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**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

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**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

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**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.

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**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.

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**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.