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## Possible role of intestinal stem cells in the pathophysiology of irritable bowel syndrome

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### Abstract

The pathophysiology of irritable bowel syndrome (IBS) is not completely understood. However, several factors are known to play a role in pathophysiology of IBS such as genetics, diet, gut microbiota, gut endocrine cells, stress and low-grade inflammation. Understanding the pathophysiology of IBS may open the way for new treatment approaches. Low density of intestinal stem cells and low differentiation toward enteroendocrine cells has been reported recently in patients with IBS. These abnormalities are believed to be the cause of the low density of enteroendocrine cells seen in patients with IBS.

Enteroendocrine cells regulate gastrointestinal motility, secretion, absorption and visceral sensitivity. Gastrointestinal dysmotility, abnormal absorption/secretion and visceral hypersensitivity are all seen in patients with IBS and have been attributed to the low density of the intestinal enteroendocrine cells in these patients. The present review conducted a literature search in Medline (PubMed) covering the last ten years until November 2019, where articles in English were included. Articles about the intestinal stem cells and their possible role in the pathophysiology of IBS are discussed in the present review. The present review discusses the assumption that intestinal stem cells play a central role in the pathophysiology of IBS and that the other factors known to contribute to the pathophysiology of IBS such as genetics, diet, gut microbiota, stress, and low-grade inflammation exert their effects through affecting the intestinal stem cells. It reports further the data that support this assumption on genetics, diet, gut microbiota, stress with depletion of glutamine, and inflammation.

**Key words:** Diet; Gut enteroendocrine cells; Gut microbiota; Low grade inflammation; Stress

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**Core tip:** The pathophysiology of irritable bowel syndrome (IBS) is not completely understood. Understanding the pathophysiology of IBS may enable us to find an effective treatment for this disorder. The density of intestinal stem cells is low in patients with IBS. Moreover, the differentiation of stem cells into enteroendocrine cells is abnormal. It seems that these abnormalities in intestinal stem cells is the cause of the low density of enteroendocrine cells seen in patients with IBS. It is believed that the low density of enteroendocrine cells is behind the gastrointestinal dysmotility, abnormal secretion/absorption and hypersensitivity observed in patients with IBS. This review presents the observations that suggest that the factors known to contribute to the pathophysiology of IBS may exert their effects through affecting the intestinal stem cells.

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## INTRODUCTION

Irritable bowel syndrome (IBS) is a wide spread condition affecting 12.1% of the world population<sup>[1,2]</sup>. The prevalence of IBS differs considerably between different parts of the world with the lowest prevalence in Asia and the highest in South America<sup>[1]</sup>. The cardinal symptom of IBS is intermittent abdominal pain accompanied by altered bowel habits and abdominal bloating/distention<sup>[3]</sup>. There is no biochemical, radiological or clinical test/examination for diagnosing IBS and the IBS diagnosis is based on symptoms assessment<sup>[4]</sup>. IBS reduces significantly the patients' quality of life in the same degree as major chronic diseases such heart failure, renal failure, diabetes, and inflammatory bowel disease<sup>[2,3]</sup>. It has been reported that 12%-14% of primary care patient visit, and 28% of referrals to gastroenterologists are IBS patients<sup>[5-7]</sup> and consequently IBS patients are more common in the healthcare than patients with diabetes, hypertension or asthma<sup>[8,9]</sup>. There is no effective treatment for IBS and the available treatment in clinic is directed to symptom relief<sup>[4]</sup>.

Several factors are known to play pivot role in pathophysiology of IBS. These factors are genetics, diet, gut microbiota, gut endocrine cells, stress and low-grade inflammation<sup>[2,10]</sup>. Abnormalities in the intestinal stem cells has been reported recently<sup>[11-13]</sup>. The present review aimed at discussing the possibility that the factors known to contribute to the pathophysiology of IBS may exert their effects through affecting the intestinal stem cells. The present review conducted a literature search in MEDLINE (PubMed) covering the last ten years until November 2019, where articles in English were included. Articles about the intestinal stem cells and their possible role in the pathophysiology of IBS are discussed.

## FCACORS INVOLVED IN THE PATHOPHYSIOLOGY OF IBS

### Genetics

Studies of family history and family cluster as well as twin studies provided strong evidences that IBS is hereditary<sup>[14-21]</sup>. However, the possible mutant gene(s) responsible for IBS is/are not found yet<sup>[2]</sup>.

### Diet

Patients with IBS avoid certain food items as they believe they worsen/trigger their symptoms<sup>[22-26]</sup>. However, there is no difference in intake of calories, or the meal patterns between IBS patients and community controls<sup>[23,27,28]</sup>.

The effect of diet on IBS symptoms cannot be explained by food allergy/intolerance<sup>[29]</sup>. However, it is generally accepted that poorly absorbed carbohydrates and fibers play an important role in development IBS symptoms<sup>[29,30]</sup>. The intake of low fermentable oligo-, di-, monosaccharides and polyols-diet and National Institute for Health and Care Excellence-modified diet improve both symptoms and quality of life in IBS patients<sup>[22,29,31,32]</sup>. However, a recent review and meta-analysis showed that there is very low quality evidence showing that low fermentable oligo-, di-,

monosaccharides and polyols diet relieves IBS symptoms<sup>[33]</sup>.

Based on a case report published in 1978, non-celiac gluten sensitivity was coined<sup>[34-36]</sup>. In this case, a patient without celiac disease, suffered from abdominal pain and diarrhea who experienced symptoms improved when she used gluten-free diet. Several studies showed that withdrawal of wheat products in patients with non-celiac IBS-like symptoms improve these symptoms<sup>[37-42]</sup>. However, a double-blind placebo-controlled study showed that it is fructan in the wheat rather than gluten that trigger IBS symptoms<sup>[43]</sup>. In a recently published meta-analysis concluded that there is insufficient evidence that gluten-free diet improves IBS symptoms<sup>[33]</sup>.

### **Gut microbiota**

The gastrointestinal microbiota comprises 12 different bacteria phyla, but most of the gut bacteria belongs to the Proteobacteria, Firmicutes, Actinobacteria and Bacteroidetes<sup>[44,45]</sup>. The anaerobic Firmicutes and Bacteroidetes phyla dominate the bacterial population in the intestinal of healthy adults, with a few members from of the Proteobacteria and Actinobacteria phyla<sup>[45,46]</sup>. A low microbial diversity in the gut (dysbiosis) has been reported to be associated with several diseases<sup>[47,48]</sup>.

In healthy subjects, the intestinal microbiota composition is affected by the individual genetic composition and environmental factors one is exposed for<sup>[44,48]</sup>. The intestinal microbiota in IBS patients differs from that of healthy subjects<sup>[48-51]</sup>, and have a lower diversity (dysbiosis)<sup>[48-51]</sup>. It is believed that this difference in the intestinal microbiota plays a pivot role in the pathophysiology of IBS<sup>[49]</sup>.

### **Gastrointestinal endocrine cells**

The gastrointestinal endocrine cells are scattered in-between the epithelial cells facing the gut lumen (Figure 1)<sup>[52-54]</sup>. These cells are localized to the stomach, small-and large intestine<sup>[53]</sup>. Among the different segments of the gastrointestinal tract the density of the endocrine cells is highest in the duodenum (Figure 2)<sup>[25]</sup>. These cells secrete over 10 different hormones that interact and integrate with the enteric, autonomic and central nervous system to regulate: Gastrointestinal motility, secretion of enzymes and bile acid, absorption of nutrients, visceral sensation, gastrointestinal cell proliferation, local immune defense and appetite<sup>[3,22,52,55-69]</sup>. These cells have sensory microvilli that project into the gastrointestinal lumen that sense gastrointestinal lumen contents and respond by releasing their hormones into the lamina propria<sup>[70-82]</sup>. These hormones can act locally on the nearby structures (paracrine mode of action) or reach the blood stream and act on far structure (endocrine mode of action)<sup>[70-82]</sup>.

Several abnormalities in different endocrine cell types of the stomach, small- and large intestine have been described in IBS patients (Figure 3)<sup>[53,83-97]</sup>. Generally, IBS patients have a lower gut endocrine cell density than healthy subjects<sup>[52]</sup>.

### **Stress**

Stress is defined as an acute threat, real or perceived, to the homeostasis of an organism<sup>[10]</sup>. Stress is a known factor that trigger/worsen the IBS symptoms<sup>[98]</sup>. The exact mechanisms by which stress affects IBS are not exactly known. However, the negative effect of stress on IBS symptoms is believed to be caused by an interaction between the gut and the central nervous system (gut-brain axis)<sup>[10]</sup>.

### **Low grade inflammation**

Intestinal low-grade inflammation is believed to be a factor that contribute to the pathophysiology of IBS<sup>[86]</sup>. Lowgrade inflammation in the intestinal mucosa occurs only in a subset of IBS, *i.e.*, post-infectious IBS, but not in sporadic (non-specific) IBS<sup>[86,99-102]</sup>.

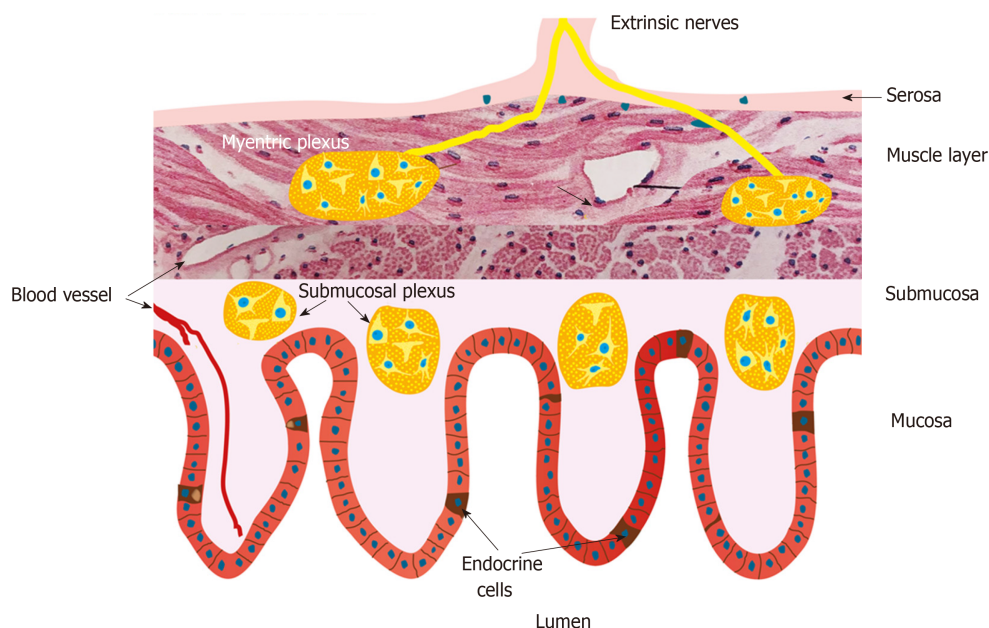
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## **THE ROLE OF INTESTINAL STEM CELLS IN THE PATHOPHYSIOLOGY OF IBS**

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### **Intestinal stem cells**

Each intestinal crypt contains four to six pluripotent (stem) cells<sup>[103]</sup>. Stem cell perform 2 activities, namely self-renewal by dividing into identical stem cell (clonogeny) to maintain a constant number of stem cells and differentiation progeny<sup>[103]</sup>. In the differentiation progeny, the stem cells differentiate into all cell types of the villus epithelium through 2 cell lineages: The secretory lineage giving raise to goblet cells, endocrine cells and Paneth cells, and the absorptive lineage giving raise to absorptive enterocytes. This differentiation takes place through a series of precursors (progenitors) (Figure 4)<sup>[68,69,104-112]</sup>.



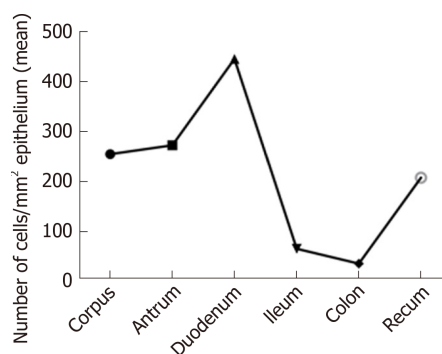
**Figure 1** Schematic illustration of the enteroendocrine cells and their anatomic relation to the enteric nervous system. The enteroendocrine cells are scattered among the epithelial cells lining the intestinal lumen. They interact and intergrade with each other's and with enteric nervous system. Reproduced from El-Salhy *et al*<sup>[54]</sup> by permission of the authors and the publisher.

### ***The relation between the abnormalities in intestinal stem cells and enteroendocrine cells***

As mentioned previously, the densities of the gastrointestinal endocrine cells are lower than that of healthy subjects<sup>[53,83-97]</sup>. The cell density of Musashi 1, and neurogenin 3 immunoreactive cells in the small and large intestine of patients with IBS are lower than that of healthy subjects (Figures 5 and 6)<sup>[11-13]</sup>. Musashi 1 is marker for intestinal stem cells and their early progeny, and neurogenin 3 is expressed in early intestinal endocrine cell progenitors originated from stem cells<sup>[103,113-118]</sup>. The low densities of enteroendocrine cells in patients with IBS could be explained by the abnormalities in intestinal stem cells<sup>[119]</sup>. Thus, low densities of Msi-1 and NEUROG3 small and large intestine in IBS patients indicate that the intestinal stem cells in these patients exhibit reduced clonogenic activity and low differentiation progeny toward endocrine cells<sup>[119,120]</sup>.

## **HYPOTHESIS**

Based on the data presented above, one may hypothesized that IBS patients may have a gene mutation controlling the number of the stem cells and/or NEUROG3 gene mutation. Furthermore, environmental factors such as diet, inflammation, stress and gut microbiota may affect the stem cells and their progeny (Figure 7). This hypothesis gets support from the following facts: (1) Low density of intestinal endocrine cells has been described in patients with congenital malabsorptive diarrhoea, which is an autosomal recessive disorder<sup>[121]</sup>. The low density of intestinal endocrine cells in this disorder is caused by loss-of-function mutations in NEUROG3 gene<sup>[121]</sup>. Similarly, low density of intestinal endocrine cells has been observed in small-intestine allograft rejection, and in NEUROG3-knockout mice<sup>[117,120]</sup>. The low density of intestinal endocrine cells in these conditions was associated with a reduction in number of intestinal neurogenin 3 cells<sup>[117,120]</sup>; (2) Changing from the common Norwegian diet to a National Institute for Health and Care Excellence-modified diet, which improved symptoms and quality of life in IBS patients is associated with changes in the densities of gastrointestinal cells<sup>[91,122-127]</sup>; (3) Modulation of the intestinal microbiota by fecal microbiota transplantation improved both symptoms and the quality of life in patients with IBS<sup>[128]</sup>. This improvement was accompanied by a change in in the densities of enteroendocrine cells<sup>[128]</sup>; (4) Glutamine is the main energy source for intestinal enterocytes and plays a major role in intestinal homeostasis and other physiological functions<sup>[129-133]</sup>. Stress, infection or inflammation cause a depletion of



**Figure 2** The density of gut endocrine cells as detected by chromogranin a immunoreactivity. Reproduced from El-Salhy *et al*<sup>[25]</sup> by permission of the authors and the publisher.

glutamine<sup>[129-133]</sup> In a randomized placebo-controlled study, dietary glutamine supplements improved symptoms in patients with post-infectious IBS<sup>[134]</sup>. Glutamine have a trophic effect on the intestinal stem cells and promotes stem cell differentiation<sup>[129,135,136]</sup>. One may speculate that stress results in the depletion of glutamine, which causes disturbance in the differentiation of the intestinal cells. This in turn would cause low density in enteroendocrine cells and the development of IBS symptoms; and (5) In animal models of human ulcerative colitis and Crohn's disease, the changes in enteroendocrine cells have been found to be strongly correlated with changes in the intestinal stem cells and their differentiation progeny toward intestinal endocrine cells<sup>[137,138]</sup>.

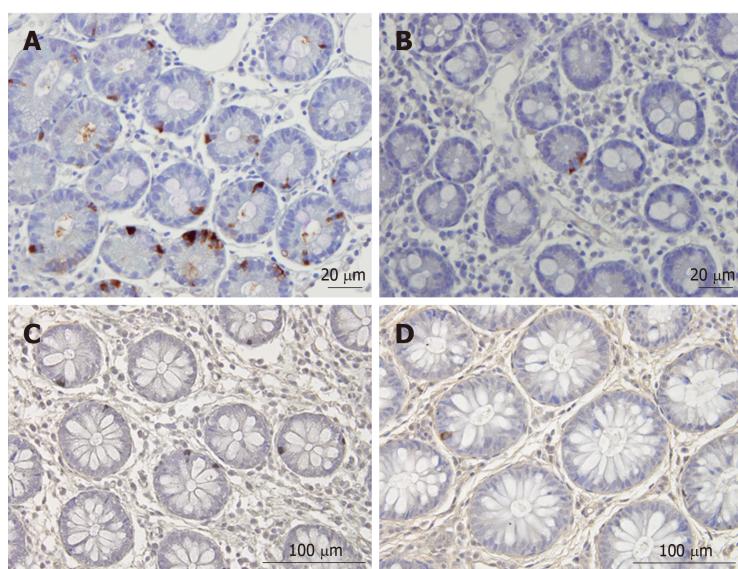
## CLINICAL IMPLICATIONS

Assuming that IBS is caused by abnormalities in stem cells, which in turn caused by genetic and environmental factors, intestinal stem cell transplantation might be an effective tool in the treatment of IBS.

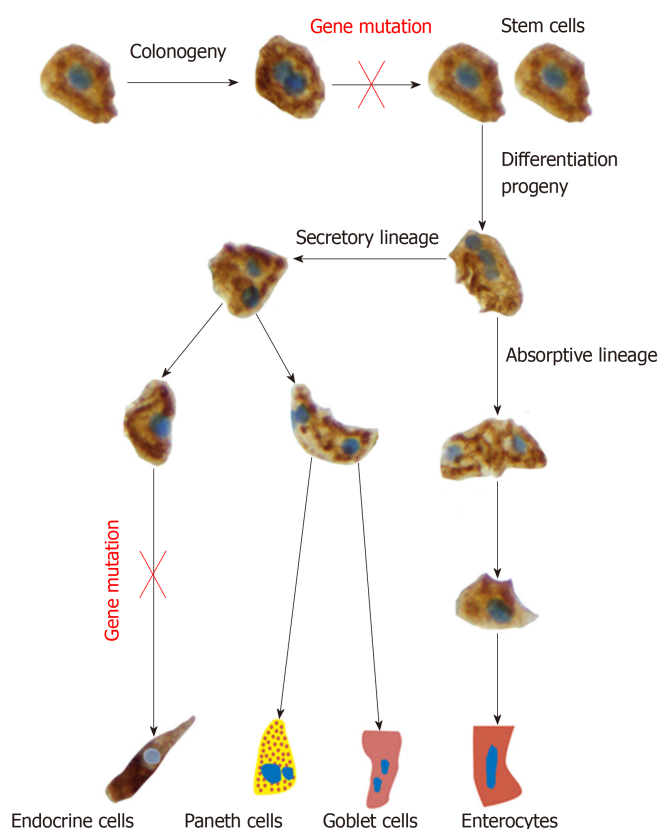
## CONCLUSION

The intestinal stem cells appear to play a central role in the pathophysiology of IBS. Factors that are known to be involved in the pathophysiology of IBS exert their effects probably through affecting the intestinal stem cells.

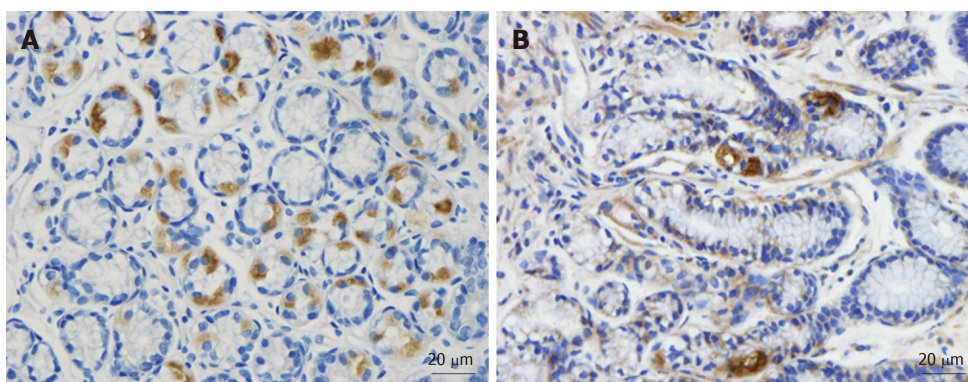




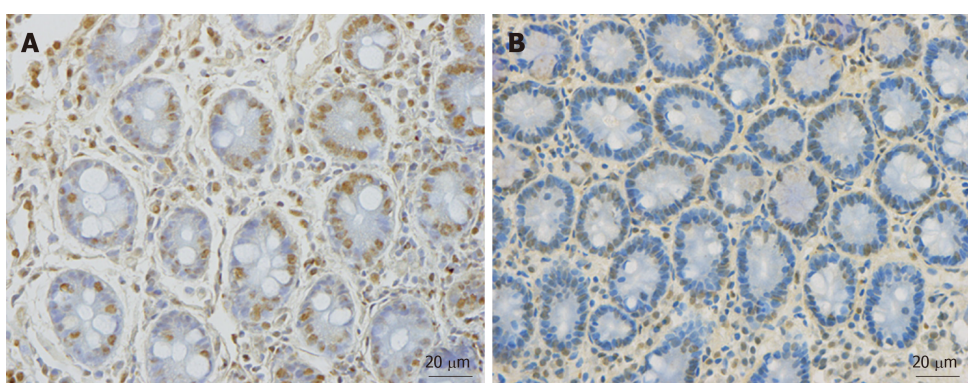
**Figure 3** Chromogranin immunoreactive cells in the duodenum of a healthy subject and of a patient with irritable bowel syndrome. A: Chromogranin immunoreactive cells in the duodenum of a healthy subject; B: Chromogranin immunoreactive cells in the duodenum of a patient with irritable bowel syndrome (IBS); C: Chromogranin A cells in the colon of a healthy control; D: Chromogranin A cells in the colon of a patient with IBS. Chromogranin A is a common marker for enteroendocrine cells. The density of Chromogranin A in the duodenum and colon of patients with IBS is lower than that of healthy subjects.



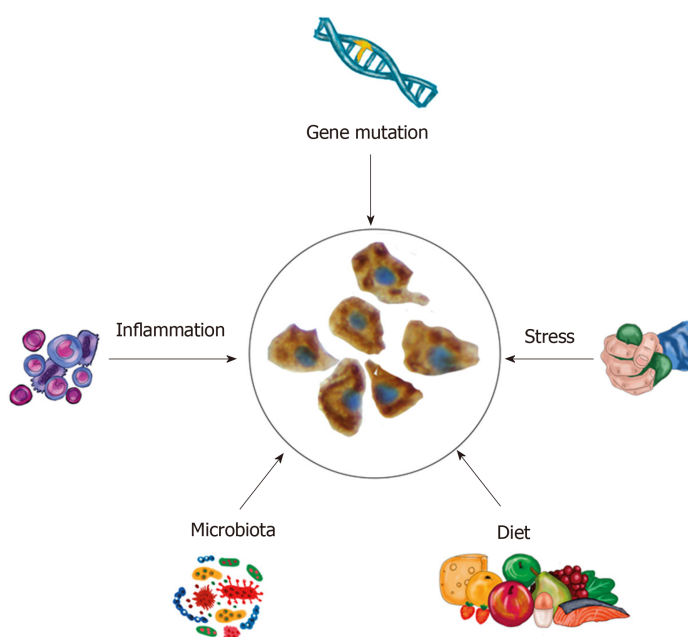
**Figure 4** The intestinal stem cell divides into 2 identical cells (clonogeny). One of these cells remain inactive, while the other stem cell differentiates into all cell types of the villus epithelium through 2 cell lineages: The secretory lineage giving raise to goblet cells, endocrine cells and Paneth cells, and the absorptive lineage giving raise to absorptive enterocytes. This differentiation occurs through a series of progenitors. The observations that the density of stem cells and progenitors for enteroendocrine cells, led to the assumption of gene mutations affecting the stem cell and neurogenin 3 gene.



**Figure 5 Musashi 1 immunoreactive cells in duodenum.** A: A healthy subject; B: A patient with irritable bowel syndrome (IBS). Musashi 1 is a marker for intestinal stem cells and their early progeny. The density of Musashi 1 cells in healthy subjects is higher than that of the IBS patients. Furthermore, Musashi 1 cells in healthy subjects appear to have more proliferation activity than that of IBS patients.



**Figure 6 Neurogenin 3 immunoreactive cells in the duodenum.** A: A healthy control; B: A patient with irritable bowel syndrome. Neurogenin 3 is expressed in the nuclei (brown) of early intestinal endocrine cell progenitors. The healthy subjects have higher density of neurogenin 3 than irritable bowel syndrome patients.



**Figure 7 Schematic drawing to illustrate the hypothesis that intestinal stem cells play a central role in the pathophysiology of irritable bowel syndrome.** The abnormalities in the intestinal stem cells can be caused by gene mutation or by environmental factors such as diet, intestinal microbiota, stress and low-grade inflammation.



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