



2016 Irritable Bowel Syndrome: Global view

## Inflammation in irritable bowel syndrome: Myth or new treatment target?

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**Author contributions:** Sinagra E designed the study; Morreale GC and Amvrosiadis G wrote the paper; Rizzo AG and Pompei G provided pictures supporting the studies; Rossi F contributed to the revision of the manuscript; Tomasello G wrote the section describing the role of endoscopy in irritable bowel syndrome; and Lo Monte AI, Cappello F and Raimondo D supervised the work.

**Conflict-of-interest statement:** All the authors declare that this research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors, thus disclosing any conflict of interests regarding such work.

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Received: June 1, 2015  
Peer-review started: June 3, 2015  
First decision: July 17, 2015  
Revised: September 28, 2015  
Accepted: December 19, 2015  
Article in press: December 19, 2015  
Published online: February 21, 2016

### Abstract

Low-grade intestinal inflammation plays a key role in the pathophysiology of irritable bowel syndrome (IBS), and this role is likely to be multifactorial. The aim of this review was to summarize the evidence on the spectrum of mucosal inflammation in IBS, highlighting the relationship of this inflammation to the pathophysiology of IBS and its connection to clinical practice. We carried out a bibliographic search in Medline and the Cochrane Library for the period of January 1966 to December 2014, focusing on publications describing an interaction between inflammation and IBS. Several evidences demonstrate microscopic and molecular abnormalities

in IBS patients. Understanding the mechanisms underlying low-grade inflammation in IBS may help to design clinical trials to test the efficacy and safety of drugs that target this pathophysiologic mechanism.

**Key words:** Inflammation; Irritable bowel syndrome; Mast cells; Neuroendocrine cells; Pathology

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**Core tip:** Low-grade intestinal inflammation plays a key role in the pathophysiology of irritable bowel syndrome, and this influence is likely multifactorial. Several evidences showed microscopic and molecular abnormalities in large subsets of patients with irritable bowel syndrome. Understanding the mechanisms underlying the low-grade inflammation in this disease may help to design clinical trials to test the efficacy and safety of drugs that target this pathophysiologic mechanism.

Sinagra E, Pompei G, Tomasello G, Cappello F, Morreale GC, Amvrosiadis G, Rossi F, Lo Monte AI, Rizzo AG, Raimondo D. Inflammation in irritable bowel syndrome: Myth or new treatment target? *World J Gastroenterol* 2016; 22(7): 2242-2255 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v22/i7/2242.htm> DOI: <http://dx.doi.org/10.3748/wjg.v22.i7.2242>

## INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic, relapsing, and remitting functional disorder of the gastrointestinal tract characterized by abdominal pain, bloating, and changes in bowel habits that lack a known structural or anatomic explanation<sup>[1]</sup>.

IBS consists of a set of altered bowel habits over a period of time and includes abdominal pain and discomfort. IBS is one of the most common diagnoses in primary care, accounting for approximately 12% of all visits<sup>[2]</sup>. In addition, a survey conducted by Russo *et al.*<sup>[3]</sup> found IBS to be the most common functional gastrointestinal diagnosis, comprising 35% of all outpatient referrals to gastroenterologists<sup>[2,3]</sup>. Therefore, IBS is also the most common diagnosis for gastroenterologists, accounting for 20%-50% of patient visits<sup>[2,4]</sup>.

With regard to the sex-related prevalence of IBS, in Western countries, the prevalence of IBS in female patients outnumbers that in male patients by 2:1<sup>[5,6]</sup>. Furthermore, the ratio of female to male IBS sufferers in the non-patient population is 2:1, and within the patient population who seek consultations with primary care physicians, females outnumber male patients by 3:1<sup>[5,7]</sup>. Finally, in tertiary-care settings, the number of female IBS patients is four- to five-times higher than the number of males<sup>[5-8]</sup>. This prevalence should not

only be strictly attributed to sex, but also to gender-related differences in healthcare-seeking behavior and sociocultural characteristics that vary between men and women with IBS as well as among different cultures<sup>[5,6]</sup>.

According to the Rome III criteria, IBS is defined based on the presence of recurrent abdominal pain or discomfort at least three days per month in the past three months associated with two or more of the following: (1) improvement with defecation; (2) onset associated with a change in frequency of stool; and (3) onset associated with a change in form (appearance) of stool. These criteria should be fulfilled for the previous three months with symptom onset at least six months before diagnosis<sup>[9]</sup>.

Rome III criteria subtype IBS according to the predominant bowel habit as IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed type, and unclassified<sup>[9]</sup>. To this end, the definition of bowel-habit type is based on the patient's description of the stool form by referring to the Bristol Stool Scale<sup>[10]</sup>. Furthermore, IBS patients can be divided into two categories: sporadic (nonspecific) and postinfectious (PI-IBS) inflammatory bowel disease-associated<sup>[11,12]</sup>.

IBS symptoms cannot be explained by structural abnormalities, and specific laboratory tests or biomarkers are not available for IBS. Therefore, IBS is classified as a functional disorder whose diagnosis depends on the history of manifested symptoms<sup>[13]</sup>.

The cause of IBS is unknown, but a single factor is not likely to be responsible for the several presentations of this complex disorder<sup>[1]</sup>; new fields of research in this area include mucosal inflammation, postinfectious low-grade inflammation, genetic and immunologic factors, alteration of the human microbiota, alterations of the intestinal permeability, and dietary and neuroendocrine factors<sup>[13]</sup>. Usually, routine histologic examinations do not show significant colonic mucosal abnormalities in the majority of IBS patients; however, recent quantitative histologic, immunohistochemical, and ultrastructural analyses have indicated subtle organic alterations in these patients.

This literature review aims to summarize the findings relating the spectrum of mucosal inflammation to IBS, highlighting their relationship to the pathophysiology of IBS and their connections, if any, to clinical practice.

## RESEARCH

We carried out a bibliographic search in MEDLINE for the period of January 1966 to July 2015, and focused on identifying publications describing an interaction between inflammation and IBS. The keywords used were: irritable bowel syndrome, inflammation, mucosal inflammation, pathology, mast cells, neuroendocrine cells, immune cells, intestinal permeability, and enteric nerves. The inclusion criteria to select articles were based on design (systematic reviews, meta-analysis,

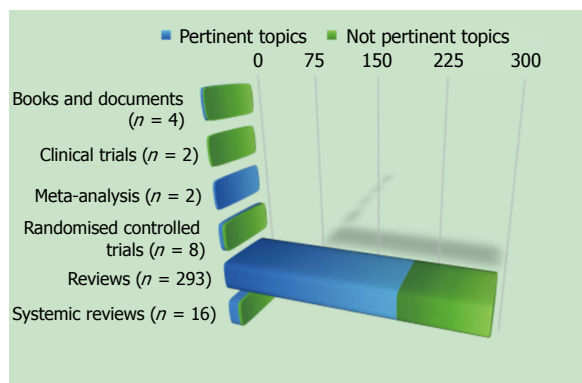


Figure 1 Literature findings on the relationship between irritable bowel syndrome and inflammation ( $n = 305$ ).

clinical trials, and experimental studies on animals) and population (adult patients > 18 years of age). We excluded articles not pertinent to this topic.

According to the aforementioned criteria, we found 305 studies, and we excluded 100 studies because they were not pertinent to this topic (Figure 1).

## ROLE OF ENDOSCOPY IN IBS

According to the American Gastroenterology Association, "a colonoscopy is recommended for patients over age 50 years (due to higher pretest probability of colon cancer), but in younger patients, performing a colonoscopy or sigmoidoscopy is determined by clinical features suggestive of disease (e.g., diarrhea, weight loss), and may not be indicated"<sup>[14]</sup>.

However, the British guidelines suggest that, "given the high frequency of colonic cancer in the population at large, an examination of the colon is advisable for a change in bowel habit over the age of 50"; the authors of these guidelines highlighted that, "as IBS patients have no increased risk of colon cancer, advice on screening for this is no different from the general population"<sup>[15]</sup>.

More recently, Japanese guidelines suggested that "colonoscopy has a diagnostic value, not only for excluding organic diseases but also for supporting the existence of pathophysiology compatible to IBS due to visceral hypersensitivity to colonoscopic procedures and colonic spasms"<sup>[16]</sup>.

A prospective, multicenter study performed by Ishihara and coworkers<sup>[17]</sup> aimed to determine the presence of organic colonic lesions in IBS patients. Their study showed that the prevalence of organic colonic diseases in IBS patients was at an acceptably low level, thus showing that the Rome III criteria are specific for the diagnosis of IBS. Conversely, another study performed by Hsiao and coworkers<sup>[18]</sup> demonstrated that IBS was not associated with the development of colon cancer in Taiwan.

Despite these recommendations, a recent Korean survey indicated that colonoscopy was the most

commonly required test (79.5%) in IBS patients<sup>[19]</sup>, whereas a study performed by Lieberman and coworkers<sup>[20]</sup> to evaluate trends in the utilization and outcomes of colonoscopy in the United States from 2000 to 2011 showed that the most common reason for colonoscopy in patients aged < 50 years was the evaluation of symptoms, such as IBS (28.7%), together with bleeding or anemia (35.3%).

Based on these updated data, IBS still represents the majority of colonoscopic biopsies seen by pathologists<sup>[21]</sup> that are usually considered either normal or near to normal on routine histologic examination. These findings provide valuable information to the physician who is suspecting a diagnosis of IBS. However, the pathologists must be aware of variations in normal tissue as well as artifacts that may result from bowel preparations or the biopsy procedure in order to not to report these variations as abnormal. Furthermore, the pathologists must consider subtle morphologic changes reported in the intestinal mucosa in IBS and associated with chronic inflammatory cells, mast cells, enteroendocrine cells, and enteric nerves<sup>[22]</sup>.

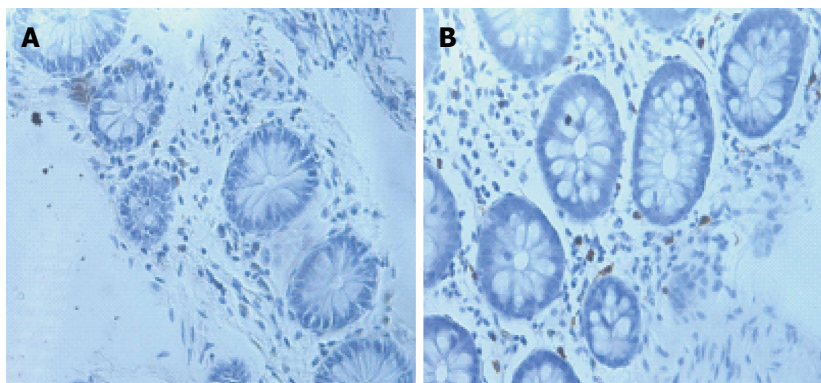
## INFLAMMATION IN IBS

The intestinal mucosa harbors a florid immune system that can be regarded as "physiologically inflamed"<sup>[23]</sup>. Thus low-grade inflammation can only be evaluated using quantitative assessments<sup>[24]</sup>. IBS patients have been shown to exhibit significant increases in lamina propria immune cells in the colonic mucosa compared with healthy subjects, which appears to be more predominant in the right than in the left colon<sup>[25]</sup>.

### Granulocytes and plasma cells

More than ten years ago, O'Sullivan *et al.*<sup>[26]</sup> evaluated the number of plasma cells, lymphocytes, eosinophils, neutrophils, and macrophages in a case-control study. Specifically, each cell type was semiquantitatively graded in hematoxylin-and-eosin-stained sections of the entire colon, and possible increases in the number of mast cells (MCs) in the colon of IBS patients compared with controls were examined using a monoclonal mouse antibody for human MC tryptase (AA1). Other than MCs, increases in cellular infiltrate were not observed in the IBS group, and the number of MCs was significantly increased in the cecum of IBS patients compared with controls.

Similarly, in 2008, Piche and coworkers<sup>[27]</sup> aimed to examine associations between fatigue, depression, and the MCs of the colonic mucosa in IBS by comparing the numbers of CD3-positive intraepithelial T lymphocytes, MCs, plasma cells, eosinophils, and neutrophils in cecal biopsies taken during colonoscopy. There was not a significant difference in the numbers of intraepithelial lymphocytes, plasma cells, eosinophils, or neutrophils between IBS patients and healthy controls, but the MC numbers per high-power field were significantly higher



**Figure 2** Immunohistochemistry for tryptase showing increases in the number of mast cells in the colonic mucosa in inflammatory bowel disease. A: Irritable bowel syndrome patient; B: Control ( $\times 40$  magnification). Courtesy of Giancarlo Pompei, personal data.

in IBS patients than in healthy controls (9.3 vs 4.0,  $P = 0.001$ ). Furthermore, the number of MCs correlated with the severity of fatigue and depression scores in IBS patients but not in healthy controls<sup>[28]</sup>.

With regard to the small bowel, Walker *et al.*<sup>[29]</sup> examined the MC, eosinophil, and intraepithelial lymphocyte populations in duodenal biopsies of subjects with IBS and functional dyspepsia. Their study showed a significant increase in the number of intraepithelial lymphocytes in biopsies from the duodenum in patients with IBS-C. However, this increase was not observed in the second part of the duodenum. Nevertheless, MC counts were also higher in IBS cases in both the first and second parts of the duodenum, but this difference was only significant for constipation-predominant IBS<sup>[28]</sup>. Interestingly, the eosinophil counts in this study did not differ between IBS patients and controls in either the first or second part of the duodenum<sup>[28]</sup>.

To date, a significant difference in the numbers of plasma cells, neutrophils, or eosinophils has not been demonstrated among IBS cases<sup>[28]</sup>. Importantly, increases in eosinophils were not identified in IBS, but the eosinophil counts were elevated in individuals with functional dyspepsia<sup>[29]</sup>. Functional dyspepsia and IBS demonstrate significant overlap in cross-sectional surveys<sup>[30]</sup>, despite attempts to classify them separately, and a biomarker to predict the presence of IBS remains elusive<sup>[31]</sup>. Therefore, this histopathologic marker may serve to distinguish the two conditions<sup>[28]</sup>.

### MCs

MCs are innate immune cells involved in food allergies, wound healing, and protection against pathogens<sup>[32]</sup>. Their functional activation consists of a degranulation process, leading to the release of various compounds, such as histamine, tryptase, and chymase<sup>[32]</sup>.

More than 40 years ago, Hiatt and Katz<sup>[33]</sup> were the first to demonstrate MC infiltration in the muscular layer of full-thickness colonic biopsy samples from four patients with "spastic colitis"<sup>[34]</sup>. Increases in the number of mucosal MCs have been observed

in IBS patients in the rectum<sup>[35,36]</sup>, rectosigmoid colon<sup>[37,38]</sup>, descending colon<sup>[39-44]</sup>, ascending colon<sup>[36]</sup>, cecum<sup>[45]</sup>, terminal ileum<sup>[25,36,46]</sup>, jejunum<sup>[47-49]</sup>, and duodenum<sup>[29,50]</sup> (Figure 2).

However, discrepancies in data obtained from these studies could be due to sex-specific differences, bowel preparation artifacts, fixation protocols, tissue orientation, sample size, or IBS-related recruitment criteria<sup>[32,43,44,51]</sup>. Furthermore, clinical studies have also yielded conflicting evidence correlating MC numbers with the onset of abdominal pain<sup>[32]</sup>.

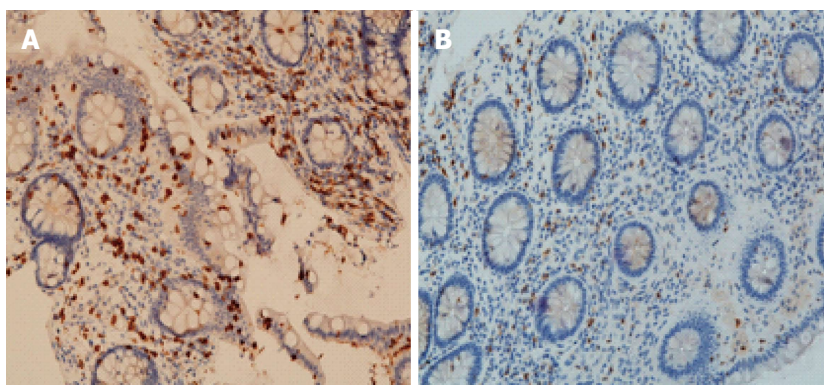
The number of functionally active MCs (exhibiting changes in the release of tryptase and histamine), rather than the absolute number of MCs, plays a pivotal role in IBS<sup>[43,50]</sup>. Consequently, the role of MCs in IBS may be affected by cells that are functionally active and form close connections with enteric and extrinsic nerve terminals, thus determining visceral hypersensitivity and altered gut function<sup>[47]</sup>.

### Lymphocytes

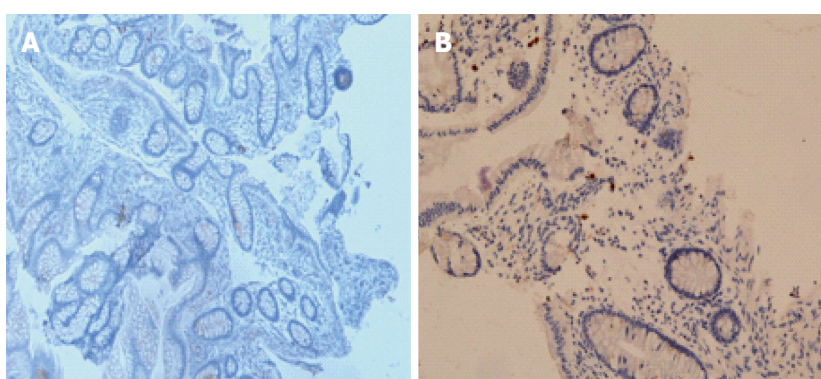
The aforementioned inflammatory changes described in the mucosa of IBS patients show that immune activation may play a role in IBS pathophysiology<sup>[34]</sup>. Mucosal T- and B-type lymphocytes are also part of the gut adaptive immune response to pathogens<sup>[32]</sup>.

An increased density of T lymphocytes in the mucosa of IBS patients has been widely demonstrated. Specifically, the T-cell density is higher in the rectum<sup>[35,36,52]</sup>, rectosigmoid colon<sup>[53]</sup>, colon<sup>[38,48,54]</sup>, cecum<sup>[26]</sup>, jejunum<sup>[55]</sup>, and duodenum<sup>[56]</sup>. Like for MCs, several studies showed that IBS patients exhibit a normal lymphocyte density in different intestinal tissue segments<sup>[19,36,38,53,57-61]</sup>. These discrepancies may be due to differences in the immunostaining techniques, quantification methods, and IBS-related recruitment criteria (Figure 3)<sup>[32]</sup>.

Conversely, the density of B-cells in the rectum<sup>[19,36]</sup>, colon<sup>[19,43,53,62]</sup>, cecum<sup>[19,20]</sup>, ileum<sup>[36]</sup>, or jejunum<sup>[60]</sup> did not differ in IBS patients. However, Forshammar and coworkers<sup>[62]</sup> and others<sup>[32]</sup> found a decrease in secretory B cells in the colon (Figure 4).



**Figure 3** Immunohistochemistry for CD3 showing increase in the number of intraepithelial T-lymphocytes in the large bowel in inflammatory bowel disease. A: Irritable bowel syndrome patient; B: Normal distribution of T-lymphocytes, which are mainly distributed within the lamina propria of the large bowel of a control patient (× 20 magnification). Courtesy of Giancarlo Pompei, personal data.



**Figure 4** Immunohistochemical staining for CD20. An equivalent distribution of B lymphocytes in the lamina propria was seen in the large intestine. A: Patient with irritable bowel syndrome; B: Control patient (× 20 magnification). Courtesy of Giancarlo Pompei, personal data.

With regard to intraepithelial lymphocytes, several discrepancies have been reported in studies assessing the density of these cells in IBS patients. An increase in density has been demonstrated in the rectum<sup>[35,36,57]</sup>, colon<sup>[57]</sup>, jejunum<sup>[55,49]</sup>, and duodenum<sup>[56]</sup>, but these increases were not confirmed by other groups<sup>[20,32,45,49,59,61]</sup>.

#### **Dendritic cells and macrophages**

Dendritic cells are antigen-presenting cells that are usually located at the surveillance interfaces of the human body, such as the skin or mucosa, and play a pivotal role in the generation and regulation of immune responses<sup>[63]</sup>. In fact, they represent the link between allergen uptake and the clinical manifestations of intestinal inflammation<sup>[64,65]</sup>. Furthermore, the gut also harbors abundant macrophages. These cells do not function as typical antigen-presenting cells and lack the cellular machinery for the production of pro-inflammatory cytokines and induction of potent adaptive immune responses. However, they show very potent phagocytic activity<sup>[65]</sup>.

In a *Trichinella spiralis* mouse model of PI-IBS, Long and coworkers<sup>[66]</sup> reported numerical and phenotypic alterations in the lamina propria dendritic cells following acute *T. spiralis* infection. In their study,

the lamina propria dendritic cells expressed increased levels of costimulatory molecules and exhibited a greater ability to migrate and induce CD4<sup>+</sup> T-cell proliferation<sup>[66]</sup>. Consequently, these changes favored increased levels of pro-inflammatory interferon- $\gamma$ , interleukin-23, and tumor necrosis factor- $\alpha$  production in the so-called "PI-IBS stage"<sup>[66,67]</sup>.

With regard to macrophages, the numbers of resident CD68<sup>+</sup> macrophages are reduced in PI-IBS cases following *Campylobacter jejuni* infection, probably due to the cytotoxic nature of the pathogen inside host cells<sup>[50]</sup>. Similarly, *Shigella* spp.<sup>[68,69]</sup> and *Salmonella* infections have also been shown to be involved in PI-IBS, and both of these organisms are intracellular pathogens that induce phagocytosis by macrophages<sup>[70,71]</sup>. Furthermore, *Salmonella* seems to be less cytotoxic to macrophages<sup>[72]</sup> and also causes a marked interleukin-18 response<sup>[72]</sup> with important implications in exerting paracrine effects on surrounding immune cells (inducing interferon- $\gamma$  expression). These changes result in increased levels of activated T cells in the infected intestine<sup>[47,52,54,55,57]</sup>.

#### **Enteroendocrine cells**

Enteroendocrine cells (residing among the epithelial

cells of the mucosa in all gut segments, with the exception of the esophagus) secrete multiple regulatory molecules that control several functions, such as postprandial secretion and motility<sup>[12,73,74]</sup>. Animal experimental studies have demonstrated abnormalities in the function of enteroendocrine cells in the setting of gastrointestinal infection<sup>[73]</sup>. Enteroendocrine cells seem to be involved in visceral hypersensitivity, disturbed gastrointestinal motility, and abnormal gut secretion<sup>[12]</sup> that patients with IBS usually present<sup>[75-77]</sup>.

In fact, visceral hypersensitivity has been shown in the colon of IBS patients<sup>[78-85]</sup>, but the correlation of this disturbance with the severity of abdominal pain is currently poorly understood<sup>[12]</sup>. Some authors hypothesize the involvement of a peripheral mechanism in visceral hypersensitivity in IBS<sup>[86-88]</sup>. Because the gut mucosa can produce high levels of serotonin<sup>[88]</sup>, a reduction in serotonin impairs intracellular uptake and degradation in the gut epithelial cells and consequently increases serotonin availability of in the gut mucosa<sup>[89-92]</sup>. Therefore, the amount of serotonin available at its receptors is markedly increased<sup>[12,87,88]</sup>. Due to this mechanism, the development of visceral hypersensitivity in PI-IBS patients may be due to the increase in serotonin at the 5-hydroxytryptamine 3 receptors of the sensory neurons of the enteric nervous system.

Dysmotility has also been shown in the small and large bowel of IBS patients, as evidenced by the involvement of cholecystokinin, ghrelin, secretin, serotonin, and peptide YY<sup>[12]</sup>. Both esophageal motility abnormalities and abnormal gastric emptying have been observed in IBS patients with conflicting results<sup>[93-108]</sup>. Specifically, IBS-C patients exhibit delayed gastric emptying, whereas accelerated gastric emptying was observed in IBS-D patients<sup>[77,98]</sup>. In this setting, ghrelin was shown to stimulate gastric and small- and large-bowel motility<sup>[106-117]</sup>. Conversely, serotonin relaxes the stomach through a nitrergic pathway and consequently delays gastric emptying<sup>[118-120]</sup>. Moreover, cholecystokinin<sup>[121-123]</sup> and secretin<sup>[124,125]</sup> were shown to relax the proximal stomach, which inhibited gastric emptying in a manner similar to secretin; furthermore, small-bowel transit was also found to be delayed overall in IBS-C patients and accelerated in IBS-D patients<sup>[126-131]</sup>, but conflicting results have been reported<sup>[132-139]</sup>.

Ghrelin, which is involved in the stimulation of small-bowel motility, and peptide YY, a regulator of the ileal brakes<sup>[140-145]</sup>, play pivotal roles in gastric emptying by stimulating the absorption of water and electrolytes and inhibiting prostaglandin E2 and vasoactive intestinal polypeptide<sup>[146-148]</sup>. Therefore, ghrelin cell density is reportedly low in the stomach, and that of peptide YY is reported to be high in the ileal mucosa of IBS-C patients, whereas the ghrelin cell density is reported to be high in the stomach, and that

of secretin is reported to be low in the duodenum of IBS-D patients<sup>[12]</sup>. Furthermore, colorectal transit was found to be delayed in IBS-C patients and accelerated in IBS-D patients<sup>[80,125,126,149-154]</sup>, but contradictory results have been reported<sup>[112,105,152,154-176]</sup>.

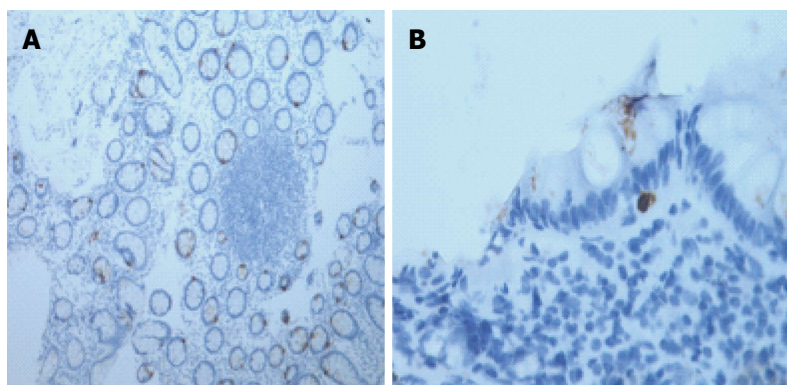
Finally, abnormal gastrointestinal secretion is common in IBS patients. Among the abnormalities in the enteroendocrine cells in IBS patients, low levels of duodenal cholecystokinin (which stimulates the secretion of digestive enzymes from pancreatic exocrine glands) and secretin (which stimulates pancreatic bicarbonate and fluid secretions)<sup>[122,123]</sup>, as well as high levels of ileal peptide YY (which stimulates the absorption of water and electrolytes), were reported in IBS-C patients<sup>[12]</sup>.

### **Intestinal permeability**

The term "mucosal barrier" was adopted by Cummings *et al.*<sup>[177]</sup> in 2004 to describe "the complex structure that separates the internal milieu from the luminal environment, consisting of the vascular endothelium, the epithelial cell lining, and the mucus layer, next to which digestive secretions, immune molecules, cell products such as cytokines, inflammatory mediators, and antimicrobial peptides, are found, mainly produced by Paneth cells in the crypts of the small intestine"<sup>[177,178]</sup>.

Conversely, impaired intestinal permeability is defined as "an altered permeability being nontransiently changed compared to the normal permeability leading to a loss of intestinal homeostasis, functional impairments and disease"<sup>[178]</sup>. Increases in the numbers of MCs in the gut of IBS patients were found to be related to changes in gut permeability<sup>[32,179-181]</sup>. In IBS patients, the assessment of permeability via the urinary recovery of orally administered markers has demonstrated increases in the permeability of the small and in the large bowels<sup>[45,182-184]</sup>, but results have been contradictory<sup>[185-187]</sup>. Furthermore, rectal permeability was also reportedly increased in IBS-D patients following exposure to MC tryptase<sup>[188]</sup>. Finally, recent studies of the permeability of the epithelial barrier have reported a decrease in the colonic expression of the tight junction proteins occludin, claudin-1, and zonula occludens-1 in IBS patients<sup>[42,189]</sup> (Figure 5).

Several aliments, as well as microbiota and bile acids, have been proposed to cause low-grade inflammation and altered permeability in IBS. In fact, in some patients, IBS was related to food allergy<sup>[190]</sup>. Furthermore, endogenous triggers, such as MC-derived histamine, proteases, and eicosanoids, could increase intestinal permeability, either directly or via the stimulation of neurons of the enteric nervous system<sup>[183]</sup>. Moreover, serotonin was also identified as an endogenous trigger of pain, inflammation, and increased permeability in IBS<sup>[40]</sup>; therefore, LX1031, an oral inhibitor of tryptophan hydroxylase, the principal enzyme needed for mucosal serotonin synthesis, has been successful for treatment of patients with non-



**Figure 5** Immunohistochemistry for chromogranin A showing increased expression in nerve terminals at the level of the basal membrane in the large intestine in inflammatory bowel disease. A: Irritable bowel syndrome patient; B: Control patient ( $\times 40$  magnification). Courtesy of Giancarlo Pompei, personal data.

constipating IBS<sup>[191]</sup>.

### Enteric nerves

Few studies have investigated the role of calcitonin gene related peptide and substance P. Wang *et al.*<sup>[37]</sup> investigated the incidence of IBS in patients who had recovered from bacillary dysentery by focusing on neuroimmunologic changes, including changes in interleukins, MCs, neuropeptides, and the relationship between MCs and intestinal nerves<sup>[50]</sup>. The density of substance P-immunoreactive fibers was increased in both the ileal and the rectosigmoid samples of IBS patients<sup>[37]</sup>, but the density of calcitonin gene related peptide-containing fibers remained unchanged. Palsson and coworkers<sup>[192]</sup> reported similar findings, and Kerkhoffs and coworkers<sup>[193]</sup> reported an increase of rectal substance P. However, these findings have not been universal<sup>[192,194]</sup>, possibly reflecting region-specific discrepancies<sup>[51]</sup>.

Neuronal plasticity in the enteric nervous system has also been investigated<sup>[195]</sup>. Akbar *et al.*<sup>[38]</sup> investigated the capsaicin receptor transient receptor potential vanilloid 1-immunoreactive nerve fibers in colonic biopsies from patients with IBS. Specifically, they demonstrated that the number of nerve fibers exhibiting immunoreactivity for substance P and transient receptor potential vanilloid 1 was increased in IBS patients. Moreover, the number of these fibers did not differ by IBS subtype, but significantly correlated with patient pain scores<sup>[50,196]</sup>.

Nerve growth factor has also been suggested to play a central role in promoting the growth and differentiation of primary afferent fibers<sup>[50]</sup>. Specifically, its expression was found to be markedly increased in rectal biopsies from pediatric<sup>[197]</sup> and adult IBS patients<sup>[198]</sup>, suggesting both the sprouting of sensory afferent fibers expressing transient receptor potential vanilloid 1 and increases in receptor sensitivity in IBS, which consequently induced visceral hyperalgesia<sup>[50]</sup>. More recently, Dothel *et al.*<sup>[199]</sup> also showed that nerve fiber density and sprouting, as well as the expression of nerve growth and neurotrophic tyrosine

kinase receptor type 1, are significantly increased in the mucosal tissues of patients with IBS. Mucosal mediators participate in these neuroplastic changes.

Finally, the morphology of enteric glia, which are known to regulate intestinal barrier integrity and neuronal activity<sup>[200]</sup> has only been examined in one study of human intestinal biopsy samples from IBS patients and was found to be unchanged<sup>[50,201]</sup>.

## CONCLUSION

Low-grade intestinal inflammation plays a key role in the pathophysiology of IBS, and this role is likely multifactorial<sup>[202]</sup>. Several studies demonstrated microscopic and molecular abnormalities in IBS patients<sup>[202,203]</sup>.

The above-reported evidence provides a rationale to test the efficacy of intestinal anti-inflammatory compounds in patients with IBS. Previously, treatment with corticosteroids was found to be ineffective in PI-IBS patients<sup>[204]</sup>; however, MC stabilizers have produced promising results, particularly in IBS-D, suggesting that immune mechanisms and MCs are involved in the generation of IBS symptoms<sup>[205,206]</sup>. Based on this approach, Clarke and coworkers<sup>[207]</sup> recently conducted a phase 3, multicenter, tertiary setting, randomized, double-blind, placebo-controlled trial in patients with Rome III-confirmed IBS to evaluate the efficacy and safety of mesalazine in patients with IBS. In this study, mesalazine treatment was not superior to placebo based on the study primary endpoint (68.6% vs 67.4%, 95%CI: 12.8-15.1,  $P = 0.870$ ). However, the placebo response was high in this trial and this study enrolled both male and female subjects and patients with mild symptoms<sup>[207]</sup>, which likely masked drug efficacy. Furthermore, a subgroup of patients with IBS showed a sustained therapy response and benefits from mesalazine therapy<sup>[207]</sup>.

As mentioned above, abnormalities in the enteric nervous system of the gut may alter digestion, gastrointestinal motility, and visceral hypersensitivity, which contribute to symptom onset and play a pivotal

role in the pathogenesis of IBS<sup>[12]</sup>.

The enteric nervous system of the gut seems to be affected by genetic differences, diet, intestinal flora, and inflammation<sup>[12]</sup>. For example, the food content of FODMAPs and fibers, which interacts with the intestinal flora and drives subsequent fermentation, may increase intestinal osmotic pressure to induce hormonal and serotonin release<sup>[12]</sup>. Targeting these known factors may improve the control of IBS symptoms by acting on mechanisms that trigger these symptoms and regulate the pathophysiology of IBS. Finally, probiotics have also been found to be effective in select IBS patients, as suggested by several recent systematic reviews, guidelines and meta-analyses, by improving intestinal permeability<sup>[208-212]</sup>.

In conclusion, a high proportion of IBS patients show low-grade inflammation, which is a multifactorial process, in the intestinal mucosa. Understanding the mechanisms underlying the low-grade inflammation in IBS may allow the design of clinical trials that test the efficacy and safety of drugs that target the pathophysiological mechanism of this disease.

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