Journal of Inflammation Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Low-Grade Inflammation: Pathophysiological Mechanisms and Drug Targets in Irritable Bowel Syndrome with Diarrhea

Baibai Ye[1], Ziyu Fu[1], Xin Zhou[1], Shengmei Wang[1], Linqi Ouyang[1], Zhen Chen[1], Guiming Deng[1,2]

[1]The First Hospital of Hunan University of Chinese Medicine, Changsha, Hunan, People's Republic of China; [2]The Second Hospital of Hunan University of Chinese Medicine, Changsha, Hunan, People's Republic of China

Correspondence: Zhen Chen; Guiming Deng, The First Hospital of Hunan University of Chinese Medicine, Hunan, People's Republic of China, Email chenzhen@hnucm.edu.cn; dengguiming@hnucm.edu.cn

Abstract: Irritable bowel syndrome with diarrhea (IBS-D) is a prevalent functional gastrointestinal disorder. Emerging evidence suggests that chronic low-grade inflammation is a significant pathophysiological mechanism, playing a pivotal role in disrupting intestinal homeostasis and driving disease pathogenesis in a subset of patients. Key contributing factors include intestinal immune dysregulation, gut microbiota imbalance, prior infections, and brain-gut axis dysfunction. Within this complex interplay of physiological and pathological processes, the core mechanisms involve abnormal immune cell activation, release of inflammatory mediators, and engagement of key inflammatory signaling pathways. Although current IBS-D management remains largely symptomatic, with no curative approaches available, the growing insight into low-grade inflammatory mechanisms offers new therapeutic prospects. Targeting intestinal low-grade inflammation is emerging as a highly attractive direction for creating novel treatment strategies. Further research is necessary to identify effective inhibitors of low-grade inflammation in IBS-D and to assess whether treatment aimed at this inflammation can prevent or alleviate the development and progression of the disease.

Keywords: irritable bowel syndrome with diarrhea, low-grade inflammation, intestinal immune imbalance, microbiota dysbiosis, infections, dysfunction of the brain-gut axis

Introduction

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by recurrent symptoms, primarily abdominal pain or discomfort, which is often accompanied by alterations in bowel habits, such as diarrhea or constipation. According to the Rome IV criteria,[1–3] IBS is classified into four common subtypes: IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), IBS with mixed symptoms of constipation and diarrhea (IBS-M), and unsubtyped IBS (IBS-U). It is crucial to emphasize that the Rome criteria are symptom-based and define IBS as a chronic condition, while they do not specify a singular pathophysiology. The etiology of IBS, particularly IBS-D, is recognized as multifactorial. In recent years, the prevalence of gastrointestinal diseases has been rising, influenced by dietary patterns and environmental factors. The global prevalence of IBS is approximately 3.8% according to the Rome IV criteria, with the IBS-D subtype accounting for roughly 30–40% of all IBS cases.[4–6] This translates to an estimated global population prevalence for IBS-D of about 1.1% to 1.5%. In China, the pooled prevalence of IBS based on Rome IV criteria is reported to be around 6.1%, with IBS-D being the most common subtype.[6] For instance, a large-scale study in Guangdong Province, China, indicated that IBS-D accounted for 74.1% of the identified IBS cases.[7] These figures significantly impact patients' quality of life. Notably, the proportion of affected females is considerably higher than that of males, with IBS-D being the most prevalent subtype.[8] Currently, the pathogenesis of IBS-D remains incompletely understood, as no single factor can fully elucidate its etiology and symptoms. Contemporary research suggests a complex interplay of multiple mechanisms, including visceral hypersensitivity, dysregulation of the brain-gut axis, altered gut microbiota, impaired intestinal barrier

https://doi.org/10.2147/JIR.S578822
Received: 5 November 2025
Accepted: 9 January 2026
Published: 30 January 2026

function, genetic predisposition, and psychosocial factors.[9] Notably, accumulating evidence positions chronic low-grade intestinal inflammation as a pivotal pathophysiological hub that may interconnect many of these mechanisms and contribute significantly to symptom generation in a substantial subset of IBS-D patients.

Chronic low-grade inflammation refers to a mild pathological condition characterized by an imbalance in the immune system, triggered by prolonged exposure to low-dose specific immunogens. This type of inflammation exhibits a degree that is slightly elevated compared to normal mucosa, yet lacks any overt external manifestations. Low-grade intestinal inflammation specifically denotes a chronic inflammatory response occurring within the intestine. Although this condition involves a mild inflammatory reaction, observable pathological changes such as congestion, edema, or mucosal erosion of the intestinal lining are not detectable by the naked eye. Consequently, low-grade intestinal inflammation is increasingly recognized as being closely associated with the pathogenesis of IBS-D.[10] Enck et al have suggested that low-grade intestinal inflammation, along with immune response imbalances and other contributing factors, may play a crucial role in the pathophysiology of IBS.[11] Furthermore, expert consensus indicates that low-grade intestinal inflammation may contribute to the pathogenesis of IBS-D by activating intestinal immunity.[7] Currently, the management of IBS-D primarily focuses on symptomatic treatment, which alleviates symptoms but often leads to relapse upon discontinuation of medication. This approach has proven to be suboptimal, leading to a waste of medical resources and imposing a financial burden on patients. Therefore, there is a pressing need to explore new therapeutic methods and pharmacological options for IBS-D.

This review was conducted based on a comprehensive literature search of electronic databases, including PubMed, Web of Science, Google Scholar, and CNKI, for relevant articles published between January 2010 and May 2025. The search utilized a combination of keywords such as “irritable bowel syndrome with diarrhea”, “IBS-D”, “low-grade inflammation”, “intestinal barrier”, and “gut microbiota”, among others. To ensure the inclusion of high-quality evidence, we excluded reviews and studies with small sample sizes or unclear diagnostic criteria. The eligible evidence was synthesized to provide a coherent overview of the current understanding of low-grade inflammation in IBS-D. This review elaborates on the clinical significance of low-grade intestinal inflammation in IBS-D and examines its underlying causes. It also discusses potential molecular mechanisms, highlights the critical role of low-grade inflammation in the pathophysiology of IBS-D, and explores its potential as a therapeutic target.

Importance of Low-Grade Intestinal Inflammation in IBS-D

IBS-D and ulcerative colitis (UC) exhibit similar clinical manifestations; however, IBS-D is not typically classified as an inflammatory bowel disease (IBD) due to the absence of organic damage to the colonic tissue. According to the Rome IV criteria, the diagnosis of IBS-D requires the presence of recurrent abdominal pain for at least 1 day per week in the last 3 months, with symptom onset at least 6 months before diagnosis. The pain must be associated with two or more of the following: related to defecation, associated with a change in stool frequency, or associated with a change in stool form. Furthermore, to be classified as the IBS-D, more than 25% of bowel movements must be of Bristol stool types 6 or 7, and less than 25% of types 1 or 2. The symptoms of IBS-D, particularly chronic diarrhea and abdominal pain, overlap with several other gastrointestinal disorders, making differential diagnosis crucial to avoid misdiagnosis and ensure appropriate treatment. A summary of the key distinguishing features between IBS-D and other common diarrheal diseases is provided in Table 1.

Increasing evidence indicates that inflammation may play a significant role in the pathophysiology of IBS-D. The timing of inflammation, the plausibility of underlying mechanisms, and findings from animal models with genetic defects in specific inflammatory molecules collectively suggest that inflammation could play a critical role in the pathogenesis of IBS-D. However, this inflammation is notably distinct from the classic inflammatory bowel diseases such as UC. The inflammation observed in IBS-D is typically chronic and low-grade, and it is believed to involve an immune response.[9,12] For instance, inflammatory plasma protein levels (compared to healthy controls) increase to a lesser extent in the blood and intestinal mucus of patients with IBS-D than in those with UC. Low-grade inflammation of the intestinal mucosa was first identified in patients with post-infectious IBS (PI-IBS). Subsequently, increased inflammatory cells and factors in the intestinal mucosa were also observed in some IBS patients, particularly those with IBS-D.[13–15] This low-grade intestinal inflammation appears to play a crucial role in the pathophysiology of IBS-D.[16] Research has demonstrated that clinical

Table 1 Differential Diagnosis of IBS-D and Common Diarrheal Diseases

Disease	Key Clinical Features	Key Diagnostic Methods/Biomakers	Distinguishing Characteristics & Notes
IBS-D	Recurrent abdominal pain relieved by defecation. No red flags (eg, no rectal bleeding, weight loss, or nocturnal symptoms). Loose/mushy stools (Bristol 6–7).	Positive diagnosis based on Rome IV criteria. Primarily a diagnosis of exclusion in the absence of alarm features. Normal routine blood tests, colonoscopy, and biopsies.	A functional disorder (disorder of gut-brain interaction). No structural or biochemical abnormalities. Pain is a central requirement.
UC	Bloody diarrhea, urgency, tenesmus, systemic symptoms (fever, weight loss).	Colonoscopy with biopsy shows continuous mucosal inflammation, ulceration, and crypt abscesses starting from the rectum. Fecal calprotectin is typically elevated (>150-200 μg/g).	Presence of mucosal inflammation and bleeding. Histology is diagnostic. Distinguishing feature is continuous inflammation from the rectum.
Crohn's Disease	Chronic diarrhea, abdominal pain (often right lower quadrant), weight loss, fatigue. It may present with perianal lesions (fissures, fistulas).	Colonoscopy with biopsy shows patchy, transmural inflammation, skip lesions. Imaging (CT/MRI enterography) can show wall thickening and complications.	Inflammation can affect any part of the GI tract (mouth to anus). Transmural involvement leads to strictures and fistulas.
Celiac Disease	Diarrhea, bloating, weight loss, fatigue, anemia. Symptoms are triggered by gluten-containing foods.	A diagnosis of celiac disease is established through positive serology (anti-tissue transglutaminase IgA) and confirmatory duodenal biopsy evidence of villous atrophy and intraepithelial lymphocytes.	Specific response to a gluten-free diet. Characteristic serological and histological markers.
BAD	Watery diarrhea, urgency, postprandial exacerbation. It often occurs after cholecystectomy	A definitive diagnosis of bile acid diarrhea rests on the SeHCAT scan, supported by serum biomarkers 7αC4 and FGF-19, or a positive response to a therapeutic trial with bile acid sequestrants like colestyramine.	Due to bile acid malabsorption. Diagnosis relies on functional tests or response to specific therapy. Note: Diagnostic availability (eg, SeHCAT) varies by region.

Abbreviations: BS-D, Irritable bowel syndrome with diarrhea; UC, Ulcerative colitis; BAD, Bile Acid Diarrhea.

symptoms such as abdominal pain and diarrhea in IBS-D patients are closely associated with low-grade intestinal inflammation.[17] In fact, this low-grade intestinal inflammation, which can be detected through modern sequencing and analytical methods such as immunohistochemistry, is a common feature in IBS-D. In contrast to the robust inflammation seen in UC, the immune cell infiltration in IBS-D—while evident—is far more subtle. It is characterized by a modest increase in lymphocytes and mast cells within the mucosa, and is accompanied by signs of a systemic low-grade inflammatory response detectable in the blood.[18]

Molecular evidence of low-grade intestinal inflammation continues to accumulate in patients with IBS-D. Recent studies have demonstrated that in individuals with IBS-D, blood, tissue, and intestinal mucus exhibit increased levels of not only serotonin (5-HT) and cytokines but also inflammatory mediators produced by goblet cells, mucus-secreting cells, and mast cells, among others. However, it is important to note that these increases are relatively modest compared to those observed in patients with UC.[19,20] Furthermore, the association between the pathology of IBS-D and various inflammatory markers has been explored in dedicated IBS-D cohorts. For example, elevations in serum calprotectin, interleukin-6 (IL-6), and C-reactive protein (CRP) have been reported in IBS-D patients compared to healthy controls.[20,21] It is critical to distinguish these levels from those in IBD; while fecal calprotectin levels in IBS-D cohorts are typically within the normal range or only slightly elevated (often <100 μg/g), they are significantly lower than the thresholds indicative of IBD (usually >150-200 μg/g).[20,22] Similarly, increases in CRP and IL-6 in IBS-D are generally subtle and remain within the low-normal to mildly elevated range, lacking the magnitude seen in active IBD. Thus, while these biomarkers may hold promise for understanding pathophysiology, their diagnostic utility for IBS-D primarily lies in differentiating it from IBD, rather than in absolute diagnosis. Current evidence suggests that therapeutic strategies

targeting low-grade intestinal inflammation could potentially prevent or mitigate multiple pathological features of IBS-D, thereby slowing the progression of the disease.

Triggers of Low-Grade Intestinal Inflammation in IBS-D

Low-grade intestinal inflammation is characterized by the presence of inflammatory cells in the intestinal mucosa, occurring without evident structural changes, destruction, or other abnormalities. Currently, this concept is relatively new, and the levels of pro-inflammatory factors are elevated by 2 to 3 times above the standard. Although the stimulation from these pro-inflammatory factors is mild, it exerts a long-term effect, typically without manifesting obvious clinical symptoms.[23] When there is an accumulation of inflammatory cells and lymphocytes, along with the activation of cells leading to secondary tissue damage, this constitutes a pathological inflammatory reaction. Low-grade intestinal inflammation is a hallmark of IBS-D and may contribute to its pathogenesis through mechanisms involving intestinal immune activation and the nervous system.[9,10] Research has indicated that factors such as intestinal immune imbalance, dysbiosis, intestinal infections, abnormalities in the brain-gut axis, stress responses, as well as dietary and psychological influences, can all contribute to the development of low-grade intestinal inflammation (Figure 1).

Immune Imbalance Triggers Low-Grade Intestinal Inflammation in IBS-D

Intestinal immune imbalance is a primary trigger for the low-grade inflammation characteristic of IBS-D. Under physiological conditions, the intestinal immune system maintains a delicate equilibrium, tolerating commensal flora

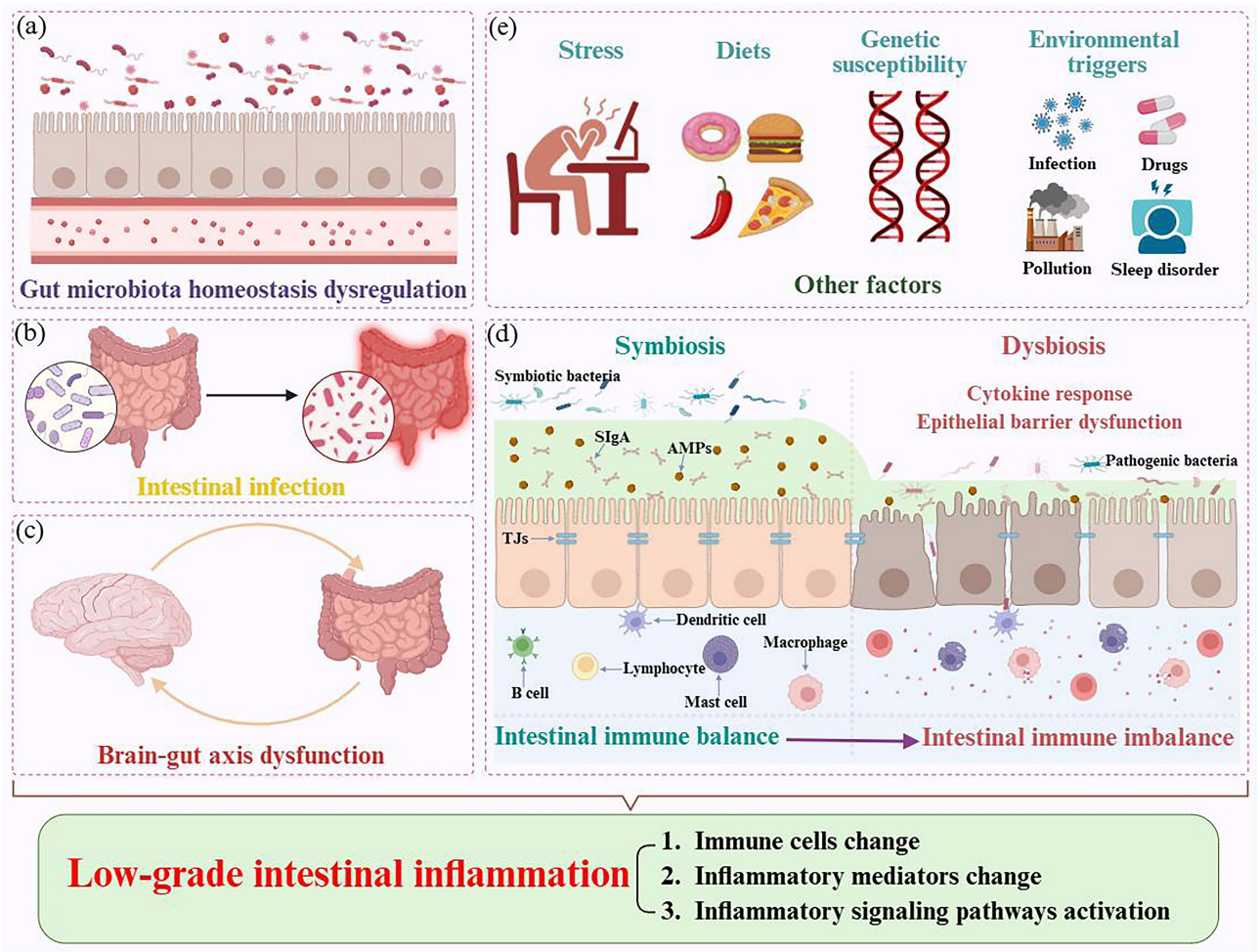

Figure 1 The causes of low-grade intestinal inflammation. (**a**) Gut microbiota homeostasis dysregulation, (**b**)Intestinal infection, (**c**) Brain-gut axis dysfunction, (**d**) Intestinal immune imbalance and (**e**) Other factors.

while defending against pathogens. In IBS-D, this balance is disrupted, leading to a state of chronic, low-level immune activation.[24,25] This activation is a key pathological event that initiates and sustains inflammation.

The aberrant immune response is evidenced by alterations in inflammatory mediators, such as elevated levels of pro-inflammatory cytokines, which will be discussed in detail in Inflammatory Mediators Can Induce Low-Grade Intestinal Inflammation in IBS-D.[26,27] Importantly, this response is notably milder than the overt inflammation seen in inflammatory bowel disease. The critical role of immune imbalance as a trigger is further supported by evidence showing that interventions which restore immune homeostasis, such as certain probiotics, can alleviate low-grade inflammation and IBS-D symptoms.[28,29] Therefore, intestinal immune imbalance acts as a cornerstone in the pathogenesis of IBS-D, translating various etiological factors into a sustained low-grade inflammatory response.

Dysregulation of Gut Microbiota Homeostasis Also Plays an Important Role in Low-Grade Intestinal Inflammation of IBS-D

The gut microbiota comprises a large and complex community of microbes that colonize the human gut, co-evolving with the host to establish a symbiotic relationship. These microorganisms play a crucial role in maintaining the mucosal barrier, providing essential nutrients, regulating immune function, and resisting pathogens. Typically, they exist in a balanced state with the human body and its external environment, which is vital for overall health.[30,31] However, dysregulation in the composition and abundance of these microbes can disrupt this equilibrium and contribute to various diseases. IBS is associated with the diversity of bacterial communities, with different subtypes of IBS patients exhibiting distinct microbial profiles.[32,33] An imbalance in intestinal flora is prevalent among patients with IBS-D, primarily characterized by reduced bacterial diversity, a decrease in dominant bacterial populations, and an increase in pathogenic bacteria.[34–36] It is important to note that microbial signatures can vary significantly between studies, influenced by factors such as geography, diet, and methodology. Furthermore, differences exist between the luminal and mucosa-associated microbiota, which may have distinct functional implications for host immunity and barrier function. Specific changes at the phylum level, such as a reported decrease in Firmicutes and an increase in Bacteroidetes, have been described in some cohorts,[37] but these findings are not uniform across all studies, highlighting the heterogeneity of IBS-D. Data regarding *Actinobacteria* and *Bifidobacteria* remain inconsistent,[33,38–41] underscoring the complexity of the gut microbiota in relation to the varying pathological features of IBS-D.[39,42] Consequently, the onset of IBS-D is widely believed to be closely linked to an imbalance in intestinal flora,[43] evidenced by a reduction in beneficial intestinal bacteria such as *Bifidobacterium* and *Lactobacillus*, alongside an increase in potentially pathogenic bacteria such as *Enterobacteriaceae, Streptococcus*, and *Fusobacterium*.[33,44,45] These shifts in the microbiota are associated with core symptoms of the disorder, including diarrhea, abdominal pain, and bloating.

The pathophysiological mechanisms connecting dysbiosis to symptoms involve intestinal barrier dysfunction, immune activation, and low-grade inflammation.[43,46] Patients with IBS-D have been reported to not only exhibit altered microbiota but also increased intestinal permeability characteristic of this subtype.[47,48] Dysbiosis can impair the intestinal barrier through multiple pathways—such as delaying epithelial cell renewal, suppressing antimicrobial protein expression, and increasing mucosal permeability.[9,49–51] When the intestinal barrier is compromised, vascular permeability increases, allowing a significant influx of pathogenic bacteria and endotoxins into the bloodstream, which activates the immune system and elevates cytokine concentrations in the colonic mucosa. Zhong W et al reported that lipopolysaccharide (LPS), a cell wall component of *Proteobacteria*, can form a complex with its receptor CD14 and be recognized by TLR4 receptors on immune cell surfaces, thereby activating the immune system in a moderate manner and promoting the release of pro-inflammatory factors, this can induce an inflammatory response.[41] Increased levels of pro-inflammatory cytokines such as IL-1β, IL-10, and IL-6 released by monocytes have also been observed in peripheral blood. Furthermore, when overproliferating pathogenic bacteria colonize the submucosa, they degrade glycoproteins and rapidly disrupt colonic mucus production, leading to further alterations in intestinal barrier function, specifically increased permeability, which facilitates significant mucosal translocation of pathogens.[52] Jabbar KS et al reported an increase in *Brachyspira*, a potential pathogen, within the colon tissue of patients with IBS-D, resulting in mild inflammation characterized by elevated plasma cells, eosinophils, and mast cells.[53] This finding underscores the particular importance

of investigating mucosa-associated microbes. Pathogenic bacteria can provoke systemic immune responses and localized inflammatory reactions, particularly in the colon, by colonizing the submucosa.[54,55] These alterations place the intestinal mucosa in a state of persistent inflammation, which subsequently contributes to symptoms such as abdominal pain and diarrhea. Consequently, an imbalance in intestinal flora may activate the immune system, leading to low-grade intestinal inflammation through increased intestinal permeability and enhanced release of LPS.

Physiologically, the gut barrier underpins the ongoing colonization and symbiotic functions of commensal microorganisms. When the integrity of this barrier is compromised, its protective effects are diminished, leading to an imbalance in immune homeostasis and disturbances in the intestinal microecology. This disruption can trigger a cascade of non-specific inflammatory responses, resulting in a state of low-grade intestinal inflammation.

Intestinal Infection Tends to Cause Low-Grade Intestinal Inflammation in IBS-D

Low-grade mucosal inflammation resulting from intestinal infection is a potential pathogenic factor in IBS-D. A significant number of patients with infectious enteritis also experience complications associated with IBS, leading to a condition known as post-infectious IBS (PI-IBS). For example, Klem F et al conducted a comprehensive meta-analysis of 45 studies on PI-IBS published between 1994 and 2015, revealing that approximately 10% of intestinal infections among 21,421 patients with enteritis progress to IBS. Individuals with a history of intestinal infection are at a 4.2 times higher risk of developing IBS compared to those without such a history.[56] It is also noteworthy that a range of demographic, clinical, and psychological factors significantly modify the risk of developing PI-IBS. The key risk modifiers identified in the meta-analysis by Klem et al and supporting studies are summarized in Table 2.[56,57] In susceptible individuals, exposure to pathogenic microorganisms induces significant alterations in gut microbiota and leads to long-term changes in host-microbiota interactions. These alterations can, in turn, impact the gut-brain axis and visceral sensitivity, disrupt the intestinal barrier, modify neuromuscular function, trigger persistent low-grade inflammation, and sustain the manifestation of IBS-D symptoms.

Currently, the specific pathogenesis of PI-IBS requires further investigation. However, it can be hypothesized that immune dysfunction resulting from intestinal infection, an imbalance of inflammatory factors, and damage to the intestinal mucosal barrier may contribute to its development. Following intestinal infection, it is likely that Toll-like receptors (TLRs) and pattern recognition receptors (PRRs) composed of TLRs are up-regulated in intestinal epithelial cells, thereby activating both innate and adaptive immunity by recognizing pathogen-associated molecular patterns.[58–60] Furthermore, infection can induce an "ecological dysbiosis" within the intestinal mucosa, where the overgrowth of microbial communities results in increased intestinal permeability, low-grade inflammation, reduced bile salt absorption, and alterations in long neural system activity.[12,49,61] Once the integrity of the intestinal mucosal barrier is compromised, bacteria can interact with the host immune system, triggering a cascade of immune responses that lead to low-grade inflammation of the intestinal mucosa. During this process, TLRs detect specific microbial patterns, prompting host cells to produce a variety of inflammation-related cytokines, which further impact the intestinal barrier in patients with IBS-D.[62] It is reported that there is a high incidence of intestinal mucosal colonization by Brachyspira in IBS-D patients, with

Table 2 Risk Modifiers for PI-IBS and Their Effect sizes[56]

Risk Modifier		Association with PI-IBS Risk	Effect Size (OR)	95% CI
Female sex		Significantly increased	2.19	1.57–3.07
Acute illness severity	Diarrhea >7 days	Significantly increased	2.62	1.48–4.61
	Bloody stools		1.86	1.14–3.03
	Abdominal pain		3.26	1.30–8.14
Antibiotic use		Increased	1.69	1.20–2.37
Psychological factors	Anxiety	Increased	1.97	1.32–2.94
	Depression		1.49	1.17–1.90

Abbreviations: OR, Odds ratio; CI, Confidence interval.

the attachment of *Brachyspira* to the apical membrane of colon cells observed in 20% of IBS patients, and this colonization was associated with alterations in molecular pathways, including mild mucosal inflammation and mast cell activation.[53] Compared to healthy individuals, patients with PI-IBS exhibit differences in cytokines such as IL-6, IL-7, IL-8, IL-1β, MIP-1β, and in their antibody responses to microbial antigens.[63,64] Additionally, there is a significant increase in the expression of CD4+ and CD8+ lymphocytes within the intestinal mucosa.[65] These findings suggest that local low-grade inflammation and immune activation in PI-IBS are primarily induced and sustained by specific cytokines, which are crucial components of the pathophysiology of this condition. During the period of visceral hypersensitivity following recovery from intestinal infection, the intestine remains in a state of continuous immune activation, leading to a long-term, sustained low-grade inflammatory response.[27,66–68] Consequently, intestinal infection is regarded as the primary trigger for the onset and maintenance of persistent low-grade intestinal inflammation.

Dysfunction of the Brain-Gut Axis Makes a Prominent Contribution to Low-Grade Intestinal Inflammation in IBS-D

The brain-gut axis is a complex bidirectional pathway established between the central nervous system and the enteric nervous system, involving multiple levels of neurotransmission, endocrine regulation, and immune response. Specifically, within this system, the nervous system utilizes neurotransmitters such as dopamine, 5-HT, and GABA for the rapid communication of information that influences mood and cognition. Notably, it is striking that over 90% of 5-HT in the human body is synthesized by chromaffin cells in the intestinal mucosa, underscoring the gut's critical role in the synthesis of neurotransmitters. As a result, abnormal secretion of 5-HT can lead to depression, anxiety, and gastrointestinal dysfunction.[69–71] The immune system conveys signals through cytokines and is involved in inflammatory responses and immune regulation. Meanwhile, the endocrine system modulates the body's stress response and emotional state through hormones such as cortisol. At present it is widely accepted that dysfunction of the brain-gut axis, caused by various factors, leads to alterations in related pathophysiological mechanisms, which may be central to the symptoms of IBS-D.[72,73] In addition to this, additional contributing factors include changes in gastrointestinal motility, increased intestinal mucosal permeability, immune activation, and alterations in intestinal microecology.[74] Consequently, there appears to be a close relationship between brain-gut axis dysfunction and low-grade intestinal inflammation, which impacts the functions of both the gut and brain through various mechanisms, thereby promoting the development of low-grade inflammation.[75]

Current studies suggest that the brain-gut axis does not directly regulate low-grade intestinal inflammation; rather, it exerts its effects indirectly through mechanisms such as an imbalance in intestinal flora and dysfunction of the intestinal barrier resulting from its impairment.[76] Research has demonstrated that, compared to healthy controls, patients with IBS-D exhibit significant abnormalities in the neural activity of relevant brain regions when subjected to visceral stimulation (eg, rectal balloon distension) during functional magnetic resonance imaging (fMRI) paradigms.[77] These neuroimaging findings often map onto specific symptom clusters; for instance, altered activity in brain regions involved in affective processing (eg, anterior cingulate cortex, insula) has been correlated with pain severity, while changes in areas related to sensory-motor integration may be more closely associated with bowel habit alterations.[78] Dysfunction of the brain-gut axis leads to an imbalance in the secretion of neurotransmitters such as 5-HT and dopamine, which not only disrupts the normal motor and sensory functions of the intestine—resulting in symptoms like diarrhea and abdominal pain—but also impacts the emotion regulation center of the brain, exacerbating anxiety and depression in patients and creating a vicious cycle.[79–81] This strongly supports the notion of the brain-gut axis as a central hub in the pathophysiological processes associated with IBS-D. Furthermore, external stressors, poor dietary habits, intestinal infections, and other factors can disrupt the delicate regulatory balance of the brain-gut axis, triggering a cascade of downstream pathophysiological changes. These include abnormal gastrointestinal motility, increased intestinal mucosal permeability, intestinal immune activation, and microecological imbalance, which are key drivers of low-grade intestinal inflammation in IBS-D. For instance, dysfunction of the brain-gut axis may disturb the balance of intestinal flora, leading to abnormal secretion of metabolites such as short-chain fatty acids and neurotransmitters, which can subsequently affect brain function and mood. Additionally, these disruptions may compromise intestinal health, contributing to low-grade inflammation of the

intestinal mucosa.[82–84] The dysfunction of the brain-gut axis may impair intestinal barrier function, allowing pathogens and their toxic components to easily enter the bloodstream and induce a systemic immune inflammatory response.[85] Therefore, while brain-gut axis dysfunction is not directly synonymous with low-grade intestinal inflammation, there exists a significant correlation between the two.

Other Predisposing Factors for Low-Grade Intestinal Inflammation in IBS-D

The complex physiological regulation system of the human body reveals that the stress response, induced by prolonged negative emotional states such as mental stress and anxiety, can disrupt the homeostasis of the neuroendocrine system, subsequently impacting the normal functioning of the intestinal tract.[86,87] This stress response activates the HPA axis, leading to the release of stress hormones. Chief among these are glucocorticoids (primarily cortisol in humans) and catecholamines (eg, epinephrine and norepinephrine). These hormones mediate a bidirectional dialogue along the brain-gut axis. Systemically, they act on the central nervous system to modulate perception, mood, and behavioral responses to stress. Locally within the gut, they exert direct effects: The release of these hormones can impair the intestinal mucosal barrier function, disrupt the normal functions and activities of both innate and adaptive immune cells in the intestine, and potentially trigger or exacerbate low-grade intestinal inflammation.

Consequently, the intestinal tract may remain in a microenvironment characterized by subclinical inflammation for an extended period.[75,88,89] Furthermore, existing studies have highlighted the intricate links between the stress response and intestinal flora, indicating that stress can significantly alter the ecological balance of intestinal microbiota.[90–92] As a core component of the intestinal microecosystem, intestinal flora is particularly sensitive to stress. Fluctuations in stress hormone levels may alter the physical and chemical environment within the intestinal tract, including pH and REDOX potential, thereby affecting the colonization, growth, and metabolism of intestinal flora. These changes can modify the composition, abundance, and diversity of intestinal microbiota, disrupting the original symbiotic balance and further compromising intestinal health.[93,94] Additionally, dietary factors play a crucial role in the development of low-grade intestinal inflammation. For instance, long-term consumption of high-fat and high-sugar diets leads to excessive production of adipokines, which stimulate the proliferation of intestinal wall cells and promote inflammatory cell infiltration. Moreover, spicy and greasy foods can irritate the intestinal mucosa, resulting in mucosal damage and increased permeability.[34,95–97]

In conclusion, low-grade intestinal inflammation is a characteristic feature of IBS-D, marked by the presence of inflammatory cells without evident structural damage, a mild excess of pro-inflammatory factors, and a predominantly asymptomatic state. This condition is associated with various factors, including immune imbalance, gut microbiota dysbiosis, intestinal infections, abnormalities of the brain-gut axis, and stress responses. Immune imbalance leads to altered levels of immune cells and inflammatory mediators, while intestinal dysbiosis is characterized by reduced microbial diversity and an increase in pathogenic bacteria. Following intestinal infection, low-grade mucosal inflammation may persist due to abnormal immune function and damage to the intestinal mucosal barrier. Dysfunction of the brain-gut axis impacts neurotransmitter secretion, exacerbates emotional issues, and creates a vicious cycle. Prolonged mental stress and stress responses affect the intestinal mucosal barrier and immune function through the HPA axis, while poor dietary habits directly stimulate the intestinal wall and increase permeability. These interrelated factors contribute to the development of low-grade intestinal inflammation and the manifestation of IBS-D symptoms. Consequently, low-grade intestinal inflammation represents a multifaceted process involving the interplay of immune, microbial, neurological, and psychological factors, as shown in Figure 2.

Molecular Mechanisms of Low-Grade Intestinal Inflammation in IBS-D

In the intestinal tissue of individuals with IBS-D, background conditions such as immune imbalance, dysbiosis, intestinal infections, and dysfunction of the brain-gut axis can initiate a progressive cycle of changes in local intestinal tissue permeability and low-grade inflammation. Over time, these changes contribute to intestinal barrier dysfunction. Numerous molecular components and mechanisms are involved in this process, which will be discussed in the following sections (Figure 3).

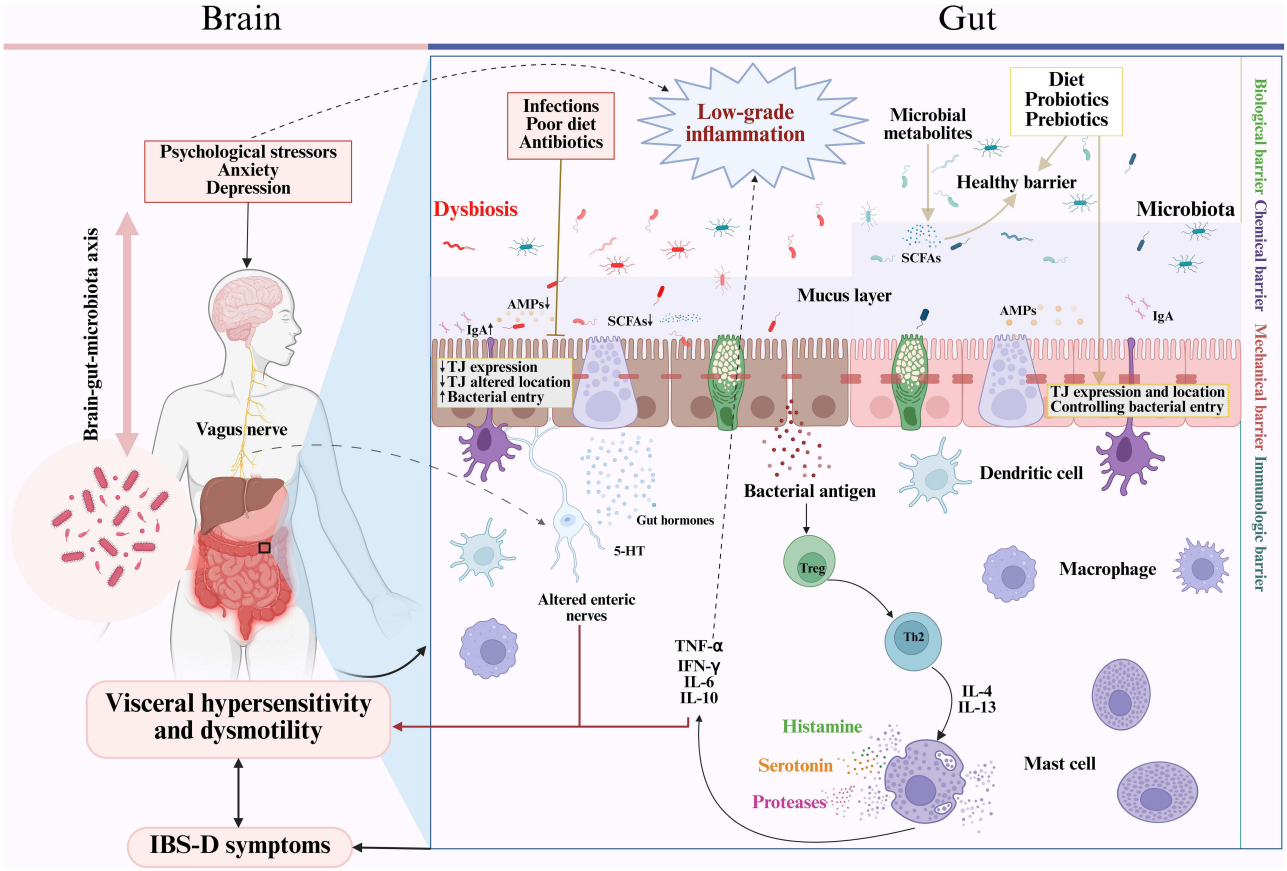

Figure 2 Comparison of IBS-D and normal intestines.

Abnormal Activation of Immune Cells Can Lead to Low-Grade Intestinal Inflammation in IBS-D

Patients with IBS-D do not exhibit morphological abnormalities; however, there is notable infiltration of immune cells, including mast cells, macrophages, dendritic cells, T lymphocytes, and plasma cells. This infiltration contributes to a sustained non-specific low-grade inflammatory state within the intestinal tract.[98] Research indicates that mucosal immune cell infiltration in IBS patients is influenced by sex; specifically, mast cell infiltration is more pronounced in female patients, whereas the number of T cells is greater in male patients.[99] The relationship between these immune cells and low-grade intestinal inflammation in IBS-D will be discussed briefly below.

Mast Cells and Macrophages

Innate immune cells, including mast cells and macrophages, are found to be increased and activated in the colon tissues of patients with IBS-D.[100–103] The local microenvironment and central pressure can facilitate the activation and degranulation of mast cells, leading to the release of tryptase, histamine, 5-HT, and other inflammatory mediators and cytokines, which contribute to the pathological processes associated with IBS-D.[104–106] For instance, LPS and tryptase can stimulate intestinal mucosal mast cells to release prostaglandin E2 (PGE2) and cyclooxygenase-2 (COX-2), which in turn upregulates 5-HT, resulting in symptoms such as diarrhea and abdominal pain.[107] Histamine, a key inflammatory mediator released upon mast cell activation, can activate vascular endothelial cells. This increased vascular permeability facilitates the exudation of plasma proteins and immune cells into the interstitial space, thereby triggering an inflammatory response. Macrophages can differentiate into M1 and M2 phenotypes, which are closely linked to the inflammatory response and play a crucial role in maintaining intestinal immune homeostasis.[108] LPS and IFN-γ promote the polarization of macrophages towards the M1 phenotype, resulting in the release of pro-inflammatory cytokines such as IL-6, IL-

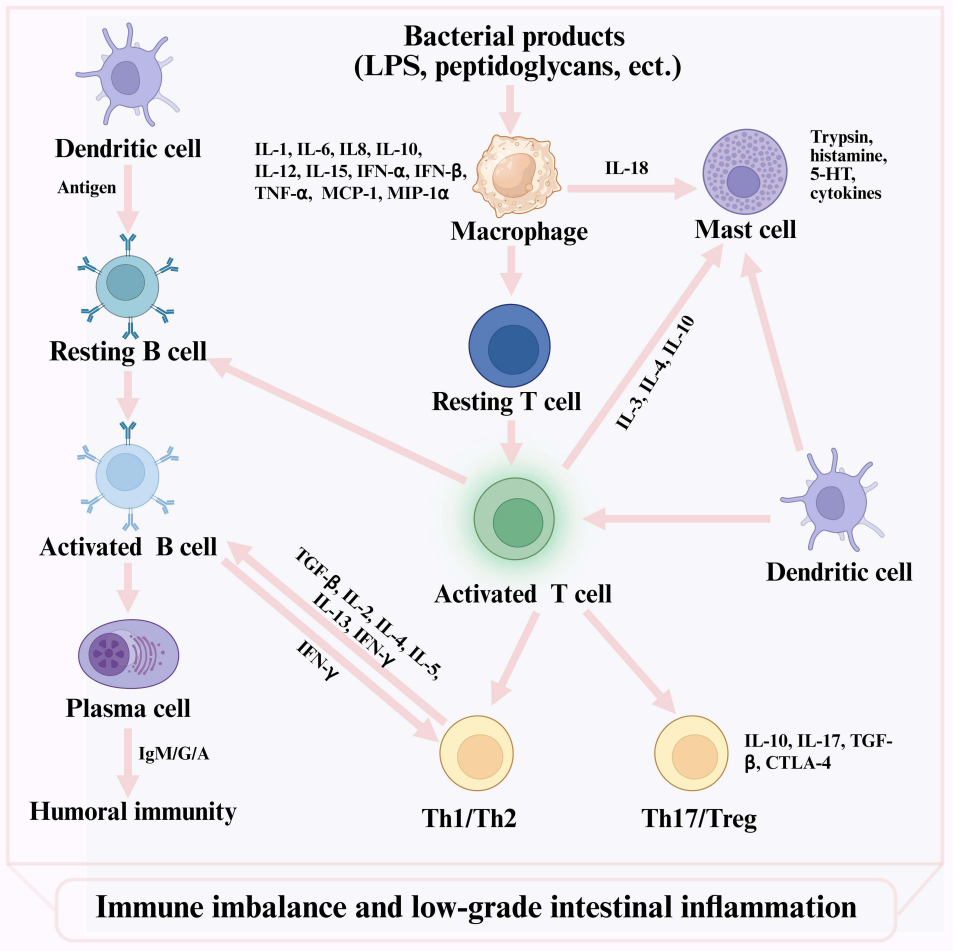

Figure 3 Immune cells and inflammatory mediators of low-grade intestinal inflammation in IBS-D.

12 and TNF-α. Conversely, anti-inflammatory cytokines such as IL-4 and IL-10 drive macrophages towards the M2 phenotype, which is involved in the anti-inflammatory response and the repair of damaged tissues.[109–111] While this M1/M2 paradigm is well-established in vitro and in animal models, evidence from human colonic biopsies in IBS-D is still emerging and often shows considerable heterogeneity. Some studies report an increase in markers associated with M1 polarization in IBS-D mucosa, but a clear and consistent polarization profile has not been definitively established, highlighting the complexity and likely plasticity of macrophage phenotypes in the human gut microenvironment.[111,112]

Dendritic Cells

DCs are the most potent professional antigen-presenting cells in the body, capable of not only initiating immune responses but also inducing immune tolerance. They play a crucial role in the immune system by bridging innate and adaptive immunity. In rats with IBS-D, the number of DCs is significantly increased, which can stimulate $CD4^+$ T cells to promote IL-4 secretion and induce mast cell degranulation.[113,114] However, the mechanisms by which DCs operate in IBS-D remain unclear, necessitating further studies to elucidate this relationship.

T Lymphocytes and Plasma Cells

In the intestinal mucosa of patients with IBS-D, moderate infiltration of adaptive immune cells, including T lymphocytes and plasma cells, has been observed within the epithelial layer and lamina propria.[98] T lymphocytes utilize the T cell receptor (TCR) on their surface to recognize the major histocompatibility complex (MHC) presented by antigen-presenting cells (APCs) after binding to antigenic peptides. During episodes of intestinal inflammation, DCs and macrophages function as APCs, capturing pathogen antigens in the gut, self-antigens released from damaged cells, and

abnormal antigens generated by an imbalance in intestinal flora. In IBS-D patients, the proportion of Th cells subsets is dysregulated, and both the function and quantity of regulatory T cells (Tregs) may be compromised.[115] Research indicates that a balance exists between Th1 and Th2 cells in the human body; when this balance is disrupted, Th1 cells tend to proliferate and secrete increased levels of IFN-γ and TNF-α.[116] Tregs are essential for maintaining intestinal immune tolerance, as cytokines such as IL-10 and TGF-β secreted by Tregs can suppress immune responses.[117] The excessive activation of Th1 cells, coupled with the insufficient functionality of Tregs, leads to an imbalance in immune regulation. In IBS-D patients, the number or function of Tregs is often reduced or impaired, failing to adequately inhibit the immune response elicited by Th1 cells, which results in the secretion of TNF-α and a shift in intestinal immune balance towards a pro-inflammatory state. T lymphocytes play a critical role in compromising the intestinal barrier and regulating the balance of intestinal flora. When T lymphocytes are overactivated, they secrete cytokines that diminish the expression or impair the function of tight junction proteins such as occludin and claudin, thereby exacerbating low-grade intestinal inflammation.[118,119] The cytokines secreted by over-activated T lymphocytes alter the intestinal environment, making it challenging for probiotics that typically thrive in a normal intestinal setting to survive. This alteration exacerbates the imbalance of intestinal flora, creating a vicious cycle that perpetuates low-grade intestinal inflammation.[120] Plasma cells, also referred to as effector B cells, are immune system cells responsible for the release of a significant quantity of antibodies. Notably, plasma cell activation and IgG concentrations were observed to be higher in patients with IBS-D compared to healthy controls, indicating a close relationship between humoral immune imbalance and barrier dysfunction. However, further studies are necessary to substantiate this hypothesis.[121,122]

Inflammatory Mediators Can Induce Low-Grade Intestinal Inflammation in IBS-D

As outlined previously, immune activation in IBS-D results in the release of diverse inflammatory mediators. Rather than acting in isolation, these mediators—including bioactive amines, cytokines, and chemokines—form a complex network that collectively drives the pathogenesis of low-grade intestinal inflammation by disrupting epithelial barrier function, dysregulating immune responses, and altering the enteric microenvironment.

Bioactive Amines: Initiators and Coordinators in the Inflammatory Network

As a prime example of interacting inflammatory mediators, bioactive amines—including 5-HT, histamine, dopamine, and norepinephrine—play a significant role in IBS-D. In patients with IBS-D, the expression levels of 5-HT and histamine are notably elevated, as evidenced by increased mucosal 5-HT content and elevated histamine concentrations in stool samples analyzed by ELISA.[123,124] Within the intestinal environment of IBS-D, bioactive amines do not function independently; rather, they interact with one another, contributing to the induction of low-grade intestinal inflammation. For instance, an increase in 5-HT promotes the degranulation of mast cells, leading to the release of histamine, which can subsequently feedback to regulate the release and action of 5-HT. Histamine serves as a potent mediator of inflammation, enhancing vascular permeability and facilitating the exudation of plasma proteins and immune cells to sites of inflammation. By activating specific 5-HT receptors, 5-HT influences immune cells, including mast cells, lymphocytes, and macrophages, prompting the release of cytokines and thereby initiating and sustaining low-grade intestinal inflammation.[125]

Cytokines: A Dysregulated Network Sustaining Inflammation

In IBS-D, a profound imbalance in the cytokine milieu is a hallmark feature, characterized by a shift towards proinflammatory signaling that overwhelms anti-inflammatory mechanisms.[126] This dysregulation is not merely an elevation or reduction of individual cytokines but represents a functionally interconnected network that perpetuates low-grade inflammation through several key aspects:

Epithelial Barrier Breakdown: Proinflammatory cytokines, particularly IFN-γ, TNF-α, and IL-1β, act in concert to compromise intestinal barrier integrity.[127] They disrupt the synthesis and distribution of tight junction proteins, with TNF-α additionally promoting epithelial cell apoptosis via the NF-κB pathway.[128–130] This breach allows increased permeation of luminal antigens, further fueling immune activation.

Immune Cell Activation and Polarization: The cytokine imbalance directly shapes the activity and differentiation of immune cells. Elevated serum IL-6 levels, measured by ELISA, disrupt immune homeostasis by impairing dendritic cell function and promoting the differentiation of pro-inflammatory Th cell subsets (Th1, Th17) over regulatory T cells.[131,132] This leads to a feed-forward cycle of inflammation, as Th1-derived IFN-γ and Th17-derived IL-17 further activate other immune cells like macrophages and sustain barrier dysfunction.[133] IL-17, while protective at normal levels, contributes to microbial dysbiosis when overexpressed.[134]

Failure of Anti-inflammatory Control: The deficit in anti-inflammatory cytokines, notably IL-4 and IL-10, is critical for the persistence of inflammation.[135–137] IL-10, essential for maintaining immune tolerance and barrier homeostasis. While some studies have observed no significant difference in circulating IL-10 levels in plasma or serum by ELISA, others have documented a contrasting pattern of significantly reduced IL-10 mRNA and protein levels in the colonic mucosa of IBS-D patients.[138–140] This loss impairs the negative feedback on proinflammatory cytokine production from antigen-presenting cells and weakens the mucosal barrier, creating a permissive environment for chronic, low-grade inflammation.[141]

In summary, the cytokine network in IBS-D functions as a self-sustaining system where barrier disruption, proinflammatory immune cell polarization, and impaired regulatory control interact synergistically to maintain a state of chronic low-grade inflammation.

Chemokines: Recruiting and Activating Immune Cells to Perpetuate Inflammation

Chemokines are central to the pathogenesis of IBS-D by orchestrating the targeted recruitment of leukocytes into the intestinal mucosa, thereby amplifying and sustaining the low-grade inflammatory response. This process creates a vicious cycle that links immune activation, barrier dysfunction, and even microbial dysbiosis.

A key player in this process is IL-8. Studies measuring IL-8 by ELISA have demonstrated elevated levels in both the colonic mucosa and serum of IBS-D patients compared to healthy controls, providing direct human evidence for its involvement.[142] IL-8 functions as a potent chemoattractant for neutrophils.[143] The recruitment and activation of neutrophils at the inflammatory site lead to the release of reactive oxygen species and proteases, which directly compromise the integrity of the intestinal epithelial barrier.[144] This breach further allows for increased antigen penetration, perpetuating immune activation. Similarly, monocyte chemoattractant protein-1 (MCP-1/CCL2) is over-expressed specifically in the intestinal mucosa of IBS-D patients, leading to the influx of monocytes/macrophages.[145,146] Once recruited, these cells become a significant source of pro-inflammatory cytokines, such as TNF-α and IL-1β. This creates a critical link between chemokine signaling and the cytokine network: the recruited cells exacerbate the existing inflammatory milieu, which in turn can stimulate further chemokine production by resident cells, forming a positive feedback loop that chronicizes inflammation.[147] Other chemokine axes also contribute to this network. For instance, elevated levels of the CXCL11/CXCR3 axis, which is implicated in recruiting Th1 cells, have been observed in the peripheral blood of IBS-D cohorts.[148] While data on MIP-1β (CCL4) in IBS-D are more limited, its potential role is suggested by studies in related functional GI disorders. Importantly, the chemokine response is not isolated; it can be directly influenced by the intestinal microbiota. Certain bacterial components can stimulate the production of chemokines like IL-8 and CXCL11, thereby linking microbial dysbiosis to the ongoing immune cell recruitment and inflammation in IBS-D.[149–151]

In conclusion, rather than acting independently, chemokines function as crucial amplifiers within the inflammatory mediator network of IBS-D. By directing the influx of specific immune cells, they directly contribute to barrier damage and reinforce the pro-inflammatory cytokine cascade, ultimately sustaining the state of low-grade intestinal inflammation.

Signaling Pathways Associated with Low-Grade Intestinal Inflammation in IBS-D

Now, the most extensively studied inflammation-related pathway in IBS-D is the TLRs/NF-κB signaling pathway (Figure 4). To begin with, TLRs are vital pattern recognition receptors (PRRs), primarily expressed on the cell membrane surfaces of immune cells, such as macrophages and dendritic cells, as well as non-immune cells, including intestinal epithelial cells. As key components of the innate immune system, TLRs recognize various pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), thereby triggering immune responses.

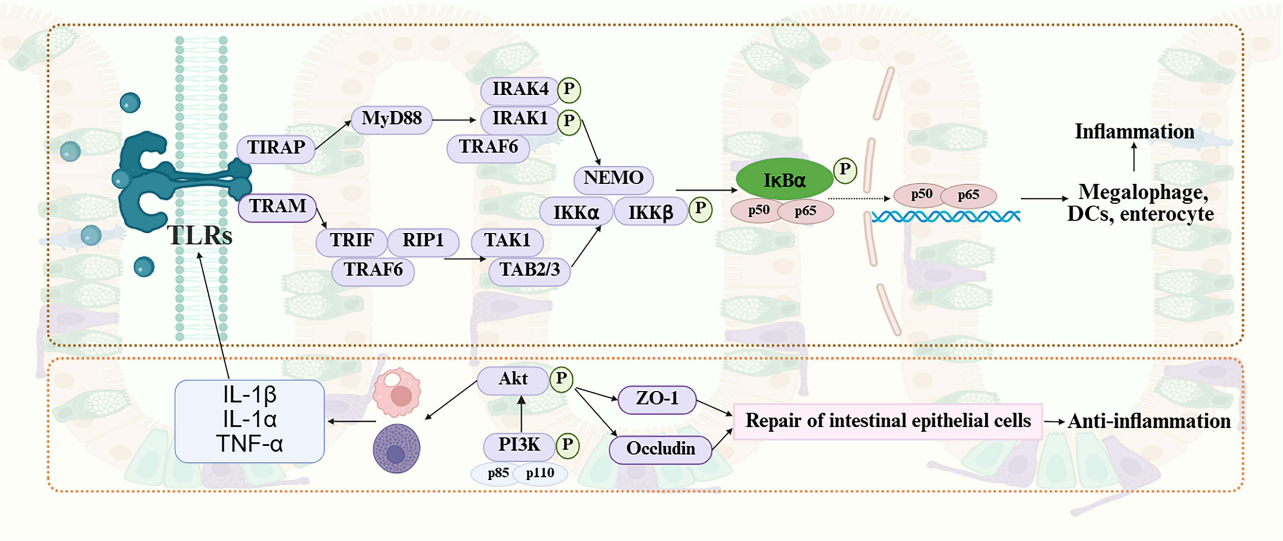

Figure 4 Inflammatory signaling pathways of low-grade intestinal inflammation in IBS-D.

Meanwhile, NF-κB, a protein complex, regulates DNA transcription, cytokine production, and cell survival, playing a crucial role in modulating immune and inflammatory responses. In the context of IBS-D, TLRs are closely associated with immune activation and the secretion of cytokines and chemokines.[152] Specifically, the activation of the TLRs signaling pathway promotes the activation and proliferation of immune cells, such as macrophages and DCs, leading to the release of numerous inflammatory factors, including TNF-α, IL-1β, and IL-6, which are elevated in the intestinal mucosa of IBS-D patients. Furthermore, TLRs activate downstream signaling molecules, such as NF-κB and MAPK, through a series of adaptor proteins including MyD88. This activation, in turn, enhances the production of cytokines and chemokines, contributing to a low-grade inflammatory response. Research has demonstrated that the expression of TLR-2, TLR-4, and TLR-5 is elevated in the colonic tissues of IBS-D patients. More specifically, the upregulation of TLR-4 and TLR-5 mediates an increase in pro-inflammatory cytokines while decreasing anti-inflammatory cytokines, thereby inducing low-grade intestinal inflammation.[17,153]

The PI3K/Akt signaling pathway is a crucial signal transduction pathway in cells, playing a significant role in various physiological processes, including cell growth, proliferation, survival, metabolism, and migration.[154,155] The relationship between PI3K/Akt and NF-κB is context-dependent and can appear paradoxical, as this pathway can exert both pro-inflammatory and anti-inflammatory effects.[156] In intestinal epithelial cells, which are critical for maintaining barrier integrity, Akt activation can promote cell survival and contribute to barrier repair, which is fundamentally an anti-inflammatory process. Under specific conditions, Akt can also phosphorylate and inhibit specific components of the NF-κB pathway, thereby exerting a restraining effect on inflammation.[157,158] However, in immune cells such as macrophages and mast cells—which are key drivers of inflammation in IBS-D—the effect of PI3K/Akt signaling is predominantly pro-inflammatory.[112] In these cells, Akt acts as a key driver of NF-κB activation, enhancing the transcription of pro-inflammatory cytokines like TNF-α and IL-1β.[159] This immune cell-mediated, pro-inflammatory role is highly relevant in the context of IBS-D. For instance, in the state of microbiota dysbiosis, bacterial products like LPS can activate PI3K/Akt in mucosal immune cells, leading to NF-κB-driven production of inflammatory mediators and contributing to the observed low-grade inflammation.[160] Furthermore, the PI3K/Akt pathway is integral to regulating the intestinal mucosal barrier. Studies by Chen et al demonstrated that this pathway is essential for maintaining the expression of tight junction proteins (eg, ZO-1, occludin) in intestinal epithelial cells, and its inhibition compromises barrier integrity.[161] Therefore, a dysregulated PI3K/Akt pathway in IBS-D may have a dual impact: it can directly promote inflammation via immune cell activation while simultaneously creating a permissive environment for inflammation by impairing the epithelial barrier, thus allowing increased translocation of luminal antigens.

https://doi.org/10.2147/JIR.S578822

Harnessing Low-Grade Inflammation as a Therapeutic Linchpin in IBS-D

Current Integrative Strategies in East-West Therapeutic Paradigms for IBS-D

Currently, treatment strategies for IBS-D primarily focus on symptom management, with no definitive cure available for the condition. The main objective of IBS-D treatment is to alleviate symptoms and enhance the quality of life, which thus necessitates an individualized and comprehensive treatment approach. Management options for IBS-D encompass dietary adjustments, lifestyle improvements, the use of probiotics, fecal microbial transplantation, psychotherapy, and pharmacological interventions aimed at symptom relief. This article summarizes the current status comparison of drug therapy for IBS-D according to *AGA (American Gastroenterological Association) Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome With Diarrhea*, as summarized in Table 3. The guidelines offer clear recommendations for eluxadoline, rifaximin, alosetron, and tricyclic antidepressants (TCAs) based on robust clinical evidence. Specifically, eluxadoline is recommended for IBS-D. In two Phase 3 trials, eluxadoline (100 mg twice daily) significantly improved the FDA composite endpoint (≥30% reduction in worst abdominal pain and ≥50% reduction in days with BSFS type 6/7 stools) compared to placebo (RR 0.87, 95% CI 0.83–0.92). It also improved stool consistency, urgency, and IBS-QOL. However, discontinuation due to adverse events was higher with eluxadoline (8%) than placebo (4%), and it is contraindicated in patients without a gallbladder or those consuming >3 alcoholic beverages/day due to risks of pancreatitis and sphincter of Oddi spasm. Moreover, rifaximin is recommended for initial treatment and retreatment upon recurrence. Rifaximin (550 mg TID for 14 days) improves global symptoms and bloating, with a safety profile similar to placebo, and retreatment is effective and safe for recurrent symptoms. Additionally, alosetron is suggested for women with severe IBS-D under a risk-management program, and it improves global symptoms, pain, and stool consistency but carries risks of ischemic colitis and constipation. Meanwhile, TCAs are suggested for IBS. TCAs improve global symptoms and abdominal pain but are associated with higher adverse events (eg, dry mouth, sedation) leading to discontinuation. The AGA suggests against SSRIs due to lack of significant benefit. Evidence for loperamide and antispasmodics is limited, and they are not specifically recommended for IBS-D.[162]

Moreover, this paper also provides a simple interpretation of the *Expert Consensus on the Diagnosis and Treatment of Irritable Bowel Syndrome in Traditional Chinese Medicine*, issued by the Spleen and Stomach Disease Branch of the Chinese Association of Traditional Chinese Medicine in 2025. It summarizes the classification and treatment methods for IBS-D in traditional Chinese medicine (TCM). This consensus offers an authoritative framework for the diagnosis and treatment of IBS-D within the realm of TCM.[7] It details how IBS-D is categorized into various syndrome types based on the patient's constitution, symptoms, and etiology, leading to the formulation of individualized treatment plans. According to TCM theory, IBS-D can be divided into four TCM syndrome patterns, including syndrome of liver depression and spleen deficiency, syndrome of spleen deficiency and dampness excess, spleen-kidney yang deficiency syndrome and large intestinal dampness-heat syndrome. For each TCM syndrome pattern, it gives the corresponding recommendations of Chinese patent medicine, such as Tongxiening granules, Qizhi weitong granules or tablets can be selected for syndrome of liver depression and spleen deficiency; and Ginseng spleen-strengthening pills or tablets, Shenling Baizhu granules can be used for syndrome of spleen deficiency and dampness excess; and Sishen pills, Guben Yichang tablets can be selected for spleen-kidney yang deficiency syndrome; and Gegen Qinlian pills, Coptis tablets, Fengliang Changweikang granules can be used for large intestinal dampness-heat syndrome. By employing a comprehensive approach that includes Chinese herbal medicine, acupuncture, massage, and other characteristic therapies, the aim is to restore the balance of Yin and Yang in patients and enhance the function of the spleen and stomach.[163–166] These approaches seek to effectively alleviate the symptoms of IBS-D and improve patients' quality of life. Despite the availability of various drugs and methods currently used to relieve symptoms in IBS-D patients, existing treatment options still struggle to address all the complexities associated with the condition. Therefore, there is an urgent need to develop new therapies that can alleviate the suffering of IBS-D patients while minimizing the risk of adverse reactions.

Targeting Low-Grade Inflammation is a Promising Approach in IBS-D

In recent years, advancements in biomedical research have significantly enhanced our understanding of the mechanisms underlying inflammation. This complex biological process involves the interaction of various cells, molecules, and

Table 3 Summary of Pharmacological Agents for IBS-D from AGA guideline[162]

Agents	AGA Recommendation & Evidence Certainty	Key Efficacy Endpoint (vs Placebo)	Trial Duration	Key Adverse Events & Discontinuation	Regulatory & Safety Notes
Eluxadoline	Conditional recommendation and Moderate certainty	FDA responder, RR 0.87 (0.83–0.92).	26 weeks	1. Common: constipation (8%), nausea (7%). 2. Serious: pancreatitis, sphincter of Oddi spasm. 3. Discontinuation due to AEs: 8% vs 4% (placebo).	1. FDA-approved for IBS-D. 2. Contraindications: No gallbladder; history of pancreatitis/ Sphincter of Oddi disease; severe hepatic impairment; alcohol abuse (>3 drinks/day).
Rifaximin	Conditional recommendation and Moderate certainty	FDA responder, RR 0.85 (0.78–0.94).	2-week treatment +4-week follow-up (initial); Retreatment studied.	1. AEs similar to placebo. 2. Drug-related AEs: 12.1% vs 10.7% (placebo). 3. Rare C. *difficile* colitis reported.	1. FDA-approved for IBS-D. 2. Approved for retreatment (up to 2 cycles) upon symptom recurrence.
Alosetron	Conditional recommendation and Moderate certainty	Global Symptom Improvement, RR 0.60 (0.54–0.67).	12-48 weeks	Serious: Ischemic colitis (~1.03/1000 patient-years), serious complications of constipation (~0.25/1000 patient-years).	1. FDA-approved with restrictions. 2. Indicated only for women with severe IBS-D inadequately responsive to conventional therapy. 3. Available only through a Risk Management Program.
TCAs	Conditional recommendation and Low certainty	Global Symptom Improvement, RR 0.67 (0.54–0.82).	6-12 weeks	1. Common: Anticholinergic effects (dry mouth, sedation, constipation). 2. Withdrawal due to AEs: RR 2.11 vs placebo.	1. Used off-label for IBS. 2. Dosing is typically lower than for depression.
Loperamide	Conditional recommendation and Very low certainty	Abdominal Pain Relief, RR 0.41 (0.20–0.84).	3-5 weeks	Data insufficient from old, small trials.	1. FDA-approved for diarrhea. 2. Used off-label for IBS-D. 3. Not recommended for relief of abdominal pain or global symptoms.
SSRIs	Conditional against recommendation and Low certainty	Global Symptom Improvement, RR 0.74 (0.52–1.06).	6-12 weeks	No significant difference from placebo in available studies.	1. Used off-label for IBS. 2. Evidence does not support efficacy for core IBS symptoms.
Antispasmodics	Conditional recommendation and Low certainty	Global Symptom Improvement, RR 0.67 (0.55–0.80).	Varies (often short-term)	Common: Dry mouth, dizziness, blurred vision.	1. Used off-label for IBS. 2. 2. A heterogeneous drug class; hyoscine, dicyclomine, and peppermint oil are available in the US.

Abbreviations: RR, relative risk, 95% CI; AEs, Adverse Events.

signaling pathways.[167,168] In states of low-grade inflammation, although the inflammatory response is less intense than in acute inflammation, persistent inflammatory factors and immune cells can still pose a potential threat to the body. Consequently, researchers are focusing on the development of new anti-inflammatory drugs that can effectively inhibit the inflammatory response with high specificity and minimal side effects. This includes biological agents that specifically target key inflammatory molecules to reduce adverse effects and improve efficacy.[169,170] Significant progress has been made in targeting low-grade inflammation across various disease fields, particularly in osteoarthritis, type 2 diabetes,

tumors, NLRP3 inflammasome-related diseases, and immune-mediated inflammatory bowel disease (IBD).[171–173] Biologics such as anti-TNF-α monoclonal antibodies, anti-integrin monoclonal antibodies, and anti-IL monoclonal antibodies have been approved worldwide for the treatment of IBD.[174–176] Although the low-grade inflammation of the intestinal mucosa in IBS-D is not as pronounced as that in IBD, persistent inflammation can disrupt normal intestinal function, leading to a range of typical symptoms including abdominal pain, diarrhea, and abdominal distension. Given the critical role of low-grade inflammation in IBS-D, and considering the successful strategies targeting low-grade inflammation in immune-mediated IBD, new anti-inflammatory therapies may offer promising opportunities for the treatment of IBS-D.[177]

Conclusions and Prospects

Research to date increasingly positions chronic low-grade intestinal inflammation as a central, actionable pathophysiological hub in IBS-D, interconnecting diverse triggers such as immune dysregulation, gut microbiota imbalance, brain-gut axis dysfunction, and environmental stressors. This mechanistic understanding offers a pivotal shift in perspective: IBS-D is not merely a functional disorder of unexplained symptoms, but may encompass a spectrum of conditions with varying degrees of inflammatory drive. This recognition has direct clinical implications. First, it underscores the urgent need for diagnostic refinement. Moving beyond the current, purely symptom-based Rome criteria, future diagnostics should integrate objective biomarkers of low-grade inflammation—such as specific mucosal transcriptomic signatures, panels of inflammatory mediators in serum or stool, or spatial metrics of immune cell activity—to identify the "inflammatory subtype" of IBS-D. This stratification is the critical first step toward personalized medicine. Second, and most consequentially, this understanding redefines the therapeutic goal from symptomatic management to targeted, mechanism-based intervention. For patients stratified into an inflammatory subtype, therapy can be directed at the causative inflammatory pathways themselves. The most promising avenues for such causative therapy include: (1) the repurposing and refinement of targeted immunomodulators (eg, mast cell stabilizers, specific cytokine inhibitors against IL-1β, IL-6, or TNF-α, or leukocyte trafficking inhibitors) in biomarker-defined subgroups; (2) the development of novel agents targeting upstream triggers, such as next-generation prebiotics/probiotics or defined microbial consortia to correct inflammation-inducing dysbiosis, alongside compounds that directly enhance intestinal barrier integrity; and (3) the validation of multi-modal strategies that combine gut-directed anti-inflammatory agents with treatments modulating the brain-gut axis (eg, neuromodulators, psychotherapy) to address the systemic nature of the disorder.

In summary, the future of IBS-D management lies in deconstructing its heterogeneity through inflammatory subtyping. By prioritizing the validation of precise biomarkers and subsequently testing targeted anti-inflammatory therapies in the identified patient subgroups, research can fundamentally change the therapeutic paradigm from blanket symptomatic control to tailored, causative therapy, ultimately improving long-term outcomes.

Data Sharing Statement

No new data were generated or analyzed in this study. This article is a review of existing published literature.

Author Contributions

Baibai Ye, Conceptualization, Writing-original draft; Ziyu Fu, Investigation, Methodology; Xin Zhou, Investigation, Project administration; Shengmei Wang, Project administration, Formal analysis; Linqi Ouyang, Software, Supervision; Zhen Chen, Validation, Writing-review & editing; Guiming Deng, Supervision, Funding acquisition and Writing-review & editing. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the National Natural Science Foundation of China [Number 82374424], the Furong Laboratory of Hunan Province Science and Technology Department [Number 2023SK2102] and the Natural Science Foundation of Hunan Province [Number 2022JJ70028].

Disclosure

The authors report there are no competing interests to declare.

References

1. Stanghellini V. Functional dyspepsia and irritable bowel syndrome: beyond Rome IV. *Dig Dis*. 2017;35 Suppl 1:14–17. doi:10.1159/000485408
2. Mearin F, Lacy BE, Chang L, et al. Bowel Disorders. *Gastroenterology*. 2016:S0016–5085(16)00222–00225. doi:10.1053/j.gastro.2016.02.031
3. Greer KB, Sultan S. Irritable bowel syndrome. *Ann Intern Med*. 2025;178(8):ITC113–ITC128. doi:10.7326/ANNALS-25-01965
4. Sperber AD, Bangdiwala SI, Drossman DA, et al. Worldwide prevalence and burden of functional gastrointestinal disorders, results of Rome Foundation Global Study. *Gastroenterology*. 2021;160(1):99–114.e3. doi:10.1053/j.gastro.2020.04.014
5. Oka P, Parr H, Barberio B, Black CJ, Savarino EV, Ford AC. Global prevalence of irritable bowel syndrome according to Rome III or IV criteria: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2020;5(10):908–917. doi:10.1016/S2468-1253(20)30217-X
6. Ray G, Ghoshal UC. Epidemiology of disorders of the gut-brain interaction: an appraisal of the Rome IV criteria and beyond. *Gut Liver*. 2024;18(4):578–592. doi:10.5009/gnl230396
7. Medicine DSDPCo CAoI. [Expert consensuson integrated Traditional Chinese and Western Medicine Diagnosis and Treatment of irritable bowel syndrome(2025)]. *Chin J Integr Trad West Med Dig*. 2025;33(03):183–194. Danish
8. Palsson OS, Tack J, Drossman DA, et al. Worldwide population prevalence and impact of sub-diagnostic gastrointestinal symptoms. *Aliment Pharmacol Ther*. 2024;59(7):852–864. doi:10.1111/apt.17894
9. Yuan Y, Wang X, Huang S, Wang H, Shen G. Low-level inflammation, immunity, and brain-gut axis in IBS: unraveling the complex relationships. *Gut Microbes*. 2023;15(2):2263209. doi:10.1080/19490976.2023.2263209
10. McKernan DP, Gaszner G, Quigley EM, Cryan JF, Dinan TG. Altered peripheral toll-like receptor responses in the irritable bowel syndrome. *Aliment Pharmacol Ther*. 2011;33(9):1045–1052. doi:10.1111/j.1365-2036.2011.04624.x
11. Enck P, Aziz Q, Barbara G, et al. Irritable bowel syndrome. *Nat Rev Dis Primers*. 2016;2:16014. doi:10.1038/nrdp.2016.14
12. Burns GL, Talley NJ, Keely S. Immune responses in the irritable bowel syndromes: time to consider the small intestine. *BMC Med*. 2022;20 (1):115. doi:10.1186/s12916-022-02301-8
13. Lee YY, Annamalai C, Rao S. Post-infectious irritable bowel syndrome. *Curr Gastroenterol Rep*. 2017;19(11):56. doi:10.1007/s11894-017-0595-4
14. Gwee KA. Post-infectious irritable bowel syndrome, an inflammation-immunological model with relevance for other IBS and functional dyspepsia. *J Neurogastroenterol Motil*. 2010;16(1):30–34. doi:10.5056/jnm.2010.16.1.30
15. Carco C, Young W, Gearry RB, Talley NJ, McNabb WC, Roy NC. Increasing Evidence That Irritable Bowel Syndrome and Functional Gastrointestinal Disorders Have a Microbial Pathogenesis. *Front Cell Infect Microbiol*. 2020;10:468. doi:10.3389/fcimb.2020.00468
16. Collins SM. Is the irritable gut an inflamed gut. *Scand J Gastroenterol Suppl*. 1992;192:102–105. doi:10.3109/00365529209095988
17. Shukla R, Ghoshal U, Ranjan P, Ghoshal UC. Expression of toll-like receptors, pro-, and anti-inflammatory cytokines in relation to gut microbiota in irritable bowel syndrome: the evidence for its micro-organic basis. *J Neurogastroenterol Motil*. 2018;24(4):628–642. doi:10.5056/jnm18130
18. Matricon J, Meleine M, Gelot A, et al. Review article: associations between immune activation, intestinal permeability and the irritable bowel syndrome. *Aliment Pharmacol Ther*. 2012;36(11–12):1009–1031. doi:10.1111/apt.12080
19. Di Giovangiulio M, Verheijden S, Bosmans G, Stakenborg N, Boeckxstaens GE, Matteoli G. The neuromodulation of the intestinal immune system and its relevance in inflammatory bowel disease. *Front Immunol*. 2015;6:590. doi:10.3389/fimmu.2015.00590
20. Huong BT, Hien NM, Dung NT, et al. Role of calprotectin, IL-6, and CRP in distinguishing between inflammatory bowel disease and diarrhea predominant irritable bowel syndrome. *Med Arch*. 2024;78(2):105–111. doi:10.5455/medarh.2024.78.105-111
21. Nardo GD, Barbara G, Borrelli O, et al. Italian guidelines for the management of irritable bowel syndrome in children and adolescents: joint Consensus from the Italian Societies of: gastroenterology, Hepatology and Pediatric Nutrition (SIGENP), Pediatrics (SIP), Gastroenterology and Endoscopy (SIGE) and Neurogastroenterology and Motility (SINGEM). *Ital J Pediatr*. 2024;50(1):51. doi:10.1186/s13052-024-01607-y
22. Black CJ, Ford AC. Rational investigations in irritable bowel syndrome. *Frontline Gastroenterol*. 2020;11(2):140–147. doi:10.1136/flgastro-2019-101211
23. Wei Wei Tian BHT, Li Liu DMY, Hua H. Research progress on curcumin improving chronic low-grade inflammation and related diseases. *China J Chin Materia Medica*. 2024;49(10):2607–2618. doi:10.19540/j.cnki.cjcmm.20240208.602
24. Song Y, Li J, Wu Y. Evolving understanding of autoimmune mechanisms and new therapeutic strategies of autoimmune disorders. *Signal Transduct Target Ther*. 2024;9(1):263. doi:10.1038/s41392-024-01952-8
25. Liu J, Zhang P, Zheng Z, et al. GABAergic signaling between enteric neurons and intestinal smooth muscle promotes innate immunity and gut defense in Caenorhabditis elegans. *Immunity*. 2023;56(7):1515–1532.e9. doi:10.1016/j.immuni.2023.06.004
26. Mitselou A, Grammeniatis V, Varouktsi A, Papadatos SS, Katsanos K, Galani V. Proinflammatory cytokines in irritable bowel syndrome: a comparison with inflammatory bowel disease. *Intest Res*. 2020;18(1):115–120. doi:10.5217/ir.2019.00125
27. Aguilera-Lizarraga J, Hussein H, Boeckxstaens GE. Immune activation in irritable bowel syndrome: what is the evidence. *Nat Rev Immunol*. 2022;22(11):674–686. doi:10.1038/s41577-022-00700-9
28. Wenfeng Wang HS, Meihui F. Effects of Sijunzi Decoction and Tongxie Yaofang on intestinal immunity and mucosal barrier function of PI-IBS mice with liver depression and spleen deficiency syndrome. *Tianjin J Trad Chin Med*. 2021;38(11):1449–1455.
29. Ying Chan XF, Quanwei Di GD, Wenwen Yan AZ, Tingting J. Dynamic changes of intestinal mucosal barrier function in mice with post-infectious irritable bowel syndrome. *Chin J Clin Gastroenterol*. 2021;33(06):428–432.
30. Thursby E, Juge N. Introduction to the human gut microbiota. *Biochem J*. 2017;474(11):1823–1836. doi:10.1042/BCJ20160510
31. Donovan SM. Introduction to the special focus issue on the impact of diet on gut microbiota composition and function and future opportunities for nutritional modulation of the gut microbiome to improve human health. *Gut Microbes*. 2017;8(2):75–81. doi:10.1080/19490976.2017.1299309

32. Han L, Zhao L, Zhou Y, et al. Altered metabolome and microbiome features provide clues in understanding irritable bowel syndrome and depression comorbidity. *ISME J*. 2022;16(4):983–996. doi:10.1038/s41396-021-01123-5
33. Jacobs JP, Lagishetty V, Hauer MC, et al. Multi-omics profiles of the intestinal microbiome in irritable bowel syndrome and its bowel habit subtypes. *Microbiome*. 2023;11(1):5. doi:10.1186/s40168-022-01450-5
34. Altomare A, Di Rosa C, Imperia E, Emerenziani S, Cicala M, Guarino M. Diarrhea Predominant-Irritable Bowel Syndrome (IBS-D): effects of Different Nutritional Patterns on Intestinal Dysbiosis and Symptoms. *Nutrients*. 2021;13(5):1506. doi:10.3390/nu13051506
35. Lagier JC, Hugon P, Khelaifia S, Fournier PE, La Scola B, Raoult D. The rebirth of culture in microbiology through the example of culturomics to study human gut microbiota. *Clin Microbiol Rev*. 2015;28(1):237–264. doi:10.1128/CMR.00014-14
36. Liu HN, Wu H, Chen YZ, Chen YJ, Shen XZ, Liu TT. Altered molecular signature of intestinal microbiota in irritable bowel syndrome patients compared with healthy controls: a systematic review and meta-analysis. *Dig Liver Dis*. 2017;49(4):331–337. doi:10.1016/j.dld.2017.01.142
37. Xiao L, Liu Q, Luo M, Xiong L. Gut microbiota-derived metabolites in irritable bowel syndrome. *Front Cell Infect Microbiol*. 2021;11:729346. doi:10.3389/fcimb.2021.729346
38. Zhao L, Yang W, Chen Y, et al. A Clostridia-rich microbiota enhances bile acid excretion in diarrhea-predominant irritable bowel syndrome. *J Clin Invest*. 2020;130(1):438–450. doi:10.1172/JCI130976
39. Su Q, Tun HM, Liu Q, et al. Gut microbiome signatures reflect different subtypes of irritable bowel syndrome. *Gut Microbes*. 2023;15 (1):2157697. doi:10.1080/19490976.2022.2157697
40. Tap J, Derrien M, Törnblom H, et al. Identification of an intestinal microbiota signature associated with severity of irritable bowel syndrome. *Gastroenterology*. 2017;152(1):111–123.e8. doi:10.1053/j.gastro.2016.09.049
41. Zhong W, Lu X, Shi H, et al. Distinct microbial populations exist in the mucosa-associated microbiota of diarrhea predominant irritable bowel syndrome and ulcerative colitis. *J Clin Gastroenterol*. 2019;53(9):660–672. doi:10.1097/MCG.0000000000000961
42. Chao G, Zhang S. The characteristics of intestinal flora of IBS-D with different syndromes. *Immun Inflamm Dis*. 2020;8(4):615–628. doi:10.1002/iid3.348
43. Jeffery IB, O'Herlihy E, Shanahan F, O' Toole PW. Microbiome alterations in IBS. *Gut*. 2020;69(12):2263–2264. doi:10.1136/gutjnl-2020-320919
44. Leyi H. [The changes of intestinal microflora in patients with irritable bowel syndrome and the effect of antibiotic rifaximin]. 2013.
45. Sciavilla P, Strati F, Di Paola M, et al. Gut microbiota profiles and characterization of cultivable fungal isolates in IBS patients. *Appl Microbiol Biotechnol*. 2021;105(8):3277–3288. doi:10.1007/s00253-021-11264-4
46. Ringel Y. The gut microbiome in irritable bowel syndrome and other functional bowel disorders. *Gastroenterol Clin North Am*. 2017;46 (1):91–101. doi:10.1016/j.gtc.2016.09.014
47. Dunlop SP, Coleman NS, Blackshaw E, et al. Abnormalities of 5-hydroxytryptamine metabolism in irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2005;3(4):349–357. doi:10.1016/s1542-3565(04)00726-8
48. Ford AC, Talley NJ. Mucosal inflammation as a potential etiological factor in irritable bowel syndrome: a systematic review. *J Gastroenterol*. 2011;46(4):421–431. doi:10.1007/s00535-011-0379-9
49. Di Tommaso N, Gasbarrini A, Ponziani FR. Intestinal barrier in human health and disease. *Int J Environ Res Public Health*. 2021;18(23):12836. doi:10.3390/ijerph182312836
50. Shumei Lai LW. Research progress of relationship between intestinal flora disorder and irritable bowel syndrome. *Contemp Med*. 2018;24 (03):182–184.
51. Xiaowei Xing JT, Shu Jiang XW, Xiang Cui DQ, Jinao D. The impacts of intestinal microflora on the structure and functions of intestinal mucosal barrier: Research progress. *Chin J Microecol*. 2018;30(06):725–730. doi:10.13381/j.cnki.cjm.201806026
52. Qu S, Zheng Y, Huang Y, et al. Excessive consumption of mucin by over-colonized Akkermansia muciniphila promotes intestinal barrier damage during malignant intestinal environment. *Front Microbiol*. 2023;14:1111911. doi:10.3389/fmicb.2023.1111911
53. Jabbar KS, Dolan B, Eklund L, et al. Association between Brachyspira and irritable bowel syndrome with diarrhoea. *Gut*. 2021;70 (6):1117–1129. doi:10.1136/gutjnl-2020-321466
54. Yihan Xu ZG, Weiming Z. Pathogenic mechanism of adhesion-induced invasive Escherichia coli and its role in Crohn′s disease. *Chin J Inflamm Bowel Dis*. 2020;04(4):333–336. doi:10.3760/cma.j.cn101480-20190527-00077
55. Grabauskas G, Gao J, Wu X, Zhou SY, Turgeon DK, Owyang C. Gut microbiota alter visceral pain sensation and inflammation via modulation of synthesis of resolvin D1 in colonic tuft cells. *Gastroenterology*. 2022:S0016–5085(22)00829–00820[pii]. doi:10.1053/j.gastro.2022.07.053
56. Klem F, Wadhwa A, Prokop LJ, et al. Prevalence, risk factors, and outcomes of irritable bowel syndrome after infectious enteritis: a systematic review and meta-analysis. *Gastroenterology*. 2017;152(5):1042–1054.
57. Erying Zhao JZ, Haiyun Chu SL, Yanjie Y. Epidemiology and pathogenic factors of irritable bowel syndrome: a review on research progress. *Chin J Public Health*. 2021;37(04):764–768.
58. Yan Jiang CS, Chunhong Xu DZ, Jinling S. Relationship between expression of NOD2, TLR2 and TLR4 and intestinal mucosal function in intestinal epithelial cells of young rats. *J Clin Exp Med*. 2020;19(11):1162–1165.
59. Huang Y, Chen Z. Inflammatory bowel disease related innate immunity and adaptive immunity. *Am J Transl Res*. 2016;8(6):2490–2497.
60. Burgueño JF, Abreu MT. Epithelial Toll-like receptors and their role in gut homeostasis and disease. *Nat Rev Gastroenterol Hepatol*. 2020;17 (5):263–278. doi:10.1038/s41575-019-0261-4
61. Takakura W, Pimentel M. Small intestinal bacterial overgrowth and irritable bowel syndrome - an update. *Front Psychiatry*. 2020;11:664. doi:10.3389/fpsyt.2020.00664
62. van Thiel I, Botschuijver S, de Jonge WJ, Seppen J. Painful interactions: microbial compounds and visceral pain. *Biochim Biophys Acta Mol Basis Dis*. 2020;1866(1):165534. doi:10.1016/j.bbadis.2019.165534
63. Pike BL, Paden KA, Alcala AN, et al. Immunological biomarkers in postinfectious irritable bowel syndrome. *J Travel Med*. 2015;22 (4):242–250. doi:10.1111/jtm.12218
64. Yang B, Zhou X, Lan C. Changes of cytokine levels in a mouse model of post-infectious irritable bowel syndrome. *BMC Gastroenterol*. 2015;15:43. doi:10.1186/s12876-015-0272-8
65. Sundin J, Rangel I, Kumawat AK, Hultgren-Hörnquist E, Brummer RJ. Aberrant mucosal lymphocyte number and subsets in the colon of post-infectious irritable bowel syndrome patients. *Scand J Gastroenterol*. 2014;49(9):1068–1075. doi:10.3109/00365521.2014.926982

66. Ohman L, Simrén M. Pathogenesis of IBS: role of inflammation, immunity and neuroimmune interactions. *Nat Rev Gastroenterol Hepatol*. 2010;7(3):163–173. doi:10.1038/nrgastro.2010.4
67. Chabbi-Achengli Y, Coman T, Collet C, et al. Serotonin is involved in autoimmune arthritis through Th17 immunity and bone resorption. *Am J Pathol*. 2016;186(4):927–937. doi:10.1016/j.ajpath.2015.11.018
68. Long Y, Wang W, Wang H, Hao L, Qian W, Hou X. Characteristics of intestinal lamina propria dendritic cells in a mouse model of postinfectious irritable bowel syndrome. *J Gastroenterol Hepatol*. 2012;27(5):935–944. doi:10.1111/j.1440-1746.2011.07046.x
69. Yano JM, Yu K, Donaldson GP, et al. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell*. 2015;161(2):264–276. doi:10.1016/j.cell.2015.02.047
70. Ziyu Liu CM, Weiyun Z. Research advances in interaction between gut microbiota and serotonin. *Acta Microbiologica Sinica*. 2022;62(4):1334–1344. doi:10.13343/j.cnki.wsxb.20210524
71. Wang X, Fu SQ, Yuan X, et al. A GAPDH serotonylation system couples CD8(+) T cell glycolytic metabolism to antitumor immunity. *Mol Cell*. 2024;84(4):760–775.e7. doi:10.1016/j.molcel.2023.12.015
72. Jiahui Li QL, Shiyang Liang JS, Jingjie W. Research advances in brain-gut-microbiome axis in pathogenesis of irritable bowel syndrome. *Acad J Chin PLA Med School*. 2023;44(12):1403–1409. doi:10.12435/j.issn.2095-5227.2023.110
73. Pellegrino R, Gravina AG. Irritable bowel syndrome remains a complex disorder of gut-brain interaction: too many actors on stage. *World J Gastroenterol*. 2025;31(8):101357. doi:10.3748/wjg.v31.i8.101357
74. Gwee KA, Ghoshal UC, Chen M. Irritable bowel syndrome in Asia: pathogenesis, natural history, epidemiology, and management. *J Gastroenterol Hepatol*. 2018;33(1):99–110. doi:10.1111/jgh.13987
75. Agirman G, Yu KB, Hsiao EY. Signaling inflammation across the gut-brain axis. *Science*. 2021;374(6571):1087–1092. doi:10.1126/science.abi6087
76. Grover M, Vanuytsel T, Chang L. Intestinal permeability in disorders of gut-brain interaction: from bench to bedside. *Gastroenterology*. 2025;168(3):480–495. doi:10.1053/j.gastro.2024.08.033
77. Dickhaus B, Mayer EA, Firooz N, et al. Irritable bowel syndrome patients show enhanced modulation of visceral perception by auditory stress. *Am J Gastroenterol*. 2003;98(1):135–143. doi:10.1111/j.1572-0241.2003.07156.x
78. Su Q, Liu L, Hua T, et al. Selective disruption of gray matter volume covariance in orbitofrontal cortex subregions among patients with functional constipation. *Sci Rep*. 2025;15(1):15440. doi:10.1038/s41598-025-00148-6
79. Staudacher HM, Black CJ, Teasdale SB, Mikocka-Walus A, Keefer L. Irritable bowel syndrome and mental health comorbidity - approach to multidisciplinary management. *Nat Rev Gastroenterol Hepatol*. 2023;20(9):582–596. doi:10.1038/s41575-023-00794-z
80. Shaohua H. Advances in the study on brain-gut axis mechanism of common mental disorders and clinical intervention. *Sichuan Mental Health*. 2023;36(3):193–196. doi:10.11886/scjsws20230525001
81. Feng Yu FJ, Shuai Xu JW, Xianliang Z. Mechanism of exercise regulating neurological function by gut microbiota-gut-brain axis. *J Shanghai Univ Sport*. 2021;45(01):66–77. doi:10.16099/j.sus.2021.01.007
82. Wu H, Zhan K, Rao K, et al. Comparison of five diarrhea-predominant irritable bowel syndrome (IBS-D) rat models in the brain-gut-microbiota axis. *Biomed Pharmacother*. 2022;149:112811. doi:10.1016/j.biopha.2022.112811
83. Mamieva Z, Poluektova E, Svistushkin V, et al. Antibiotics, gut microbiota, and irritable bowel syndrome: what are the relations. *World J Gastroenterol*. 2022;28(12):1204–1219. doi:10.3748/wjg.v28.i12.1204
84. Sabo CM, Dumitrascu DL. Microbiota and the irritable bowel syndrome. *Minerva Gastroenterol*. 2021;67(4):377–384. doi:10.23736/S2724-5985.21.02923-5
85. Zhan K, Wu H, Xu Y, et al. The function of the gut microbiota-bile acid-TGR5 axis in diarrhea-predominant irritable bowel syndrome. *mSystems*. 2024;9(3):e0129923. doi:10.1128/msystems.01299-23
86. Fadgyas-Stanculete M, Buga AM, Popa-Wagner A, Dumitrascu DL. The relationship between irritable bowel syndrome and psychiatric disorders: from molecular changes to clinical manifestations. *J Mol Psychiatry*. 2014;2(1):4. doi:10.1186/2049-9256-2-4
87. Fond G, Loundou A, Hamdani N, et al. Anxiety and depression comorbidities in irritable bowel syndrome (IBS): a systematic review and meta-analysis. *Eur Arch Psychiatry Clin Neurosci*. 2014;264(8):651–660. doi:10.1007/s00406-014-0502-z
88. Chidambaram SB, Essa MM, Rathipriya AG, et al. Gut dysbiosis, defective autophagy and altered immune responses in neurodegenerative diseases: tales of a vicious cycle. *Pharmacol Ther*. 2022;231:107988. doi:10.1016/j.pharmthera.2021.107988
89. Kaser A, Lee AH, Franke A, et al. XBP1 links ER stress to intestinal inflammation and confers genetic risk for human inflammatory bowel disease. *Cell*. 2008;134(5):743–756. doi:10.1016/j.cell.2008.07.021
90. Góralczyk-Bińkowska A, Szmajda-Krygier D, Kozłowska E. The microbiota-gut-brain axis in psychiatric disorders. *Int J Mol Sci*. 2022;23(19):11245. doi:10.3390/ijms231911245
91. Clark A, Mach N. Exercise-induced stress behavior, gut-microbiota-brain axis and diet: a systematic review for athletes. *J Int Soc Sports Nutr*. 2016;13:43. doi:10.1186/s12970-016-0155-6
92. Gubert C, Kong G, Renoir T, Hannan AJ. Exercise, diet and stress as modulators of gut microbiota: implications for neurodegenerative diseases. *Neurobiol Dis*. 2020;134:104621. doi:10.1016/j.nbd.2019.104621
93. Shandilya S, Kumar S, Kumar Jha N, Kumar Kesari K, Ruokolainen J. Interplay of gut microbiota and oxidative stress: perspective on neurodegeneration and neuroprotection. *J Adv Res*. 2022;38:223–244. doi:10.1016/j.jare.2021.09.005
94. Gao X, Cao Q, Cheng Y, et al. Chronic stress promotes colitis by disturbing the gut microbiota and triggering immune system response. *Proc Natl Acad Sci U S A*. 2018;115(13):E2960–E2969. doi:10.1073/pnas.1720696115
95. Wielgosz-Grochowska JP, Domanski N, Drywień ME. Efficacy of an irritable bowel syndrome diet in the treatment of small intestinal bacterial overgrowth: a narrative review. *Nutrients*. 2022;14(16):3382. doi:10.3390/nu14163382
96. Lacy BE, Pimentel M, Brenner DM, et al. ACG clinical guideline: management of irritable bowel syndrome. *Am J Gastroenterol*. 2021;116(1):17–44. doi:10.14309/ajg.0000000000001036
97. Halmos EP, Power VA, Shepherd SJ, Gibson PR, Muir JG. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. *Gastroenterology*. 2014;146(1):67–75.e5. doi:10.1053/j.gastro.2013.09.046
98. Dyadyk OO, Snisarevskyi PP, Snisarevska TP. Morphological features of cellular infiltration in the mucosa of large intestine in ulcerative colitis and irritable bowel syndrome. *Wiad Lek*. 2021;74(1):57–63.

99. Cremon C, Gargano L, Morselli-Labate AM, et al. Mucosal immune activation in irritable bowel syndrome: gender-dependence and association with digestive symptoms. *Am J Gastroenterol*. 2009;104(2):392–400. doi:10.1038/ajg.2008.94
100. Guilarte M, Santos J, de Torres I, et al. Diarrhoea-predominant IBS patients show mast cell activation and hyperplasia in the jejunum. *Gut*. 2007;56(2):203–209. doi:10.1136/gut.2006.100594
101. Bashashati M, Moossavi S, Cremon C, et al. Colonic immune cells in irritable bowel syndrome: a systematic review and meta-analysis. *Neurogastroenterol Motil*. 2018;30(1). doi:10.1111/nmo.13192
102. Katsumata R, Ishii M, Lee S, et al. Cytokine profile and immunoglobulin E-mediated serological food hypersensitivity in patients with irritable bowel syndrome with diarrhea. *J Neurogastroenterol Motil*. 2018;24(3):415–421. doi:10.5056/jnm17114
103. Boyer J, Saint-Paul MC, Dadone B, et al. Inflammatory cell distribution in colon mucosa as a new tool for diagnosis of irritable bowel syndrome: a promising pilot study. *Neurogastroenterol Motil*. 2018;30(1). doi:10.1111/nmo.13223
104. Gao J, Xiong T, Grabauskas G, Owyang C. Mucosal serotonin reuptake transporter expression in irritable bowel syndrome is modulated by gut microbiota via mast cell-prostaglandin E2. *Gastroenterology*. 2022;162(7):1962–1974.e6. doi:10.1053/j.gastro.2022.02.016
105. An S, Zong G, Wang Z, Shi J, Du H, Hu J. Expression of inducible nitric oxide synthase in mast cells contributes to the regulation of inflammatory cytokines in irritable bowel syndrome with diarrhea. *Neurogastroenterol Motil*. 2016;28(7):1083–1093. doi:10.1111/nmo.12811
106. Decraecker L, Cuende Estévez M, Van Remoortel S, et al. Characterisation of MRGPRX2+ mast cells in irritable bowel syndrome. *Gut*. 2025;74(7):1068–1077. doi:10.1136/gutjnl-2024-334037
107. Grabauskas G, Wu X, Gao J, Li JY, Turgeon DK, Owyang C. Prostaglandin E(2), produced by mast cells in colon tissues from patients with irritable bowel syndrome, contributes to visceral hypersensitivity in mice. *Gastroenterology*. 2020;158(8):2195–2207.e6. doi:10.1053/j.gastro.2020.02.022
108. Pan X, Zhu Q, Pan LL, Sun J. Macrophage immunometabolism in inflammatory bowel diseases: from pathogenesis to therapy. *Pharmacol Ther*. 2022;238:108176. doi:10.1016/j.pharmthera.2022.108176
109. Yunna C, Mengru H, Lei W, Weidong C. Macrophage M1/M2 polarization. *Eur J Pharmacol*. 2020;877:173090. doi:10.1016/j.ejphar.2020.173090
110. Cutolo M, Campitiello R, Gotelli E, Soldano S. The role of M1/M2 macrophage polarization in rheumatoid arthritis synovitis. *Front Immunol*. 2022;13:867260. doi:10.3389/fimmu.2022.867260
111. Rodríguez-Fandiño OA, Hernández-Ruiz J, López-Vidal Y, Charúa-Guindic L, Escobedo G, Schmulson MJ. Maturation phenotype of peripheral blood monocyte/macrophage after stimulation with lipopolysaccharides in irritable bowel syndrome. *J Neurogastroenterol Motil*. 2017;23(2):281–288. doi:10.5056/jnm16137
112. Meng EX, Verne GN, Zhou Q. Macrophages and Gut barrier function: guardians of gastrointestinal health in post-inflammatory and post-infection responses. *Int J Mol Sci*. 2024;25(17). doi:10.3390/ijms25179422
113. Li M, Zhang L, Lu B, et al. Role of dendritic cell-mediated abnormal immune response in visceral hypersensitivity. *Int J Clin Exp Med*. 2015;8(8):13243–13250.
114. Zhang L, Wang HL, Zhang YF, et al. Stress triggers irritable bowel syndrome with diarrhea through a spermidine-mediated decline in type I interferon. *Cell Metab*. 2024:S1550–4131(24)00366–00368[pii]. 10.1016/j.cmet.2024.09.002.
115. Zhang MM, Dang M, Wu X, et al. Da-Jian-Zhong decoction alleviates diarrhea-predominant irritable bowel syndrome via modulation of gut microbiota and Th17/Treg balance. *J Ethnopharmacol*. 2024;331:118275. doi:10.1016/j.jep.2024.118275
116. Shang Q, Yu X, Sun Q, Li H, Sun C, Liu L. Polysaccharides regulate Th1/Th2 balance: a new strategy for tumor immunotherapy. *Biomed Pharmacother*. 2024;170:115976. doi:10.1016/j.biopha.2023.115976
117. Ramanan D, Pratama A, Zhu Y, et al. Regulatory T cells in the face of the intestinal microbiota. *Nat Rev Immunol*. 2023;23(11):749–762. doi:10.1038/s41577-023-00890-w
118. Yuting Zhong ZW, Lichao Z. Advances in the study of natural small molecules to protect the intestinal epithelial tight junction barrier in inflammatory bowel disease. *Chin Pharmacolog Bull*. 2023;39(12):2205–2210. doi:10.12360/CPB202204046
119. Paradis T, Bègue H, Basmaciyan L, Dalle F, Bon F. Tight junctions as a key for pathogens invasion in intestinal epithelial cells. *Int J Mol Sci*. 2021;22(5):2506. doi:10.3390/ijms22052506
120. Shim JA, Ryu JH, Jo Y, Hong C. The role of gut microbiota in T cell immunity and immune mediated disorders. *Int J Biol Sci*. 2023;19(4):1178–1191. doi:10.7150/ijbs.79430
121. Pardo-Camacho C, Ganda Mall JP, Martínez C, et al. Mucosal plasma cell activation and proximity to nerve fibres are associated with glycocalyx reduction in diarrhoea-predominant irritable bowel syndrome: jejunal barrier alterations underlying clinical manifestations. *Cells*. 2022;11(13):2046. doi:10.3390/cells11132046
122. Vicario M, González-Castro AM, Martínez C, et al. Increased humoral immunity in the jejunum of diarrhoea-predominant irritable bowel syndrome associated with clinical manifestations. *Gut*. 2015;64(9):1379–1388. doi:10.1136/gutjnl-2013-306236
123. Zhai L, Huang C, Ning Z, et al. Ruminococcus gnavus plays a pathogenic role in diarrhea-predominant irritable bowel syndrome by increasing serotonin biosynthesis. *Cell Host Microbe*. 2023;31(1):33–44.e5. doi:10.1016/j.chom.2022.11.006
124. Magen E, Chikovani T. Possible therapeutic role of IgE blockade in irritable bowel syndrome. *World J Gastroenterol*. 2016;22(43):9451–9456. doi:10.3748/wjg.v22.i43.9451
125. Keszthelyi D, Troost FJ, Jonkers DM, et al. Serotonergic reinforcement of intestinal barrier function is impaired in irritable bowel syndrome. *Aliment Pharmacol Ther*. 2014;40(4):392–402. doi:10.1111/apt.12842
126. Choghakhori R, Abbasnezhad A, Hasanvand A, Amani R. Inflammatory cytokines and oxidative stress biomarkers in irritable bowel syndrome: association with digestive symptoms and quality of life. *Cytokine*. 2017;93:34–43. doi:10.1016/j.cyto.2017.05.005
127. Gryka-Marton M, Grabowska AD, Szukiewicz D. Breaking the barrier: the role of proinflammatory cytokines in BBB dysfunction. *Int J Mol Sci*. 2025;26(8). doi:10.3390/ijms26083532
128. Awad K, Barmeyer C, Bojarski C, et al. Epithelial barrier dysfunction in diarrhea-predominant irritable bowel syndrome (IBS-D) via downregulation of claudin-1. *Cells*. 2023;12(24):2846. doi:10.3390/cells12242846
129. Foerster EG, Mukherjee T, Cabral-Fernandes L, Rocha J, Girardin SE, Philpott DJ. How autophagy controls the intestinal epithelial barrier. *Autophagy*. 2022;18(1):86–103. doi:10.1080/15548627.2021.1909406

130. Chen S, Liu H, Li Z, et al. Epithelial PBLD attenuates intestinal inflammatory response and improves intestinal barrier function by inhibiting NF-κB signaling. *Cell Death Dis*. 2021;12(6):563. doi:10.1038/s41419-021-03843-0
131. Bashashati M, Moradi M, Sarosiek I. Interleukin-6 in irritable bowel syndrome: a systematic review and meta-analysis of IL-6 (-G174C) and circulating IL-6 levels. *Cytokine*. 2017;99:132–138. doi:10.1016/j.cyto.2017.08.017
132. Zhang S, Tian D, Xia Z, et al. Chang-Kang-Fang alleviates diarrhea predominant irritable bowel syndrome (IBS-D) through inhibiting TLR4/NF-κB/NLRP3 pathway. *J Ethnopharmacol*. 2024;330:118236. doi:10.1016/j.jep.2024.118236
133. Duan J, Matute JD, Unger LW, et al. Endoplasmic reticulum stress in the intestinal epithelium initiates purine metabolite synthesis and promotes Th17 cell differentiation in the gut. *Immunity*. 2023;56(5):1115–1131.e9. doi:10.1016/j.immuni.2023.02.018
134. Omenetti S, Pizarro TT. The Treg/Th17 axis: a dynamic balance regulated by the gut microbiome. *Front Immunol*. 2015;6:639. doi:10.3389/fimmu.2015.00639
135. Czogalla B, Schmitteckert S, Houghton LA, et al. A meta-analysis of immunogenetic Case-Control Association Studies in irritable bowel syndrome. *Neurogastroenterol Motil*. 2015;27(5):717–727. doi:10.1111/nmo.12548
136. Kumar A, Rani L, Mhaske ST, et al. IL-3 receptor expression on activated human th cells is regulated by IL-4, and IL-3 synergizes with IL-4 to enhance Th2 cell differentiation. *J Immunol*. 2020;204(4):819–831. doi:10.4049/jimmunol.1801629
137. Zhu SW, Liu ZJ, Sun QH, Duan LP. Effect of the interleukin 10 polymorphisms on interleukin 10 production and visceral hypersensitivity in Chinese patients with diarrhea-predominant irritable bowel syndrome. *Chin Med J*. 2019;132(13):1524–1532. doi:10.1097/CM9.0000000000000306
138. Dong L, Xie J, Wang Y, et al. Mannose ameliorates experimental colitis by protecting intestinal barrier integrity. *Nat Commun*. 2022;13(1):4804. doi:10.1038/s41467-022-32505-8
139. Kim W, Lee EJ, Bae IH, et al. Lactobacillus plantarum-derived extracellular vesicles induce anti-inflammatory M2 macrophage polarization in vitro. *J Extracell Vesicles*. 2020;9(1):1793514. doi:10.1080/20013078.2020.1793514
140. Schmulson M, Pulido-London D, Rodriguez O, et al. Lower serum IL-10 is an independent predictor of IBS among volunteers in Mexico. *Am J Gastroenterol*. 2012;107(5):747–753. doi:10.1038/ajg.2011.484
141. Xie Y, Zhan X, Tu J, et al. Atractylodes oil alleviates diarrhea-predominant irritable bowel syndrome by regulating intestinal inflammation and intestinal barrier via SCF/c-kit and MLCK/MLC2 pathways. *J Ethnopharmacol*. 2021;272:113925. doi:10.1016/j.jep.2021.113925
142. Linsalata M, Prospero L, Ignazzi A, et al. Depression in Diarrhea-Predominant IBS Patients: exploring the Link Between Gut Barrier Dysfunction and Erythrocyte Polyunsaturated Fatty Acid Levels. *J Clin Med*. 2025;14(7). doi:10.3390/jcm14072483
143. Caviglia GP, Tucci A, Pellicano R, et al. Clinical response and changes of cytokines and zonulin levels in patients with diarrhoea-predominant irritable bowel syndrome treated with bifidobacterium longum ES1 for 8 or 12 weeks: a preliminary report. *J Clin Med*. 2020;9(8):2353. doi:10.3390/jcm9082353
144. Zhen Y, Chu C, Zhou S, Qi M, Shu R. Imbalance of tumor necrosis factor-α, interleukin-8 and interleukin-10 production evokes barrier dysfunction, severe abdominal symptoms and psychological disorders in patients with irritable bowel syndrome-associated diarrhea. *Mol Med Rep*. 2015;12(4):5239–5245. doi:10.3892/mmr.2015.4079
145. Singh S, Anshita D, Ravichandiran V. MCP-1: function, regulation, and involvement in disease. *Int Immunopharmacol*. 2021;101(Pt B):107598. doi:10.1016/j.intimp.2021.107598
146. Nabavi-Rad A, Sadeghi A, Asadzadeh Aghdaei H, Yadegar A, Smith SM, Zali MR. The double-edged sword of probiotic supplementation on gut microbiota structure in Helicobacter pylori management. *Gut Microbes*. 2022;14(1):2108655. doi:10.1080/19490976.2022.2108655
147. Huang X, Li A, Long P, Liu Y, Zhou Z, Pan Y. The neutrophil-to-albumin ratio (NAR): a novel index in relation to clinical symptoms, quality of life, and psychological status in diarrhea-predominant irritable bowel syndrome (IBS-D). *J Inflamm Res*. 2024;17:3685–3695. doi:10.2147/JIR.S458363
148. Hayatbakhsh MM, Gowhari Shabgah A, Pishgouyi S, Tavakol Afshari J, Zeidabadi H, Mohammadi M. The Serum Levels of CCL2 and CCL16 Expression in Patients with Irritable Bowel Syndrome. *Rep Biochem Mol Biol*. 2019;8(1):9–14.
149. Yoshimoto T, Oshima T, Huang X, Tomita T, Fukui H, Miwa H. Microinflammation in the intestinal mucosa and symptoms of irritable bowel syndrome. *J Gastroenterol*. 2022;57(2):62–69. doi:10.1007/s00535-021-01838-4
150. Rizzello F, Ricci C, Scandella M, et al. Dietary geraniol ameliorates intestinal dysbiosis and relieves symptoms in irritable bowel syndrome patients: a pilot study. *BMC Complement Altern Med*. 2018;18(1):338. doi:10.1186/s12906-018-2403-6
151. Schmidt C, Häuser W, Giese T, Stallmach A. Irritable pouch syndrome is associated with depressiveness and can be differentiated from pouchitis by quantification of mucosal levels of proinflammatory gene transcripts. *Inflamm Bowel Dis*. 2007;13(12):1502–1508. doi:10.1002/ibd.20241
152. Kim HJ. Do toll-like receptors play a new role as a biomarker of irritable bowel syndrome. *J Neurogastroenterol Motil*. 2018;24(4):510–511. doi:10.5056/jnm18153
153. Koçak E, Akbal E, Köklü S, Ergül B, Can M. The colonic tissue levels of TLR2, TLR4 and nitric oxide in patients with irritable bowel syndrome. *Intern Med*. 2016;55(9):1043–1048. doi:10.2169/internalmedicine.55.5716
154. He Y, Sun MM, Zhang GG, et al. Targeting PI3K/Akt signal transduction for cancer therapy. *Signal Transduct Target Ther*. 2021;6(1):425. doi:10.1038/s41392-021-00828-5
155. Glaviano A, Foo A, Lam HY, et al. PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer. *Mol Cancer*. 2023;22(1):138. doi:10.1186/s12943-023-01827-6
156. Zhang X, Zhang F, Li Y, et al. Blockade of PI3K/AKT signaling pathway by Astragaloside IV attenuates ulcerative colitis via improving the intestinal epithelial barrier. *J Transl Med*. 2024;22(1):406. doi:10.1186/s12967-024-05168-w
157. Wang L, Chen H, DU Y, et al. Yiqi Zishen Formula ameliorates inflammation in mice with chronic obstructive pulmonary disease by inhibiting the PI3K/Akt/NF-κB signaling pathway. *Nan Fang Yi Ke Da Xue Xue Bao*. 2025;45(7):1409–1422. doi:10.12122/j.issn.1673-4254.2025.07.07
158. Tang P, Ding Q, Lin J, et al. Pen yan jing tablets alleviates pelvic inflammatory disease by inhibiting Akt/NF-κB pathway. *Int J Med Sci*. 2023;20(11):1386–1398. doi:10.7150/ijms.87433
159. Liao C, Lai T, Lin Y, et al. Inhibition of Polyinosinic-polycytidylic acid-induced acute pulmonary inflammation and NF-κB activation in mice by a banana plant extract. *Int J Med Sci*. 2024;21(1):107–122. doi:10.7150/ijms.88748

160. Samakova A, Gazova A, Sabova N, Valaskova S, Jurikova M, Kyselovic J. The PI3k/Akt pathway is associated with angiogenesis, oxidative stress and survival of mesenchymal stem cells in pathophysiologic condition in ischemia. *Physiol Res*. 2019;68(Suppl 2):S131–S138. doi:10.33549/physiolres.934345
161. Chen S, Huang J, Liu T, et al. PI3K/Akt signaling pathway mediates the effect of low-dose boron on barrier function, proliferation and apoptosis in rat intestinal epithelial cells. *Sci Rep*. 2024;14(1):393. doi:10.1038/s41598-023-50800-2
162. Lembo A, Sultan S, Chang L, Heidelbaugh JJ, Smalley W, Verne GN. AGA clinical practice guideline on the pharmacological management of irritable bowel syndrome with diarrhea. *Gastroenterology*. 2022;163(1):137–151. doi:10.1053/j.gastro.2022.04.017
163. Qianxin Lou MT, Yan Tang SQ. Progress of Traditional Chinese Medicine treating irritable bowels syndrome-D. *Liaoning J Trad Chin Med*. 2020;47(10):206–208. doi:10.13192/j.issn.1000-1719.2020.10.061
164. Jingyi Liu CS, Yueying Q. Progress in TCM treatment of diarrhea-predominant irritable bowel syndrome. *Xinjiang J Trad Chin Med*. 2024;42 (04):140–143.
165. Jiaojiao wang HL, Xiaoyuan L. Research progress in the treatment of diarrheal irritable bowel syndrome with traditional Chinese medicine classic formulae. *Acta Chin Med Pharmacol*. 2024;52(04):112–116. doi:10.19664/j.cnki.1002-2392.240084
166. Pengfei Liu WZ, Yaozhou T. Research progress of external treatment of traditional Chinese medicine in the treatment of diarrhea-predominant irritable bowel syndrome. *Jiangxi J Trad Chin Med*. 2020;51(01):78–80.
167. Saller BS, Wöhrle S, Fischer L, et al. Acute suppression of mitochondrial ATP production prevents apoptosis and provides an essential signal for NLRP3 inflammasome activation. *Immunity*. 2024:S1074–7613(24)00492–00498. doi:10.1016/j.immuni.2024.10.012
168. Lamkanfi M, Dixit VM. Mechanisms and functions of inflammasomes. *Cell*. 2014;157(5):1013–1022. doi:10.1016/j.cell.2014.04.007
169. Botz B, Bölcskei K, Helyes Z. Challenges to develop novel anti-inflammatory and analgesic drugs. *Wiley Interdiscip Rev Nanomed Nanobiotechnol*. 2017;9(3). doi:10.1002/wnan.1427
170. Wang W, Gao Y, Zhang M, Li Y, Tang BZ. Neutrophil-like Biomimic AIE Nanoparticles with High-Efficiency Inflammatory Cytokine Targeting Enable Precise Photothermal Therapy and Alleviation of Inflammation. *ACS Nano*. 2023;17(8):7394–7405. doi:10.1021/acsnano.2c11762
171. Wang B, Li J, Tian F. Downregulation of lncRNA SNHG14 attenuates osteoarthritis by inhibiting FSTL-1 mediated NLRP3 and TLR4/NF-κB pathway through miR-124-3p. *Life Sci*. 2021;270:119143. doi:10.1016/j.lfs.2021.119143
172. Liu N, Chen L, Yan M, et al. *Eubacterium rectale* improves the efficacy of Anti-PD1 immunotherapy in melanoma via l-Serine-Mediated NK cell activation. *Research*. 2023;6:0127. doi:10.34133/research.0127
173. Li X, Yi H, Jin Z, et al. MCRS1 sensitizes T cell-dependent immunotherapy by augmenting MHC-I expression in solid tumors. *J Exp Med*. 2024;221(12):e20240959. doi:10.1084/jem.20240959
174. Neurath MF. Strategies for targeting cytokines in inflammatory bowel disease. *Nat Rev Immunol*. 2024;24(8):559–576. doi:10.1038/s41577-024-01008-6
175. Liu J, Di B, Xu LL. Recent advances in the treatment of IBD: targets, mechanisms and related therapies. *Cytokine Growth Factor Rev*. 2023;71-72:1–12. doi:10.1016/j.cytogfr.2023.07.001
176. Stallmach A, Atreya R, Grunert PC, Stallhofer J, de Laffolie J, Schmidt C. Treatment Strategies in Inflammatory Bowel Diseases. *Dtsch Arztebl Int*. 2023;120(45):768–778. doi:10.3238/arztebl.m2023.0142
177. Wellens J, Sabino J, Vanuytsel T, Tack J, Vermeire S. Recent advances in clinical practice: mastering the challenge-managing IBS symptoms in IBD. *Gut*. 2025;74(2):312–321. doi:10.1136/gutjnl-2024-333565