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REVIEW

Regulation of the serotonin transporter in the pathogenesis of irritable bowel syndrome

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Abstract

Serotonin (5-HT) and the serotonin transporter (SERT) have earned a tremendous amount of attention regarding the pathogenesis of irritable bowel syndrome (IBS). Considering that enteric 5-HT is responsible for the secretion, motility and perception of the bowel, the involvement of altered enteric 5-HT metabolism in the pathogenesis of IBS has been elucidated. Higher 5-HT availability is commonly associated with depressed SERT mRNA in patients with IBS compared with healthy controls. The expression difference of SERT between IBS patients and healthy controls might suggest that SERT plays an essential role in IBS pathogenesis, and SERT 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 are provided, including aspects of SERT gene polymorphisms, microRNAs, immunity and inflammation, gut microbiota, growth factors, among others. Potential SERT-directed therapies for IBS are also described. The potential regulators of SERT are of clinical importance and are important for better understanding IBS pathophysiology and therapeutic strategies.

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

Core tip: The serotonin transporter (SERT) participates in metabolizing serotonin in the gut and plays a crucial role in the pathogenesis of irritable bowel syndrome (IBS). This review summarizes the relevant evidence on the factors that might regulate SERT, including SERT gene polymorphisms, microRNAs, immunity and inflammation, gut microbiota and growth factors. This review also reveals several 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 disorder with complex symptoms appearing as abdominal pain/discomfort and altered bowel patterns[1-3]. A growing number of people suffer from IBS, with an estimated 5.8%-17.5% prevalence, especially in females[4,5]. IBS causes a tremendous decline in the health-related quality of life and brings a considerable socioeconomic burden of up to $19 billion[2,6]. The Rome III criteria have been improved to help with the diagnosis and differential diagnosis of the syndrome[7-10]. According to these 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 6-year follow-up study showed that approximately 10% of patients with infective gastroenteritis suffer from post-infective IBS (PI-IBS)[13]. Because IBS is considered to be a multifactorial and heterogeneous disease with various phenotypes, no single mechanism entirely explains the pathophysiology of the disorder. Some possible mechanisms involve the initiation, persistence and severity of symptom flares, including inflammation, immunity, infection[14,15], the gut microbiota[16,17], psychosocial stress[16,18,19] and an abnormal brain-gut axis[16,20]. Recent discoveries have revealed that genetic susceptibility[21], diet/drug intolerances[22] and environmental pollutants[23] are closely associated with IBS pathogenesis. Although the etiology of IBS is largely elusive, there are some characteristic symptoms of the disorder, including visceral hypersensitivity[16,24], intestinal barrier dysfunction[25] and gut motility disorder[16,17,26].

As a signal transducer and a neurotransmitter, serotonin (5-HT) mediates intercellular signaling transmission in the gut, and most of the 5-HT in the body is in the gut. Enteric 5-HT is synthesized by enterochromaffin (EC) cells (90%) and enteric serotonergic neurons of the myenteric plexus (10%)[27]. Therefore, EC cells are the main source of enteric 5-HT in the gastrointestinal (GI) tract[28,29]. 5-HT inactivation is as important as 5-HT release for maintaining 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 5-HT inactivation by removing 5-HT from the interstitial space in the lamina propria into mucosal enterocytes and presynaptic neurons that are responsible for catabolism[30,31]. Coates *et al*[31] first characterized a significantly decreased level of SERT in IBS. However, there was another conflicting finding of increased SERT expression in IBS[32,33]. Taking the significant differences in the analytical methodology used and the heterogeneity of phenotypes into account, most researchers, such as Faure *et al*[34], have demonstrated that IBS patients have a remarkably attenuated level of SERT expression in the intestinal lining, which conforms to a remarkably decreased capacity of enterocytes to reuptake 5-HT. It is generally accepted that there is a significant inverse correlation targeting the level of availability between SERT and 5-HT.

SERT plays a critical role in the uptake and internalization of extracellular 5-HT. Previous studies have provided support to the concept that SERT is regulated by transcriptional and posttranslational mechanisms. To date, an association between SERT gene polymorphisms and IBS susceptibility has been inconsistent among different ethnic groups and even among different populations[35]. Despite the lack of consensus on the wide range of roles of potential factors, immunity activation, inflammatory response, gut microbiota and their relationships have been suggested to regulate SERT expression in PI-IBS[36]. Probiotics are also notable for linking inflammation-immune systems and gut microbiota in IBS patients[37]. Recent studies have also shed light on the fascinating roles of microRNAs, growth factors and other factors 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, 5-HT 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 studies have proven that 5-HT acts upon mucosal sensory transduction, responding to pressure and luminal stimuli derived from diet and bacteria[41]. The release of 5-HT acting on a series of 5-HT receptors initiates secretory reflexes, peristaltic reflexes and, if pronounced, diarrhea, by stimulating intrinsic primary afferent neurons and myenteric interneurons[41-43]. Furthermore, by stimulating extrinsic sensory nerves, 5-HT can also transmit the sensation of discomfort to

Table 1 Summary of potential regulators of the serotonin transporter in irritable bowel syndrome

Regulatory factors	Ref.	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 polymorphisms; 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.

the central nervous system along the gut–brain axis in IBS. Therefore, 5-HT is closely related to 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) are considered to be possible treatments for IBS. In 2014, a systematic review declared that antidepressants are effective in treating IBS[46]. However, in 2015, a meta-analysis with conflicting results found that the efficacy of SSRIs to treat IBS was inconclusive[47]. One study showed that IBS patients with a psychiatric comorbidity had a greater probability of carrying SERT variants[48]. The possibilities underpinning antidepressants, such as SSRIs and other factors that regulate SERT, require further elaboration.

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

POTENTIAL REGULATORY FACTORS OF SERT

Both genetic and non-genetic factors are implicated in the up-regulation or down-regulation of SERT expression in IBS (Table 1). It is becoming clear that genetic predisposition might underlie IBS in individuals[53]. A large-scale study between monozygotic twins and dizygotic twins proved that both heredity and the environment contribute to the development of IBS. Furthermore, it appeared that environmental influence was more important for individuals than heredity in IBS[54]. In the present article, the potential regulatory factors of SERT expression are presented and discussed, and these factors might be involved in the pathophysiology and/or etiology of IBS.

SERT gene polymorphisms

As Hotoleanu *et al*[55] demonstrated using twin studies, familial aggregation and epidemiology, genetic factors contribute to IBS, especially polymorphisms of the SERT gene. In other words, a low-expression SERT genotype might underlie a genetic predisposition to IBS[56,57]. Furthermore, Kohen *et al*[58] reported a trend

towards an 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 the SERT gene was normal in IBS. Galligan *et al*[60] found increased serotonin availability in SERT knockout rats associated with visceral hypersensitivity. The *SERT* gene, solute carrier family 6 member 4 (SLC6A4), localizes to chromosome 17q11.2. SLC6A4 spans approximately 40 KB, contains 14 exons and ultimately encodes a 603-amino acid protein[61-63]. There are a series of polymorphic regions that might affect the expression or function of SERT[59,64-67] and further alter 5-HT reuptake, reaching up to 40-fold *in vitro*[68]. Current research mainly focuses on positive associations of the SLC6A4 genetic polymorphisms with the etiology of IBS, including 5-HTTLPR[69], a 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 between the three aspects has not yet been determined[58].

The most frequently studied variant, a 5-HTTLPR insertion/deletion polymorphism of approximately 44 base pairs, is subdivided into long (L) and short (S) alleles[69,72]. Furthermore, 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 that the L/L genotype leading to a higher SERT level appeared more frequently in IBS-C individuals than in IBS-D and healthy individuals[73]. Yeo *et al*[74] reported that the 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 with 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 subtype. However, because of insufficient patients participating in these studies, there was still no consistent conclusion. A meta-analysis containing thousands of IBS cases found ethnic differences in the relationship between 5-HTTLPR and IBS; moreover, the L/L genotype, or rather the L allele, was more relevant to IBS-C in East Asians than in Caucasians[78]. Similarly, another meta-analysis showed that the SLC6A4 polymorphism is associated with a reduced risk of IBS in American and Asian populations[35].

Another SERT gene polymorphism, called variable number of tandem repeats STin2, or simply "STin2 VNTR" for short, is located in intron 2 and consists of an indeterminate number of 17-bp segments (*i.e.*, 9, 10 or 12 repeats)[65,70]. Our previous study reported that the 10/12 genotype might contribute to IBS[79], although other reports regarding the association between STin2 VNTRs and IBS were controversial and inconclusive[74,80]. With regard to functional SNPs within the VNTR promoter, Kohen *et al*[58] found that compared with the more frequent A-allele, the comparatively rare rs25531 G-allele decreased SERT transcription and thus increased the IBS risk by approximately 3-fold. 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 mRNA and protein expression by suppressing the human SERT (hSERT) promoter 1[81]. The development of SERT gene-specific therapeutics to regulate SERT expression in the treatment of multiple disorders, including IBS, is realizable. Clinicians could put individualized treatment into effect according to different SERT genotypes as one of the factors.

MicroRNAs

Posttranscriptional gene regulation by microRNAs (miRNAs) can greatly contribute to miRNA-targeted gene translation[82,83]. miRNAs, endogenous about 22 nucleotide (nt) noncoding RNAs, pair with and then silence target mRNAs and achieve fine adjustments of protein outputs[84-86]. Of interest, nearly all aspects of biological processes, including development and cellular homeostasis, are under the influence of miRNAs. Moreover, miRNAs can facilitate the development of several types of diseases when they dysregulate targeted gene expression[83-85,87]. Despite insufficient studies focusing on the 3'-untranslated region (3'-UTR) of SLC6A4, miRNA binding to the 3'-UTR of SERT mRNAs by incomplete complementary base pairing is crucial for SERT mRNA translation, localization and stability[38,88].

During the past several years, it has been shown that SERT is a target of microRNA-16 (miR-16). The highly conserved miR-16 among mammalian species has high expression levels in the heart, brain, small intestine, lung and kidney[89,90]. Baudry *et al*[38] investigated if SERT expression was decreased by miRNAs in monoaminergic neurons utilizing the 1C11 neuroectodermal cell line expressing SERT transcripts. The results showed a 40% decline in the numbers of [^{3}H]-paroxetine (SSRI) binding sites after transfection with a high level of miR-16. SSRI fluoxetine down-regulated SERT expression by increasing the level of miR-16 in 1C11$^{5\text{-HT}}$ cells (1C11 neuroectodermal cells differentiate into serotonergic neuronal cells)[38]. Similar findings were obtained in the hippocampus, showing that fluoxetine treatment resulted in down-regulated miR-16 and 5-fold increased SERT expression, with further illustration that the level of miR-16 was regulated by SSRI antidepressants and was increased or decreased according to the different regions in

the brain. Furthermore, the neutralization of miR-16 played an antidepressant role in the hippocampus[91]. Direct injection of anti-miR-16 had an antidepressant effect similar to fluoxetine[91,92]. A study investigating acute lung injury also drew the same conclusions that decreased miR-16 levels contributed to increased SERT expression and therefore promoted the pathogenesis of pulmonary edema[93].

miR-16 might not be the only modulatory miRNA involved in the translational repression of SERT. For example, Jensen and colleagues[94] found that SERT expression in the HeLa cell line was also regulated by miR-545, and a U to G SNP in the 3'-UTR of the SERT mRNA had no effect on miR-545 binding and SERT down-regulation. 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 the brain tissue of Wistar rat pups highlighted that *Cronobacter sakazakii* infection up-regulated miR-16 expression interacting with SERT mRNA, which led to decreased levels of 5-HT and SERT expression[95]. Recently, a study directly illuminated that increased miR-24 expression in the enterocytes of IBS patients and mouse models promoted IBS-D pathogenesis by down-regulating SERT expression[96]. Discovering novel miRNAs related to posttranscriptional SERT gene regulation and elucidating the underlying mechanisms provide a new strategy to expand our understanding of miRNAs in the development and treatment of IBS.

Immunity and inflammation

Given that accumulating evidence points to a critical role for immune activation of the gut mucosa in EC 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]. It is generally accepted that there are increased levels of mucosal immune cell infiltration and proinflammatory cytokines in IBS patients. Furthermore, the inflammatory state of the 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 with healthy controls[41,103]. Foley *et al*[52] found that the reduced level of mucosal SERT mRNA in IBS-D patients was correlated with increased numbers of mucosal intraepithelial lymphocytes (IELs) and mast cells compared with healthy controls. A study from Wheatcroft and colleagues[104] evaluated post-*Trichinella spiralis* infection of T cell receptor (TCR) knockout mice with respect to EC cell numbers and SERT expression. The authors demonstrated that deficiencies of all T cells decreased infection-induced EC cell hyperplasia and extinguished mastocytosis, with a drastic reduction in jejunal SERT expression. Paradoxically, despite the general presence of inflammatory infiltrates, Faure *et al*[34] detected no differences in the numbers of IELs and $CD3^+$ cells located in the lamina propria between IBS patients and healthy controls.

Accumulating evidence has demonstrated that proinflammatory mediators, such as interferon-γ and tumor necrosis factor (TNF)-α, and not solely a non-specific change of inflammatory damage on epithelial cells, induce significant reductions in SERT mRNA, SERT protein levels and SERT function in Caco2 cells[105]. However, prostaglandin E_2 and interleukin-12 (IL-12) had no effect on the SERT mRNA and protein levels[105]. Furthermore, treatment with Shugan decoction, a type of traditional Chinese medicine used to treat IBS-D patients, resulted in a decreased TNF-α level with up-regulated SERT gene and protein levels in colonic tissue, which suggested underlying interactions between TNF-α and SERT expression[106]. A protective cytokine, transforming growth factor-β1, can activate SERT activity and inhibit intestinal inflammation *via* PI3K and syntaxin 3[107]. These studies provide an overview of immune mechanisms involved in SERT regulation in a subset of IBS patients.

Gut microbiota

It is 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 involved in the pathogenesis of IBS because of the convincing findings that predisposed individuals following infectious gastroenteritis suffer from PI-IBS and resemble patients with IBS-D[110,111]. Because of the rapid evolution of analytical techniques, such as 16S rRNA-based microbiota analyses for profiling bacteria in the GI tract, not just in culture, it has been shown that mucosal and fecal gut microbial community composition differs between patients with IBS and healthy controls[112]. Albeit with significant differences in methods, many studies have found that the relative abundances of the genera *Lactobacillus*, *Bifidobacterium*, *Actinobacteria* and *Bacteroidetes* were decreased, while *Proteobacteria*, *Firmicutes* and *Firmicutes*: *Bacteroidetes* ratios were increased in fecal samples of IBS-D patients[110,113,114]. Malinen *et al*[115] even found an association between altered bacterial composition and subtypes of IBS, with a decreased amount of *Lactobacillus spp.* among IBS-D patients and an elevated amount of *Veillonella spp.* among IBS-C patients. However, the lack of large sample sizes and the heterogeneity of IBS symptoms represent limitations of these studies.

As noted previously, particular gut microbes and microbial metabolites regulate tryptophan metabolism, the serotonergic system and brain-gut axis functions and thereby alter the levels of 5-HT in the colon and blood, which might suggest a critical role for

the intestinal flora in regulating SERT and ultimately influencing the pathogenesis of IBS[40,112,116,117]. Yano *et al*[116] found that EC cells were promoted to synthesize and secrete 5-HT by endogenous bacteria, such as spore-forming bacteria and their metabolites in germ-free mice. 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 levels, apical SERT activity, 5-HT uptake and mucosal 5-HT content. An investigation by Nzakizwanayo *et al*[119] demonstrated that the exposure of mouse ileal tissue to *E. coli* Nissle 1917 *in vitro* 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. Similarly, in IBS, reduced 5-HIAA levels and 5-HIAA/5-HT ratios elucidate serotonergic system dysbiosis with regard to both synthesis and metabolism[120]. Our previous study suggested that the supernatant of probiotics, such as *Lactobacillus rhamnosus GG*, up-regulated the SERT mRNA level as much as 9.4-fold in enterocytes and mouse intestinal tissues in a concentration- and time-dependent manner[121,122]. Our research also found that a protein derived from LGG, known as p40, activated epidermal growth factor receptor (EGFR), which suggested that LGG up-regulated SERT possibly by activating EGFR[123].

Therapeutic strategies targeting the gut microbiota to recover the decreased diversity and stability might be a viable treatment strategy for IBS and other 5-HT-related brain-gut-microbiota axis disorders[40,116]. To date, scientists and clinicians have made a variety of creative attempts, especially using probiotics, prebiotics, antibiotics and fecal microbiota transplantation (FMT), to increase the relative abundance of commensals (such as *Lactobacilli* and *Bifidobacteria*, *etc*.) and conversely, to decrease the relative abundance of those bacterial species exacerbating IBS symptoms (*Clostridium*, *E. coli*, *Salmonella*, *Shigella* and *Pseudomonas*)[108,124]. Both a low-carbohydrate diet and the probiotic LGG have been proven effective in IBS patients[122,125]. *Lactococcus lactis*, which is effective in suppressing colon inflammation by secreting IL-10, restores colonic 5-HT concentrations, given that the 5-HT level is increased in a dinitro-benzenesulfonic-acid micro-inflammation model[102]. Similarly, Martín *et al*[126] found that the probiotic *Faecalibacterium prausnitzii* strain A2-165 (a type of commensal bacterium) or its supernatant had anti-inflammatory effects, with down-regulation of 5-HT levels to restore the normal state. Rifaximin, the most studied antibiotic in IBS, increased the relative abundance of *Lactobacillus* in the ileum, which relieved the mucosal inflammatory state and visceral hyperalgesia of the rat model[127]. There is growing evidence regarding the efficacy of FMT in relieving symptoms in IBS patients, even in patients with longstanding refractory IBS-D, *via* restoring the intestinal microbiota[128-131]. However, no study has demonstrated a 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, the feasibility and reliability of FMT remain to be determined.

Growth factors

There is growing evidence regarding the role of growth factors, such as EGF[132], basic fibroblast growth factor[133] and nerve growth factor[134], in the up-regulation of SERT expression. At present, EGF has been the most studied of these factors. As a polypeptide with 53 amino acid residues and growth hormone[135], EGF plays multiple biological roles by combining with a specific EGFR located on the basolateral surface of enterocytes[135-138]. There is evidence to suggest that EGF is involved in 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 the GI tract from intestinal inflammation[137], little is known about a potential correlation between EGF signaling and IBS pathogenesis.

In response to SERT regulation, as Gill *et al*[144] first suggested, EGF acting on EGFR activates the hSERT promoter and upregulates SERT mRNA levels and function in enterocytes through transcriptional mechanisms in a dose- and time-dependent manner. Two types of alternate promoters of the *SERT* gene, hSERTp1 and hSERTp2[145], are both active in Caco-2 cells by approximately 2- to 2.5-fold, respectively, compared with the transfected results of the pGL2 empty vector alone[144]. Accumulating evidence suggests that EGF promotes SERT gene expression. Kekuda *et al*[132] found that the treatment of human placental choriocarcinoma cells with EGF increased the levels of SERT transcriptional activity, SERT mRNA expression and SERT function, likely by activating the EGF receptor through tyrosine phosphorylation. Kubota *et al*[133] reached similar conclusions about EGF and basic fibroblast growth factor using human glial cells (astrocytes). However, the positive effects of EGF on both distinct promoters of the SERT gene (hSERTp1 and hSERTp2) are counteracted by inhibiting EGFR tyrosine kinase activity[132,144]. Decreased plasma and colonic tissue EGF levels were observed in IBS patients and in a rat model with visceral hypersensitivity[146]. Therefore, decreased EGF correlates with decreased SERT activity, which is consistent with the conclusions that decreased EGF levels result in decreased removal of 5-HT into intestinal epithelial cells, stimulating visceral sensitivity and ultimately contributing to IBS[146]. As a neuroendocrine mediator, neurotrophin nerve growth factor is increased in mucosal tissues[147,148] and could relieve intestinal barrier dysfunction and visceral hypersensitivity of IBS-D patients[149,150]. These findings

suggest that the up-regulation of SERT expression and function by growth factors might provide a better understanding of the pathogenesis and treatment of IBS.

Others

In addition, several different factors modulate SERT expression. As an agonist of tyrosine-kinase receptors, aurintricarboxylic acid plays a role in the upregulation of SERT, similar to EGF[132]. Although studies have 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*.) regulate SERT, it remains to be determined if these factors are involved in IBS pathogenesis.

FUTURE PROSPECTS

It is now believed that 5-HT signaling is essential to the pathogenesis of IBS. As a result, new therapeutic strategies targeting the abnormal expression of SERT might represent a breakthrough to relieve the symptoms of this excruciating disease[28,109]. At present, therapeutic approaches targeting gut microbiota, immune activation and the inflammatory response have received adequate attention to regulate SERT. There is no doubt that these potential regulators of SERT hold great promise for the development of treatments for IBS.

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