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

Hyland NP *et al*. Microbiota-host interactions in IBS

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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.

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**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 1013 to 1014 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 NFκB 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 cellsby 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 TH17 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 animalshighlight 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 (CH4), hydrogen sulphide (H2S) 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 CH4 production[77], suggesting that, in a subgroup of constipation-predominant IBS patients, bacterial-derived CH4 contributes to the pathophysiology of the disorder. Moreover, CH4, produced mainly by *Methanobrevibacter. smithii* in humans, has been associated with alterations in intestinal motility. In an animal model, CH4 significantly reduces intestinal transit following *in vivo* infusion[78], and *in vitro* recordings suggesting that one of the mechanisms by which CH4 influences the ileal contractile response is *via* regulatory control of sensory neurotransmission[79]. Like CH4, H2S also exerts an inhibitory effect on intestinal neuromuscular function[80,81]. Sulphate reducing bacteria, responsible for the disposal of H2, and subsequent generation of H2S, are also relevant in the context of IBS[82]. H2S exerts an inhibitory effect on neuromuscular activity[83]. Further studies confirmed an inhibitory role for H2S on motor complexes and also indicated that this effect was independent of the ENS[84]. Moreover, H2S-induced inhibitory responses were sensitive to potassium (K) channel and, in particular KCa+ 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 H2, CO2 and CH4[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.

**REFERENCES**

1 **Guarner F**, Malagelada JR. Gut flora in health and disease. *Lancet* 2003; **361**: 512-519 [PMID: 12583961 DOI: 10.1016/S0140-6736(03)12489-0]

2 **Codling C**, O'Mahony L, Shanahan F, Quigley EM, Marchesi JR. A molecular analysis of fecal and mucosal bacterial communities in irritable bowel syndrome. *Dig Dis Sci* 2010; **55**: 392-397 [PMID: 19693670 DOI: 10.1007/s10620-009-0934-x]

3 **Jeffery IB**, Quigley EM, Öhman L, Simrén M, O'Toole PW. The microbiota link to irritable bowel syndrome: an emerging story. *Gut Microbes* 2012; **3**: 572-576 [PMID: 22895081 DOI: 10.4161/gmic.21772]

4 **Quigley EM**. Therapies aimed at the gut microbiota and inflammation: antibiotics, prebiotics, probiotics, synbiotics, anti-inflammatory therapies. *Gastroenterol Clin North Am* 2011; **40**: 207-222 [PMID: 21333908 DOI: 10.1016/j.gtc.2010.12.009]

5 **Choung RS**, Locke GR. Epidemiology of IBS. *Gastroenterol Clin North Am* 2011; **40**: 1-10 [PMID: 21333897 DOI: 10.1016/j.gtc.2010.12.006]

6 **Clarke G**, Quigley EM, Cryan JF, Dinan TG. Irritable bowel syndrome: towards biomarker identification. *Trends Mol Med* 2009; **15**: 478-489 [PMID: 19811951 DOI: 10.1016/j.molmed.2009.08.001]

7 **Longstreth GF**, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* 2006; **130**: 1480-1491 [PMID: 16678561 DOI: 10.1053/j.gastro.2005.11.061]

8 **Quigley EM**, Abdel-Hamid H, Barbara G, Bhatia SJ, Boeckxstaens G, De Giorgio R, Delvaux M, Drossman DA, Foxx-Orenstein AE, Guarner F, Gwee KA, Harris LA, Hungin AP, Hunt RH, Kellow JE, Khalif IL, Kruis W, Lindberg G, Olano C, Moraes-Filho JP, Schiller LR, Schmulson M, Simrén M, Tzeuton C. A global perspective on irritable bowel syndrome: a consensus statement of the World Gastroenterology Organisation Summit Task Force on irritable bowel syndrome. *J Clin Gastroenterol* 2012; **46**: 356-366 [PMID: 22499071 DOI: 10.1097/MCG.0b013e318247157c]

9 **Quigley EM**. Bugs on the brain; brain in the gut--seeking explanations for common gastrointestinal symptoms. *Ir J Med Sci* 2013; **182**: 1-6 [PMID: 23179664 DOI: 10.1007/s11845-012-0865-y]

10 **Thabane M**, Kottachchi DT, Marshall JK. Systematic review and meta-analysis: The incidence and prognosis of post-infectious irritable bowel syndrome. *Aliment Pharmacol Ther* 2007; **26**: 535-544 [PMID: 17661757 DOI: 10.1111/j.1365-2036.2007.03399.x]

11 **Farhadi A**, Banan A, Fields J, Keshavarzian A. Intestinal barrier: an interface between health and disease. *J Gastroenterol Hepatol* 2003; **18**: 479-497 [PMID: 12702039]

12 **Goto Y**, Ivanov II. Intestinal epithelial cells as mediators of the commensal-host immune crosstalk. *Immunol Cell Biol* 2013; **91**: 204-214 [PMID: 23318659 DOI: 10.1038/icb.2012.80]

13 **Zyrek AA**, Cichon C, Helms S, Enders C, Sonnenborn U, Schmidt MA. Molecular mechanisms underlying the probiotic effects of Escherichia coli Nissle 1917 involve ZO-2 and PKCzeta redistribution resulting in tight junction and epithelial barrier repair. *Cell Microbiol* 2007; **9**: 804-816 [PMID: 17087734 DOI: 10.1111/j.1462-5822.2006.00836.x]

14 **Ulluwishewa D**, Anderson RC, McNabb WC, Moughan PJ, Wells JM, Roy NC. Regulation of tight junction permeability by intestinal bacteria and dietary components. *J Nutr* 2011; **141**: 769-776 [PMID: 21430248 DOI: 10.3945/jn.110.135657]

15 **Petersson J**, Schreiber O, Hansson GC, Gendler SJ, Velcich A, Lundberg JO, Roos S, Holm L, Phillipson M. Importance and regulation of the colonic mucus barrier in a mouse model of colitis. *Am J Physiol Gastrointest Liver Physiol* 2011; **300**: G327-G333 [PMID: 21109593 DOI: 10.1152/ajpgi.00422.2010]

16 **Ohland CL**, Macnaughton WK. Probiotic bacteria and intestinal epithelial barrier function. *Am J Physiol Gastrointest Liver Physiol* 2010; **298**: G807-G819 [PMID: 20299599 DOI: 10.1152/ajpgi.00243.2009]

17 **Natividad JM**, Verdu EF. Modulation of intestinal barrier by intestinal microbiota: pathological and therapeutic implications. *Pharmacol Res* 2013; **69**: 42-51 [PMID: 23089410 DOI: 10.1016/j.phrs.2012.10.007]

18 **Dunlop SP**, Hebden J, Campbell E, Naesdal J, Olbe L, Perkins AC, Spiller RC. Abnormal intestinal permeability in subgroups of diarrhea-predominant irritable bowel syndromes. *Am J Gastroenterol* 2006; **101**: 1288-1294 [PMID: 16771951 DOI: 10.1111/j.1572-0241.2006.00672.x]

19 **Frese SA**, Benson AK, Tannock GW, Loach DM, Kim J, Zhang M, Oh PL, Heng NC, Patil PB, Juge N, Mackenzie DA, Pearson BM, Lapidus A, Dalin E, Tice H, Goltsman E, Land M, Hauser L, Ivanova N, Kyrpides NC, Walter J. The evolution of host specialization in the vertebrate gut symbiont Lactobacillus reuteri. *PLoS Genet* 2011; **7**: e1001314 [PMID: 21379339 DOI: 10.1371/journal.pgen.1001314]

20 **Bertiaux-Vandaële N**, Youmba SB, Belmonte L, Lecleire S, Antonietti M, Gourcerol G, Leroi AM, Déchelotte P, Ménard JF, Ducrotté P, Coëffier M. The expression and the cellular distribution of the tight junction proteins are altered in irritable bowel syndrome patients with differences according to the disease subtype. *Am J Gastroenterol* 2011; **106**: 2165-2173 [PMID: 22008894 DOI: 10.1038/ajg.2011.257]

21 **Martínez C**, Lobo B, Pigrau M, Ramos L, González-Castro AM, Alonso C, Guilarte M, Guilá M, de Torres I, Azpiroz F, Santos J, Vicario M. Diarrhoea-predominant irritable bowel syndrome: an organic disorder with structural abnormalities in the jejunal epithelial barrier. *Gut* 2013; **62**: 1160-1168 [PMID: 22637702 DOI: 10.1136/gutjnl-2012-302093]

22 **Villani AC**, Lemire M, Thabane M, Belisle A, Geneau G, Garg AX, Clark WF, Moayyedi P, Collins SM, Franchimont D, Marshall JK. Genetic risk factors for post-infectious irritable bowel syndrome following a waterborne outbreak of gastroenteritis. *Gastroenterology* 2010; **138**: 1502-1513 [PMID: 20044998 DOI: 10.1053/j.gastro.2009.12.049]

23 **Nicholson JK**, Holmes E, Lindon JC, Wilson ID. The challenges of modeling mammalian biocomplexity. *Nat Biotechnol* 2004; **22**: 1268-1274 [PMID: 15470467 DOI: 10.1038/nbt1015]

24 **Zeng J**, Li YQ, Zuo XL, Zhen YB, Yang J, Liu CH. Clinical trial: effect of active lactic acid bacteria on mucosal barrier function in patients with diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther* 2008; **28**: 994-1002 [PMID: 18671775 DOI: 10.1111/j.1365-2036.2008.03818.x]

25 **Vivinus-Nébot M**, Frin-Mathy G, Bzioueche H, Dainese R, Bernard G, Anty R, Filippi J, Saint-Paul MC, Tulic MK, Verhasselt V, Hébuterne X, Piche T. Functional bowel symptoms in quiescent inflammatory bowel diseases: role of epithelial barrier disruption and low-grade inflammation. *Gut* 2014; **63**: 744-752 [PMID: 23878165 DOI: 10.1136/gutjnl-2012-304066]

26 **Magalhaes JG**, Tattoli I, Girardin SE. The intestinal epithelial barrier: how to distinguish between the microbial flora and pathogens. *Semin Immunol* 2007; **19**: 106-115 [PMID: 17324587 DOI: 10.1016/j.smim.2006.12.006]

27 **Medzhitov R**. Origin and physiological roles of inflammation. *Nature* 2008; **454**: 428-435 [PMID: 18650913 DOI: 10.1038/nature07201]

28 **O'Hara AM**, Shanahan F. Gut microbiota: mining for therapeutic potential. *Clin Gastroenterol Hepatol* 2007; **5**: 274-284 [PMID: 17368226 DOI: 10.1016/j.cgh.2006.12.009]

29 **Thomas CM**, Versalovic J. Probiotics-host communication: Modulation of signaling pathways in the intestine. *Gut Microbes* 2010; **1**: 148-163 [PMID: 20672012]

30 **Lyons A**, O'Mahony D, O'Brien F, MacSharry J, Sheil B, Ceddia M, Russell WM, Forsythe P, Bienenstock J, Kiely B, Shanahan F, O'Mahony L. Bacterial strain-specific induction of Foxp3+ T regulatory cells is protective in murine allergy models. *Clin Exp Allergy* 2010; **40**: 811-819 [PMID: 20067483 DOI: 10.1111/j.1365-2222.2009.03437.x]

31 **Sibartie S**, O'Hara AM, Ryan J, Fanning A, O'Mahony J, O'Neill S, Sheil B, O'Mahony L, Shanahan F. Modulation of pathogen-induced CCL20 secretion from HT-29 human intestinal epithelial cells by commensal bacteria. *BMC Immunol* 2009; **10**: 54 [PMID: 19814810 DOI: 10.1186/1471-2172-10-54]

32 **McCarthy J**, O'Mahony L, O'Callaghan L, Sheil B, Vaughan EE, Fitzsimons N, Fitzgibbon J, O'Sullivan GC, Kiely B, Collins JK, Shanahan F. Double blind, placebo controlled trial of two probiotic strains in interleukin 10 knockout mice and mechanistic link with cytokine balance. *Gut* 2003; **52**: 975-980 [PMID: 12801954]

33 **Rachmilewitz D**, Katakura K, Karmeli F, Hayashi T, Reinus C, Rudensky B, Akira S, Takeda K, Lee J, Takabayashi K, Raz E. Toll-like receptor 9 signaling mediates the anti-inflammatory effects of probiotics in murine experimental colitis. *Gastroenterology* 2004; **126**: 520-528 [PMID: 14762789]

34 **Jijon H**, Backer J, Diaz H, Yeung H, Thiel D, McKaigney C, De Simone C, Madsen K. DNA from probiotic bacteria modulates murine and human epithelial and immune function. *Gastroenterology* 2004; **126**: 1358-1373 [PMID: 15131797]

35 **Sheil B**, McCarthy J, O'Mahony L, Bennett MW, Ryan P, Fitzgibbon JJ, Kiely B, Collins JK, Shanahan F. Is the mucosal route of administration essential for probiotic function? Subcutaneous administration is associated with attenuation of murine colitis and arthritis. *Gut* 2004; **53**: 694-700 [PMID: 15082588]

36 **O'Mahony L**, O'Callaghan L, McCarthy J, Shilling D, Scully P, Sibartie S, Kavanagh E, Kirwan WO, Redmond HP, Collins JK, Shanahan F. Differential cytokine response from dendritic cells to commensal and pathogenic bacteria in different lymphoid compartments in humans. *Am J Physiol Gastrointest Liver Physiol* 2006; **290**: G839-G845 [PMID: 16293657 DOI: 10.1152/ajpgi.00112.2005]

37 **Abreu MT**. Toll-like receptor signalling in the intestinal epithelium: how bacterial recognition shapes intestinal function. *Nat Rev Immunol* 2010; **10**: 131-144 [PMID: 20098461 DOI: 10.1038/nri2707]

38 **Kamdar K**, Nguyen V, DePaolo RW. Toll-like receptor signaling and regulation of intestinal immunity. *Virulence* 2013; **4**: 207-212 [PMID: 23334153 DOI: 10.4161/viru.23354]

39 **Neish AS**, Gewirtz AT, Zeng H, Young AN, Hobert ME, Karmali V, Rao AS, Madara JL. Prokaryotic regulation of epithelial responses by inhibition of IkappaB-alpha ubiquitination. *Science* 2000; **289**: 1560-1563 [PMID: 10968793]

40 **Round JL**, Lee SM, Li J, Tran G, Jabri B, Chatila TA, Mazmanian SK. The Toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota. *Science* 2011; **332**: 974-977 [PMID: 21512004 DOI: 10.1126/science.1206095]

41 **Wang Y**, Devkota S, Musch MW, Jabri B, Nagler C, Antonopoulos DA, Chervonsky A, Chang EB. Regional mucosa-associated microbiota determine physiological expression of TLR2 and TLR4 in murine colon. *PLoS One* 2010; **5**: e13607 [PMID: 21042588 DOI: 10.1371/journal.pone.0013607]

42 **Brint EK**, MacSharry J, Fanning A, Shanahan F, Quigley EM. Differential expression of toll-like receptors in patients with irritable bowel syndrome. *Am J Gastroenterol* 2011; **106**: 329-336 [PMID: 21102570 DOI: 10.1038/ajg.2010.438]

43 **Belmonte L**, Beutheu Youmba S, Bertiaux-Vandaële N, Antonietti M, Lecleire S, Zalar A, Gourcerol G, Leroi AM, Déchelotte P, Coëffier M, Ducrotté P. Role of toll like receptors in irritable bowel syndrome: differential mucosal immune activation according to the disease subtype. *PLoS One* 2012; **7**: e42777 [PMID: 23028414 DOI: 10.1371/journal.pone.0042777]

44 **McKernan DP**, Nolan A, Brint EK, O'Mahony SM, Hyland NP, Cryan JF, Dinan TG. Toll-like receptor mRNA expression is selectively increased in the colonic mucosa of two animal models relevant to irritable bowel syndrome. *PLoS One* 2009; **4**: e8226 [PMID: 20011045 DOI: 10.1371/journal.pone.0008226]

45 **Tattoli I**, Petitta C, Scirocco A, Ammoscato F, Cicenia A, Severi C. Microbiota, innate immune system, and gastrointestinal muscle: ongoing studies. *J Clin Gastroenterol* 2012; **46 Suppl**: S6-11 [PMID: 22955360 DOI: 10.1097/MCG.0b013e318265ea7d]

46 **Macsharry J**, O'Mahony L, Fanning A, Bairead E, Sherlock G, Tiesman J, Fulmer A, Kiely B, Dinan TG, Shanahan F, Quigley EM. Mucosal cytokine imbalance in irritable bowel syndrome. *Scand J Gastroenterol* 2008; **43**: 1467-1476 [PMID: 18752146 DOI: 10.1080/00365520802276127]

47 **Lee BJ**, Bak YT. Irritable bowel syndrome, gut microbiota and probiotics. *J Neurogastroenterol Motil* 2011; **17**: 252-266 [PMID: 21860817 DOI: 10.5056/jnm.2011.17.3.252]

48 **Rousseaux C**, Thuru X, Gelot A, Barnich N, Neut C, Dubuquoy L, Dubuquoy C, Merour E, Geboes K, Chamaillard M, Ouwehand A, Leyer G, Carcano D, Colombel JF, Ardid D, Desreumaux P. Lactobacillus acidophilus modulates intestinal pain and induces opioid and cannabinoid receptors. *Nat Med* 2007; **13**: 35-37 [PMID: 17159985 DOI: 10.1038/nm1521]

49 **Kuhn KA**, Stappenbeck TS. Peripheral education of the immune system by the colonic microbiota. *Semin Immunol* 2013; **25**: 364-369 [PMID: 24169518 DOI: 10.1016/j.smim.2013.10.002]

50 **Falk PG**, Hooper LV, Midtvedt T, Gordon JI. Creating and maintaining the gastrointestinal ecosystem: what we know and need to know from gnotobiology. *Microbiol Mol Biol Rev* 1998; **62**: 1157-1170 [PMID: 9841668]

51 **O'Mahony C**, Scully P, O'Mahony D, Murphy S, O'Brien F, Lyons A, Sherlock G, MacSharry J, Kiely B, Shanahan F, O'Mahony L. Commensal-induced regulatory T cells mediate protection against pathogen-stimulated NF-kappaB activation. *PLoS Pathog* 2008; **4**: e1000112 [PMID: 18670628 DOI: 10.1371/journal.ppat.1000112]

52 **Ochoa-Repáraz J**, Mielcarz DW, Ditrio LE, Burroughs AR, Begum-Haque S, Dasgupta S, Kasper DL, Kasper LH. Central nervous system demyelinating disease protection by the human commensal Bacteroides fragilis depends on polysaccharide A expression. *J Immunol* 2010; **185**: 4101-4108 [PMID: 20817872 DOI: 10.4049/jimmunol.1001443]

53 **Corr SC**, Li Y, Riedel CU, O'Toole PW, Hill C, Gahan CG. Bacteriocin production as a mechanism for the antiinfective activity of Lactobacillus salivarius UCC118. *Proc Natl Acad Sci U S A* 2007; **104**: 7617-7621 [PMID: 17456596 DOI: 10.1073/pnas.0700440104]

54 **Rea MC**, Sit CS, Clayton E, O'Connor PM, Whittal RM, Zheng J, Vederas JC, Ross RP, Hill C. Thuricin CD, a posttranslationally modified bacteriocin with a narrow spectrum of activity against Clostridium difficile. *Proc Natl Acad Sci U S A* 2010; **107**: 9352-9357 [PMID: 20435915 DOI: 10.1073/pnas.0913554107]

55 **Castagliuolo I**, Riegler MF, Valenick L, LaMont JT, Pothoulakis C. Saccharomyces boulardii protease inhibits the effects of Clostridium difficile toxins A and B in human colonic mucosa. *Infect Immun* 1999; **67**: 302-307 [PMID: 9864230]

56 **Ohman L**, Lindmark AC, Isaksson S, Posserud I, Strid H, Sjövall H, Simrén M. B-cell activation in patients with irritable bowel syndrome (IBS). *Neurogastroenterol Motil* 2009; **21**: 644-50, e27 [PMID: 19222763 DOI: 10.1111/j.1365-2982.2009.01272.x]

57 **Ohman L**, Isaksson S, Lindmark AC, Posserud I, Stotzer PO, Strid H, Sjövall H, Simrén M. T-cell activation in patients with irritable bowel syndrome. *Am J Gastroenterol* 2009; **104**: 1205-1212 [PMID: 19367268 DOI: 10.1038/ajg.2009.116]

58 **Cremon C**, Pallotti F, Bacchilega M, Stanghellini V, Corinaldesi R, Barbara G. Antiflagellin antibodies suggest infective participation in irritable bowel syndrome pathogenesis. *Expert Rev Gastroenterol Hepatol* 2008; **2**: 735-740 [PMID: 19090734 DOI: 10.1586/17474124.2.6.735]

59 **Schoepfer AM**, Schaffer T, Seibold-Schmid B, Müller S, Seibold F. Antibodies to flagellin indicate reactivity to bacterial antigens in IBS patients. *Neurogastroenterol Motil* 2008; **20**: 1110-1118 [PMID: 18694443 DOI: 10.1111/j.1365-2982.2008.01166.x]

60 **Langhorst J**, Junge A, Rueffer A, Wehkamp J, Foell D, Michalsen A, Musial F, Dobos GJ. Elevated human beta-defensin-2 levels indicate an activation of the innate immune system in patients with irritable bowel syndrome. *Am J Gastroenterol* 2009; **104**: 404-410 [PMID: 19174795 DOI: 10.1038/ajg.2008.86]

61 **O'Mahony L**, McCarthy J, Kelly P, Hurley G, Luo F, Chen K, O'Sullivan GC, Kiely B, Collins JK, Shanahan F, Quigley EM. Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology* 2005; **128**: 541-551 [PMID: 15765388]

62 **Diaz Heijtz R**, Wang S, Anuar F, Qian Y, Björkholm B, Samuelsson A, Hibberd ML, Forssberg H, Pettersson S. Normal gut microbiota modulates brain development and behavior. *Proc Natl Acad Sci U S A* 2011; **108**: 3047-3052 [PMID: 21282636 DOI: 10.1073/pnas.1010529108]

63 **Neufeld KM**, Kang N, Bienenstock J, Foster JA. Reduced anxiety-like behavior and central neurochemical change in germ-free mice. *Neurogastroenterol Motil* 2011; **23**: 255-64, e119 [PMID: 21054680 DOI: 10.1111/j.1365-2982.2010.01620.x]

64 **Cryan JF**, O'Mahony SM. The microbiome-gut-brain axis: from bowel to behavior. *Neurogastroenterol Motil* 2011; **23**: 187-192 [PMID: 21303428 DOI: 10.1111/j.1365-2982.2010.01664.x]

65 **Fleshner M**. The gut microbiota: a new player in the innate immune stress response? *Brain Behav Immun* 2011; **25**: 395-396 [PMID: 21168480 DOI: 10.1016/j.bbi.2010.12.007]

66 **Wang SX**, Wu WC. Effects of psychological stress on small intestinal motility and bacteria and mucosa in mice. *World J Gastroenterol* 2005; **11**: 2016-2021 [PMID: 15800998]

67 **Cryan JF**, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nat Rev Neurosci* 2012; **13**: 701-712 [PMID: 22968153 DOI: 10.1038/nrn3346]

68 **Desbonnet L**, Garrett L, Clarke G, Kiely B, Cryan JF, Dinan TG. Effects of the probiotic Bifidobacterium infantis in the maternal separation model of depression. *Neuroscience* 2010; **170**: 1179-1188 [PMID: 20696216 DOI: 10.1016/j.neuroscience.2010.08.005]

69 **Bravo JA**, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, Bienenstock J, Cryan JF. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc Natl Acad Sci U S A* 2011; **108**: 16050-16055 [PMID: 21876150 DOI: 10.1073/pnas.1102999108]

70 **Clarke G**, Grenham S, Scully P, Fitzgerald P, Moloney RD, Shanahan F, Dinan TG, Cryan JF. The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. *Mol Psychiatry* 2013; **18**: 666-673 [PMID: 22688187 DOI: 10.1038/mp.2012.77]

71 **Tillisch K**, Labus J, Kilpatrick L, Jiang Z, Stains J, Ebrat B, Guyonnet D, Legrain-Raspaud S, Trotin B, Naliboff B, Mayer EA. Consumption of fermented milk product with probiotic modulates brain activity. *Gastroenterology* 2013; **144**: 1394-401, 1401.e1-4 [PMID: 23474283 DOI: 10.1053/j.gastro.2013.02.043]

72 **Barajon I**, Serrao G, Arnaboldi F, Opizzi E, Ripamonti G, Balsari A, Rumio C. Toll-like receptors 3, 4, and 7 are expressed in the enteric nervous system and dorsal root ganglia. *J Histochem Cytochem* 2009; **57**: 1013-1023 [PMID: 19546475 DOI: 10.1369/jhc.2009.953539]

73 **Scirocco A**, Matarrese P, Petitta C, Cicenia A, Ascione B, Mannironi C, Ammoscato F, Cardi M, Fanello G, Guarino MP, Malorni W, Severi C. Exposure of Toll-like receptors 4 to bacterial lipopolysaccharide (LPS) impairs human colonic smooth muscle cell function. *J Cell Physiol* 2010; **223**: 442-450 [PMID: 20112289 DOI: 10.1002/jcp.22053]

74 **Hooper LV**, Wong MH, Thelin A, Hansson L, Falk PG, Gordon JI. Molecular analysis of commensal host-microbial relationships in the intestine. *Science* 2001; **291**: 881-884 [PMID: 11157169 DOI: 10.1126/science.291.5505.881]

75 **Verdú EF**, Bercík P, Bergonzelli GE, Huang XX, Blennerhasset P, Rochat F, Fiaux M, Mansourian R, Corthésy-Theulaz I, Collins SM. Lactobacillus paracasei normalizes muscle hypercontractility in a murine model of postinfective gut dysfunction. *Gastroenterology* 2004; **127**: 826-837 [PMID: 15362038]

76 **Husebye E**, Hellström PM, Sundler F, Chen J, Midtvedt T. Influence of microbial species on small intestinal myoelectric activity and transit in germ-free rats. *Am J Physiol Gastrointest Liver Physiol* 2001; **280**: G368-G380 [PMID: 11171619]

77 **Kim G**, Deepinder F, Morales W, Hwang L, Weitsman S, Chang C, Gunsalus R, Pimentel M. Methanobrevibacter smithii is the predominant methanogen in patients with constipation-predominant IBS and methane on breath. *Dig Dis Sci* 2012; **57**: 3213-3218 [PMID: 22573345 DOI: 10.1007/s10620-012-2197-1]

78 **Pimentel M**, Lin HC, Enayati P, van den Burg B, Lee HR, Chen JH, Park S, Kong Y, Conklin J. Methane, a gas produced by enteric bacteria, slows intestinal transit and augments small intestinal contractile activity. *Am J Physiol Gastrointest Liver Physiol* 2006; **290**: G1089-G1095 [PMID: 16293652 DOI: 10.1152/ajpgi.00574.2004]

79 **Lee HR**, Pimentel M. Bacteria and irritable bowel syndrome: the evidence for small intestinal bacterial overgrowth. *Curr Gastroenterol Rep* 2006; **8**: 305-311 [PMID: 16836942]

80 **Linden DR**, Levitt MD, Farrugia G, Szurszewski JH. Endogenous production of H2S in the gastrointestinal tract: still in search of a physiologic function. *Antioxid Redox Signal* 2010; **12**: 1135-1146 [PMID: 19769466 DOI: 10.1089/ars.2009.2885]

81 **Fiorucci S**, Distrutti E, Cirino G, Wallace JL. The emerging roles of hydrogen sulfide in the gastrointestinal tract and liver. *Gastroenterology* 2006; **131**: 259-271 [PMID: 16831608 DOI: 10.1053/j.gastro.2006.02.033]

82 **Carbonero F**, Benefiel AC, Gaskins HR. Contributions of the microbial hydrogen economy to colonic homeostasis. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 504-518 [PMID: 22585131 DOI: 10.1038/nrgastro.2012.85]

83 **Teague B**, Asiedu S, Moore PK. The smooth muscle relaxant effect of hydrogen sulphide in vitro: evidence for a physiological role to control intestinal contractility. *Br J Pharmacol* 2002; **137**: 139-145 [PMID: 12208769 DOI: 10.1038/sj.bjp.0704858]

84 **Gallego D**, Clavé P, Donovan J, Rahmati R, Grundy D, Jiménez M, Beyak MJ. The gaseous mediator, hydrogen sulphide, inhibits in vitro motor patterns in the human, rat and mouse colon and jejunum. *Neurogastroenterol Motil* 2008; **20**: 1306-1316 [PMID: 19019033 DOI: 10.1111/j.1365-2982.2008.01201.x]

85 **Salminen S**, Bouley C, Boutron-Ruault MC, Cummings JH, Franck A, Gibson GR, Isolauri E, Moreau MC, Roberfroid M, Rowland I. Functional food science and gastrointestinal physiology and function. *Br J Nutr* 1998; **80 Suppl 1**: S147-S171 [PMID: 9849357]

86 **Thompson JS**, Quigley EM, Adrian TE. Qualitative changes in enteric flora and short-chain fatty acids after intestinal resection. *Dig Dis Sci* 1998; **43**: 624-631 [PMID: 9539660]

87 **Canani RB**, Costanzo MD, Leone L, Pedata M, Meli R, Calignano A. Potential beneficial effects of butyrate in intestinal and extraintestinal diseases. *World J Gastroenterol* 2011; **17**: 1519-1528 [PMID: 21472114 DOI: 10.3748/wjg.v17.i12.]

88 **Treem WR**, Ahsan N, Kastoff G, Hyams JS. Fecal short-chain fatty acids in patients with diarrhea-predominant irritable bowel syndrome: in vitro studies of carbohydrate fermentation. *J Pediatr Gastroenterol Nutr* 1996; **23**: 280-286 [PMID: 8890079]

89 **Soret R**, Chevalier J, De Coppet P, Poupeau G, Derkinderen P, Segain JP, Neunlist M. Short-chain fatty acids regulate the enteric neurons and control gastrointestinal motility in rats. *Gastroenterology* 2010; **138**: 1772-1782 [PMID: 20152836 DOI: 10.1053/j.gastro.2010.01.053]

90 **Haschke G**, Schafer H, Diener M. Effect of butyrate on membrane potential, ionic currents and intracellular Ca2+ concentration in cultured rat myenteric neurones. *Neurogastroenterol Motil* 2002; **14**: 133-142 [PMID: 11975713]

91 **Tazoe H**, Otomo Y, Kaji I, Tanaka R, Karaki SI, Kuwahara A. Roles of short-chain fatty acids receptors, GPR41 and GPR43 on colonic functions. *J Physiol Pharmacol* 2008; **59 Suppl 2**: 251-262 [PMID: 18812643]

92 **Lesniewska V**, Rowland I, Laerke HN, Grant G, Naughton PJ. Relationship between dietary-induced changes in intestinal commensal microflora and duodenojejunal myoelectric activity monitored by radiotelemetry in the rat in vivo. *Exp Physiol* 2006; **91**: 229-237 [PMID: 16263800 DOI: 10.1113/expphysiol.2005.031708]

93 **Durbán A**, Abellán JJ, Jiménez-Hernández N, Artacho A, Garrigues V, Ortiz V, Ponce J, Latorre A, Moya A. Instability of the faecal microbiota in diarrhoea-predominant irritable bowel syndrome. *FEMS Microbiol Ecol* 2013; **86**: 581-589 [PMID: 23889283 DOI: 10.1111/1574-6941.12184]

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