**Name of Journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 25990**

**Manuscript Type: TOPIC HIGHLIGHT**

**2016 Irritable Bowel Syndrome: Global view**

**regulation of** **serotonin transporter** **in the** **pathogenesis of** **irritable bowel syndrome**

Jin DC *et al*. SERT regulation in IBS

Duo-Chen Jin, Hai-Long Cao, Meng-Que Xu, Si-Nan Wang, Yu-Ming Wang, Fang Yan, Bang-Mao Wang

**Duo-Chen Jin, Hai-Long Cao, Meng-Que Xu, Si-Nan Wang, Yu-Ming Wang, Fang Yan, Bang-Mao Wang,** Department of Gastroenterology and Hepatology, General Hospital, Tianjin Medical University, Tianjin 300052, China

**Hai-Long Cao, Fang Yan,** Division of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN 37232­0696, United States

**Author contributions:** Jin DC, Cao HL and Wang BM designed the review; Jin DC, Cao HL, Xu MQ, Wang SN and Wang YM collected and analyzed the literature; Jin DC and Cao HL wrote the paper; Jin DC, Cao HL, Xu MQ, Wang SN, Yan F and Wang BM identified the manuscript; All authors were involved in the final approval of the article.

**supported by** National Natural Science Foundation of China, No. 81300272 (to Cao HL), No. 81470796 (to Yan F), No. 81570489 (to Wang YM) and No. 81570478 (to Wang BM); and Tianjin Research Program of Application Foundation and Advanced Technology of China, No. 15JCZDJC36600 (to Yan F).

**Conflict-of-interest statement:** The authors have no conflict of interest.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Correspondence to:** **Hai-long Cao, MD,** **PhD,** Department of Gastroenterology and Hepatology, General Hospital, Tianjin Medical University, 154 Anshan Road, Heping District, Tianjin 300052, China. cao\_hailong@163.com

**Telephone**: +86-22-60362608

**Fax**: +86-22-27813550

**Received:** March 27, 2016

**Peer-review started:** March 28, 2016

**First decision:** May 12, 2016

**Revised:** May 28, 2016

**Accepted:** June 15, 2016

**Article in press:**

**Published online:**

**Abstract**

Serotonin (5-HT) and serotonin transporter (SERT) have exerted a tremendous fascination in the pathogenesis of irritable bowel syndrome (IBS). Considering enteric serotonin is responsible for the secretion, motility and perception of the bowel, altered enteric serotonin metabolism involving in the pathogenesis of IBS has been elucidated. It is becoming clear that a higher 5-HT availability associated with depressed SERT mRNA can be found in patients with IBS compared to healthy controls. Expression difference of SERT between IBS patients and healthy controls might suggest that SERT played an essential role in IBS pathogenesis, which was expected to be a novel therapeutic target for IBS. Progress in this area has begun to illuminate the complex regulatory mechanisms of SERT in the etiology of IBS. In this article, current insights regarding the regulation of SERT in IBS were provided, including the aspects of SERT gene polymorphisms, microRNAs, immunity and inflammation, gut microbiota, growth factors, *etc*. Moreover, potential SERT-directed therapeutic implications for IBS were also involved. These potential factors regulating SERT are of clinical importance, and are conducive to understand the pathophysiology and therapeutic strategies of IBS better.

**Key words:** Irritable bowel syndrome; Serotonin transporter;Serotonin; Regulation; Therapy

**© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Serotonin transporter (SERT) participating in metabolizing serotonin in the gut plays a crucial role in the pathogenesis of irritable bowel syndrome (IBS). This review summarized the relevant evidence on the feasible regulation factors of SERT, including SERT gene polymorphisms, microRNAs, immunity and inflammation, gut microbiota, growth factors, *etc*. It also revealed some potential treatments targeting SERT for IBS patients.

Jin DC, Cao HL, Xu MQ, Wang SN, Wang YM, Yan F, Wang BM. regulation of serotonin transporter in the pathogenesis of irritable bowel syndrome. *World J Gastroenterol* 2016; In press

**INTRODUCTION**

As a functional bowel disorder, irritable bowel syndrome (IBS) has the highest incidence rate worldwide. IBS is defined as a complex symptom-based disorder for showing up as abdominal pain/discomfort and altered bowel pattern[1-3]. A growing number of people are suffering from IBS with an estimated 5.8%-17.5% prevalence, especially in female[4,5]. IBS causes a tremendous decline in the health-related quality of life and brings with considerable socioeconomic burden up to $19 billion[2,6]. So far, the Rome III criteria have been improved to help diagnose and differential diagnose the syndrome[7-10]. According to this criteria, IBS can be divided into 4 subtypes, namely IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), IBS mixed type (IBS-M) and IBS unsubtyped (IBS-U)[11,12]. Furthermore, a follow-up study for six years showed that approximately 10% patients with infective gastroenteritis suffered from post-infective IBS (PI-IBS) ultimately[13]. Since IBS is considered to be a multifactorial and heterogeneous disease seen with the various phenotypes, no single mechanism entirely explains pathophysiology of the disorder. Some possible mechanisms are involved in the initiation, persistence and severity of symptom flares including inflammation, immunity, infection[14,15], the gut microbiota[16,17], psychosocial stress[16,18,19], abnormal brain-gut axis[16,20]. Also, recent discoveries have revealed that genetic susceptibility[21], diet/drugs intolerances[22] and environment pollutions[23] are closely associated with IBS pathogenesis. Although the aetiology of IBS is largely elusive, there are still some characteristic symptoms of the disorder including visceral hypersensitivity[16,24], intestinal barrier dysfunction[25] and gut motility disorder[16,17,26].

In the gut, as a signal transducer and a neurotransmitter, serotonin mediates intercellular signaling transmission. Most of serotonin of the body is in the gut. Enteric serotonin is synthesized by enterochromaffin (EC) cells (90%) and enteric serotonergic neurons of myenteric plexus (10%)[27]. Hence, EC cells are the main source of enteric 5-HT existing in the gastrointestinal (GI) tract[28,29]. Serotonin inactivation is as important as serotonin release in order to keep dynamic equilibrium. As a number of neurotransmitter sodium symporters or the solute carrier superfamily 6, the serotonin reuptake transporter (SERT) plays an irreplaceable role in serotonin inactivation by removing it from interstitial space in the lamina propria into mucosal enterocytes and presynaptic neurons where are responsible for catabolism[30,31]. Coates *et al*[31] characterized the first time that there was a significant decreased level of SERT in IBS. However, there was a conflicting finding of increased SERT expression in IBS[32,33]. Taking the significant differences of analytical methodology used and the heterogeneity of phenotypes into account, most researchers like C. Faure *et al*[34] demonstrated that IBS patients had a remarkably attenuated level of SERT expression in intestinal lining, which conformed to a remarkably decreased capacity of enterocytes to retake 5-HT. In other words, it’s generally accepted that there is a significant inverse correlation targeting the level availability between SERT and 5-HT.

SERT plays a critical role in uptake and internalization of extracellular 5-HT. Previous studies have provided support to the concept that SERT is regulated by transcriptional and posttranslational mechanisms. Until now, association between SERT gene polymorphisms and IBS susceptibility has been found inconsistently among different ethnic groups, even among different populations[35]. Despite the lack of consensus on the wide range of the roles of potential factors, immunity activation, inflammatory response, gut microbiota, and their relationship have been suggested to regulate SERT expression in PI-IBS[36]. Probiotics are also notable for linking with inflammation-immune systems and gut microbiota in IBS patients[37]. Profoundly, recent studies also have shed a fascinating light on their roles of microRNAs, growth factors and others in regulating SERT[38].

**Role of SERT in IBS**

5-HT expands its regulatory functions outside the central nervous system as a neurotransmitter. In the gut, serotonin is also a key signal transducer[39,40]. Although the complex roles of 5-HT in the gut have not yet been clearly and completely elucidated, current researches have proved that 5-HT acts upon mucosal sensory transduction responding to pressure and luminal stimuli deriving from diet and bacteria[41]. The release of serotonin acting on a series of serotonin receptors initiates secretory reflexes, peristaltic reflexes, and if pronounced, even diarrhea, by stimulating intrinsic primary afferent neurons and myenteric interneurons[41-43]. Furthermore, by stimulating extrinsic sensory nerves, it also can transmit sensation of discomfort to the central nervous system along the gut–brain axis in IBS. Thus, 5-HT is closely related to the secretion, motility and sensation in the gut[28,31]. Shufflebotham *et al*[44] highlighted the importance of 5-HT dysfunction in IBS symptoms and psychophysiological manifestation with the use of the acute tryptophan depletion paradigm. Moreover, increasing evidence suggests that psychiatric comorbidities are highly prevalent in IBS patients[45]. Antidepressant selective serotonin reuptake inhibitors (SSRIs), could be considerable treatments for IBS. In 2014, a systematic review declared that antidepressants are effective to treat IBS[46]. However, in 2015, a meta-analysis with conflicting results found that the efficacy of SSRIs to treat IBS was inconclusive[47]. Promisingly, one study manifested that IBS patients with psychiatric comorbidity had a greater probability of carrying SERT variants[48]. The possibilities underpinning antidepressants like SSRIs and other factors to regulate SERT require further elaboration.

The termination of the serotonin signal is as important as the initiate of that, therefore, SERTs on the cell membrane of enterocytes are vital to transport 5-HT from extracellularly into intracellularly, where 5-HT is metabolized by monamino-oxidases[49]. Chen *et al*[50] demonstrated nearly all of the intestinal epithelial cells on the surface of the lumen expressed SERT availably using the mice with a targeted deletion of SERT. As a result, it is not surprising that the intestinal mucosa has a huge capacity for taking up serotonin from interstitial space. Hence, 5-HT is transported into enterocytes by SERT after releasing from EC cells and acting on local selected receptors[30].As a kind of membrane-embedded transporter, SERT is crucial for modulating amplitude and duration of the serotonin signaling[51].As discussed above, a significant correlation has been observed between abnormalities of serotonin signaling and IBS-like symptom pathogenesis. Furthermore, it is now believed that altered SERT expression is responsible for the disorganized serotonin signaling. When dysregulated SERT increases mucosal 5-HT availability, high-levels of gut secretion and motility may accelerate the development of IBS-D[52]. It’s generally accepted that the abnormalities of SERT expression make a contribution to IBS development. However, the regulation of SERT expression in IBS and the mechanisms underlying are not fully understood.

**Potential regulation factors of SERT**

Both genetic and nongenetic factors are implicated in the upregulation or downregulation of SERT expression in IBS (Table 1). It is becoming clear that genetic predisposition may underlie IBS in individuals[53]. The large-scale study between monozygotic twins and dizygotic twins proved that both heredity and environment contributed to the development of IBS. What’s more, it seemed that environmental influence was more crucial for the individuals than heredity in IBS[54]. In this article, the potential regulation factors on SERT expression were presented and discussed, which may involve in the pathophysiology and/or etiology of IBS.

***SERT gene polymorphisms***

As Hotoleanu *et al*[55] pointed out, genetic factor contributed to IBS based on twin studies, familial aggregation and epidemiology, especially the polymorphisms of SERT gene. In other words, a low-expression SERT genotype may underlie a genetic predisposition of IBS[56,57]. Furthermore, Kohen *et al*[58] reported a trend towards association between 5-HT-transporter-gene-linked polymorphic region (5-HTTLPR) L/L genotype and IBS. However, Camilleri *et al*[59] found that colonic mucosal expression of SERT gene was normal in IBS. Galligan *et al*[60] found that there was increased serotonin availability in SERT KO rats associated with visceral hypersensitivity. SERT gene, solute carrier family 6 member 4 (SLC6A4), localizes to chromosome 17q11.2. SLC6A4 spans approximately 40 KB and contains 14 exons, which encodes a 603-amino acid protein ultimately[61-63]. There are a series of polymorphic regions that may affect the expression or function of SERT gene[59,64-67], and further alter 5-HT retake reaching up to 40-fold *in vitro*[68]. Current researches mainly focus on whether there are positive associations of the SLC6A4 genetic polymorphisms with the etiology of IBS, including 5-HTTLPR[69], variable number of tandem repeats (VNTR) STin2[65] and functional single nucleotide polymorphisms (SNPs; rs25531 and rs25532, *etc*.)[58,70,71]. However, the presence of linkage disequilibrium (LD) between the three aspects has not yet been determined[58].

The most frequently studied variant, 5-HTTLPR insertion/deletion polymorphism about 44 base pairs, is subdivided into long (L) and short (S) alleles[69,72]. Furthermore, as such, compared with the L/S and S/S genotypes, the transcriptional efficiency of the L/L genotype is significantly higher[73]. Our previous study found the L/L genotype which led to a higher SERT level appeared more frequently in IBS-C individuals than IBS-D and healthy individuals[73]. Yeo *et al*[74] reported 5-HTTLPR polymorphism was highly related to female patients with IBS. The S allele leading to decreased transcription of SLC6A4 and attenuated expression of SERT protein resulted in a reduced reuptake of 5-HT and a higher 5-HT level, which was consistent with manifestations of IBS-D compared to other subtypes of IBS and controls[75]. Contradictorily, Sikander *et al*[76] and Pata *et al*[77] reported that the S/S genotype had a significant correlation with IBS-C patients in the Indian and Turkish population, and Wendelbo *et al*[33] concluded an increased content of SERT availability in ileal epithelia facilitating the pathogenesis of IBS, regardless of the subtypes. However, for the insufficient numbers of patients participated in these studies, there was still no consistent conclusion. A meta-analysis containing thousands of IBS cases found that there existed ethnic difference in the relationship between 5-HTTLPR and IBS, moreover, L/L genotype was more relevant to IBS-C in East Asians than in Caucasians, or rather L allele[78]. Similarly, another meta-analysis showed that SLC6A4 polymorphism caused a reduced risk of IBS population in America and Asia[35].

There is another SERT gene polymorphism, called variable number of tandem repeats STin2, or simply "STin2 VNTR" for short, which is located in intron 2, consisting of an indeterminate number of 17-bp segments, *i.e.*, 9, 10, or 12 repeats availability[65,70]. Our previous study reported that 10/12 genotype may contribute to IBS[79], while other reports about the association between STin2 VNTRs and IBS were controversial and inconclusive[74,80]. When it comes to functional SNPs within the promoter VNTR, Kohen *et al*[58] found that compared to the more frequent A-allele, the comparatively rare rs25531 G-allele decreased SERT transcription level and thus increased IBS risk by approximately threefold. Of note, SERT gene promoter polymorphisms have been implicated in the treatment effects of histone deacetylase inhibitors (butyrate or trichostatin) in cultured colonic epithelial cells (Caco-2 cells), which resulted in reduced SERT mRNAs and proteins by suppressing human SERT (hSERT) promoter 1[81]. In the long run, the development of SERT gene-specific therapeutics to regulate SERT expression in the treatment of multiple disorders including IBS is realizable. Clinicians may put individual treatment into effect according to the different genotypes of SERT gene as one of the factors.

***MicroRNAs***

Posttranscriptional gene regulation affected by an enormous amount of microRNAs (miRNAs) is one of pivotal regulation mode contributing to miRNAs-targeted genes translation[82,83]. MiRNAs, endogenous ~22 nucleotides (nt) noncoding RNAs, pair to and then silence target mRNAs and thus achieve fine adjustments of protein outputs[84-86]. It is of interest that, nearly all aspects of biological processes, including development and cellular homeostasis, are under the influence of miRNAs. Moreover, it will facilitate the development of some kind of diseases when miRNAs dysregulate targeted gene expression[83-85,87]. Despite insufficient researches focusing on 3’ untranslated region (3’-UTR) of SLC6A4, miRNAs binding to 3’-UTR of SERT mRNAs by incompletely complementary base pairing are crucial for SERT mRNAs translation, localization and stability[38,88].

Intriguingly, during the past several years it was clearly showed that SERT was such a target of microRNA-16 (miR-16). Highly conserved miR-16 among mammalian species has high expression levels in heart, brain, small intestine, lung, and kidney[89,90]. Baudry *et al*[38] investigated whether SERT expression was depressed by miRNAs in monoaminergic neurons utilizing the 1C11 neuroectodermal cell line expressing SERT transcripts. The results showed 40% declines in the numbers of [3H]-paroxetine (SSRI) binding sites after transfected with high level of miR-16. The SSRI fluoxetine downregulated SERT expression by increasing the level of miR-16 in 1C115-HT cells (1C11 neuroectodermal cells differentiate into serotonergic neuronal cells)[38]. Subsequently, the similar findings were obtained in hippocampus that fluoxetine treatment resulting in downregulated miR-16, led to increased SERT expression fivefold, with further illustration that the level of miR-16 regulated by SSRI antidepressants, increased or decreased, depended on the different regions in the brain, and neutralization of miR-16 played an antidepressant role in the hippocampus[91]. Likewise, direct injection of anti-miR-16 had an antidepressant effect like fluoxetine[91,92]. A study investigating acute lung injury also drew the same conclusions that a decreased miR-16 level contributed to an increased SERT expression and hence promoted the pathogenesis of pulmonary edema[93]

MiR-16 may not be the only modulatory miRNA in translational repression of SERT. For example, Jensen KP and colleagues found that SERT expression in Hela cell lines was regulated additionally by miR-545, and it seemed that U to G SNP in 3’UTR of SERT mRNA had no difference in binding with miR-545 and downregulated effects[94]. In addition, miR-15a contiguously located at chromosome 13q14.3 with miR-16 also regulated SERT expression in rat and human cells[62,89]. More concerning, the observed results from brain tissue of wistar rat pups highlighted that *Cronobacter sakazakii* infection upregulated miR-16 expression interacting with SERT mRNA, which led to the decreased levels of 5-HT and SERT expression[95]. Recently, a study directly illuminated that increased miR-24 expression in enterocytes of IBS patients and mice models promoted IBS-D pathogenesis by downregulating SERT expression[96]. In a word, discovering novel miRNAs relating to posttranscriptional SERT gene regulation, and elucidating the underlying mechanisms provide a new strategy to expand understandings of miRNAs implications in the development and treatment of IBS.

***Immunity and inflammation***

Given accumulating evidence points to a critical role of immune activation for gut mucosa resulting in enterochromaffin cell hyperplasia and reduced SERT activity in IBS-D patients or post-infectious IBS (PI-IBS) patients[97], it is not surprising that mucosal 5-HT is increased in IBS-D patients[41,52,98,99] and PI-IBS patients[41,98,100,101]. Indeed, it’s generally accepted that there are increased levels of mucosal immune cell infiltration and proinflammatory cytokines in IBS patients. Furthermore, inflammatory state of intestinal mucosa promotes visceral hypersensitivity[14,34,102]. Evidence suggests that 50% of IBS patients exhibit a drastic 72% increase of immunocytes in colonic mucosa, including CD3+, CD4+, and CD8+ T cells and mast cells, compared to healthy controls[41,103]. More concerning, Foley *et al*[52] found that the reduced level of mucosal SERT mRNA in IBS-D folks was correlated with the increased numbers of mucosal intraepithelial lymphocytes (IELs) and mast cells compared with healthy controls. Besides, a study from Wheatcroft J and colleagues evaluated post-Trichinella spiralis infection of T-cell receptor knock out (TCR KO) mice with respects to EC numbers and SERT expression. As the authors pointed out, deficiencies of all T cells decreased infection-induced enterochromaffin cell hyperplasia and extinguished mastocytosis, with drastic reduction in jejunal SERT expression[104]. However paradoxically, despite the general presence of inflammatory infiltrate more or less, Faure *et al*[34] detected no differences in the numbers of IELs and CD3+ cells located in the lamina propria between IBS folks and healthy folks.

Accumulating evidence demonstrated that proinflammatory mediators, such as interferon-γ and tumor necrosis factor α, not just a nonspecific change of inflammatory damage on epithelial cells, induced significant reductions in SERT mRNA, SERT protein level and SERT function in Caco2 cells[105]. While prostaglandin E2 (PGE2) and interleukin-12 (IL-12) had no effect on SERT mRNA and protein levels[105]. Further, Shugan decoction (SGD) is a kind of traditional Chinese medicine that is used to treat IBS-D patients. The treatment with SGD decreased TNF-α level with upregulated SERT gene and protein levels in colonic tissue, which suggested the underlying interactions between TNF-α and SERT expression[106]. Inversely, a protective cytokine named transforming growth factor-β1 (TGF-β1) could activate SERT activity and protect from intestinal inflammation via PI3K and syntaxin 3[107]. These studies provide an overview of immune mechanisms involving in SERT regulation in a subset of IBS patients.

***Gut microbiota***

It’s generally accepted that gut microbiota dysbiosis is responsible for intestinal ecology disturbances, which could be a significant catalyst in the development of functional bowel disorders[108,109]. The current insight is that gut host-microbial interactions are important elements involving in the pathogenesis of IBS, because of the most convincing findings that predisposed individuals following infectious gastroenteritis would suffer from PI-IBS resembling those of IBS-D[110,111]. Because of the rapid evolution of analytical techniques such as 16S rRNA-based microbiota analyses for profiling of the bacteria in the GI tract, not just culture, it has shown that mucosal and fecal gut microbial community composition differed between patients with IBS and healthy controls[112]. Albeit with significant differences in methods, many studies have found that relative abundance of the genera *Lactobacillus*, *Bifidobacterium*, *Actinobacteria* and *Bacteroidetes* were decreased while *Proteobacteria*, *Firmicutes* and *Firmicutes*: *Bacteroidetes* ratios were increased in fecal sample of IBS-D patients[110,113,114]. Malinen *et al*[115] even found that there was an association between altered bacteria composition and subtypes of IBS, with a decreased amount of *Lactobacillus spp.* among IBS-D patients whereas an elevated amount of *Veillonella spp.* among IBS-C patients. However, the lack of large sample and the heterogeneity of IBS symptoms represented a limitation of these studies.

As noted earlier, particular gut microbes and microbial metabolites regulate tryptophan metabolism, the serotonergic system, and brain-gut axis functions and thereby alter levels of 5-HT in the colon and blood, which may suggest the critical role of intestinal flora in regulating SERT, and ultimately influencing the pathogenesis of IBS[40,112,116,117]. Yano JM and colleagues found that ECs were promoted to synthesize and secrete 5-HT by indigenous bacteria such as spore-forming bacteria and their metabolites in germ-free mice[116]. On the one hand, Esmaili *et al*[118] found that Caco-2 cells and mice infected by enteropathogenic *E coli* to simulate infectious diarrheal diseases (PI-IBS and enteric infections), had decreased SERT mRNA level, apical SERT activity, 5-HT uptake and mucosal 5-HT content. On the other hand, an investigation provided by Nzakizwanayo *et al*[119] demonstrated that the exposure of mouse ileal tissue *in vitro* to *Escherichia coli* Nissle 1917 (EcN) increased 5-HT bioavailability and decreased its metabolite level (5-hydroxy indole acetic acid, 5-HIAA), which suggested the underlying mechanisms for clearing 5-HT by SERT. As a correlation, in IBS, the reductions of 5-HIAA level and 5-HIAA/5-HT ratio elucidate serotonergic system dysbiosis in both respects for synthesis and metabolism[120]. Indeed, our previous study suggested that the supernatant of probiotics like *Lactobacillus rhamnosus GG* (LGG-s) upregulated SERT mRNA level as much as 9.4-fold in enterocytes and mice intestinal tissues in a concentration and time dependent manner[121,122]. Our research also found that a protein called p40 derived from LGG activated EGFR (epidermal growth factor receptor), which suggested that LGG upregulated SERT possibly by activating EGFR[123].

Therapeutic strategies targeting the gut microbiota in order to recover the decreased diversity and stability might be a viable treatment strategy for IBS and other serotonin-related brain-gut-microbiota axis disorders[40,116]. To date, the scientists and clinicians have made a variety of creative attempts, especially probiotics, prebiotics, antibiotics and FMT, to increase the relative abundance of commensals (like *Lactobacilli* and *Bifidobacteria*, *etc*.), and conversely, decrease the relative abundance of those bacterial species exacerbating IBS symptoms (*Clostridium*, *Escherichia coli*, *Salmonella*, *Shigella* and *Pseudomonas*)[108,124]. On the one hand, both a low-carbohydrate diet and the probiotic LGG have been proven effective in IBS patients respectively[122,125]. *Lactococcus lactis*, which is effective in suppressing colon inflammation by secreting IL-10, restores colonic 5-HT concentrations, given 5-HT level is increased in DiNitro-Benzenesulfonic-acid (DNBS) micro-inflammation model[102]. And similarly, Martín *et al*[126] found that probiotics *Faecalibacterium prausnitzii* strain A2-165 (a type of commensal bacterium) or its supernatant, had anti-inflammatory effect with a downregulated 5-HT level to restore normal. Rifaximin, the most studied antibiotic in IBS, increased the relative abundance of *Lactobacillus* in the ileum, which relieved mucosal inflammatory state and visceral hyperalgesia of rat model[127]. Promisingly, there is growing evidence regarding FMT in relieving symptoms in IBS patients, even in these with longstanding refractory IBS-D via restoring the intestinal microbiota[128-131]. However, no study has demonstrated the relationship between FMT and SERT in IBS. Further studies are necessary to determine new classes of probiotics and underlying mechanisms contributing to the treatment of IBS, meanwhile, it remains to be determined the feasibility and reliability of FMT.

***Growth factors***

There is growing evidence regarding some growth factors in the upregulation of SERT expression, such as EGF[132], basic fibroblast growth factor[133], nerve growth factor[134]. At present, EGF has been mostly studied. As a polypeptide with 53 amino acid residues and growth hormone[135], EGF plays multifarious biological functions via combining with specific EGFR located on the basolateral surface of enterocytes[135-138]. There is identical evidence to suggest that, EGF involves in a great many normal physiological processes (stimulating intestinal epithelium cell proliferation, differentiation and maturation[136,139-141], *etc*.) and pathophysiologic situations (maintenance of homeostasis[142], protection and regeneration of gastrointestinal mucosa[136,140,143]). Given that EGF signaling protects GI tract from intestinal inflammation[137], little is known whether there is a correlation between EGF signaling and IBS pathogenesis.

Responding to SERT regulation, as Gill *et al*[144] pointed out, for the first time, EGF acting on EGFR activated promoter hSERT and upregulated SERT mRNA level and function in enterocytes through transcriptional mechanisms in a dose and time dependent manner. Two types of alternate promoters of SERT gene, hSERTp1 and hSERTp2[145], are both active in Caco-2 cells by approximately 2- to 2.5-fold, compared with the transfected results of the pGL2 empty vector alone [144]. Afterwards, accumulating evidence suggests EGF promotes SERT gene expression level. Kekuda *et al*[132,144] found that treatment of human placental choriocarcinoma cells with EGF increased the levels of SERT gene transcriptional activity, SERT mRNA expression and SERT function, most likely by activating the EGF receptor through tyrosine phosphorylation. Kubota *et al*[133] reached the similar conclusions about EGF and basic fibroblast growth factor using human glial cells (astrocytes). On the other hand, the upregulated effects of EGF on the both distinct promoters of SERT gene (hSERTp1 and hSERTp2), are counteracted by inhibiting EGFR tyrosine kinase activity[132,144]. The decreased plasma and colonic tissues EGF levels were observed in IBS patients, as well as in a rat model with visceral hypersensitivity[146]. Therefore, decreased level of EGF correlated to decreased level of SERT activity, which was consistent with the conclusions that a decrease in EGF level resulted in a decrease in removing 5-HT into intestinal epithelial cells, stimulating visceral sensitivity, and ultimately contributing to IBS[146]. Interestingly, as a kind of neuroendocrine mediator, neurotrophin nerve growth factor is increased in mucosal tissues[147,148], and can relieve intestinal barrier dysfunction and visceral hypersensitivity of IBS-D patients[149,150]. These findings suggest that the upregulation of SERT expression and function by growth factors might provide a better understanding of the pathogenesis and treatment of IBS.

***Others***

In addition, there are some different factors modulating SERT expression. As an agonist of tyrosine-kinase receptor, aurintricarboxylic acid plays a similar role in the upregulation of SERT, just like EGF[132]. Although studies found that some factors (CCAAT/enhancer binding protein beta[151], heterogeneous nuclear ribonucleoprotein K[152], 10(-7)M 4-β-12-tetradecanoylphorbol-13-acetate[153], *etc*.) regulated SERT, it remained to be determined whether these factors involved in IBS pathogenesis.

**Future prospects**

It is now believed that serotonin signaling is essential to the pathogenesis of IBS. As a result, new therapeutic strategies targeting the abnormal expression of SERT may be a new breakthrough and benefit to relieve symptoms from this excruciating disease[28,109]. At present, therapeutic approaches targeting gut microbiota, immune activation and inflammatory response have received an adequate attention to regulate SERT. There is no doubt that these potential regulation factors of SERT have a broad developing prospect in the treatment of IBS.

**References**

1 **Jarrett ME**, Han CJ, Cain KC, Burr RL, Shulman RJ, Barney PG, Naliboff BD, Zia J, Heitkemper MM. Relationships of abdominal pain, reports to visceral and temperature pain sensitivity, conditioned pain modulation, and heart rate variability in irritable bowel syndrome. *Neurogastroenterol Motil* 2016; Epub ahead of print [PMID: 26993039 DOI: 10.1111/nmo.12812]

2 **Sayuk GS**, Gyawali CP. Irritable bowel syndrome: modern concepts and management options. *Am J Med* 2015; **128**: 817-827 [PMID: 25731138 DOI: 10.1016/j.amjmed.2015.01.036]

3 **Guagnozzi D**, Arias Á, Lucendo AJ. Systematic review with meta-analysis: diagnostic overlap of microscopic colitis and functional bowel disorders. *Aliment Pharmacol Ther* 2016; Epub ahead of print [PMID: 26913568 DOI: 10.1111/apt.13573]

4 **Kaji M**, Fujiwara Y, Shiba M, Kohata Y, Yamagami H, Tanigawa T, Watanabe K, Watanabe T, Tominaga K, Arakawa T. Prevalence of overlaps between GERD, FD and IBS and impact on health-related quality of life. *J Gastroenterol Hepatol* 2010; **25**: 1151-1156 [PMID: 20594232 DOI: 10.1111/j.1440-1746.2010.06249.x]

5 **Sperber AD**, Dumitrascu D, Fukudo S, Gerson C, Ghoshal UC, Gwee KA, Hungin AP, Kang JY, Minhu C, Schmulson M, Bolotin A, Friger M, Freud T, Whitehead W. The global prevalence of IBS in adults remains elusive due to the heterogeneity of studies: a Rome Foundation working team literature review. *Gut* 2016; Epub ahead of print [PMID: 26818616 DOI: 10.1136/gutjnl-2015-311240]

6 **Wilson A**, Longstreth GF, Knight K, Wong J, Wade S, Chiou CF, Barghout V, Frech F, Ofman JJ. Quality of life in managed care patients with irritable bowel syndrome. *Manag Care Interface* 2004; **17**: 24-8, 34 [PMID: 15038690]

7 **Ford AC**, Bercik P, Morgan DG, Bolino C, Pintos-Sanchez MI, Moayyedi P. Validation of the Rome III criteria for the diagnosis of irritable bowel syndrome in secondary care. *Gastroenterology* 2013; **145**: 1262-70.e1 [PMID: 23994201 DOI: 10.1053/j.gastro.2013.08.048]

8 **Engsbro AL**, Begtrup LM, Kjeldsen J, Larsen PV, de Muckadell OS, Jarbøl DE, Bytzer P. Patients suspected of irritable bowel syndrome--cross-sectional study exploring the sensitivity of Rome III criteria in primary care. *Am J Gastroenterol* 2013; **108**: 972-980 [PMID: 23419383 DOI: 10.1038/ajg.2013.15]

9 **Wang X**, Luscombe GM, Boyd C, Kellow J, Abraham S. Functional gastrointestinal disorders in eating disorder patients: altered distribution and predictors using ROME III compared to ROME II criteria. *World J Gastroenterol* 2014; **20**: 16293-16299 [PMID: 25473186 DOI: 10.3748/wjg.v20.i43.16293]

10 **Koloski NA**, Jones M, Young M, Talley NJ. Differentiation of functional constipation and constipation predominant irritable bowel syndrome based on Rome III criteria: a population-based study. *Aliment Pharmacol Ther* 2015; **41**: 856-866 [PMID: 25736433 DOI: 10.1111/apt.13149]

11 **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]

12 **Engsbro AL**, Simren M, Bytzer P. Short-term stability of subtypes in the irritable bowel syndrome: prospective evaluation using the Rome III classification. *Aliment Pharmacol Ther* 2012; **35**: 350-359 [PMID: 22176384 DOI: 10.1111/j.1365-2036.2011.04948.x]

13 **Neal KR**, Barker L, Spiller RC. Prognosis in post-infective irritable bowel syndrome: a six year follow up study. *Gut* 2002; **51**: 410-413 [PMID: 12171965]

14 **O'Malley D**. Immunomodulation of enteric neural function in irritable bowel syndrome. *World J Gastroenterol* 2015; **21**: 7362-7366 [PMID: 26139983 DOI: 10.3748/wjg.v21.i24.7362]

15 **Ohman L**, Simrén M. Pathogenesis of IBS: role of inflammation, immunity and neuroimmune interactions. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 163-173 [PMID: 20101257 DOI: 10.1038/nrgastro.2010.4]

16 **Moloney RD**, Johnson AC, O'Mahony SM, Dinan TG, Greenwood-Van Meerveld B, Cryan JF. Stress and the Microbiota-Gut-Brain Axis in Visceral Pain: Relevance to Irritable Bowel Syndrome. *CNS Neurosci Ther* 2016; **22**: 102-117 [PMID: 26662472 DOI: 10.1111/cns.12490]

17 **Ringel-Kulka T**, Choi CH, Temas D, Kim A, Maier DM, Scott K, Galanko JA, Ringel Y. Altered Colonic Bacterial Fermentation as a Potential Pathophysiological Factor in Irritable Bowel Syndrome. *Am J Gastroenterol* 2015; **110**: 1339-1346 [PMID: 26303129 DOI: 10.1038/ajg.2015.220]

18 **Mawe GM**, Coates MD, Moses PL. Review article: intestinal serotonin signalling in irritable bowel syndrome. *Aliment Pharmacol Ther* 2006; **23**: 1067-1076 [PMID: 16611266 DOI: 10.1111/j.1365-2036.2006.02858.x]

19 **Qin HY**, Cheng CW, Tang XD, Bian ZX. Impact of psychological stress on irritable bowel syndrome. *World J Gastroenterol* 2014; **20**: 14126-14131 [PMID: 25339801 DOI: 10.3748/wjg.v20.i39.14126]

20 **Fichna J**, Storr MA. Brain-Gut Interactions in IBS. *Front Pharmacol* 2012; **3**: 127 [PMID: 22783191 DOI: 10.3389/fphar.2012.00127]

21 **Gazouli M**, Wouters MM, Kapur-Pojskić L, Bengtson MB, Friedman E, Nikčević G, Demetriou CA, Mulak A, Santos J, Niesler B. Lessons learned--resolving the enigma of genetic factors in IBS. *Nat Rev Gastroenterol Hepatol* 2016; **13**: 77-87 [PMID: 26726033 DOI: 10.1038/nrgastro.2015.206]

22 **Gibson PR**, Varney J, Malakar S, Muir JG. Food components and irritable bowel syndrome. *Gastroenterology* 2015; **148**: 1158-74.e4 [PMID: 25680668 DOI: 10.1053/j.gastro.2015.02.005]

23 **Marynowski M**, Likońska A, Zatorski H, Fichna J. Role of environmental pollution in irritable bowel syndrome. *World J Gastroenterol* 2015; **21**: 11371-11378 [PMID: 26523104 DOI: 10.3748/wjg.v21.i40.11371]

24 **Labus JS**, Mayer EA, Jarcho J, Kilpatrick LA, Kilkens TO, Evers EA, Backes WH, Brummer RJ, van Nieuwenhoven MA. Acute tryptophan depletion alters the effective connectivity of emotional arousal circuitry during visceral stimuli in healthy women. *Gut* 2011; **60**: 1196-1203 [PMID: 21402618 DOI: 10.1136/gut.2010.213447]

25 **Camilleri M**. Peripheral mechanisms in irritable bowel syndrome. *N Engl J Med* 2012; **367**: 1626-1635 [PMID: 23094724 DOI: 10.1056/NEJMra1207068]

26 **Törnblom H**, Van Oudenhove L, Tack J, Simrén M. Interaction between preprandial and postprandial rectal sensory and motor abnormalities in IBS. *Gut* 2014; **63**: 1441-1449 [PMID: 24142965 DOI: 10.1136/gutjnl-2013-305853]

27 **Sikander A**, Rana SV, Prasad KK. Role of serotonin in gastrointestinal motility and irritable bowel syndrome. *Clin Chim Acta* 2009; **403**: 47-55 [PMID: 19361459 DOI: 10.1016/j.cca.2009.01.028]

28 **Gershon MD**, Tack J. The serotonin signaling system: from basic understanding to drug development for functional GI disorders. *Gastroenterology* 2007; **132**: 397-414 [PMID: 17241888 DOI: 10.1053/j.gastro.2006.11.002]

29 **Chin A**, Svejda B, Gustafsson BI, Granlund AB, Sandvik AK, Timberlake A, Sumpio B, Pfragner R, Modlin IM, Kidd M. The role of mechanical forces and adenosine in the regulation of intestinal enterochromaffin cell serotonin secretion. *Am J Physiol Gastrointest Liver Physiol* 2012; **302**: G397-G405 [PMID: 22038827 DOI: 10.1152/ajpgi.00087.2011]

30 **Bjerregaard H**, Severinsen K, Said S, Wiborg O, Sinning S. A dualistic conformational response to substrate binding in the human serotonin transporter reveals a high affinity state for serotonin. *J Biol Chem* 2015; **290**: 7747-7755 [PMID: 25614630 DOI: 10.1074/jbc.M114.573477]

31 **Coates MD**, Mahoney CR, Linden DR, Sampson JE, Chen J, Blaszyk H, Crowell MD, Sharkey KA, Gershon MD, Mawe GM, Moses PL. Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and irritable bowel syndrome. *Gastroenterology* 2004; **126**: 1657-1664 [PMID: 15188158]

32 **Kerckhoffs AP**, Ter Linde JJ, Akkermans LM, Samsom M. Trypsinogen IV, serotonin transporter transcript levels and serotonin content are increased in small intestine of irritable bowel syndrome patients. *Neurogastroenterol Motil* 2008; **20**: 900-907 [PMID: 18363639 DOI: 10.1111/j.1365-2982.2008.01100.x]

33 **Wendelbo I**, Mazzawi T, El-Salhy M. Increased serotonin transporter immunoreactivity intensity in the ileum of patients with irritable bowel disease. *Mol Med Rep* 2014; **9**: 180-184 [PMID: 24213511 DOI: 10.3892/mmr.2013.1784]

34 **Faure C**, Patey N, Gauthier C, Brooks EM, Mawe GM. Serotonin signaling is altered in irritable bowel syndrome with diarrhea but not in functional dyspepsia in pediatric age patients. *Gastroenterology* 2010; **139**: 249-258 [PMID: 20303355 DOI: 10.1053/j.gastro.2010.03.032]

35 **Areeshi MY**, Haque S, Panda AK, Mandal RK. A serotonin transporter gene (SLC6A4) polymorphism is associated with reduced risk of irritable bowel syndrome in American and Asian population: a meta-analysis. *PLoS One* 2013; **8**: e75567 [PMID: 24069428 DOI: 10.1371/journal.pone.0075567]

36 **Sundin J**, Rangel I, Repsilber D, Brummer RJ. Cytokine Response after Stimulation with Key Commensal Bacteria Differ in Post-Infectious Irritable Bowel Syndrome (PI-IBS) Patients Compared to Healthy Controls. *PLoS One* 2015; **10**: e0134836 [PMID: 26366730 DOI: 10.1371/journal.pone.0134836]

37 **Goulet O**. Potential role of the intestinal microbiota in programming health and disease. *Nutr Rev* 2015; **73** Suppl 1: 32-40 [PMID: 26175488 DOI: 10.1093/nutrit/nuv039]

38 **Baudry A**, Mouillet-Richard S, Schneider B, Launay JM, Kellermann O. miR-16 targets the serotonin transporter: a new facet for adaptive responses to antidepressants. *Science* 2010; **329**: 1537-1541 [PMID: 20847275 DOI: 10.1126/science.1193692]

39 **Berger M**, Gray JA, Roth BL. The expanded biology of serotonin. *Annu Rev Med* 2009; **60**: 355-366 [PMID: 19630576 DOI: 10.1146/annurev.med.60.042307.110802]

40 **O'Mahony SM**, Clarke G, Borre YE, Dinan TG, Cryan JF. Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. *Behav Brain Res* 2015; **277**: 32-48 [PMID: 25078296 DOI: 10.1016/j.bbr.2014.07.027]

41 **Spiller R**. Serotonin and GI clinical disorders. *Neuropharmacology* 2008; **55**: 1072-1080 [PMID: 18687345 DOI: 10.1016/j.neuropharm.2008.07.016]

42 **Gershon MD**. Serotonin is a sword and a shield of the bowel: serotonin plays offense and defense. *Trans Am Clin Climatol Assoc* 2012; **123**: 268-80; discussion 280 [PMID: 23303993]

43 **Keszthelyi D**, Troost FJ, Masclee AA. Understanding the role of tryptophan and serotonin metabolism in gastrointestinal function. *Neurogastroenterol Motil* 2009; **21**: 1239-1249 [PMID: 19650771 DOI: 10.1111/j.1365-2982.2009.01370.x]

44 **Shufflebotham J**, Hood S, Hendry J, Hince DA, Morris K, Nutt D, Probert C, Potokar J. Acute tryptophan depletion alters gastrointestinal and anxiety symptoms in irritable bowel syndrome. *Am J Gastroenterol* 2006; **101**: 2582-2587 [PMID: 17029611 DOI: 10.1111/j.1572-0241.2006.00811.x]

45 **Lee YT**, Hu LY, Shen CC, Huang MW, Tsai SJ, Yang AC, Hu CK, Perng CL, Huang YS, Hung JH. Risk of Psychiatric Disorders following Irritable Bowel Syndrome: A Nationwide Population-Based Cohort Study. *PLoS One* 2015; **10**: e0133283 [PMID: 26222511 DOI: 10.1371/journal.pone.0133283]

46 **Ford AC**, Quigley EM, Lacy BE, Lembo AJ, Saito YA, Schiller LR, Soffer EE, Spiegel BM, Moayyedi P. Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: systematic review and meta-analysis. *Am J Gastroenterol* 2014; **109**: 1350-165; quiz 1366 [PMID: 24935275 DOI: 10.1038/ajg.2014.148]

47 **Xie C**, Tang Y, Wang Y, Yu T, Wang Y, Jiang L, Lin L. Efficacy and Safety of Antidepressants for the Treatment of Irritable Bowel Syndrome: A Meta-Analysis. *PLoS One* 2015; **10**: e0127815 [PMID: 26252008 DOI: 10.1371/journal.pone.0127815]

48 **Kohen R**, Tracy JH, Haugen E, Cain KC, Jarrett ME, Heitkemper MM. Rare Variants of the Serotonin Transporter Are Associated With Psychiatric Comorbidity in Irritable Bowel Syndrome. *Biol Res Nurs* 2016; Epub ahead of print [PMID: 26912503]

49 **Keating C**, Beyak M, Foley S, Singh G, Marsden C, Spiller R, Grundy D. Afferent hypersensitivity in a mouse model of post-inflammatory gut dysfunction: role of altered serotonin metabolism. *J Physiol* 2008; **586**: 4517-4530 [PMID: 18653657 DOI: 10.1113/jphysiol.2008.156984]

50 **Chen JJ**, Li Z, Pan H, Murphy DL, Tamir H, Koepsell H, Gershon MD. Maintenance of serotonin in the intestinal mucosa and ganglia of mice that lack the high-affinity serotonin transporter: Abnormal intestinal motility and the expression of cation transporters. *J Neurosci* 2001; **21**: 6348-6361 [PMID: 11487658]

51 **Kerckhoffs AP**, ter Linde JJ, Akkermans LM, Samsom M. SERT and TPH-1 mRNA expression are reduced in irritable bowel syndrome patients regardless of visceral sensitivity state in large intestine. *Am J Physiol Gastrointest Liver Physiol* 2012; **302**: G1053-G1060 [PMID: 22323131 DOI: 10.1152/ajpgi.00153.2011]

52 **Foley S**, Garsed K, Singh G, Duroudier NP, Swan C, Hall IP, Zaitoun A, Bennett A, Marsden C, Holmes G, Walls A, Spiller RC. Impaired uptake of serotonin by platelets from patients with irritable bowel syndrome correlates with duodenal immune activation. *Gastroenterology* 2011; **140**: 1434-43.e1 [PMID: 21315720 DOI: 10.1053/j.gastro.2011.01.052]

53 **Adam B**, Liebregts T, Holtmann G. Mechanisms of disease: genetics of functional gastrointestinal disorders--searching the genes that matter. *Nat Clin Pract Gastroenterol Hepatol* 2007; **4**: 102-110 [PMID: 17268545 DOI: 10.1038/ncpgasthep0717]

54 **Levy RL**, Jones KR, Whitehead WE, Feld SI, Talley NJ, Corey LA. Irritable bowel syndrome in twins: heredity and social learning both contribute to etiology. *Gastroenterology* 2001; **121**: 799-804 [PMID: 11606493]

55 **Hotoleanu C**, Popp R, Trifa AP, Nedelcu L, Dumitrascu DL. Genetic determination of irritable bowel syndrome. *World J Gastroenterol* 2008; **14**: 6636-6640 [PMID: 19034965]

56 **Camilleri M**, Atanasova E, Carlson PJ, Ahmad U, Kim HJ, Viramontes BE, McKinzie S, Urrutia R. Serotonin-transporter polymorphism pharmacogenetics in diarrhea-predominant irritable bowel syndrome. *Gastroenterology* 2002; **123**: 425-432 [PMID: 12145795]

57 **Park JM**, Choi MG, Park JA, Oh JH, Cho YK, Lee IS, Kim SW, Choi KY, Chung IS. Serotonin transporter gene polymorphism and irritable bowel syndrome. *Neurogastroenterol Motil* 2006; **18**: 995-1000 [PMID: 17040410 DOI: 10.1111/j.1365-2982.2006.00829.x]

58 **Kohen R**, Jarrett ME, Cain KC, Jun SE, Navaja GP, Symonds S, Heitkemper MM. The serotonin transporter polymorphism rs25531 is associated with irritable bowel syndrome. *Dig Dis Sci* 2009; **54**: 2663-2670 [PMID: 19125330 DOI: 10.1007/s10620-008-0666-3]

59 **Camilleri M**, Andrews CN, Bharucha AE, Carlson PJ, Ferber I, Stephens D, Smyrk TC, Urrutia R, Aerssens J, Thielemans L, Göhlmann H, van den Wyngaert I, Coulie B. Alterations in expression of p11 and SERT in mucosal biopsy specimens of patients with irritable bowel syndrome. *Gastroenterology* 2007; **132**: 17-25 [PMID: 17241856 DOI: 10.1053/j.gastro.2006.11.020]

60 **Galligan JJ**, Patel BA, Schneider SP, Wang H, Zhao H, Novotny M, Bian X, Kabeer R, Fried D, Swain GM. Visceral hypersensitivity in female but not in male serotonin transporter knockout rats. *Neurogastroenterol Motil* 2013; **25**: e373-e381 [PMID: 23594365 DOI: 10.1111/nmo.12133]

61 **Lesch KP**, Balling U, Gross J, Strauss K, Wolozin BL, Murphy DL, Riederer P. Organization of the human serotonin transporter gene. *J Neural Transm Gen Sect* 1994; **95**: 157-162 [PMID: 7865169]

62 **Moya PR**, Wendland JR, Salemme J, Fried RL, Murphy DL. miR-15a and miR-16 regulate serotonin transporter expression in human placental and rat brain raphe cells. *Int J Neuropsychopharmacol* 2013; **16**: 621-629 [PMID: 22564678 DOI: 10.1017/S1461145712000454]

63 **Ye R**, Quinlan MA, Iwamoto H, Wu HH, Green NH, Jetter CS, McMahon DG, Veestra-VanderWeele J, Levitt P, Blakely RD. Physical Interactions and Functional Relationships of Neuroligin 2 and Midbrain Serotonin Transporters. *Front Synaptic Neurosci* 2015; **7**: 20 [PMID: 26793096 DOI: 10.3389/fnsyn.2015.00020]

64 **Wendland JR**, Martin BJ, Kruse MR, Lesch KP, Murphy DL. Simultaneous genotyping of four functional loci of human SLC6A4, with a reappraisal of 5-HTTLPR and rs25531. *Mol Psychiatry* 2006; **11**: 224-226 [PMID: 16402131 DOI: 10.1038/sj.mp.4001789]

65 **MacKenzie A**, Quinn J. A serotonin transporter gene intron 2 polymorphic region, correlated with affective disorders, has allele-dependent differential enhancer-like properties in the mouse embryo. *Proc Natl Acad Sci USA* 1999; **96**: 15251-15255 [PMID: 10611371]

66 **Ozaki N**, Goldman D, Kaye WH, Plotnicov K, Greenberg BD, Lappalainen J, Rudnick G, Murphy DL. Serotonin transporter missense mutation associated with a complex neuropsychiatric phenotype. *Mol Psychiatry* 2003; **8**: 933-936 [PMID: 14593431 DOI: 10.1038/sj.mp.4001365]

67 **Prasad HC**, Zhu CB, McCauley JL, Samuvel DJ, Ramamoorthy S, Shelton RC, Hewlett WA, Sutcliffe JS, Blakely RD. Human serotonin transporter variants display altered sensitivity to protein kinase G and p38 mitogen-activated protein kinase. *Proc Natl Acad Sci USA* 2005; **102**: 11545-11550 [PMID: 16055563 DOI: 10.1073/pnas.0501432102]

68 **Murphy DL**, Moya PR. Human serotonin transporter gene (SLC6A4) variants: their contributions to understanding pharmacogenomic and other functional G×G and G×E differences in health and disease. *Curr Opin Pharmacol* 2011; **11**: 3-10 [PMID: 21439906 DOI: 10.1016/j.coph.2011.02.008]

69 **Lesch KP**, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, Benjamin J, Müller CR, Hamer DH, Murphy DL. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 1996; **274**: 1527-1531 [PMID: 8929413]

70 **Yuan J**, Kang C, Wang M, Wang Q, Li P, Liu H, Hou Y, Su P, Yang F, Wei Y, Yang J. Association study of serotonin transporter SLC6A4 gene with Chinese Han irritable bowel syndrome. *PLoS One* 2014; **9**: e84414 [PMID: 24392134 DOI: 10.1371/journal.pone.0084414]

71 **Murdoch JD**, Speed WC, Pakstis AJ, Heffelfinger CE, Kidd KK. Worldwide population variation and haplotype analysis at the serotonin transporter gene SLC6A4 and implications for association studies. *Biol Psychiatry* 2013; **74**: 879-889 [PMID: 23510579 DOI: 10.1016/j.biopsych.2013.02.006]

72 **Hu XZ**, Lipsky RH, Zhu G, Akhtar LA, Taubman J, Greenberg BD, Xu K, Arnold PD, Richter MA, Kennedy JL, Murphy DL, Goldman D. Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. *Am J Hum Genet* 2006; **78**: 815-826 [PMID: 16642437 DOI: 10.1086/503850]

73 **Wang YM**, Chang Y, Chang YY, Cheng J, Li J, Wang T, Zhang QY, Liang DC, Sun B, Wang BM. Serotonin transporter gene promoter region polymorphisms and serotonin transporter expression in the colonic mucosa of irritable bowel syndrome patients. *Neurogastroenterol Motil* 2012; **24**: 560-55, 560-55, [PMID: 22435794 DOI: 10.1111/j.1365-2982.2012.01902.x]

74 **Yeo A**, Boyd P, Lumsden S, Saunders T, Handley A, Stubbins M, Knaggs A, Asquith S, Taylor I, Bahari B, Crocker N, Rallan R, Varsani S, Montgomery D, Alpers DH, Dukes GE, Purvis I, Hicks GA. Association between a functional polymorphism in the serotonin transporter gene and diarrhoea predominant irritable bowel syndrome in women. *Gut* 2004; **53**: 1452-1458 [PMID: 15361494 DOI: 10.1136/gut.2003.035451]

75 **Kumar S**, Ranjan P, Mittal B, Ghoshal UC. Serotonin transporter gene (SLC6A4) polymorphism in patients with irritable bowel syndrome and healthy controls. *J Gastrointestin Liver Dis* 2012; **21**: 31-38 [PMID: 22457857]

76 **Sikander A**, Rana SV, Sinha SK, Prasad KK, Arora SK, Sharma SK, Singh K. Serotonin transporter promoter variant: Analysis in Indian IBS patients and control population. *J Clin Gastroenterol* 2009; **43**: 957-961 [PMID: 19687750 DOI: 10.1097/MCG.0b013e3181b37e8c]

77 **Pata C**, Erdal ME, Derici E, Yazar A, Kanik A, Ulu O. Serotonin transporter gene polymorphism in irritable bowel syndrome. *Am J Gastroenterol* 2002; **97**: 1780-1784 [PMID: 12135035 DOI: 10.1111/j.1572-0241.2002.05841.x]

78 **Zhang ZF**, Duan ZJ, Wang LX, Yang D, Zhao G, Zhang L. The serotonin transporter gene polymorphism (5-HTTLPR) and irritable bowel syndrome: a meta-analysis of 25 studies. *BMC Gastroenterol* 2014; **14**: 23 [PMID: 24512255 DOI: 10.1186/1471-230X-14-23]

79 **Wang BM**, Wang YM, Zhang WM, Zhang QY, Liu WT, Jiang K, Zhang J. [Serotonin transporter gene polymorphism in irritable bowel syndrome]. *Zhonghua Nei Ke Za Zhi* 2004; **43**: 439-441 [PMID: 15312441]

80 **Li Y**, Nie Y, Xie J, Tang W, Liang P, Sha W, Yang H, Zhou Y. The association of serotonin transporter genetic polymorphisms and irritable bowel syndrome and its influence on tegaserod treatment in Chinese patients. *Dig Dis Sci* 2007; **52**: 2942-2949 [PMID: 17394071 DOI: 10.1007/s10620-006-9679-y]

81 **Gill RK**, Kumar A, Malhotra P, Maher D, Singh V, Dudeja PK, Alrefai W, Saksena S. Regulation of intestinal serotonin transporter expression via epigenetic mechanisms: role of HDAC2. *Am J Physiol Cell Physiol* 2013; **304**: C334-C341 [PMID: 23195070 DOI: 10.1152/ajpcell.00361.2012]

82 **Brennecke J**, Stark A, Russell RB, Cohen SM. Principles of microRNA-target recognition. *PLoS Biol* 2005; **3**: e85 [PMID: 15723116 DOI: 10.1371/journal.pbio.0030085]

83 **Krol J**, Loedige I, Filipowicz W. The widespread regulation of microRNA biogenesis, function and decay. *Nat Rev Genet* 2010; **11**: 597-610 [PMID: 20661255 DOI: 10.1038/nrg2843]

84 **Bartel DP**. MicroRNAs: target recognition and regulatory functions. *Cell* 2009; **136**: 215-233 [PMID: 19167326 DOI: 10.1016/j.cell.2009.01.002]

85 **Liu B**, Li J, Cairns MJ. Identifying miRNAs, targets and functions. *Brief Bioinform* 2014; **15**: 1-19 [PMID: 23175680 DOI: 10.1093/bib/bbs075]

86 **Zhang R**, Su B. Small but influential: the role of microRNAs on gene regulatory network and 3'UTR evolution. *J Genet Genomics* 2009; **36**: 1-6 [PMID: 19161940 DOI: 10.1016/S1673-8527(09)60001-1]

87 **Croce CM**. Causes and consequences of microRNA dysregulation in cancer. *Nat Rev Genet* 2009; **10**: 704-714 [PMID: 19763153 DOI: 10.1038/nrg2634]

88 **Millan MJ**. MicroRNA in the regulation and expression of serotonergic transmission in the brain and other tissues. *Curr Opin Pharmacol* 2011; **11**: 11-22 [PMID: 21345728 DOI: 10.1016/j.coph.2011.01.008]

89 **Yue J**, Tigyi G. Conservation of miR-15a/16-1 and miR-15b/16-2 clusters. *Mamm Genome* 2010; **21**: 88-94 [PMID: 20013340 DOI: 10.1007/s00335-009-9240-3]

90 **Song MF**, Dong JZ, Wang YW, He J, Ju X, Zhang L, Zhang YH, Shi JF, Lv YY. CSF miR-16 is decreased in major depression patients and its neutralization in rats induces depression-like behaviors via a serotonin transmitter system. *J Affect Disord* 2015; **178**: 25-31 [PMID: 25779937 DOI: 10.1016/j.jad.2015.02.022]

91 **Launay JM**, Mouillet-Richard S, Baudry A, Pietri M, Kellermann O. Raphe-mediated signals control the hippocampal response to SRI antidepressants via miR-16. *Transl Psychiatry* 2011; **1**: e56 [PMID: 22833211 DOI: 10.1038/tp.2011.54]

92 **Dwivedi Y**. Evidence demonstrating role of microRNAs in the etiopathology of major depression. *J Chem Neuroanat* 2011; **42**: 142-156 [PMID: 21515361 DOI: 10.1016/j.jchemneu.2011.04.002]

93 **Tamarapu Parthasarathy P**, Galam L, Huynh B, Yunus A, Abuelenen T, Castillo A, Kollongod Ramanathan G, Cox R, Kolliputi N. MicroRNA 16 modulates epithelial sodium channel in human alveolar epithelial cells. *Biochem Biophys Res Commun* 2012; **426**: 203-208 [PMID: 22940131 DOI: 10.1016/j.bbrc.2012.08.063]

94 **Jensen KP**, Covault J, Conner TS, Tennen H, Kranzler HR, Furneaux HM. A common polymorphism in serotonin receptor 1B mRNA moderates regulation by miR-96 and associates with aggressive human behaviors. *Mol Psychiatry* 2009; **14**: 381-389 [PMID: 18283276 DOI: 10.1038/mp.2008.15]

95 **Sivamaruthi BS**, Madhumita R, Balamurugan K, Rajan KE. Cronobacter sakazakii infection alters serotonin transporter and improved fear memory retention in the rat. *Front Pharmacol* 2015; **6**: 188 [PMID: 26388777 DOI: 10.3389/fphar.2015.00188]

96 **Liao XJ**, Mao WM, Wang Q, Yang GG, Wu WJ, Shao SX. MicroRNA-24 inhibits serotonin reuptake transporter expression and aggravates irritable bowel syndrome. *Biochem Biophys Res Commun* 2016; **469**: 288-293 [PMID: 26631964 DOI: 10.1016/j.bbrc.2015.11.102]

97 **Spiller R**, Lam C. An Update on Post-infectious Irritable Bowel Syndrome: Role of Genetics, Immune Activation, Serotonin and Altered Microbiome. *J Neurogastroenterol Motil* 2012; **18**: 258-268 [PMID: 22837873 DOI: 10.5056/jnm.2012.18.3.258]

98 **Spiller RC**, Jenkins D, Thornley JP, Hebden JM, Wright T, Skinner M, Neal KR. Increased rectal mucosal enteroendocrine cells, T lymphocytes, and increased gut permeability following acute Campylobacter enteritis and in post-dysenteric irritable bowel syndrome. *Gut* 2000; **47**: 804-811 [PMID: 11076879]

99 **Lee KJ**, Kim YB, Kim JH, Kwon HC, Kim DK, Cho SW. The alteration of enterochromaffin cell, mast cell, and lamina propria T lymphocyte numbers in irritable bowel syndrome and its relationship with psychological factors. *J Gastroenterol Hepatol* 2008; **23**: 1689-1694 [PMID: 19120860 DOI: 10.1111/j.1440-1746.2008.05574.x]

100 **Wang H**, Steeds J, Motomura Y, Deng Y, Verma-Gandhu M, El-Sharkawy RT, McLaughlin JT, Grencis RK, Khan WI. CD4+ T cell-mediated immunological control of enterochromaffin cell hyperplasia and 5-hydroxytryptamine production in enteric infection. *Gut* 2007; **56**: 949-957 [PMID: 17303597 DOI: 10.1136/gut.2006.103226]

101 **Chadwick VS**, Chen W, Shu D, Paulus B, Bethwaite P, Tie A, Wilson I. Activation of the mucosal immune system in irritable bowel syndrome. *Gastroenterology* 2002; **122**: 1778-1783 [PMID: 12055584]

102 **Martín R**, Chain F, Miquel S, Natividad JM, Sokol H, Verdu EF, Langella P, Bermúdez-Humarán LG. Effects in the use of a genetically engineered strain of Lactococcus lactis delivering in situ IL-10 as a therapy to treat low-grade colon inflammation. *Hum Vaccin Immunother* 2014; **10**: 1611-1621 [PMID: 24732667 DOI: 10.4161/hv.28549]

103 **Cremon C**, Gargano L, Morselli-Labate AM, Santini D, Cogliandro RF, De Giorgio R, Stanghellini V, Corinaldesi R, Barbara G. Mucosal immune activation in irritable bowel syndrome: gender-dependence and association with digestive symptoms. *Am J Gastroenterol* 2009; **104**: 392-400 [PMID: 19174797 DOI: 10.1038/ajg.2008.94]

104 **Wheatcroft J**, Wakelin D, Smith A, Mahoney CR, Mawe G, Spiller R. Enterochromaffin cell hyperplasia and decreased serotonin transporter in a mouse model of postinfectious bowel dysfunction. *Neurogastroenterol Motil* 2005; **17**: 863-870 [PMID: 16336502 DOI: 10.1111/j.1365-2982.2005.00719.x]

105 **Foley KF**, Pantano C, Ciolino A, Mawe GM. IFN-gamma and TNF-alpha decrease serotonin transporter function and expression in Caco2 cells. *Am J Physiol Gastrointest Liver Physiol* 2007; **292**: G779-G784 [PMID: 17170025 DOI: 10.1152/ajpgi.00470.2006]

106 **Shi HL**, Liu CH, Ding LL, Zheng Y, Fei XY, Lu L, Zhou XM, Yuan JY, Xie JQ. Alterations in serotonin, transient receptor potential channels and protease-activated receptors in rats with irritable bowel syndrome attenuated by Shugan decoction. *World J Gastroenterol* 2015; **21**: 4852-4863 [PMID: 25944998 DOI: 10.3748/wjg.v21.i16.4852]

107 **Nazir S**, Kumar A, Chatterjee I, Anbazhagan AN, Gujral T, Priyamvada S, Saksena S, Alrefai WA, Dudeja PK, Gill RK. Mechanisms of Intestinal Serotonin Transporter (SERT) Upregulation by TGF-β1 Induced Non-Smad Pathways. *PLoS One* 2015; **10**: e0120447 [PMID: 25954931 DOI: 10.1371/journal.pone.0120447]

108 **Distrutti E**, Monaldi L, Ricci P, Fiorucci S. Gut microbiota role in irritable bowel syndrome: New therapeutic strategies. *World J Gastroenterol* 2016; **22**: 2219-2241 [PMID: 26900286 DOI: 10.3748/wjg.v22.i7.2219]

109 **Jalanka J**, Salonen A, Fuentes S, de Vos WM. Microbial signatures in post-infectious irritable bowel syndrome--toward patient stratification for improved diagnostics and treatment. *Gut Microbes* 2015; **6**: 364-369 [PMID: 26512631 DOI: 10.1080/19490976.2015.1096486]

110 **Simrén M**, Barbara G, Flint HJ, Spiegel BM, Spiller RC, Vanner S, Verdu EF, Whorwell PJ, Zoetendal EG. Intestinal microbiota in functional bowel disorders: a Rome foundation report. *Gut* 2013; **62**: 159-176 [PMID: 22730468 DOI: 10.1136/gutjnl-2012-302167]

111 **Jalanka-Tuovinen J**, Salojärvi J, Salonen A, Immonen O, Garsed K, Kelly FM, Zaitoun A, Palva A, Spiller RC, de Vos WM. Faecal microbiota composition and host-microbe cross-talk following gastroenteritis and in postinfectious irritable bowel syndrome. *Gut* 2014; **63**: 1737-1745 [PMID: 24310267 DOI: 10.1136/gutjnl-2013-305994]

112 **Ringel Y**, Ringel-Kulka T. The Intestinal Microbiota and Irritable Bowel Syndrome. *J Clin Gastroenterol* 2015; **49** Suppl 1: S56-S59 [PMID: 26447966 DOI: 10.1097/MCG.0000000000000418]

113 **Mayer EA**, Savidge T, Shulman RJ. Brain-gut microbiome interactions and functional bowel disorders. *Gastroenterology* 2014; **146**: 1500-1512 [PMID: 24583088 DOI: 10.1053/j.gastro.2014.02.037]

114 **Krogius-Kurikka L**, Lyra A, Malinen E, Aarnikunnas J, Tuimala J, Paulin L, Mäkivuokko H, Kajander K, Palva A. Microbial community analysis reveals high level phylogenetic alterations in the overall gastrointestinal microbiota of diarrhoea-predominant irritable bowel syndrome sufferers. *BMC Gastroenterol* 2009; **9**: 95 [PMID: 20015409 DOI: 10.1186/1471-230X-9-95]

115 **Malinen E**, Rinttilä T, Kajander K, Mättö J, Kassinen A, Krogius L, Saarela M, Korpela R, Palva A. Analysis of the fecal microbiota of irritable bowel syndrome patients and healthy controls with real-time PCR. *Am J Gastroenterol* 2005; **100**: 373-382 [PMID: 15667495 DOI: 10.1111/j.1572-0241.2005.40312.x]

116 **Yano JM**, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, Nagler CR, Ismagilov RF, Mazmanian SK, Hsiao EY. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell* 2015; **161**: 264-276 [PMID: 25860609 DOI: 10.1016/j.cell.2015.02.047]

117 **Reigstad CS**, Salmonson CE, Rainey JF, Szurszewski JH, Linden DR, Sonnenburg JL, Farrugia G, Kashyap PC. Gut microbes promote colonic serotonin production through an effect of short-chain fatty acids on enterochromaffin cells. *FASEB J* 2015; **29**: 1395-1403 [PMID: 25550456 DOI: 10.1096/fj.14-259598]

118 **Esmaili A**, Nazir SF, Borthakur A, Yu D, Turner JR, Saksena S, Singla A, Hecht GA, Alrefai WA, Gill RK. Enteropathogenic Escherichia coli infection inhibits intestinal serotonin transporter function and expression. *Gastroenterology* 2009; **137**: 2074-2083 [PMID: 19747920 DOI: 10.1053/j.gastro.2009.09.002]

119 **Nzakizwanayo J**, Dedi C, Standen G, Macfarlane WM, Patel BA, Jones BV. Escherichia coli Nissle 1917 enhances bioavailability of serotonin in gut tissues through modulation of synthesis and clearance. *Sci Rep* 2015; **5**: 17324 [PMID: 26616662 DOI: 10.1038/srep17324]

120 **Thijssen AY**, Mujagic Z, Jonkers DM, Ludidi S, Keszthelyi D, Hesselink MA, Clemens CH, Conchillo JM, Kruimel JW, Masclee AA. Alterations in serotonin metabolism in the irritable bowel syndrome. *Aliment Pharmacol Ther* 2016; **43**: 272-282 [PMID: 26538292 DOI: 10.1111/apt.13459]

121 **Wang YM**, Ge XZ, Wang WQ, Wang T, Cao HL, Wang BL, Wang BM. Lactobacillus rhamnosus GG supernatant upregulates serotonin transporter expression in intestinal epithelial cells and mice intestinal tissues. *Neurogastroenterol Motil* 2015; **27**: 1239-1248 [PMID: 26088715 DOI: 10.1111/nmo.12615]

122 **Pedersen N**, Andersen NN, Végh Z, Jensen L, Ankersen DV, Felding M, Simonsen MH, Burisch J, Munkholm P. Ehealth: low FODMAP diet vs Lactobacillus rhamnosus GG in irritable bowel syndrome. *World J Gastroenterol* 2014; **20**: 16215-16226 [PMID: 25473176 DOI: 10.3748/wjg.v20.i43.16215]

123 **Wang L**, Cao H, Liu L, Wang B, Walker WA, Acra SA, Yan F. Activation of epidermal growth factor receptor mediates mucin production stimulated by p40, a Lactobacillus rhamnosus GG-derived protein. *J Biol Chem* 2014; **289**: 20234-20244 [PMID: 24895124 DOI: 10.1074/jbc.M114.553800]

124 **Didari T**, Mozaffari S, Nikfar S, Abdollahi M. Effectiveness of probiotics in irritable bowel syndrome: Updated systematic review with meta-analysis. *World J Gastroenterol* 2015; **21**: 3072-3084 [PMID: 25780308 DOI: 10.3748/wjg.v21.i10.3072]

125 **Halmos EP**, Christophersen CT, Bird AR, Shepherd SJ, Gibson PR, Muir JG. Diets that differ in their FODMAP content alter the colonic luminal microenvironment. *Gut* 2015; **64**: 93-100 [PMID: 25016597 DOI: 10.1136/gutjnl-2014-307264]

126 **Martín R**, Miquel S, Chain F, Natividad JM, Jury J, Lu J, Sokol H, Theodorou V, Bercik P, Verdu EF, Langella P, Bermúdez-Humarán LG. Faecalibacterium prausnitzii prevents physiological damages in a chronic low-grade inflammation murine model. *BMC Microbiol* 2015; **15**: 67 [PMID: 25888448 DOI: 10.1186/s12866-015-0400-1]

127 **Xu D**, Gao J, Gillilland M, Wu X, Song I, Kao JY, Owyang C. Rifaximin alters intestinal bacteria and prevents stress-induced gut inflammation and visceral hyperalgesia in rats. *Gastroenterology* 2014; **146**: 484-96.e4 [PMID: 24161699 DOI: 10.1053/j.gastro.2013.10.026]

128 **Zoller V**, Laguna AL, Prazeres Da Costa O, Buch T, Göke B, Storr M. [Fecal microbiota transfer (FMT) in a patient with refractory irritable bowel syndrome]. *Dtsch Med Wochenschr* 2015; **140**: 1232-1236 [PMID: 26261935 DOI: 10.1055/s-0041-103798]

129 **Rebizak E**, Sierant K, Łabuzek K, Okopień B. [Fecal transplantation the future therapy?]. *Pol Merkur Lekarski* 2015; **39**: 73-76 [PMID: 26319378]

130 **Pinn DM**, Aroniadis OC, Brandt LJ. Is fecal microbiota transplantation (FMT) an effective treatment for patients with functional gastrointestinal disorders (FGID)? *Neurogastroenterol Motil* 2015; **27**: 19-29 [PMID: 25424663 DOI: 10.1111/nmo.12479]

131 **Xu MQ**, Cao HL, Wang WQ, Wang S, Cao XC, Yan F, Wang BM. Fecal microbiota transplantation broadening its application beyond intestinal disorders. *World J Gastroenterol* 2015; **21**: 102-111 [PMID: 25574083 DOI: 10.3748/wjg.v21.i1.102]

132 **Kekuda R**, Torres-Zamorano V, Leibach FH, Ganapathy V. Human serotonin transporter: regulation by the neuroprotective agent aurintricarboxylic acid and by epidermal growth factor. *J Neurochem* 1997; **68**: 1443-1450 [PMID: 9084414]

133 **Kubota N**, Kiuchi Y, Nemoto M, Oyamada H, Ohno M, Funahashi H, Shioda S, Oguchi K. Regulation of serotonin transporter gene expression in human glial cells by growth factors. *Eur J Pharmacol* 2001; **417**: 69-76 [PMID: 11301061]

134 **Gil C**, Najib A, Aguilera J. Serotonin transport is modulated differently by tetanus toxin and growth factors. *Neurochem Int* 2003; **42**: 535-542 [PMID: 12590935]

135 **Carpenter G**, Cohen S. Epidermal growth factor. *J Biol Chem* 1990; **265**: 7709-7712 [PMID: 2186024]

136 **Dvorak B**. Milk epidermal growth factor and gut protection. *J Pediatr* 2010; **156**: S31-S35 [PMID: 20105663 DOI: 10.1016/j.jpeds.2009.11.018]

137 **Niederlechner S**, Baird C, Petrie B, Wischmeyer E, Wischmeyer PE. Epidermal growth factor receptor expression and signaling are essential in glutamine's cytoprotective mechanism in heat-stressed intestinal epithelial-6 cells. *Am J Physiol Gastrointest Liver Physiol* 2013; **304**: G543-G552 [PMID: 23275616 DOI: 10.1152/ajpgi.00418.2012]

138 **Danielsen AJ**, Maihle NJ. The EGF/ErbB receptor family and apoptosis. *Growth Factors* 2002; **20**: 1-15 [PMID: 11999214]

139 **Ménard D**, Corriveau L, Arsenault P. Differential effects of epidermal growth factor and hydrocortisone in human fetal colon. *J Pediatr Gastroenterol Nutr* 1990; **10**: 13-20 [PMID: 2324874]

140 **Carpenter G**. Epidermal growth factor is a major growth-promoting agent in human milk. *Science* 1980; **210**: 198-199 [PMID: 6968093]

141 **Miettinen PJ**, Berger JE, Meneses J, Phung Y, Pedersen RA, Werb Z, Derynck R. Epithelial immaturity and multiorgan failure in mice lacking epidermal growth factor receptor. *Nature* 1995; **376**: 337-341 [PMID: 7630400 DOI: 10.1038/376337a0]

142 **Fraguas S**, Barberán S, Cebrià F. EGFR signaling regulates cell proliferation, differentiation and morphogenesis during planarian regeneration and homeostasis. *Dev Biol* 2011; **354**: 87-101 [PMID: 21458439 DOI: 10.1016/j.ydbio.2011.03.023]

143 **Jones MK**, Tomikawa M, Mohajer B, Tarnawski AS. Gastrointestinal mucosal regeneration: role of growth factors. *Front Biosci* 1999; **4**: D303-D309 [PMID: 10077540]

144 **Gill RK**, Anbazhagan AN, Esmaili A, Kumar A, Nazir S, Malakooti J, Alrefai WA, Saksena S. Epidermal growth factor upregulates serotonin transporter in human intestinal epithelial cells via transcriptional mechanisms. *Am J Physiol Gastrointest Liver Physiol* 2011; **300**: G627-G636 [PMID: 21273531 DOI: 10.1152/ajpgi.00563.2010]

145 **Linden DR**, White SL, Brooks EM, Mawe GM. Novel promoter and alternate transcription start site of the human serotonin reuptake transporter in intestinal mucosa. *Neurogastroenterol Motil* 2009; **21**: 534-41, e10-1 [PMID: 19222758 DOI: 10.1111/j.1365-2982.2008.01247.x]

146 **Cui XF**, Zhou WM, Yang Y, Zhou J, Li XL, Lin L, Zhang HJ. Epidermal growth factor upregulates serotonin transporter and its association with visceral hypersensitivity in irritable bowel syndrome. *World J Gastroenterol* 2014; **20**: 13521-13529 [PMID: 25309082 DOI: 10.3748/wjg.v20.i37.13521]

147 **Willot S**, Gauthier C, Patey N, Faure C. Nerve growth factor content is increased in the rectal mucosa of children with diarrhea-predominant irritable bowel syndrome. *Neurogastroenterol Motil* 2012; **24**: 734-79, e347 [PMID: 22625872 DOI: 10.1111/j.1365-2982.2012.01933.x]

148 **Dothel G**, Barbaro MR, Boudin H, Vasina V, Cremon C, Gargano L, Bellacosa L, De Giorgio R, Le Berre-Scoul C, Aubert P, Neunlist M, De Ponti F, Stanghellini V, Barbara G. Nerve fiber outgrowth is increased in the intestinal mucosa of patients with irritable bowel syndrome. *Gastroenterology* 2015; **148**: 1002-1011.e4 [PMID: 25655556 DOI: 10.1053/j.gastro.2015.01.042]

149 **Matricon J**, Muller E, Accarie A, Meleine M, Etienne M, Voilley N, Busserolles J, Eschalier A, Lazdunski M, Bourdu S, Gelot A, Ardid D. Peripheral contribution of NGF and ASIC1a to colonic hypersensitivity in a rat model of irritable bowel syndrome. *Neurogastroenterol Motil* 2013; **25**: e740-e754 [PMID: 23902154 DOI: 10.1111/nmo.12199]

150 **Xu XJ**, Liu L, Yao SK. Nerve growth factor and diarrhea-predominant irritable bowel syndrome (IBS-D): a potential therapeutic target? *J Zhejiang Univ Sci B* 2016; **17**: 1-9 [PMID: 26739521 DOI: 10.1631/jzus.B1500181]

151 **Zimmermann K**, van Phi VD, Brase A, Phi-van L. Inhibition of serotonin transporter expression by C/EBPβ in LPS-activated macrophage cells (HD11). *Innate Immun* 2015; **21**: 406-415 [PMID: 25213348 DOI: 10.1177/1753425914547434]

152 **Yoon Y**, McKenna MC, Rollins DA, Song M, Nuriel T, Gross SS, Xu G, Glatt CE. Anxiety-associated alternative polyadenylation of the serotonin transporter mRNA confers translational regulation by hnRNPK. *Proc Natl Acad Sci USA* 2013; **110**: 11624-11629 [PMID: 23798440 DOI: 10.1073/pnas.1301485110]

153 **Giannaccini G**, Betti L, Palego L, Schmid L, Fabbrini L, Pelosini C, Gargini C, Da Valle Y, Lanza M, Marsili A, Maffei M, Santini F, Vitti P, Pinchera A, Lucacchini A. Human serotonin transporter expression during megakaryocytic differentiation of MEG-01 cells. *Neurochem Res* 2010; **35**: 628-635 [PMID: 20041293 DOI: 10.1007/s11064-009-0112-8]

**P-Reviewer:** O'Malley D, Shiotani A, Yang YK **S-Editor:** Ma YJ **L-Editor:** **E-Editor:**

**Table 1 Summary of potential regulation factors of serotonin transporter in irritable bowel syndrome**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Regulation factors** | | **Authors** | **Publication year** | | **Study type** |
| **SERT gene polymorphisms** | | | |  |  |
| 5-HTTLPR | | Zhang *et al*[78] | | 2014 | Meta-analysis |
|  | | Areeshi *et al*[35] | | 2013 | Meta-analysis |
|  | | Wang *et al*[73] | | 2012 | Case-control study |
|  | | Yeo *et al*[74] | | 2004 | Case-control study |
|  | | Kumar *et al*[75] | | 2012 | Case-control study |
|  | | Sikander *et al*[76] | | 2009 | Case-control study |
|  | | Pata *et al*[77] | | 2002 | Case-control study |
| STin2 VNTRs | | Wang *et al*[79] | | 2004 | Case-control study |
|  | | Yeo *et al*[74] | | 2004 | Case-control study |
| SNPs | | Kohen *et al*[58] | | 2009 | Case-control study |
| **MicroRNAs** (↓) | | | |  |  |
| MiR-16 | | Baudry *et al*[38] | | 2010 | Experimental study |
| MiR-545 | | Jensen *et al*[94] | | 2009 | Experimental study |
| MiR-15a | | Moya *et al*[62] | | 2013 | Experimental study |
| MiR-24 | | Liao *et al*[96] | | 2016 | Case-control study |
| **Immunity and inflammation** | | | |  |  |
| Immune cells (↓) | | | |  |  |
| IELs | | Foley *et al*[52] | | 2011 | Experimental study |
|  | | Faure *et al*[34] | | 2010 | Experimental study |
| Mast cells | | Foley *et al*[52] | | 2011 | Experimental study |
| T cells | | Wheatcroft *et al*[104] | | 2005 | Experimental study |
|  | | Faure *et al*[34] | | 2010 | Experimental study |
| Inflammatory cytokines | | | |  |  |
| IFN-γ and TNF-α (↓) | | Foley *et al*[105] | | 2007 | Experimental study |
| TGF-β1 (↑) | Nazir *et al*[107] | | | 2015 | Experimental study |
| **Gut microbiota** | |  | |  |  |
| EPEC (↓) | | Esmaili *et al*[118] | | 2009 | Experimental study |
| EcN (↓) | | Nzakizwanayo *et al*[119] | | 2015 | Experimental study |
| LGG (↑) | | Wang *et al*[121] | | 2015 | Experimental study |
| **Growth factors** (↑) | | | |  |  |
| EGF | | Kekuda *et al*[132] | | 1997 | Experimental study |
| bFGF | | Kubota *et al*[133] | | 2001 | Experimental study |
| NGF | | Gil *et al*[134] | | 2003 | Experimental study |

5-HTTLPR: 5-HT-transporter-gene-linked polymorphic region; STin2 VNTRs: Variable number of tandem repeats STin2; SNPs: Single nucleotide polymorphism; IELs: Intraepithelial lymphocytes; IFN-γ and TNF-α: Interferon-γ and tumor necrosis factor-α; TGF-β1: Transforming growth factor-β1; EPEC: Enteropathogenic *E coli*; EcN: *Escherichia coli* Nissle 1917; LGG: *Lactobacillus rhamnosus GG* supernatant; EGF: Epidermal growth factor; Bfgf: Basic fibroblast growth factor; NGF: Nerve growth factor.