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The microbiota link to irritable bowel syndrome

An emerging story

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Irritable bowel syndrome (IBS) is a clinically heterogeneous disorder which is likely to involve a number of causative factors. The contribution of altered intestinal microbiota composition or function to this disorder is controversial, and is the subject of much current research. Until recently, the technical limitations of the methodologies available have not permitted an adequate survey of low-abundance microbial species. Recent technological developments have enabled the analysis of the global population of the microbiome using high through-put, culture independent, *16S rRNA* amplicon pyrosequencing. Using these new methodologies, we are able to gain important biological insights into the link between functional bowel disorders and the microbiome. This addendum contextualizes and summarizes the results of these studies, and defines the future challenges and opportunities in the field.

Keywords: Irritable Bowel Syndrome (IBS), microbiota, microbiome, gastroenteritis, allergy

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Introduction

IBS prevalence in the industrialised world is approximately 10% to 20% in the general population.[1,2] This makes IBS the most widespread gastrointestinal disorder and, as individuals suffering from IBS have a reduced quality of life and report more co-morbidities than the general population, it has a significant negative burden on society[1]. IBS is commonly subtyped according to predominant bowel habit into diarrhea-predominant, constipation-predominant or mixed/alternating phenotypes (IBS-D, IBS-C or IBS-M).

Although the cause of IBS is unknown, it is regarded as a multi-factorial disease, with genetic, neurobiological, and psychosocial elements all potentially contributing to symptomology. While a convincing history of the onset of IBS in relation to gastroenteritis is present in only a minority of IBS subjects,[3] a role for the microbiota in the majority can be imputed from some, albeit circumstantial, pieces of evidence which include upregulation of Toll-like receptor[4] increased levels of defensins in stool samples[5] and clinical responses to probiotics and antibiotics.[6,7] More direct evidence comes from studies of the colonic microbiota. We and others[8-10] have shown that the microbiota of the distal bowel is altered in IBS compared with healthy subjects, and that this altered microbial flora influences the symptoms of IBS. It is, therefore, conceivable that microbial functions such as the production of short chain fatty acids (SCFAs) and immunological impacts by unknown mechanisms invoke a proinflammatory microenvironment in the gut. Host determined subtleties governing humoral immunity, innate immunity, in addition to variations in gut metabolism and physiological stress, may play critical roles in the degree of severity of IBS induced by an altered gut microbiota.[11] Emerging links between host genetics,[12] and dietary patterns,[13] may also prove informative in the understanding of IBS.

Consensus and Contradictions in Recent Studies of Microbiota in IBS

Until recently, studies dealing with microbial alterations in IBS have looked at a

relatively few well-characterized species in the sub-types of IBS, and have often included sub-optimal phenotypic characterization of the subjects. The Jeffery et al. publication, to which this Addendum relates,[8] used high through-put, culture-independent *16S rRNA* gene pyrosequencing technology applied to fecal samples in order to investigate the complete microbiome in a relatively large cohort of very well characterized subjects. The study showed that the majority of the IBS subjects had an altered intestinal microbiota when compared with healthy controls, but some of the IBS samples presented no abnormalities in their microbiota composition. Of significant interest was the observation that the cohort of IBS subjects without an altered microbiota had a significantly increased incidence of depression. The overall rate of depression in the study was 22%. This was unevenly split between the IBS samples, with the majority of cases occurring in the normal-type-microbiota IBS, who exhibited a prevalence of depression of 40%. The IBS cohort with the altered microbiota composition had a rate of depression similar to that of a normal population. We, therefore, speculate that IBS subjects, in general, with an altered microbiota may have no significant increase in the incidence of depression. The association with depression in the patients with no alterations in their microbiota, suggests that other host susceptibility factors must also play a part.

Among the IBS subjects with an altered microbiota composition, two similar but distinct subgroups were identified. At the highest taxonomic level (phylum), these IBS groups were defined by an increase in Firmicutes abundance and a decrease in the Bacteroides. This IBS signature has resonance with another study published in late 2011[9] with the differentially present microbiota between the two papers being relatively consistent in relation to an increase in Firmicutes abundance that is also consistent with previous literature.[10]

The increase in Firmicutes abundance was associated with Eubacterium, Ruminococcaceae spp, and Clostridum cluster XIVa. These taxa, however, were not evenly distributed between the two IBS groups with an altered microbiota.

The first group was defined by elevated levels of the Lachnospiraceae family, Clostridum cluster XIVa and the now defunct definition *Lachnospiraceae insertea sedis*, the members of this microbial population have the predicted ability to produce pro-inflammatory flagellin proteins. One member of this population identified by the analysis of the OTUs was *R. torques*. *R. torques* produces pro-inflammatory flagellin proteins[14] and degrades mucus[15] which could potentially contribute to an altered mucus barrier function. These functional characteristics and the association of *R. torques* with IBS[14] may lead one to speculate that it may have the potential to induce a low level inflammatory response. Alternatively, its relative abundance may represent an altered mucus turnover in IBS, an interesting possibility given the prominence of the passage of mucus in the faecal content of IBS patients.

Interestingly, the second group had a non-significant 5-fold increase in another mucin degrader; *Akkermansia muciniphila*. This group was defined by a relative overabundance of uncultured Clostridiales, some of which can be grouped into the Ruminococcaceae, and Clostridium cluster IV definitions. Although the microbial members of these taxa were of a generally uncharacterizsed nature, they were generally found to be part of the normal microbiota; albeit at lower levels. A number of studies have shown an increase in short chain fatty acids (SCFA) concentration in at least a subset of IBS stool samples.[16-18] Butyrate and acetate are common SCFAs produced by commensal bacteria in the human gut and are necessary for normal functioning of host-microbiota interactions.[19] The described IBS-related microbiota, (Ruminococccaceae and Clostridium cluster XIVa) are known to be enriched in producers of SCFAs.[20] Abnormal levels of butyrate can promote visceral hypersensitivity in a rat model[21] and high concentrations of SCFAs have been shown to induce powerful contractions in the terminal ileum.[22] These are interesting observations given the clinical association of IBS symptoms with visceral hypersensitivity and dysmotility. Furthermore, the production of SCFAs has the potential to lower the pH in the colon.[23] It has also been shown that tolerance of lower pH values is a feature of a number of the Firmicutes species, especially those belonging to Clostridium cluster XIVa. This low pH tolerance is not seen among the Bacteroidetes spp. and Bifidobacterium spp. with the exception of *B. adolescentis*. The low pH and *B. adolescentis*-enriched environment correlates well with the IBS signature, as we previously reported.[8]

Common to both altered-microbiota IBS clusters were bacteria whose *16S rRNA* amplicons were 100% identical to those of *Lactobacillus ruminis*, Shigella spp., and Streptococcus spp *Lactobacillus ruminis* and Shigella spp. have both demonstrated pro-inflammatory potential.[24,25] Lactobacillus species have been reported as less abundant in the microbiota of IBS sufferers.[18] This was not observed in our study. Different Lactobacillus species and strains can demonstrate both pro-inflammatory and anti-inflammatory activities.[26,27] At this juncture, it is prudent to only regard motile flagellated Lactobacilli[28] as obligatory pro-inflammatory.

Extraneous Confounders: Diet and Lifestyle

It is also likely that symptoms in an IBS subject reflect the interplay of a number of causative factors, whose relative importance may vary considerably between individuals. Among the clinical factors that likely underlie symptoms are stress, the menstrual cycle and food ingestion. In this regard, animals studies have shown that stress and early life stress, in particular, can alter the microbiota,[29] thereby raising the possibility that changes observed in IBS are a consequence and not a cause of IBS. With regard to food and IBS, the perception that they may suffer from one or another food intolerance or allergy leads many IBS subjects to initiate a variety of dietary changes. Indeed, while the incidence of self-reported food intolerance in IBS subjects ranges from 20–70%,[30] it is only recently that dietary aspects of IBS have begun to attract serious research interest. Food hypersensitivity, a microbiota-independent reaction characterized by mucosal inflammation and impaired intestinal permeability,[31] appears to be relatively uncommon in IBS. However, when identified, the elimination of allergenic

foods from the diet can result in reduced symptom scores or complete remission, particularly in the IBS-D subtype.[32,33]

More relevant to the microbiota are recent reports of intolerance to a number of foods and poorly absorbed carbohydrates, in particular. These carbohydrates are collectively known as FODMAPS and include fructose, lactose, fructans and galactans. Low FODMAP diets have been found to provide significant relief for sufferers of IBS,[13] strengthening the notion that reduction of SCFA loads may ameliorate IBS symptoms. Similar mechanisms may underlie the impact of gluten-containing foods on IBS symptoms.[34] Diet could also be a major confounder in the interpretation of studies of the microbiota in IBS, given the impact of dietary changes on the microbiota[35] and the predilection of IBS sufferers to adopt various dietary regimens, that range from high-fiber to elimination diets, in order to alleviate symptoms.

Genetic factors appear to be important in IBS because concordance rates are higher in monozygotic twins (22.4%) than in dizygotic twins (9.1%), but the relatively low monozygotic concordance emphasizes that environmental factors weigh more heavily than genetics.[36] The interpretation of studies to date is somewhat limited by variations in study populations, IBS definition and the variable presence of a number of confounding factors.[12] With the exception of a possible genetic susceptibility to post-infectious IBS,[37] there is currently no data on possible interactions between the host genome and the microbiota in IBS. Medication was another possible environmental factor in our study, but as noted in Supplemental data, only 27% of subjects were receiving medication, and there was no correlation with any of the identified clusters. We also failed to detect any association between seasonality (of microbiota sampling and analysis) and microbiota clustering (data not shown).

Microbiota-Immune System-HPAA Interactions: Possible Roles in IBS Symptomology

At least two clinical observations support the relevance of previous or sustained low-grade inflammation to the development of IBS. Specifically, a substantial proportion of patients develop their chronic gut symptoms after an episode of gastroenteritis (post-infectious IBS),[38] and a large proportion of patients with inflammatory bowel disease (IBD) report IBS-like symptoms despite no signs of active inflammation.[39] Moreover, a large body of scientific evidence supports the importance of immune activation and low-grade inflammation in IBS patients, even though studies contradicting this also exist.[11] Abnormalities in the gut microbiota are of potential relevance to immunological alterations in IBS, because the gut microbiota is important in driving and modulating the immune response. However, there are few studies assessing a direct link between alterations in gut microbiota composition and low-grade inflammation or immune activation in the gut.

Due to the massive number of bacteria that reside in the human gastrointestinal tract, the colonic mucosa must constantly maintain homeostasis between the microbiota and the host. Commensal bacteria will interact with intestinal epithelial cells and modulate intestinal immune responses. The gut microbiota is crucial for development of the immune system. Mice bred and kept under sterile conditions (germ free) have a compromised and dysfunctional intestinal immune system.[40] Moreover, complete absence of a gut microbiota also affects extra-intestinal immune compartments, demonstrated by diminished germinal center formation in the spleen and peripheral lymph nodes and reduced levels of serum antibodies.[40,41] Mice with low gut bacterial diversity and/or complexity, or with no microbiota, are highly susceptible to enteric infections.[42,43] In addition, antibiotic treatment significantly alters microbial density and composition, and promotes opportunistic infections.[44] Interestingly, antibiotics given for non-GI infections seem to increase the risk for developing functional GI symptoms.[45]

The gut microbiota have an important role shaping the intestinal immune system by promoting both immune activity and regulatory effects. For instance, segmented filamentous bacteria (SFB) trigger intestinal inflammatory Th17 cells responses,[46] and are also potent stimulators of humoral immune responses through activation of B cells and induction of IgA secretion.[47] Elevated levels of serum antibodies specific for bacterial flagellins have been detected in patients with post-infectious IBS.[48] Moreover, increased abundance of flagellin-producing species belonging to Clostridium cluster XIVa have been demonstrated in IBS by us and others.[8,10] Immune responses to bacterial flagellin are mediated through toll like receptor 5 (TLR5), which is a cell-associated pattern-recognition molecule regulating innate immunity. Quantitative reverse transcriptase-PCR analysis has showed increased mRNA levels of TLR5 in colonic mucosa of IBS patients.[4] Thus, enhanced immune activity in IBS may be due to increased TLR5-flagellin interactions. However, the complexity of relationships between the microbiota, toll-like receptors and inflammation is illustrated by the fact that deletion of TLR5 produces a model of spontaneous colitis.[49]

Gut microbiota may also prevent intestinal pathology. *Bacteroides fragilis* has a protective effect, in part due to the production of polysaccharide A (PSA), which mediates suppression of intestinal inflammation by inducing expansion of IL-10 producing CD4+ T cells.[50] *B. fragilis,* or the bacterial product PSA, may induce CD103+ tolerogenic DCs, which, in turn, promote differentiation of T regulatory cells which suppress effector T cell functions.[51] Moreover, Clostridium strains have been demonstrated to induce colonic IL-10 producing Treg cells and, thereby, protect mice from colitis.[52] The increased SCFA production potential of the microbiota in IBS, as discussed above, may also have anti-inflammatory effects. SCFAs bind the G-protein-coupled receptor 43 (GPR43), which seems necessary for the normal resolution of certain inflammatory responses. Hence, GPR43-deficient mice have exacerbated or unresolved colitis with increased production of inflammatory mediators by Gpr43-deficient immune cells, and increased immune cell recruitment.[53]

To summarize, there are several potential pathways whereby gut microbiota can influence immune activity in the gut, potentially leading to symptom

generation and the development of IBS. However, studies specifically addressing gut microbial-immune interactions in patients with IBS are needed in order to substantiate these theories. Moreover, for both GI microbiota and immune alterations, the direct link with the symptom patterns in patients with IBS remain to be clearly established.

Open Questions and Research Challenges

Taken together, these recent studies employing deep sequencing methods indicate that the microbiota in IBS is different. Before we can ascribe a fundamental patho-physiological role to the microbiota in IBS (with the exception of post-infectious IBS) or begin to propose diagnostic or prognostic roles to fecal microbiological studies, many unanswered questions need to be addressed. First, the interpretation of available data needs to be circumspect given the relatively small sizes of the study populations involved which, therefore, preclude any meaningful interrogation of the impact of variations in IBS phenotype or patient demographics. Larger studies are needed which control, as far as possible, for such potentially confounding factors as diet, probiotic supplements and prebiotic use. To date, most studies have examined the fecal microbiota as a surrogate for the colonic bacterial population. This approach, though more clinically feasible, fails to differentiate between luminal and mucosal populations and may miss the latter completely. Given evidence that these populations may differ significantly in IBS,[54,55] as in other disorders, further studies of the juxtamucosal bacterial population in IBS are warranted. To begin to address the possible pathogenic role of the microbiota in IBS several lines of investigation need to be pursued, including both a detailed assessment of the metabolic signatures of the microbiota in IBS, as well as correlations with the host immune response and the host genome. There are opportunities to take advantage of some clinical observations such as the impact on IBS symptoms by the poorly absorbed antibiotic rifaximin[6] and some specific probiotics.[7] What changes do these therapies induce and how do any alterations in the microbiota correlate with symptomatic responses?

For now, we have some intriguing observations on the microbiota in IBS. Defining what implications these changes in the microbiota have for the diagnosis and management of this challenging disorder must await further study.

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