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EDITORIAL

Recent developments in the pathophysiology of irritable bowel syndrome

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Abstract

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder, the pathophysiology of which is not completely known, although it has been shown that genetic/social learning factors, diet, intestinal microbiota, intestinal low-grade inflammation, and abnormal gastrointestinal endocrine cells play a major role. Studies of familial aggregation and on twins have confirmed the heritability of IBS. However, the proposed IBS risk genes are thus far nonvalidated hits rather than true predisposing factors. There is no convincing evidence that IBS patients suffer from food allergy/intolerance, with the effect exerted by diet seemingly caused by intake of poorly absorbed carbohydrates and fiber. Obesity is a possible comorbidity of IBS. Differences in the microbiota between IBS patients and healthy controls have been reported, but the association between IBS symptoms and specific bacterial species is uncertain. Low-grade inflammation appears to play a role in the pathophysiology of a major subset of IBS, namely postinfectious IBS. The density of intestinal endocrine cells is reduced in patients with IBS, possibly as a result of genetic factors, diet, intestinal microbiota, and low-grade inflammation interfering with the regulatory signals controlling the intestinal stem-cell clonogenic and differentiation activities. Furthermore, there is speculation that this decreased number of endocrine cells is responsible for the visceral hypersensitivity, disturbed gastrointestinal motility, and abnormal gut secretion seen in IBS patients.

Key words: Diet; Endocrine cells; Genetic factors; Low-grade inflammation; Microbiota; Stem cells

Core tip: There are several factors that play a major role in the pathophysiology of irritable bowel syndrome

(IBS). These factors are genetic disposition, diet, the intestinal microbiota, and mucosal low-grade inflammation. These factors are known to affect the gastrointestinal endocrine cells, with the densities of intestinal endocrine cells being reduced in IBS patients. The reduction in the gastrointestinal endocrine cells seems to be caused by abnormal clonogenic and differentiation activities of the intestinal stem cells. The abnormalities in the gastrointestinal endocrine cells can explain the visceral hypersensitivity, disturbed gastrointestinal motility, and abnormal gut secretion observed in IBS patients.

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INTRODUCTION

Patients with irritable bowel syndrome (IBS) suffer from intermittent abdominal pain or discomfort in combination with altered bowel habits and abdominal distension/bloating[1-3]. These symptoms cause significant morbidity, with impaired quality of life and reduced work productivity[4,5], and is an economic burden to both the patients and society[6-12]. IBS patients can be divided into three subtypes according to the predominant bowel pattern: diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), and both diarrhea and constipation (IBS-M)[13].

The pathophysiology of IBS is incompletely understood, and there is no diagnostic test or effective treatment for this condition[14-16]. Thus, IBS patients visit doctors more frequently, undergo more diagnostic tests and examinations, consume more medications, and are hospitalized more frequently than those without IBS[6-12]. Understanding the pathophysiology of IBS is necessary in order to develop better diagnostic methods and effective treatments, and consequently reduce the economical costs both for patients and society. New data on the pathophysiology of IBS have accumulated over the past few years, improving our understanding of this disorder[1,15-20]. The aim of this review was to account for these new data and integrate them into the current knowledge on the pathophysiology of IBS.

PATHOPHYSIOLOGY OF IBS

There is evidence that several factors play a central role in the pathophysiology of IBS, such as genetic/social learning factors, diet, the intestinal microbiota, low-grade chronic intestinal inflammation, and abnormal gastrointestinal endocrine cells[1,14-20].

Heritability and social learning

Familial aggregation: Familial clustering of IBS has been noted in everyday clinical practice, with 37% of IBS patients reportedly having a family history of the disorder[21]. Moreover, it has been shown that IBS patients are more likely (33.9%) than controls (12.6%) to have a family history of IBS[22]. In a cohort of IBS patients from Olmsted County, USA, a significant association was found between IBS patients and having a first-degree family member with IBS, but not for their non-IBS spouses[23]. The prevalence of IBS was 17% among IBS patients' relatives, compared to 7% among their spouses' relatives[24]. Similarly, the prevalence rates of IBS were reported to be 21%-50% and 4%-27% among relatives of IBS patients and non-IBS controls, respectively[25,26]. In a recently published, nationwide survey of the Swedish population, the risk of IBS was found to be increased in the first-, second-, and third-degree relatives of patients with IBS compared with their non-IBS counterparts, with the risk tending to be higher in more closely related relatives[27].

Twin studies: All twin studies confirm a substantial genetic component in IBS[28-31], with one exception[32]. Among 343 Australian twin pairs, IBS was found to occur at rate of 33.3% in monozygotic twins compared to 13.3% in dizygotic twins, with 56.9% of the variance being due to additive genetic factors.[28] In two studies involving 6060 and 986 American twin pairs[29,33], the first study showed that the concordance of IBS was significantly greater in monozygotic (17.2%) than in dizygotic (8.4) twins[29], and in the second study the polychoric correlation of IBS for monozygotic twins with IBS was greater than that for dizygotic twins (47% and 17%, respectively)[33]. In Scandinavia, a study conducted involving 3286 Norwegian twin pairs found that the concordance for IBS was significantly higher among monozygotic (22.4%) than dizygotic (9.1%) twins, and that the concordance was higher (48.5%) in females[31]. However, in contrast to all other twin studies, a study of 1870 British twin pairs did not reveal any significant difference in the rates of IBS between monozygotic and dizygotic twins[32].

Genetic studies: The aforementioned epidemiological and twin studies point to a potential involvement of specific genes in the pathogenesis of IBS. Most of the genetic research has concentrated on the serotonin signaling pathways, control of immune activation, bile acid synthesis, neuropeptide activity, and intestinal secretion[34-37]. More than 60 gene candidates have been proposed to play a role in the genetic predisposition to IBS, but these risk genes have yet to be validated[38]. The most important of these gene candidates are described in detail elsewhere[39]. Several studies have focused on the *HTTLPR* genotype, which controls the expression of the SLC6A4 (serotonin transporter

protein); however, the reported association with IBS is equivocal[40-43].

The gene that is most likely to be associated with IBS, and with IBS-C in particular, is that encoding tumor necrosis factor superfamily 15 (*TNFSF15).* It was first described in Swedish and US patients, and was confirmed in patient cohorts in the UK and Canada[44-46]. However, in a genome-wide association study (GWAS) the association between *TNFSF15* and IBS was found to be nonsignificant[47]. It was suggested that this seemingly contradictory finding can be explained by the possibility that genetic effects are diluted and more difficult to detect at the general population level[47].

In a general population GWAS, a locus at 7p22.1, which includes the genes *KDELR2* and *GRID2IP*, showed consistent IBS risk effects[47]. *KDELR2* encodes a family of receptors, the most well known of which is KDELR1 [KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 1], which is an integral membrane protein that binds the Lys-Asp-Leu-Glu and Arg-Asp-Leu-Glu amino acid motifs of target proteins and mediates their retrograde transport to the endoplasmic reticulum[48-52]. *GRID2IP* encodes delphilin, which is expressed in nerve-fiber-Purkinje-cell synapses in the brain[53,54].

The reasons underlying the conflicting results yielded by genetic association studies, and especially in IBS, are discussed elsewhere[38,55]. The IBS risk genes proposed so far are nonvalidated hits rather than true predisposing factors, and the studies conducted have been largely too underpowered to capture true association signals[38]. In the future, research in this field should apply the promising GWAS approach to research candidate mechanisms rather than symptom definition[38].

Environment and social learning

Parental modeling and reinforcement of illness behaviors may play a role in the pathophysiology of IBS[29,56-59]. Having a mother with IBS accounts for as much variance as having an identical twin with IBS[56]. Aggregation of IBS among spouses to IBS patients has been reported to indicate that nongenetic - and most probably environmental factors - are responsible for IBS clustering[27]. In a more recent comprehensive review, where a careful weighing of evidence was made, concluded that social learning may be one of the factors involved in the etiology of IBS[60]. Moreover, the pain caused by visceral hypersensitivity in IBS has been attributed to atypical attention to pain as a part of illness behavior[61,62].

Diet: Most IBS patients believe that certain food items trigger their symptoms[63-71]. This has resulted in IBS patients making conscious choices to avoid foodstuffs such as milk and milk products, wheat products, caffeine, cabbage, onions, peas, beans, hot spices, and fried and smoked food[63,68,72,73].The intake of energy, carbohydrates, proteins, and fats in IBS patients does not differ from that of the general population[72-78]. However, IBS patients tend to avoid several food sources that are important to their health, especially those rich in vitamins and minerals[73]. Several factors have been discussed to explain the mechanisms by which diet plays its role in the pathophysiology of IBS, such as poorly absorbed carbohydrates and fiber, food allergy/intolerance, and the comorbidity of obesity and IBS[1,17,20,79-83].

Poorly absorbed carbohydrates and fiber: Several food items contain indigestible and poorly absorbed short-chain carbohydrates, namely fermentable oligo-, di-, and monosaccharides, and polyols (FODMAPs)[1]. FODMAPs include fructose, lactose, sugar sources (sorbitol, maltitol, mannitol, xylitol, and isomalt), fructans, and galactans[1,84], and occur in a wide range of foods such as wheat, rye, vegetables, fruits, and legumes[85-87]. These unabsorbed carbohydrates enter the distal small intestine and colon, where they increase the osmotic pressure in the luminal cavity and provide a substrate for bacterial fermentation[84,88,89]. This bacterial fermentation leads to gas production, which in turn causes abdominal distension and abdominal pain/discomfort. FODMAPs have been found to trigger gastrointestinal symptoms in IBS, and a low-FODMAPs diet reduces symptoms and improves the patient's quality of life[73,78,90-95].

Recent studies have shown that the triggering of IBS symptoms by FODMAPs is much more complicated than was originally thought. Thus, a low FODMAPs intake induces favorable changes in the intestinal microbiota[96] and gastrointestinal endocrine cells[97-100]. The change from a diet of typical Australian food to a low-FODMAPs diet was found to change the intestinal microbiota; whereas a typical Australian diet increases the relative abundance of butyrate-producing *Clostridium* cluster XIVa and the mucus-associated *Akkermansia muciniphila*, and reduces *Ruminococcus* torques, a low-FODMAPs diet reduces the total bacterial abundance[96]. Several endocrine cell types in the gastrointestinal tract of IBS patients are abnormal[101-120], and these abnormalities are considered to play a major role in the development of IBS symptoms and represent future targets for treatment[16,121]. Switching from a typical Norwegian diet to a low-FODMAPs diet has been shown to change the densities of endocrine cells in the stomach and large intestine toward normal levels[97-100].

Food allergy/intolerance: There is no convincing evidence to support the idea that IBS patients suffer from food allergy/intolerance[64,67,122-128]. The prevalence of nonceliac gluten sensitivity (NCGS) in the United States has been reported to range from 0.55% to 6%[129,130]. NCGS is defined as patients with gastrointestinal and extragastrointestinal IBS-like symptoms without celiac disease or wheat allergy, and

with symptom relief on a gluten-free diet (GFD) and relapse on gluten challenge[130-137].

NCGS was first described more than 30 years ago[138,139], and has been the focus of several recent reports[140-144]. Contradictory results have been reported regarding whether or not NCGS patients have low-grade inflammation and abnormal intestinal permeability[141,144-151]. However, in double-blind, randomized, placebo-controlled studies[141,143,144], the positive effects on symptoms in NCGS patients were actually found to be the result of wheat withdrawal rather than gluten withdrawal[152]. In a placebo-controlled, crossover study of patients with IBS-like symptoms with self-imposed GFD[153], the gastrointestinal symptoms consistently and significantly improved when the FODMAPs intake was reduced, and these symptoms were not worsened by either a low- or high-dose challenge with gluten. It therefore seems that it is the carbohydrate content (fructans and galactans) in the wheat rather than gluten that is responsible for triggering NCGS symptoms. This conclusion is supported further by the findings that in those who believed that they had NCGS, 24% had uncontrolled symptoms despite consuming a GFD, 27% were not following a GFD alone, and 65% avoided other foods that contain high levels of FODMAPs[154].

NCGS and IBS patients experience the same symptoms that are triggered by wheat intake, and both groups have a high frequency of antigliadin antibodies (AGAs) with negative tissue transglutaminase, or deamidated gliadin peptide antibodies[133,143,155-158]. AGAs have been reported to have a good sensitivity but a low specificity for celiac disease[159], and 12%-15% of healthy subjects are reportedly positive for AGAs[155,159,160]. It is thus possible to conclude that NCGS patients are IBS patients who are self-diagnosed and have self-treated by adhering to a GFD.

Obesity and IBS: There has been some concern that the onset of symptoms upon ingesting food would result in low food intake with consequent malnutrition in patients with IBS[73,161]. However, while some studies have found an association between low body mass index (BMI) and IBS[162], others have found the predominance of normal-weight or overweight IBS patients[63]. The association between IBS and obesity was found to be controversial in a comprehensive review, and the author concluded that obesity and IBS might be linked[163].

Appetite is regulated by a large number of hormones, including those secreted by the gastrointestinal endocrine cells[164]. The densities of the following five gastrointestinal endocrine cell types that secrete hormones known to regulate appetite are abnormal in patients with IBS: ghrelin, cholecystokinin, peptide YY, enteroglucagon (oxyntomodulin), and serotonin[101,103,104,107,165-171]. Ghrelin stimulates food intake and body weight gain[172,173]. The density of this endocrine cell type is increased in IBS-D patients. The densities of endocrine cells that secrete the other four hormones, which have an anorexigenic action[174-189], are reduced in patients with IBS. This would be predictive of an increased appetite and food intake in IBS patients. BMI and appetite in IBS patients have not been fully studied, and the currently available data are controversial. It is not clear whether IBS patients have an increased appetite, which is opposed by the avoidance of eating because of worsening of symptoms upon eating, or a high BMI.

Intestinal microbiota: The role of the intestinal microbiota in the pathophysiology of IBS has been discussed in detail elsewhere[190-194]. The human intestine contains about 10^{14} bacteria belonging to over 1000 species[190,195,196]. These bacteria can be present in the lumen or attached to or embedded in the mucus layer of the gastrointestinal tract[197]. The number of bacteria is lower in the small intestine than in the colon, and decreases gradually toward the upper parts of the gastrointestinal tract[198-200]. The gastrointestinal microbial composition is determined by host genetic factors and environmental factors[193]. The environmental factors include mode of delivery at birth, aging, treatment with antibiotics, and sanitation status[201]. The gastrointestinal microbiota plays a role in gastrointestinal motility, gut immune defense, digestion and metabolism, inflammation, and cell proliferation[193,202].

Several studies using culture-based and culture-independent methods have shown that the microbiota - as detected in feces samples - differs between in IBS patients and healthy controls[203-229]. However, the association between IBS symptoms and specific bacterial species is uncertain[191]. Although contradictory results have been reported, decreased levels of lactobacilli and bifidobacteria, and increased levels of anaerobic bacteria such as streptococci and *Escherichia coli*, as well as increased ratios of *Firmicutes*, *Bacteroidetes*, and *Clostridium* species have been confirmed in several studies[206,226].

Low-grade inflammation: It has been suggested that the presence of colonic mucosal low-grade inflammation plays a role in the pathophysiology of IBS[18,230]. However, studies of mucosal low-grade inflammation in the colon have yielded contradictory results[231]. There are reports of increased numbers of intraepithelial immune cells, and elevated numbers of immune cells and mast cells in lamina propria of rectal biopsies taken from patients with postinfectious IBS (PI-IBS)[116,232,233]. The densities of immune and mast cells in the mucosa of patients with sporadic (nonspecific) IBS (non-PI-IBS) did not differ from those in healthy controls[234]. An increased number of intraepithelial lymphocytes has been found in studies in which no attention was paid to the previous history of gastrointestinal infection[235-237]. However, an unchanged density of mast cells was found in studies in which no distinction was made between PI-IBS and non-PI-IBS[235,238,239]. Moreover, the mast cell density was elevated in PI-IBS but not in non-PI-

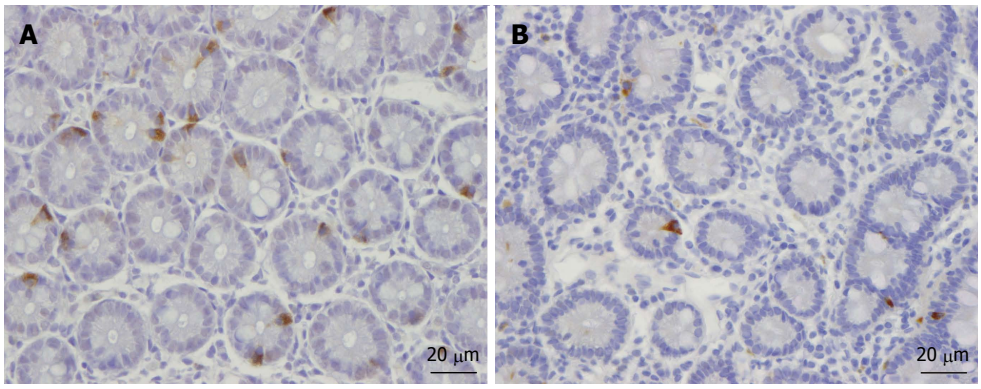

Figure 1 Chromogranin A-immunoreactive cells in (A) a healthy subject and (B) an irritable bowel syndrome patient.

IBS[118,235]. Similar to the immune cells and mast cells, inconsistent findings have been reported regarding cytokines in patients with IBS[240], whereby changes in cytokines were reported in IBS patients[240-242], but not in those with non-PI-IBS[243].

The research performed to date provides compelling evidence that low-grade inflammation occurs in a subset of IBS patients, namely those with PI-IBS, but not in those with non-PI-IBS. PI-IBS represents a considerable proportion of IBS patients, with an incidence of 7%-31% among IBS patients[244-246]. Thus, low-grade inflammation plays a significant role in the pathophysiology in a subset of IBS patients.

Abnormal gastrointestinal endocrine cells

Gastrointestinal endocrine cells: The gastrointestinal tract contains at least 15 different types of endocrine cells that are spread among the epithelial cells of the mucosa[14,78,170,247-250]. These cells, which constitute about 1% of all epithelial cells in the gastrointestinal tract[247,248,251-253], have specialized sensors in the form of microvilli that project into the lumen and respond to luminal stimuli by releasing hormones[101,254-265]. The distribution, functions, and modes of action of the most important endocrine/paracrine cells are described in detail elsewhere[15,16,170]. In brief, they secrete one or more signaling substances into the lamina propria, where these substances act directly on nearby structures (autocrine/paracrine mode) and/or indirectly *via* an endocrine mode of action (by circulating in the blood to reach distant targets)[266]. They regulate several functions of the gastrointestinal tract such as sensation, motility, secretion, absorption, local immune defense, and food intake[1,166,170,247,248]. These cells interact and integrate with each other and with the enteric nervous system and the afferent and efferent nerve fibers of the central nervous system[1,166,170,267].

Abnormal endocrine cells have been found in both sporadic IBS and PI-IBS patients. In sporadic IBS, abnormal endocrine cells were found in the stomach, proximal small intestine (duodenum), distal small intestine (ileum), colon, and rectum[111-113,167,171,268-276]. Although the densities of endocrine cell types can vary (*i.e.*, decrease or increase), the general trend of the entire intestinal endocrine cell population is toward a decrease in IBS. This becomes evident when intestinal biopsy samples are stained with chromogranin A, which is a common marker for endocrine cells. Thus, the densities of the total endocrine cells in the duodenum, ileum, and colon are reportedly decreased, while those of the stomach and rectum are unchanged (Figure 1)[102,269,271,272]. In contrast to sporadic IBS, the densities of intestinal endocrine cells in patients with PI-IBS tend to increase[109,113,114,116-120,277].

Stem cells: Each intestinal crypt contains four to six stem cells, which originate from pluripotent stem cells of endodermal origin[247,248,278]. These cells divide into new stem cells (self-renewal; clonogeny) and into cells that differentiate into all epithelial cell types including enterocytes, goblet cells, Paneth cells, and endocrine cells (differentiation progeny)[279-293]. The differentiation progeny includes two lineages: secretory and absorptive. The secretory lineage gives rise to goblet, endocrine, and Paneth cells, and the absorptive lineage to absorptive enterocytes (Figure 2)[279-293].

As mentioned above, the total density of intestinal endocrine cells is reduced in sporadic IBS. A similar reduction in the density of intestinal endocrine cells has been observed in congenital malabsorptive diarrhea, and following small-intestine allograft rejection[294,295]. The decrease in the density of endocrine cells in both conditions has been found to be caused by a mutation in the gene encoding the protein neurogenin 3 (NEUROG3), which is expressed in the endocrine progenitor cells required for intestinal endocrine development, and a reduction in the progenitors of intestinal endocrine cells that express NEUROG3 and NeuroD[294,295]. It has recently been reported that the densities of cells expressing Musashi 1 (Msi-1, expressed in both stem cells and in their early progeny; Figure 3) and NEUROG3 (expressed in early endocrine cell progenitors; Figure 4)[296] were reduced in the duodenum of sporadic IBS patients[299]. It was concluded that disturbance of the clonogenic and differentiation activities of intestinal stem cells could be responsible for the reduction of intestinal endocrine cells observed in IBS patients[296].

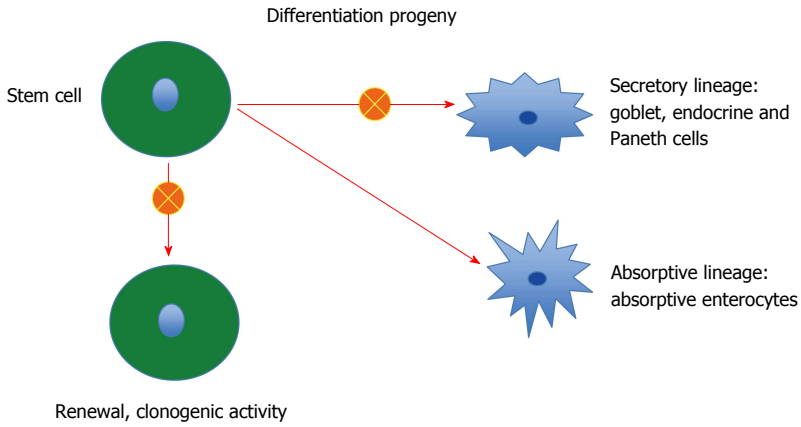

Figure 2 The intestinal stem cell exerts 2 activities: clonogenic activity, where it produce a copy of itself to maintain the number of stem cells constant in the crypts, and differentiation activity. The differentiation consists of 2 lineages: secretory lineage and absorptive lineage. Through a cascade of progenitors the secretory lineage give rise to goblet, endocrine and Paneth cells and the absorptive lineage to absorptive enterocytes. In IBS patients, both clonogenic and differentiation activities are abnormal.

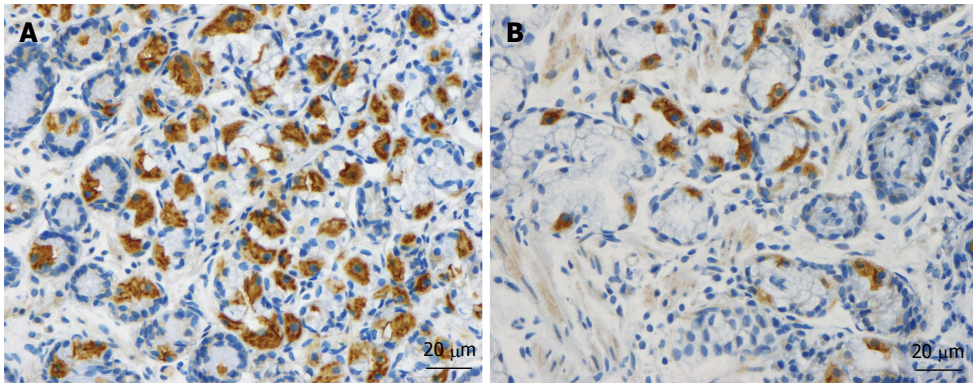

Figure 3 Msi-1-immunoreactive cells in duodenum of subjects from the (A) control, and (B) irritable bowel syndrome patient.

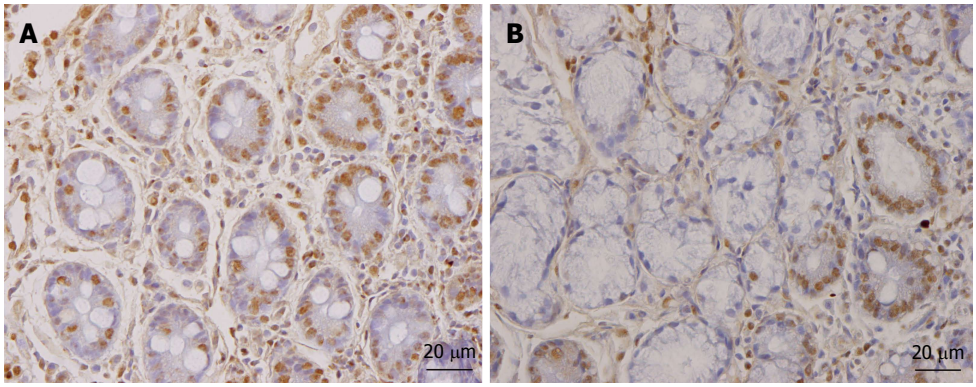

Figure 4 NEUROG3-immunoreactive cells in (A) a healthy subject and (B) an irritable bowel syndrome patient.

HYPOTHESIS

IBS patients exhibit visceral hypersensitivity, disturbed gastrointestinal motility, and abnormal gut secretion[297-301]. The gastrointestinal endocrine cells, as mentioned above, regulate several functions of the gut including sensation, motility, and secretion. The density of the intestinal endocrine cells is generally reduced in sporadic IBS. This reduction appears to be caused by a reduction in intestinal stem-cell self-renewal and proliferation. Intestinal stem-cell self-renewal (clonogeny) and proliferation are regulated by several signaling pathways[287]. As demonstrated in this review, heredity, diet, the intestinal microbiota, and low-grade inflammation play a major role in the pathophysiology of IBS. Changes in diet, intestinal bacterial flora, and inflammation have been reported to affect the density of endocrine cells in the gut[1,97,302].

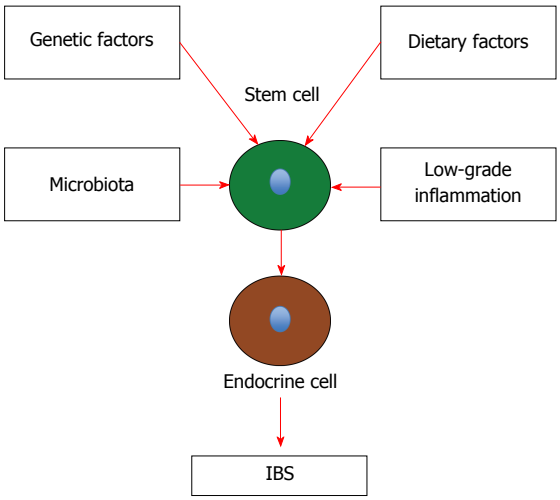

Figure 5 Schematic drawing to illustrate the possible pathophysiology of irritable bowel syndrome. Details are described in the text. IBS: Irritable bowel syndrome.

It can be speculated that the factors that have been shown to play a major role in the pathophysiology of IBS will affect the signaling pathways for stem-cell clonogenic renewal and proliferation, resulting in abnormalities in the gastrointestinal endocrine cells with the development of IBS symptoms (Figure 5).

CONCLUSION

There is compelling evidence that genetic factors, diet, the intestinal microbiota, and mucosal low-grade inflammation play a major role in the pathophysiology of IBS. These factors are known to affect the gastrointestinal endocrine cells, with the densities of intestinal endocrine cells being reduced in IBS patients. The abnormalities in the gastrointestinal endocrine cells can explain the visceral hypersensitivity, disturbed gastrointestinal motility, and abnormal gut secretion observed in IBS patients.

The reduction in intestinal endocrine cells appears to be caused by disturbance of the clonogenic and differentiation activities of the intestinal stem cells. The clonogeny and proliferation of intestinal stem cells are regulated by several signaling pathways. It is possible that genetic factors, diet, the intestinal microbiota, and mucosal low-grade inflammation interfere with the signals regulating the clonogenic and proliferation activities of stem cells, resulting in a reduction in the density of intestinal endocrine cells. This reduction of intestinal endocrine cells can in turn result in the development of IBS symptoms.

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