated with increased risk of post-infectious IBS (40). Detailed molecular studies of the epithelial barrier indicate the expression and subcellular distribution of tight junction proteins are substantially altered in IBS patients (41–44), and impaired intestinal permeability has been shown to correlate with pain/discomfort and/or bowel habit (**Table 1**) (34,37,41,43). However, impaired barrier defenses are unlikely to directly cause pain, but instead ease access of luminal contents to the GI wall, promoting inflammatory responses and modulating sensory-motor function.

ALTERATIONS IN INNATE IMMUNITY

Mast cells

Mast cells are the most studied population of immune cells in IBS. These leukocytes contain granules and are typically associated with allergic-type responses. When activated, mast cells secrete a complex mixture of inflammatory mediators, including proteases, prostaglandins, histamine, and cytokines/chemokines, many of which modulate the intestinal nerve activity (**Figure 1**). IBS patients have increased serum concentrations of interleukin (IL)-8, a chemokine primarily responsible for the attraction of mast cells and granulocytes (45–47). However, reports of variation in the absolute number of mast cells in the intestine are conflicting, as a similar number of studies indicate mast cell numbers are increased or unchanged in IBS patients (**Table 2**) (44,48–67). In those studies that observed increased mast cell numbers, correlations with symptoms are also mixed (**Table 1**) (37,41,50,52,53,55,59,63). Despite this contention, the absolute number of mast cells may not be the defining characteristic of their involvement in IBS. Mast cells have been shown to be in

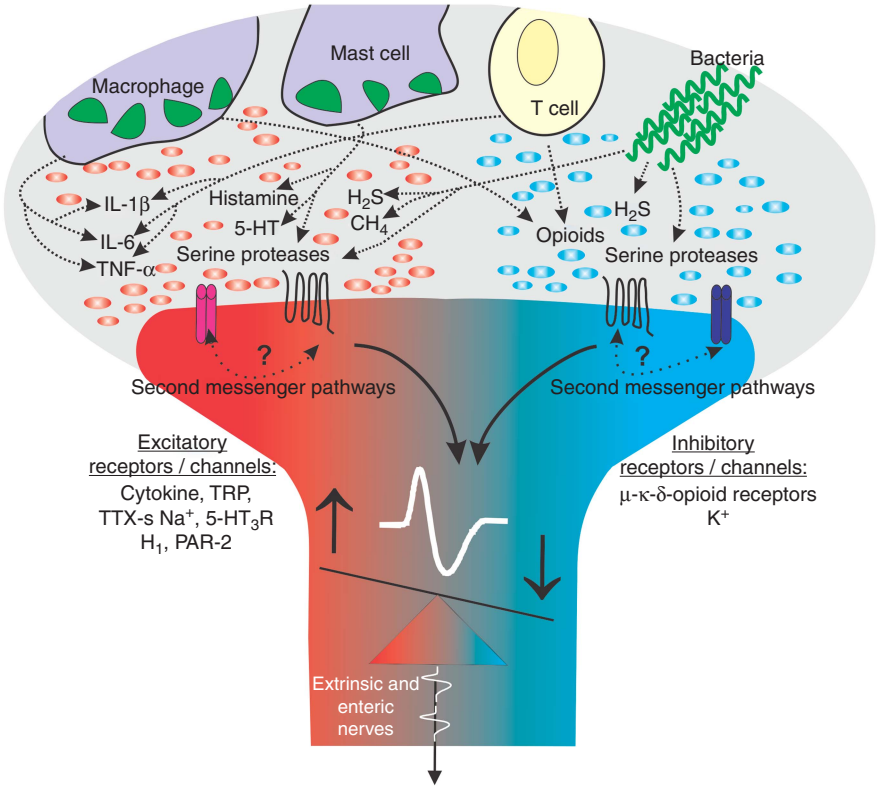

Figure 2. Altered immunity in irritable bowel syndrome has differential affects on neural activity with excitatory or inhibitory consequences. Bacteria, their products, and immune mediators bind to receptors on nerve endings. These receptors may either directly modulate nerve firing or may couple to effector ion channels to regulate the excitability of the nerve ending. The second messenger pathways involved in this coupling in the gastrointestinal (GI) tract are largely unknown. The firing of action potentials is the net result of excitatory and inhibitory inputs. IL, interleukin; TNF-α, tumor necrosis factor-α.

closer proximity to colonic nerve endings in IBS patients, a finding that correlated strongly with severity and frequency of pain (55). Further, supernatants from mucosal biopsies from IBS patients are more likely to activate intestinal nerves than those from healthy subjects (52,54,56,66,68). This nerve activation is dependent on mast cell-derived mediators, including serine proteases acting on protease-activated receptor-2, histamine acting on its H_1 receptor, and serotonin acting on its 5-HT_3 receptor (**Figure 2**), and occurs regardless of whether changes in absolute mast cell numbers are observed or not. Most interestingly, these alterations are observed across IBS-D, -C, and -A patients, suggesting common pain inducing mediator(s), although by default this excludes a role in the different motility patterns observed in these patient cohorts and concentrations of these mediators often do not correlate with symptoms (**Table 1**) (37,41,52,55). Of note, IBS patients hypersensitive to colonic distension recently showed benefit from treatment with the mast cell stabilizer and H_1 receptor antagonist Ketotifen; however, the underlying mechanisms are unclear, as this treatment did not alter mast cell numbers or cultured secretion of histamine or tryptase (67). A key remaining question is what is driving the mast cell degranulation observed in IBS patients? Levels of IgE, the classical mast cell degranulator, are typically unaltered in serum or colonic biopsies in IBS patients, although they may be raised in response to allergen (62,69–71). However, mast cell degranulation is a complex process, which also occurs independently of IgE, as different mast cell activators are able to modulate the selective release of a diverse range of mast cell mediators (72).

Antigen-presenting cells

Antigen-presenting cells, including macrophages and dendritic cells, are little investigated in IBS. Macrophages are primarily involved in phagocytosis in the GI tract, but also have antigen-presenting capabilities and secrete an array of cytokines that activate nerve endings (**Figures 1** and **2**). The concentration of macrophage-attracting chemokines secreted by intestinal biopsies and the numbers of CD68+ macrophages are decreased in IBS compared with healthy subjects, possibly indicating an impaired capacity to respond to antigenic material (**Table 2**) (62,64,73). Macrophages express Toll-like receptors (TLRs) and decreased macrophage numbers in contrast with recently found increased expression of TLR4 and TLR5 in colonic biopsies from IBS patients (74). However, epithelial cells also express TLRs, and as immune cells were not isolated in this study it is not clear whether the increased expression was observed on epithelial or immune cells, or both (75). At least two subsets of macrophages have been described, M1 and M2, based on functional differences, but much remains to be learned regarding appropriate

markers to differentiate them (76). The involvement of different macrophage subtypes may apply in IBS, as CD163 is upregulated on monocytes after activation and there is a much higher ratio of CD163:CD68 numbers in the colon of healthy subjects compared with IBS patients (62).

Eosinophils

Eosinophils are typically associated with allergic responses, but no changes in numbers in blood or intestinal biopsies or the *in situ* levels of eosinophil cationic protein are observed in IBS (50,77–79) (**Table 2**). However, several studies have linked eosinophil numbers with functional dyspepsia, a functional GI disorder associated with upper abdominal discomfort and disordered motility (79,80). Little is known about the effects eosinophil-derived mediators have on GI nerves.

ALTERATIONS IN ADAPTIVE IMMUNITY

Repeated exposure to the same antigen activates the adaptive immune system, whereby T and B cells quickly migrate from lymph nodes via the blood to sites of infection and mount stronger responses against specific antigen (**Figure 1**). Migration of immune cells from the blood to the GI tract is dictated by chemokine gradients and the binding of integrins to their specific receptors in the gut wall. The classic homing markers for lymphocytes are the interaction between MaDCAM-1 (mucosal addressin cell adhesion molecule-1) in the gut wall and the integrin complex $\alpha_4\beta_7$ on the cell surface of lymphocytes. MaDCAM-1 expression is yet to be investigated in IBS patients and little is also known about chemokines, with only one report finding decreased expression of CCL2, CXCL9, and CXCL10 in mucosal biopsies from IBS patients (73).

T cells

Circulating T cells numbers are unaltered in IBS, but studies indicate a greater proportion of T cells are homing to the GI tract and reside within the GI wall in IBS patients compared with healthy subjects (**Figure 1** and **Table 2**) (16,17,23,49–51, 53,55,63–65,81–85). Circulating T-helper (T_H) and cytotoxic T cells and T cells residing in the colon wall of IBS patients are more likely to be in an activated state, as they have increased expression of the activation markers CD69 and HLA-DR (82). Increased T-cell numbers correlate with motility-related symptoms in biopsies from the descending colon, but this was not observed in rectosigmoid biopsies (**Table 1**) (51,53,63). There is considerable divergence regarding the blood cytokine profile in IBS, with some suggesting a predominating T_H type 1 (T_H1) phenotype (↑ tumor necrosis factor-α (TNF-α), IL-1β, IL-12, IL-6, and ↓ IL-10) (23,45–47,82,85–89), whereas others show a shift toward a predominating T_H2 allergy-type phenotype (↑ IL-5, IL-10, IL-13, and ↓ TNF-α; **Table 3**) (78,84,90). On the other hand, some investigations fail to observe any change in cytokine concentrations (91). Blood levels of IL-1β, TNF-α, and IL-6 correlate positively with IBS symptoms, whereas negative correlations are observed for IL-10 and IL-12 (**Table 1**) (82,85,87,91).

Table 1. Correlation between symptoms of IBS and altered cellularity

	Measurement											
	Cellularity				Immune mediators							
					Circulating					Mucosal		
Symptom	Intest. perm.	Mast	T cell	B cell	IL-1β	IL-10	IL-12	TNF-α	IL-6	Trypt.	Hist.	5-HT
Overall severity	+ + (37)	+ + + (37)			+ (82)	– – (91)				+ + (37)		
Pain/discomfort	+ + + (34) + + (43) ↔ (33,41)	+ + (53) ↔ (41,52,55)	↔ (53)	↔ (53)	+ + + (87)			+ + + (87)	+ + + (87)	↔ (41,52,55)	↔ (52,55)	+ + + (52)
Bowel habit	+ + (41)	+ + (41) ↔ (52)	+ + (51), ↔ (53)	↔ (53)						+ + (41), ↔ (52)	↔ (52)	↔ (52)
Anxiety/depression/fatigue		+ (50) ↔ (59,63)	↔ (63)				– – (91)	+ + + (85)				

Hist, histamine; IBS, inflammatory bowel syndrome; IL, interleukin; Intest. Perm., intestinal permeability; TNF, tumor necrosis factor; Trypt, tryptase; 5-HT, serotonin.
↔ No significant associations; Pearson's correlation < + or −0.1; + weak association; correlation + or −0.3 to + or −0.5; + + + strong association; Pearson's correlation > 0.5. In all cases, positive or negative associations were determined to be significant in the original manuscripts.

Table 2. Cellularity of biopsies from IBS patients compared to healthy subjects

	Large intestine					Small intestine		
	Recto/Sigmoid	Descending	Transverse	Ascending	Cecum	Ileum	Jejunum	Duodenum
IEL	↑ (49,64) ↔ (51,63)	↑ (49)	↑ (49)	↑ (49)	↔ (37,50)		↑ (60) ↔ (41)	↑ (59)
Mast	↑ (61,81,91) ↓ (67) ↔ (48,49,51,57,63,66)	↑ (44,52–56,66) ↓ (62,67) ↔ (48,49)	↔ (49)	↑ (61) ↔ (48,49,62)	↑ (37,48,50)	↑ (57,58,61)	↑ (41,42,60)	↑ (59)
T (CD3)	↑ (49,51,63,64,81) ↔ (91)	↑ (49,53) ↔ (62)	↑ (49)	↑ (49) ↔ (62)	↑ (50)			
T_H	↔ (91)	↑ (53)						
T_C	↑ (64) ↔ (49,91)	↑ (53) ↓ (62) ↔ (49)	↔ (49)	↔ (49,62)				
B		↔ (53)						
NK	↔ (49)	↔ (49)	↔ (49)	↔ (49,62)				
Macrophage	↓ (64)	↓ (62)						
Neutrophil	↔ (49)	↔ (49)	↔ (49)	↔ (49)	↔ (50)			
Eosinophil					↔ (37,50)			

IEL, intraepithelial lymphocyte; IBS, inflammatory bowel syndrome; NK, natural killer cell; T_C, cytotoxic T cell; T_H, helper T cell.
This table demonstrates the conflicting nature of studies of IBS populations. The majority of these studies do not differentiate between IBS subgroups.

Genotyping studies of IBS patients indicate they are more likely to have alleles associated with excessive production of IL-6, IL-2, TNF-α, and TNFSF15, a member of the TNF family, whereas a recent meta-analysis indicated high IL-10 producers are less likely to develop IBS (40,90,92–96). Classification of patients according to the IBS subtype is rarely performed, but when this is done clear differences in immune profile are observed with increased concentrations of T_H1-type cytokines, including TNF-α and IL-1β, detected alongside typical T_H2 cytokines, such as IL-10, in IBS-D (85,87,88). The lack of polarization toward a T_H1 or T_H2 axis indicates the nature of immune activation in IBS is not straightforward but instead likely to be a complex phenomenon incorporating several distinct cell types and/or possibly cells with plasticity of function (97).

T_{REG} are currently little investigated in IBS, with only one report showing that numbers and suppressive capabilities of blood and colon T_{REG} are unaltered in IBS (98). The T_H17 axis is also yet to be studied in detail, and although the functions of T_H17 cytokines in intestinal homeostasis are controversial IL-17 has been shown to sensitize sensory nerves in the somatosensory system (99,100). Understanding the role and relationship of these cell types is currently of great interest in a number of inflammatory disease states, such as inflammatory bowel disease (101), but is also very likely to provide vital information regarding the maintenance of the low grade but chronic immune activation observed in IBS patients. This may be especially of interest, as we better appreciate the likely phenomenon of "post-inflammatory" IBS (2,102,103).

Table 3. Changes in circulating immune profiles in IBS observed plasma/serum or peripheral blood mononuclear cells

Cytokine	Plasma/serum	PBMC
TNF-α	↑ (86,89) ↓ (84) ↔ (45,46,91)	↑ (85,87,88) ↔ (90)
IL-1β	↑ (89) ↔ (46,91)	↑ (82,85,87,88) ↔ (90)
IL-12	↑ (89) ↔ (46,91)	↑ (23,87)
IL-2	↔ (46)	
sIL-2R		↑ (87)
IFN-γ	↔ (46,89)	↔ (82,87)
IL-6	↑ (45–47,89) ↔ (91)	↑ (85,87,88)
sIL-6R	↑ (45)	
IL-4	↔ (46)	
IL-5	↔ (46)	↑ (78)
IL-10	↓ (86) ↔ (45,46,89,91)	↑ (87,88,90) ↓ (23) ↔ (82)
IL-13	↔ (46,89)	↑ (78)
IL-8	↑ (45,46,89) ↔ (91)	↔ (87)

IBS, inflammatory bowel syndrome; IFN, interferon; IL, interleukin; PBMC, peripheral blood mononuclear cell; sIL-2R, soluble IL-2R receptor; sIL-6R, soluble IL-6 receptor; TNF, tumor necrosis factor.

B cells

Circulating B cells are also more likely to express the GI homing integrin β_7 in IBS patients compared with healthy subjects; however, numbers of B cells are unchanged in the descending colon (**Figure 1** and **Table 2**) (53,78,104). A greater proportion of B cells express the activation markers CD80 and CD86, and T-cell activation induces increased release of cytokines involved in B-cell activation in IBS compared with health (68,78). The primary role of B cells is to produce antibodies (Ig) directed against antigen, and IgG-positive B cells are increased in the blood of IBS patients relative to healthy subjects (68). Increased blood IgE and IgG concentrations are classically associated with allergy and are typically unaltered in IBS at baseline; however, in response to allergen serum IgE and IgG levels increase in IBS patients above that observed in health (37,70,71). Interestingly, increased levels of autoantibodies against neuronal channels have been observed in IBS patients; however, the clinical implications of this are yet to be determined (105,106). Indeed, patients with autoimmune diseases, including Sjogren's syndrome and type 1 diabetes, produce autoantibodies that affect GI motility via actions on calcium channels or muscarinic receptors, indicating a potential for autoantibody-mediated GI neural dysfunction (107,108).

IMMUNE MEDIATORS MODULATE COLONIC NERVE FUNCTION

As outlined above, mast cells and bacterial-derived mediators, such as serine proteases, are increased in IBS and activate colonic nerves, highlighting a potential role in symptoms (**Figure 2**). Cytokines are important signaling messengers in the immune system, but also modulate nerve function. Indeed, TNF-α, IL-1β, and IL-6 each sensitize colonic afferent and enteric nerves (**Figure 2**) (87,109–112). Interestingly, we recently showed different functional effects of these cytokines on colonic sensory afferents, whereby TNF-α caused a pronounced sensitization to mechanical stimuli, which was mediated by an interaction between TNFR1 and transient receptor potential A1 (43). IL-1β and IL-6 had more subtle effects on sensitivity to mechanical stimuli, but IL-1β caused pronounced chemosensory effects in the absence of distension, which were dependent on tetrodotoxin-sensitive sodium channels, but not on transient receptor potential A1 (43). These findings indicate cytokine receptors couple to different effector channels, most likely by different intracellular signaling pathways (**Figure 2**). Peripheral blood mononuclear cells from IBS-D patients have high concentrations of these cytokines, and we have also shown peripheral blood mononuclear cell supernatants from these patients sensitize colorectal sensory nerves to distension (57,85,87,113). Further, TNF-α, IL-1β, and IL-6 concentrations in peripheral blood mononuclear cells correlate with symptom severity in IBS-D, including the intensity and frequency of painful events and motility-associated symptoms (**Table 1**) (85,87).

Immune cells also synthesize and secrete mediators that inhibit neuronal activity, including the opioids β-endorphin, enkephalin, and dynorphin (114,115). These mediators are endogenous agonists of μ-, κ-, and δ-opioid receptors, respectively, each of which is expressed on extrinsic sensory afferent and/or enteric nerves (116). Weak μ-opioid receptor agonists are useful for treating diarrhea, whereas constipation is a common side effect of stronger pain-relieving opioids. In sensory afferents, immune-derived β-endorphin is particularly relevant in health, where it acts to set the threshold to nociceptive distension (87,117). Thus, loss of the inhibitory effect provided by immune-derived β-endorphin potentially contributes to painful sensations, as nociceptive nerves become more easily activated, and also to motility alterations via activity on enteric neurons.

CONCLUSIONS

Despite several decades of promising evidence implicating the immune system in IBS, the extent to which it is involved in clinical symptoms remains controversial and many questions remain. Foremost is causation; what is driving the immune activation—is it centrally or peripherally mediated, or a combination of both? IBS patients frequently copresent with extraintestinal and psychological comorbidities, including anxiety and depression, which correlate with altered immune function (**Table 1**), and emotional stimuli such as chronic stress are known to alter immune function (recently reviewed by Elsenbruch (118)). If peripheral mechanisms dominate what is causing the immune activation—is it driven by food allergens, perturbations in microbiota, or bacterial or viral infection? Does an allergic- or autoimmune-type response predominate? What are the mechanisms underlying the interactions between the nervous and immune systems? Which effector ion channels and signaling pathways on peripheral nerves are most important? A major unanswered question is whether alterations driving the initial changes in neuroimmune signaling are the same as those driving the maintenance of chronic symptoms. An integrated hypothesis could be that an initial peripheral insult drives changes in peripheral immune and nervous function, but also the central nervous system processing of visceral stimuli. Altered central nervous system processing may then modulate the descending innervation of the GI immune system, leading to enhanced susceptibility to luminal pathogens and chronic peripheral immune alterations, which in turn sensitize not only the peripheral nerves but also the central cognitive processes.

To answer these questions, much more information is required about both the immune system and the nervous system. The relationship between the host and the microbiome is only just beginning to be investigated in detail, and given the major function dendritic cells have in antigen presentation in the gut, it would not be surprising if their function is altered in IBS. Pain is typically regarded as a danger signal and sign of disease, yet in GI diseases symptoms and pathology frequently correlate poorly. Much effort is made to identify mediators, effector channels, and pathways that activate neural endings; however, neuronal signaling is often a balance between excitatory and inhibitory factors. Loss of inhibitory

factors conceivably contributes to painful sensations, yet little is known of endogenous inhibitory mediators. The development and characterization of animal models of visceral hypersensitivity are clearly valuable in understanding how symptoms develop and persist, but as yet no animal model concurrently demonstrates all the symptoms of IBS. Little is known about changes in the peripheral nervous system in IBS patients, mainly due to the difficulty in accessing visceral neuronal tissue in humans; however, there have been recent promising studies characterizing human GI nerve functions (54,119,120).

Patient selection can clearly confound studies and more attention needs to be placed on the reporting of patient symptoms and similarities or differences between IBS cohorts, and also the adequate selection of control subjects. Diarrhea and constipation are different extremes, and it is most likely that the underlying mechanisms differ. Critical insights have been gained from following post-infectious IBS patients, but it remains to be determined just how similar these patients are to non-post-infectious IBS. Complicating matters is the likelihood that IBS is multifactorial and patients may have alterations in several distinct underlying processes that may be linked, such as chronic stress and immune activation, or which may independently contribute to symptoms via distinct mechanisms.

Understanding how alterations in the neuroimmune axis lead to symptoms is critical to the development of new therapies for IBS. This requires a comprehensive knowledge of the nature of the changes in the immune system, and the subsequent modulation of viscerosensory and enteric nerve function by immune mediators. Answering these questions not only leads to new therapies but also potentially reveals causation, shifting the classification of IBS from a functional disease to an organic one.

CONFLICT OF INTEREST

Guarantor of the article: Patrick A. Hughes, PhD.

Specific author contributions: P.A. Hughes wrote the review and compiled the tables and figures with intellectual input and editing from each of the other authors.

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