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TOPIC HIGHLIGHT

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Microbiota-host interactions in irritable bowel syndrome: Epithelial barrier, immune regulation and brain-gut interactions

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Abstract

Irritable bowel syndrome (IBS) is a common, sometimes debilitating, gastrointestinal disorder worldwide. While altered gut motility and sensation, as well as aberrant brain perception of visceral events, are thought to contribute to the genesis of symptoms in IBS, a search for an underlying aetiology has, to date, proven unsuccessful. Recently, attention has been focused on the microbiota as a possible factor in the pathogenesis of IBS. Prompted by a number of clinical observations, such as the recognition of the *de novo* development of IBS following enteric infections, as well as descriptions of changes in colonic bacterial populations in IBS and supported by clinical responses to interventions, such as antibiotics and probiotics, that modify the microbiota, various approaches have been taken to investigating the microbiota-host response in IBS, as well as in animal models thereof. From such studies a considerable body of evidence has accumulated to indicate the activation or upregulation of both factors involved in bacterial engagement with the host as well host defence mechanisms against bacteria. Alterations in gut barrier function, occurring in response, or in parallel, to changes in the microbiota, have also been widely described and can be seen to play a pivotal role in generating and sustaining host immune responses both within and beyond the gut. In this manner a plausible hypothesis, based on an altered microbiota and/or an aberrant host response, for the pathogenesis, of at least some instances of IBS, can be generated.

Key words: Microbiota; Irritable bowel syndrome; Toll-like receptor; Epithelial barrier; Gut-brain axis

Core tip: Recent discoveries have kindled an interest in microbiota-host interactions in irritable bowel syndrome (IBS) and have led to new lines of research into this common and elusive disorder. It is clear that the microbiota is altered in IBS and that such alterations could well contribute to the pathogenesis of the disorder through, for example, increased permeability, an altered immune profile, effects on the central nervous system and modulation of gut neuromuscular function. This review will explore these host-microbe interactions and their relevance to the pathogenesis of IBS. This review will explore these interactions and their relevance to the pathogenesis of IBS.

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INTRODUCTION

The importance of the microbiota in the pathogenesis of irritable bowel syndrome (IBS) has only recently begun to be understood with alterations in the composition of the gut microbiota being increasingly investigated as a factor in the pathogenesis and pathophysiology of IBS. The human microbiota is a complex ecosystem which may contain as many as 1000 to 1150 bacterial species and between 10^{13} to 10^{14} microorganisms with the greatest density and diversity of bacteria being found in the distal small bowel and colon[1]. The number of bacteria within the gut is about 10 times that of all cells in the human body. While data remains limited, it is evident that IBS patients have an altered microbiota relative to healthy individuals. Bacterial diversity is reduced[2] and more detailed analyses have identified differences at species and strain level[3] among both children and adults with IBS. Not surprisingly, given the heterogeneity of the IBS phenotype, these results have not been consistent and the sizes of the study populations involved have not been large enough to encompass the entire symptom and demographic spectrum that is IBS. Other clinical evidence also supports a role for the microbiota in IBS, including the role of enteric infections as well as the well documented symptom responses to antibiotics, such as rifaximin, and certain probiotics[4].

IBS is one of the most common gastrointestinal ailments worldwide affecting anywhere from 5%-15% of adults in the general population[5]. Despite considerable effort, a biomarker(s) specific for IBS has not been identified[6] and its definition remains entirely clinical, based on the presence of abdominal pain/or discomfort associated with altered bowel habit, often accompanied by symptoms of bloating and distension[7]. The spectrum of symptom severity in IBS is broad with the majority of those affected never seeking medical advice but self-medicating or instituting dietary or life-style measures to control symptoms. At the other end of the spectrum are a smaller number of affected individuals whose symptoms are debilitating and impose a very significant impact on quality of life. IBS is commonly associated with other gastrointestinal ailments such as gastroesophageal reflux, functional dyspepsia and extra-intestinal disorders[8]. Over the years, altered motility, visceral hypersensitivity, immune alterations and, more recently, compromised epithelial barrier function have all been invoked to explain the genesis of symptoms in IBS. Whether considered individually or collectively, these factors undoubtedly play a role in the onset and exacerbation of symptoms in IBS, although none can satisfactorily claim to be a fundamental cause of IBS[9]. Indeed, one of the few true causes of IBS that has been identified is enteric infection; several large series attest to the de novo development of IBS following acute enteric bacterial, viral and parasitic infections[10]. This latter observation kindled an interest in microbiota-host interactions in IBS and has led to a new and surprising line of research into this common and elusive disorder. This review will explore these interactions and their relevance to the pathogenesis of IBS.

INTESTINAL EPITHELIAL BARRIER: AN INTERFACE FOR HOST-MICROBE INTERACTIONS IN IBS

Given the size of the intestine and the density of the commensal flora, the gut represents an enormous interface between the host and its' environment, and, thereby, functions as a barrier between the external environment and the internal milieu and is essential in maintaining health and preventing disease[11]. The intestinal epithelial barrier comprises a thick mucus layer and a single layer of intestinal epithelial cells (IECs) which separate commensal bacteria from the underlying submucosa and as such are a critical component of commensal-host interactions[12]. It is now well understood that IECs are not an inert component of this interaction but are both effected by, and themselves effect, the microbiota. The commensal flora has been shown to directly affect the epithelial barrier through its regulation of tight junction proteins. Examples of this include, increased expression and distribution of zonula ocludin-2[13] as well asupregulation of other gap junction proteins such as occudin2 and claudin-2 in response to a number of probiotic bacteria in several IECs[14]. Commensal flora also contribute to the production of mucus as the mucus layer is considerably reduced in the gut of germ-free mice, but recovers on exposure to bacterial products[15,16]. Given the influence of microbes on the integrity of the intestinal epithelium, this may be of relevance in the context of the compromised epithelial barrier and alterations in permeability observed in IBS[17,18]. The mechanisms underlying this increased permeability in IBS include alterations in tight junction protein expression, localisation or function, changes in the microbiota, presence of active inflammation and/or presence of pro-inflammatory cytokines and increased cell shedding[19]. In particular, reduction of the tight junction protein zonula ocludin-1 (ZO-1) and disruption of apical expression of claudin-1, occludin and ZO-1 have been observed in IBS[20,21]. In addition, single nucleotide polymorphisms in the gene encoding the tight junction protein E-cadherin (CDH1) are associated with an increased risk for the development of post-infectious IBS[22]. Of particular note, is the relationship between increased permeability and the severity of abdominal pain experienced by IBS patients[23]. Moreover, in IBS patients, Zeng and colleagues partially reversed changes in small intestinal permeability with a probiotic cocktail[24]. This increased permeability of the barrier seen in IBS patients may also contribute to the low-grade inflammation that characterises this syndrome, due to increased bacterial translocation[25].

COMMENSAL REGULATION OF IMMUNITY: RELEVANCE FOR IBS

The mucosal surface of the intestinal epithelium has evolved to allow the correct balance of responsiveness, being broadly unresponsive to the presence of the commensal bacteria in the gut lumen whilst still being able to mount an immune response to the presence of pathogenic bacteria[26]. How commensals and the immune system achieve this balance is an area of on-going investigation[27]. It seems likely that no single mechanism applies to all commensals; different strains or species employ different strategies. Nonetheless, a range of potential mechanisms have been identified[28,29]. For example, *Bifidobacterium infantis* prevents nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) and interleukin (IL)-8 activation and also inhibits the secretion of the chemokine CCL20 in response to *Salmonella typhimurium*, *Clostridium difficile*, *Mycobacterium paratuberculosis* and, even, bacterial flagellin[30,31]. Some strains, indeed, appear to exert potent anti-inflammatory effects: in an experimental animal (IL-10 knockout) model of colitis, both a *Lactobacillus* and a *Bifidobacterium* suppressed the production of the pro-inflammatory cytokines interferon-γ, tumor necrosis factor-α, and IL-12, while levels of the anti-inflammatory cytokine transforming growth factor-β were maintained[32]. Similar effects have been demonstrated for the probiotic cocktail VSL#3 in experimental models of colitis[33,34]. What is very exciting is the observation, again in an animal model, of the ability of orally administered probiotics to exert anti-inflammatory effects at sites well distant from the gut[35]. These differential cytokine responses to commensals and pathogens have also been demonstrated in man[36].

Immunological alterations are increasingly being reported in IBS with the hypothesis that there is a low-grade inflammatory state associated with this condition. Investigation of the role of the microbiota in mediating these immune alterations in IBS are in their infancy, but further study may provide some insight into the pathogenesis of IBS. Accumulating data support the presence of an immune engagement between the microbiota and the host in IBS; an interaction that involves both systemic and mucosal immunity that could generate a low-grade inflammatory response.

Toll like receptors, mucosal immunity and IBS

A number of factors may allow the epithelium to tolerate commensal organisms with the innate immune system and pattern recognition receptors (PPRs) playing a critical role. PPRs, such as toll-like receptors (TLRs), mediate the interaction between the host and the microbiota and, in doing so, facilitate both inflammatory and homeostatic processes[37]. Indeed commensal-TLR interactions in the intestine have been predominantly implicated in homeostatic events[38]. Commensal signalling through TLRs results in the inhibition of the NF-κB inflammatory pathway[39] and also in the upregulation of TLR inhibitory proteins such as PPARγ. For one commensal, *Bacteroides fragilis*, symbiosis with the host has been shown to be mediated through the activation of TLR2 on Foxp3$^+$ regulatory T cells by a PSA, produced by the bacterium, resulting in immunological tolerance[40]. The intimacy of the interaction between the microbiota and these PPR's is also illustrated by the observation that the microbiota determines expression of TLR2 in the colon[41].

Expression of TLRs has also been recently reported to be altered in IBS. Increased levels of TLRs 4 and 5 and decreased levels of TLRs 7 and 8 have been shown in colonic biopsy tissue of IBS patients[42]. The work of Belmonte *et al*[43] further characterised these changes according to IBS subtype and showed that only the IBS-mixed subgroup showed upregulation of TLRs 2 and 4. These authors also showed the alterations in expression were confined to epithelial cells. Similar alterations in expression of TLRs have been shown in a rat model of stress-induced IBS[44]. Work performed by Tattoli *et al*[45] has further demonstrated that TLR ligands can directly affect gastrointestinal motility possibly implying that disruptions in the composition of the microbiota may result in changes in gut motility, as observed in IBS patients. The colonic mucosal tissue from IBS patients also displays an altered cytokine profile possibly reflecting the alterations in TLR expression[46]. And, whilst evidence has been advanced to indicate that alterations in the microbiota are present in IBS[47], how such changes might directly affect TLR expression and cytokine production in these patients remains unclear. Moreover, the microbiota may also have the capacity to influence expression of non-TLR receptors, such as μ-opioid and cannabinoid receptors, in IECs which may be equally relevant in the context of IBS[48].

Commensals, systemic immunity and IBS

In addition to the ability of the microbiota to modulate local mucosal immune responses, extensive clinical and experimental data have been generated to indicate that commensal bacteria can also modify systemic immune responses[49]. Commensals may promote the development of T helper cells, including T_H17 cells and result in a controlled inflammatory response which is protective against pathogens, in part, through the production of IL-17[50]. Commensals, such as *Bifidobacterium infantis* and *Faecalobacterium prasunitzii*, differentially induce regulatory T cells (Tregs) and result in the production of the anti-inflammatory cytokine, IL-10[51]. Similarly, colonization of mice with *Bifidobacterium fragilis* resulted in the expansion of IL-10 producing Tregs and amelioration of the disease experimental autoimmune encephalomyelitis in a mouse model[52]. The regulation of immunity by commensals is likely to occur, not only *via* TLRs, but also through a variety of commensal-derived substances, ranging from relatively nonspecific fatty acids and peroxides to highly specific bacteriocins[53,54], which can inhibit or kill other, potentially pathogenic, bacteria[28]; meanwhile certain strains produce proteases capable of denaturing bacterial

toxins[55].

Systemic immune alterations have also been observed in IBS. B cells isolated from the blood of IBS patients display an amplified activation level[56]. Similarly, T cells isolated from both blood and colonic biopsies showed increased activation levels in IBS patients compared to healthy controls; evidenced by increased expression of the activation markers CD69 and HLA-DR[57]. Increased levels of antibodies to bacterial flagellin[58,59] and elevated levels of beta-defensin-2 in the faeces have also been demonstrated in IBS[60]. In addition, the ratio of IL-10 to IL-12 cytokines from peripheral monocytes is decreased in IBS patients compared to healthy controls; this ratio was normalised following treatment with *Bifidobacterium infantis*[61].

COMMENSAL REGULATION OF THE GUT-BRAIN AXIS: RELEVANCE FOR IBS

The ability of gut microbiota to communicate with the brain and thus modulate behaviour is emerging as an exciting concept in health and disease. Indeed, it has been proposed that the microbiota can influence the development[62] and function[63] of the central nervous system (CNS), thereby, leading to the concept of the microbiota-gut-brain axis[64,65]. Studies focusing on the impact of enteric microbiota on the host and, in particular, on the CNS are essential to our understanding of how the gut-brain axis may influence the pathogenesis of IBS[64]. Moreover, functionally, an association between psychological stress, intestinal transit and "dysbacteriosis" has been reported[66].

Influence of commensals on the central nervous system

There is clear evidence of communication between commensals and the CNS facilitated through neuroendocrine, neuroimmune, the autonomic nervous system and the enteric nervous system (ENS), collectively forming complex networks. This communication functions bidirectionally with the microbiota influencing CNS function and *vice versa*[67]. For example, oral administration of *Bifidobacterium infantis* 35624 influences the concentrations of 5-hydroxyindole acetic acid and dihydroxyphenylacetic acid in the frontal cortex and amygdala, respectively[68]. Moreover, *Bifidobacterium infantis* 35624 has been shown, in an animal model of depression and visceral hypersensitivity (the maternally-separated rat), to normalise immune responses, reverse behavioural deficits and restore basal norepinephrine concentrations in the brainstem[68]. A more recent study, describing the effects of *Lactobacillus rhamnosus* (*JB-1*) on behaviour and central expression of gamma aminobutyric acid receptors, demonstrated these effects to be vagal-dependent thereby establishing the vagus nerve as a key pathway in transducing microbe-gut to brain signals[69]. Germ-free models have also proven to be a useful tool in interrogating the influence of the gut microbiota on central nervous system function. For example, germ free mice display altered central expression of the neurotropic factor; brain derived neurotropic factor, as well as serotonin. Moreover, the latter was resistant to restoration of the microbiota in adulthood[70], implicating a role for the microbiota in early-life development and its absence with persistent long-term effects on hippocampal gene expression. The first clinical study demonstrating the influence of commensal organisms on brain activity, using a probiotic cocktail, is of particular relevance to IBS. Healthy female subjects, who consumed the probiotic cocktail containing *Bifidobacterium animalis* subsp *Lactis*, *Streptococcus thermophiles*, *Lactobacillus bulgaricus*, and *Lactococcus lactis* subsp *Lactis* twice daily for four weeks, exhibited altered activity in brain regions that control central processing of emotion and sensation[71], areas of particular relevance in the context of IBS. Collectively, these latter observations could address some of the proposed pathophysiological mechanisms associated with symptom development in IBS, namely, disturbances in the brain-gut axis.

Influence of commensals on the enteric nervous system and neuromuscular function

The ENS and human smooth muscle cells, key regulators of intestinal motility, express the machinery necessary to respond directly to commensals[72,73]. Therefore, commensals have the capacity to influence neuromuscular function, indicating a role for this interaction in IBS. Direct influence on the ENS can be inferred by studies examining peripheral TLR expression. TLR-4 and TLRs-3 and -7 are expressed in the ENS of both the murine and human intestine and colon[72]. Moreover, studies on human smooth muscle cells suggest that a direct interaction between these and the microbiota is possible, as stimulation of TLR4 induced inhibition of smooth muscle contractility[73]. While other studies have demonstrated that commensal organisms may influence neurotransmitter release and production of gamma-aminobutyric acid[74]. Of more direct relevance to IBS, manipulating the host-microbiota interaction to improve neuromuscular function was demonstrated in a study using *Lactobacillus paracasei,* in which the bacterium attenuated gut muscle hypercontractility in an animal model of post-infectious IBS[75]. This effect was strain-dependent and appeared to be mediated, in part, through a modulation of the immunological response to the initial infection and, in part, through the direct effects of the organism, or a metabolite thereof, on gut muscle. Additionally, studies interrogating the effects of several microbes on intestinal motility in germ-free animals highlight the selective and divergent effects of individual strains on intestinal motor function, with some, but not all strains, influencing transit[76].

Indirect interactions are mediated through commensal-derived factors including methane (CH_4), hydrogen sulphide (H_2S) and short-chain fatty acids. Noteworthy, in the context of IBS, levels of *Methanobrevibacter smithii* in the stools of constipation-predominant IBS patients correlate with levels of CH_4 production[77], suggesting that, in a subgroup of constipation-predominant IBS patients,

bacterial-derived CH_4 contributes to the pathophysiology of the disorder. Moreover, CH_4, produced mainly by *Methanobrevibacter. smithii* in humans, has been associated with alterations in intestinal motility. In an animal model, CH_4 significantly reduces intestinal transit following *in vivo* infusion[78], and *in vitro* recordings suggesting that one of the mechanisms by which CH_4 influences the ileal contractile response is *via* regulatory control of sensory neurotransmission[79]. Like CH_4, H_2S also exerts an inhibitory effect on intestinal neuromuscular function[80,81]. Sulphate reducing bacteria, responsible for the disposal of H_2, and subsequent generation of H_2S, are also relevant in the context of IBS[82]. H_2S exerts an inhibitory effect on neuromuscular activity[83]. Further studies confirmed an inhibitory role for H_2S on motor complexes and also indicated that this effect was independent of the ENS[84]. Moreover, H_2S-induced inhibitory responses were sensitive to potassium (K) channel and, in particular K_{Ca}^+ channel, blockade in the presence of neural inhibition *in vitro*[84].

One of the principal roles of the colonic microflora is to salvage energy from carbohydrates that have not been digested in the upper gastrointestinal tract, the major end-products of which are short-chain fatty acids (SCFA), in addition to the gaseous end-products H_2, CO_2 and CH_4[85,86]. The SCFAs include acetate, propionate and butyrate, the latter of which has multiple effects in the gastrointestinal tract, including impacts on visceral perception, motility and secreto-motor function[87]. Noteworthy, faecal bacteria from diarrhoea predominant IBS patients produce less SCFA in an *in vitro* fermentation system. Differences in SCFA production by colonic bacterial flora in patients with diarrhoea predominant IBS may be related to the development of gastrointestinal symptoms and, in particular, neuromuscular dysfunction[88]. SCFAs may also influence ENS plasticity through monocarboxylate transporters[89]. However, these plastic changes in the ENS display a level of SCFA specificity, as neither acetate nor propionate alter the neurochemical make-up of the myenteric plexus[89]. Moreover, butyrate also appears to directly influence intracellular calcium concentrations in myenteric neurons[90] as well as activating the G protein coupled receptors, GPR41 and GPR43 which are widely expressed in rat and human colon[91]. However, altering the activity of the microbiota, with prebiotics for example, supports the concept that it is not only the presence or absence of the microbiota that is capable of regulating intestinal motor physiology, but that qualitative changes in the microbiota can alter neuromuscular function[92]. The issue of differentiating between direct effects of the microbiota or its products and the secondary consequences induced by components of the microbiota is one that bedevils the interpretation of many studies in this area.

CONCLUSION

It is clear that the microbiota is altered in IBS and that such alterations could well contribute to the pathogenesis of the disorder through, for example, increased permeability, an altered immune profile, effects on the CNS and modulation of gut neuromuscular function. To date, however, there is a paucity of clinical studies in IBS patients evaluating the effects of selectively manipulating the microbiota based on preclinical evidence leading to a causality dilemma; whether changes in the microbiota are cause or effect in disorders such as IBS. It is quite unlikely in the context of IBS, given its comorbidities and variability in symptom presentation, that a single microbial alteration will be identified as causative for all IBS pathogenesis, or that one microbial intervention will universally improve all symptoms. Rather, several interventions may prove efficacious in ameliorating various subgroups or individual symptoms. Moreover, focus has moved from the description of qualitative changes in the microbiota in IBS to their metabolic activity. Such an approach has only recently been applied in the context of IBS, where the activity of the microbiota was assessed in relation to symptom presentation[93]. This approach now needs to be expanded with the expectation that data from such studies which will not only determine which microbes may be protective, or causative in IBS, but will also identify which metabolites may be effective therapeutically.

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