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Roles of G protein-coupled receptors in inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) is a complex disease with multiple pathogenic factors. Although the pathogenesis of IBD is still unclear, a current hypothesis suggests that genetic susceptibility, environmental factors, a dysfunctional immune system, the microbiome, and the interactions of these factors substantially contribute to the occurrence and development of IBD. Although existing and emerging drugs have been proven to be effective in treating IBD, none can cure IBD permanently. G protein-coupled receptors (GPCRs) are critical signaling molecules implicated in the immune response, cell proliferation, inflammation regulation and intestinal barrier maintenance. Breakthroughs in the understanding of the structures and functions of GPCRs have provided a driving force for exploring the roles of GPCRs in the pathogenesis of diseases, thereby leading to the development of GPCR-targeted medication. To date, a number of GPCRs have been shown to be associated with IBD, significantly advancing the drug discovery process for IBD. The associations between GPCRs and disease activity, disease severity, and disease phenotypes have also paved new avenues for the precise management of patients with IBD. In this review, we mainly focus on the roles of the most studied proton-sensing GPCRs, cannabinoid receptors, and estrogen-related GPCRs in the pathogenesis of IBD and their potential clinical values in IBD and some other diseases.

Key words: G protein-coupled receptors; Inflammatory bowel disease; Pathogenesis; Signaling pathway; Drug discovery

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Core tip: Inflammatory bowel disease is a complex and heterogeneous disease with unclear pathogenesis. Advances in the understanding of the structures and functions of G protein-coupled receptors (GPCRs) have been a driving force for exploring the roles of

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GPCRs in the pathogenesis of diseases, thereby leading to the development of GPCR-targeted medication. In this review, we mainly focus on the roles of GPCRs in the pathogenesis of inflammatory bowel disease and their potential values in disease diagnosis, treatment and monitoring.

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, relapsing and destructive disorder that mainly affects the gastrointestinal (GI) tract^[1]. Long-lasting inflammation and aberrant immune responses gradually lead to the development of stenosis and fistulas, which causes a dramatic increase in medical expense and negatively affects the quality of life of patients with IBD. Crohn's disease (CD) and ulcerative colitis (UC) are two major subtypes, and they share some clinical, immunologic, and pathological characteristics. Although the exact etiology of IBD is not completely understood, genetic susceptibility, environmental factors, a dysfunctional immune system, and the microbiome are believed to play multifaceted roles in the onset and progression of this disease^[1,2]. New evidence suggests that G protein-coupled receptors (GPCRs) are critical signaling molecules implicated in the immune response, cell proliferation, inflammation regulation and intestinal barrier maintenance^[3]. Significant associations between GPCRs and the pathogenesis of numerous diseases such as IBD, diabetes mellitus, Parkinson's disease and cancers have been confirmed in different studies^[4-6]. Although many agents, such as aminosalicylic acid, glucocorticoids, immunosuppressants, biological agents (infliximab, adalimumab, vedolizumab and ustekinumab), and small molecule drugs (tofacitinib), have been approved to treat IBD, but none can prevent disease flare-ups or cure IBD permanently. Moreover, side effects such as opportunistic infection, myelotoxicity and lymphoma limit their clinical application to a certain degree^[7]. The development of novel medications with good therapeutic effectiveness and few adverse events is rapidly becoming a vital part of IBD research. Therefore, an in-depth understanding of the roles of GPCRs in the pathogenic mechanisms of IBD is essential in providing the possibility of translational research on GPCR-based therapeutics. In addition, correlations between GPCRs and IBD activity, disease severity, and disease phenotypes can further help physicians manage the disease more efficiently. In this paper, we outline the basic structures, functions and signaling pathways of GPCRs, with a focus on the roles of GPCRs in the pathogenesis of IBD and their potential values in disease diagnosis, treatment and monitoring.

BASIC STRUCTURES, FUNCTIONS, AND SIGNALING PATHWAYS OF GPCRs

GPCRs are the largest and most functionally diverse membrane protein family consisting of numerous receptors. To date, more than 800 genes have been identified to be responsible for coding GPCRs in the human genome^[3]. GPCRs share common structural motifs, including the characteristic seven α -helical structured transmembrane domains, an extracellular N-terminus, and a changeable intracellular C-terminus^[8]. Ligands such as light photons, odor molecules, hormones, neurotransmitters, chemokines, *etc.*, can interact with the extracellular sites of GPCRs, creating conformational changes in the transmembrane domains and intracellular sequences^[9]. GPCRs are characteristically coupled to and activate the heterotrimeric guanine-nucleotide-binding signal transducing proteins (G proteins), which in turn are dissociated into $G\alpha$ and $G\beta\gamma$ subunits, and interact with different downstream effectors^[10]. According to the sequence similarity of $G\alpha$ subunits, the G proteins are divided into four types, namely, G_s , G_i/o , $G_q/11$ and $G_{12/13}$, which are responsible for binding to specific GPCRs^[3,10]. Therefore, G proteins are of utmost importance in

GPCR signaling transduction, determining the activations of second messengers [such as Ca^{2+} , cyclic adenosine monophosphate (cAMP), inositol 1,4,5-triphosphate (IP₃), and diacylglycerol (DG)], and influencing the activities of calmodulin, protein kinase A (PKA), protein kinase C (PKC) and mitogen-activated protein kinases (MAPKs)^[11] (Figure 1). A complex signal transduction network has made it particularly difficult for researchers to fully clarify the GPCR signaling pathways and pinpoint the pathogenic pathway for one given disease.

Two classic signaling pathways related to GPCRs have been extensively studied in the past few decades. The most important pathway is the adenylyl cyclase (AC)/cAMP signaling pathway (Figure 1). GPCRs bind to and activate Gs proteins, then stimulate AC, leading to an increased concentration of cAMP and the activation of PKA. Pathophysiological processes associated with the AC/cAMP pathway include the immunoregulation, inflammatory responses, apoptosis and autophagy. In contrast, the activation of Gi proteins has the opposite effect, causing a reduction in cAMP and inhibition of PKA^[10-12]. Another fundamental signaling cascade is the phospholipase C β (PLC- β)/ Ca^{2+} signaling pathway^[10,11] (Figure 1). Activated Gq proteins stimulate the major effector enzyme PLC- β , and then hydrolyze phosphatidylinositol 4,5-bisphosphate (PIP₂) to create two second-messengers, IP₃ and DG, which are responsible for the regulation of calcium and calmodulin-dependent protein kinase, and PKC activation, mediating the modulation of cellular growth, proliferation and division^[10,11]. It is evident that GPCR signaling pathways are involved in some critical IBD-associated biological processes, including immune responses, inflammatory reactions, apoptosis and autophagy. Therefore, identification of the roles of GPCRs in IBD will facilitate a better understanding of the intricate pathogenesis of the disease, thereby promoting an innovation in disease treatment for patients with IBD.

ROLES OF GPCRS IN THE PATHOGENESIS OF IBD

It is universally acknowledged that GPCRs play different roles in the origination and development of many diseases, including IBD, diabetes mellitus, Parkinson's disease, breast cancer, *etc.* IBD is characterized by chronicity, heterogeneity and destructiveness, which pose a challenge for physicians to manage patients effectively and precisely. Recent technological advances have substantially facilitated the process of GPCRs research in IBD, and furthermore, many IBD researchers consider GPCRs to be a major area of focus in their research, given the enormous potential of GPCRs in disease diagnosis, treatment and monitoring. In this review, we focus on the roles of the GPCRs in the pathogenesis of IBD, including proton-sensing GPCRs, cannabinoid receptors, autonomic nervous system GPCRs and estrogen-related GPCRs.

Proton-sensing GPCRs

IBD commonly presents chronic and long-lasting mucosal inflammation of the GI tract, especially of the small intestine and colon. Cellular metabolic byproducts and invasive pathogenic microorganisms induce mucosal inflammation. In turn, mucosal inflammation contributes to an increased concentration of proton and lactate products, as well as proinflammatory cytokines, chemokines and adhesion molecules in local sites and distal areas, which dramatically influences the balance between proinflammatory and anti-inflammatory responses^[13-15]. Therefore, various inflammatory diseases, including IBD, represent an acidic microenvironment with a local tissue pH below 7.0 or even 6.0^[14-16]. Available data indicate that patients with IBD manifest a more acidic intestinal lumen than patients without IBD^[14,17]. Thus, it is necessary to determine the activity and functions of cells in an acidic microenvironment and the underlying signaling pathways in IBD research. A new pH-sensing GPCR family is comprised of G protein-coupled receptor 4 (GPR4), G protein-coupled receptor 68 (GPR68 or OGR1), G protein-coupled receptor 65 (GPR65 or TDAG8), and G protein-coupled receptor 132 (GPR132 or G2A)^[18]; these proteins can sense protons near histidine residues on their extracellular regions, and then result in inflammation and immune responses. In addition, they can induce blood vessel formation and regulate metastasis and the proliferation of cancer cells^[13,19]. Several lines of evidence have suggested that proton-sensing GPCRs are involved in a wide variety of diseases, including inflammatory diseases (IBD), ischemic disease (myocardial infarction), solid tumors (ovarian cancer), *etc.*^[13,20,21]. Elucidating the roles of pH-sensing GPCRs in these diseases may be helpful for physicians to investigate the pathogenic mechanisms and evaluate the disease state more extensively. In this paper, we focus on the roles of proton-sensing GPCRs in IBD (Table 1).

GPR4: The *GPR4* gene was first identified by Mahadevan *et al*^[22] in 1995. It is located

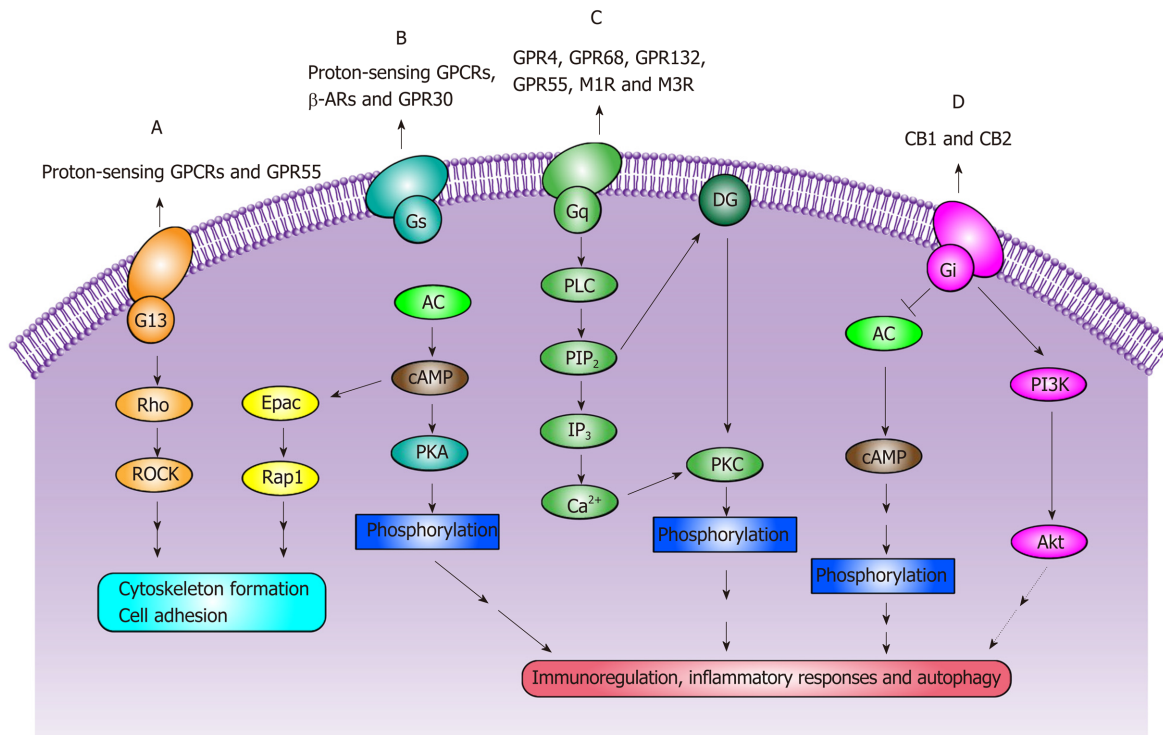


Figure 1 The main signaling pathways of G protein-coupled receptors. A: Proton-sensing G protein-coupled receptors and G protein-coupled receptor 55 are coupled to G13 proteins and are involved in G13/Rho signaling pathways, mediating the modulation of cytoskeleton formation and cell adhesion; B: Proton-sensing G protein-coupled receptors, G protein-coupled receptor 30 and β -adrenergic receptors are implicated in Gs/adenylyl cyclase/cyclic adenosine monophosphate (cAMP) signaling pathways and multiple phosphorylation events, and then mediate immunoregulation, inflammatory responses and autophagy. In addition, G protein-coupled receptor 4 is also implicated in cAMP/exchange protein activated by cAMP (Epac) signaling pathways, and then affects cell adhesion; C: G protein-coupled receptor 4, G protein-coupled receptor 68, G protein-coupled receptor 132, G protein-coupled receptor 55, type 1 muscarinic receptor and type 3 muscarinic receptor bind to Gq proteins and are involved in Gq/phospholipase C/ Ca^{2+} signaling pathways, then phosphorylate target proteins, mediating the regulation of immune response, inflammatory reaction and autophagy; D: Cannabinoid receptor 1 and cannabinoid receptor 2 are coupled to Gi proteins and are involved in immunoregulation, inflammatory responses and autophagy through Gi/adenylyl cyclase/cAMP and Gi/phosphatidylinositol 3 kinase/Akt signaling pathways. GPCRs: G protein-coupled receptors; GPR55: G protein-coupled receptor 55; ROCK: Rho associated coiled-coil containing protein kinase; GPR30: G protein-coupled receptor 30; β -ARs: β -adrenergic receptors, including β 1-, β 2- and β 3-adrenergic receptor; AC: Adenylyl cyclase; cAMP: Cyclic adenosine monophosphate; GPR4: G protein-coupled receptor 4; Epac: Exchange protein activated by cAMP; Rap1: Ras associated protein 1; PKA: Protein kinase A; GPR68: G protein-coupled receptor 68; GPR 132: G protein-coupled receptor 132; M1R: Type 1 muscarinic receptor; M3R: Type 3 muscarinic receptor; PLC: Phospholipase C; PIP₂: Phosphatidylinositol 4,5-bisphosphate; IP₃: Inositol 1,4,5-trisphosphate; DG: Diacylglycerol; PKC: Protein kinase C; CB1: Cannabinoid receptor 1; CB2: Cannabinoid receptor 2; PI3K: Phosphatidylinositol 3 kinase; Akt: Also known as protein kinase B (PKB); Proton-sensing GPCRs: GPR4, GPR68, GPR65 and GPR132; Phosphorylation: nuclear factor kappa-B (NF- κ B), extracellular signal-regulated kinase (ERK)/p38 mitogen-activated protein kinase (p38MAPK) etc.

on chromosome 19q13.3 and encodes a protein of 362 amino acids (a receptor) that can be activated by isocapnic and hypercapnic acidosis^[16,22]. GPR4 is widely expressed in various tissues, with the highest expression level in the lungs, and relatively lower expression levels in the heart, liver and intestine^[14,22]. Initially, GPR4 was found in myotonic dystrophy^[22]. Subsequent studies have also confirmed its involvement in other diseases, including IBD, rheumatoid arthritis (RA) and myocardial infarction. It is well known that the abnormal vascular inflammatory response in the intestine is a pathological hallmark of IBD. Available evidence has indicated that activation of GPR4 by isocapnic acidosis could indirectly aggravate inflammation by enhancing the adhesive ability of endothelial cells (ECs) to leukocytes through the Gs/cAMP/exchange protein activated by cAMP (Epac) signaling pathway^[18]. Other downstream pathways, such as the Gq/PLC/ Ca^{2+} and G13/Rho pathways, have also been reported in several other studies^[23] (Figure 1). In GPR4-mediated inflammatory responses, the expression levels of adhesion molecules such as E-selectin, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1) were significantly elevated^[18]. A later transcriptome analysis validated these results and revealed that GPR4, activated by acidosis, had a positive effect on the increased transcription of inflammatory genes, including nuclear factor kappa-B (NF- κ B) pathway genes (*NFKB1*, *NFKB2*, and *RELB*, etc.), and stress response genes (*ATF3* and *DDIT3*)^[16]. Moreover, the administration of a GPR4 antagonist could substantially ameliorate the acidosis-stimulated inflammatory responses^[16]. Histologic evidence has further demonstrated that, in comparison to control intestinal tissues, the mRNA

Table 1 Roles of G protein-coupled receptors in inflammatory bowel disease and the main signaling pathways of G protein-coupled receptors

GPCRs	Main signaling pathways	Roles
Proton-sensing GPCRs		
GPR4	Gs/AC/cAMP, cAMP/Epac, Gq/PLC/Ca ²⁺ , G13/Rho and NF-κB signaling pathways	Promotes leukocyte adhesion and increases the expression levels of adhesion molecules and inflammatory genes
GPR68	Gs/AC/cAMP, Gq/PLC/Ca ²⁺ , G13/Rho and ERK/p38MAPK signaling pathways	Aggravates intestinal inflammation and fibrogenesis, and improves epithelial barrier function
GPR65	Gs/AC/cAMP and G13/Rho signaling pathways	Alleviates inflammatory responses, and maintains epithelial barrier and lysosome function
GPR132	Gs/AC/cAMP, Gq/PLC/Ca ²⁺ , G13/Rho, Ras/ERK signaling pathways	Shows bidirectional effects on inflammation and controls the polarization of macrophages
Cannabinoid receptors		
CB1 and CB2	Gi/AC/cAMP, Gi/PI3K/Akt and ERK/p38MAPK signaling pathways	Inhibit intestinal motility, secretion and inflammation; increase susceptibility to IBD; and affect the course of the disease
GPR55	Gq/PLC/Ca ²⁺ and G13/Rho signaling pathways	Regulates intestinal motility and neuropathic and inflammatory pain, and shows bidirectional effects on intestinal inflammation
Autonomic nervous system GPCRs		
M1R and M3R	Gq/PLC/Ca ²⁺ , ERK/p38MAPK and NF-κB signaling pathways	Show bidirectional effects on intestinal secretion and inflammation, and maintain epithelial barrier
β-ARs	Gs/AC/cAMP signaling pathways	Alleviate inflammatory responses
Estrogen related GPCRs		
GPR30	Gs/AC/cAMP, PI3K/Akt and Src/ERK signaling pathways	Alleviates inflammatory responses

GPCRs: G protein-coupled receptors; GPR4: G protein-coupled receptor 4; AC: Adenylyl cyclase; cAMP: Cyclic adenosine monophosphate; Epac: Exchange protein activated by cAMP; PLC: Phospholipase C; NF-κB: Nuclear factor kappa-B; GPR68: G protein-coupled receptor 68; ERK: Extracellular signal-regulated kinase; p38MAPK: p38 mitogen-activated protein kinase; GPR65: G protein-coupled receptor 65; GPR132: G protein-coupled receptor 132; CB1: Cannabinoid receptor 1; CB2: Cannabinoid receptor 2; PI3K: Phosphatidylinositol 3 kinase; Akt: Also known as protein kinase B (PKB); GPR55: G protein-coupled receptor 55; M1R: Type 1 muscarinic receptor; M3R: Type 3 muscarinic receptor; β-ARs: β-adrenergic receptors; GPR30: G protein-coupled receptor 30.

expression level of GPR4 was increased in the inflamed tissues of IBD. Furthermore, in experimental acute colitis models, GPR4-deficient mice showed lower expression levels of adhesion molecules and inflammatory genes than wild-type mice, and thus, GPR4-deficient mice presented with less severe colitis than control mice^[14]. Recently, it was reported that GPR4^{-/-}/IL-10^{-/-}-double-knockout mice with chronic colitis manifested decreased histology scores and myeloperoxidase activity, as well as diminished CD4⁺ T helper cell infiltration and lower expression levels of inflammatory molecules than GPR4^{+/+}/IL-10^{-/-} mice. This finding further reinforces the positive regulatory effect of GPR4 activation on inflammatory activity^[24]. Collectively, GPR4 exerts proinflammatory effects on intestinal inflammation in a pH-dependent fashion. It should be emphasized that GPR4 was predominantly expressed in endothelial cells, while other cells such as monocytes, macrophages and smooth muscle cells in the intestine also demonstrated expression of GPR4^[14]. Further efforts should be made to elaborate the functional roles of GPR4 in these cells. In addition, critical modulators of IBD, such as TNF-α and reactive oxygen species (H₂O₂), can also independently stimulate the expression of GPR4, which makes the acidosis-induced inflammation in IBD more complex^[25]. Further efforts are needed to explore a possible interaction between GPR4 and other inflammatory modulators.

GPR4 is undoubtedly a promising therapeutic target as it can mediate the interaction between leukocytes and ECs, which is critical to inflammatory processes. Drugs targeting leukocyte adhesion and extravasation, such as vedolizumab and natalizumab, have been developed and approved for the treatment of IBD. GPR4 small molecule inhibitors have also been found to alleviate the inflammatory response of ECs in basic experiments, while therapeutics specifically targeting GPR4 for IBD and other inflammatory diseases have not been developed^[16]. Recently, Fukuda *et al.*^[20] developed a selective GPR4 antagonist to treat myocardial infarction in mice with great effects, providing a basis for drug development in IBD treatment. Given the substantial effect of GPR4 on the inflammatory process, GPR4-targeted agents may

work as an alternative to disease treatment. Thus, further studies on GPR4-related drug development are of paramount importance.

GPR68 (OGR1): GPR68, also known as OGR1, is not only a receptor for sphingosylphosphorylcholine, but also serves as a proton-sensing receptor implicated in pH homeostasis. It has a negligible activity at pH 7.8 and is fully activated at pH 6.8^[26]. Stimulated by extracellular acidosis, OGR1 is coupled to Gq/11 proteins, and then activates the PLC/Ca²⁺ signaling pathway in multiple cellular responses^[21,26]. In addition to Gq/11 proteins, OGR1 also binds to Gs and G13 proteins, and is involved in the Gs/cAMP and Rho/Rho associated coiled-coil containing protein kinase (ROCK) signaling pathways, respectively^[27,28] (Figure 1). Among these diverse cellular responses, inflammation has been of long-standing interest for researchers.

Previous studies of OGR1 in human airway smooth muscle cells have shed light on its positive regulatory role in inflammation. Ichimonji *et al.*^[29] reported that OGR1 could stimulate the production of proinflammatory cytokines (such as IL-6) upon extracellular acidification, which was associated with the phosphorylation signaling of extracellular signal-regulated kinase (ERK) and p38 MAPK. OGR1, induced by extracellular acidification, mediates the increased expression of several genes that are implicated in inflammatory regulation, immune responses, actin cytoskeleton formation and cell-adhesion modulation. To identify the effects of OGR1 in IBD, a later study found an elevated mRNA expression level of OGR1 in patients with IBD (approximately 2-fold increase) compared to the level in controls without IBD^[13]. Animal experiments further showed that OGR1^{-/-}/IL-10^{-/-}-double-knock-out mice had a lower inflammation score in the intestine and a delayed rectal prolapse than OGR1^{+/+}/IL-10^{-/-} mice^[13]. These data indicated that OGR1 deficiency could confer a protective effect on spontaneous inflammation of the intestine. In addition, it was also observed that inhibition of NF-κB activity could reverse the TNF-stimulated overexpression of OGR1, suggesting the involvement of the NF-κB signaling pathway in OGR1 regulation^[13]. It is known that the NF-κB transduction pathway is one of the important pathways that are linked with IBD. In addition, OGR1 contributes significantly to intestinal fibrogenesis. In comparison with the non-fibrotic tissues of patients with IBD, fibrosis-affected terminal ileum tissues showed an increased expression level of fibrosis markers, which was accompanied by elevated OGR1 expression^[30]. In mouse models of chronic colitis, OGR1-deficient mice had a marked reduction in collagen deposition and mRNA expression levels of fibrosis markers compared to the deposition and expression in wild-type mice^[30]. From this point of view, OGR1 may serve as a fibrosis marker and affect disease phenotypes (stricturing phenotypes) of IBD to some degree. The critical role of OGR1 in intestinal fibrosis makes it an appealing target for treating fibrotic stricture, especially given that intestinal fibrosis is a key cause of morbidity and mortality in patients with IBD. Furthermore, it is noteworthy that OGR1 not only influences intestinal inflammation and fibrosis, but also affects the intestinal epithelial barrier function. Stimulation of OGR1 by acidification could markedly improve intestinal barrier function by modifying the actin cytoskeleton and strengthening cell adhesion^[31]. It is known that the intestinal epithelial barrier of patients with IBD is damaged, especially in patients with UC^[32,33]. The conflicting effects of OGR1 in IBD make it difficult for researchers to explain its clear role in the pathogenesis of IBD. Therefore, the pathogenic and/or protective effects of OGR1 in IBD warrant further exploration. Clarification of the roles of OGR1 in different disease states (active or inactive state) and other disease locations is also needed.

Considering that OGR1 signaling pathways are implicated in a multitude of IBD-associated cellular processes, including inflammatory responses, fibrosis and cell adhesion, therapeutics targeting OGR1 are potentially of great importance^[13]. Available evidence suggests that the progression of intestinal fibrosis not only relies on the presence of inflammation but also on sustained mucosal acidification^[34]. Controlling the inflammatory activity alone may not fully prevent intestinal fibrogenesis. Thus, there is a pressing need to develop drugs which specifically block the activation of OGR1, along with other anti-inflammatory agents, to prevent the development of intestinal fibrosis^[30]. However, no drug targeting OGR1 has been developed or approved for human disease including IBD. Therefore, a close collaboration between researchers, drug developers, physicians, and data analysts should be organized, with the aim of promoting progress in translational research and drug discovery.

GPR65 (TDAG8): A large-scale meta-analysis of more than 75000 cases and controls identified TDAG8 (I231L, rs3742704) as a susceptibility locus of IBD^[35]. TDAG8 mRNA is widely expressed in different organs and cells, including peripheral blood leukocytes, lymph nodes, the spleen and the intestine, with the highest expression

level being in immune cells^[36,37]. The glycosphingolipid psychosine and some other related glycosphingolipids are ligands for TDAG8.

TDAG8 shares a high amino acid sequence homology with GPR4 and OGR1, suggesting that it has the potential to respond to changes in extracellular pH. Ishii *et al.*^[38] first demonstrated that TDAG8 was a proton-sensing receptor, and of importance in cAMP accumulation, Rho activation, and stress fiber formation. TDAG8 is involved in the AC/cAMP signaling pathway *via* Gs proteins, and the Rho signaling pathway through G12/13 proteins^[39] (Figure 1). Available evidence suggests that pH-dependent stimulation of TDAG8 is lower in monocytes of patients with IBD compared with that of healthy controls. In 2009, Mogi *et al.*^[40] identified TDAG8 as a negative regulator of inflammation in mouse peritoneal macrophages. Induced by extracellular acidification, TDAG8 exerts its anti-inflammatory effects by inhibiting the production of proinflammatory cytokines (TNF- α and IL-6). A subsequent study drew a similar conclusion and discovered that it positively regulated the anti-inflammatory cytokine (IL-10) in T cells and macrophages. Recently, Tcymbarevich *et al.*^[41] proved that TDAG8-deficient mice with dextran sodium sulfate (DSS)-induced colitis had markedly increased levels of IFN- γ , IL-6, and iNOS in comparison with wild-type mice. In addition, a lack of TDAG8 also leads to increased infiltration of macrophages and neutrophils in colonic tissues, which further exacerbates intestinal inflammation and destroys the intestinal epithelial barrier function. All of the aforementioned results demonstrated that activation of TDAG8 could diminish immune-mediated inflammation and maintain intestinal epithelial barrier function. It should be pointed out, however, that in addition to extracellular acidification, intracellular acidification might also have an impact on the inhibition of proinflammatory cytokine production^[42]. Whether or not the target of intracellular acidification is TDAG8 remains to be determined. Therefore, additional research efforts should be made to clarify the molecular mechanisms of TDAG8 in the acidification-mediated modulation of inflammation. It is noteworthy that TDAG8 is not only involved in the regulation of cytokine production and intestinal epithelial barrier, but also plays a critical role in the modulation of autophagy. It is well known that intracellular bacterial defense processes and autophagy are defective in patients with IBD. Serological evidence also suggested that macrophages from patients with IBD (especially patients with CD) exhibit impaired secretion of TNF- α in response to bacterial infection^[43]. Recently, a functional genomic study claimed that cells (in patients with IBD) expressing GPR65 I231L exhibited aberrant lysosomal pH, lower lysosomal activity, impaired defenses against pathogens, and greater accumulation of lipid droplets, which were associated with cellular toxicity and inflammation. In comparison with wild-type mice, GPR65-deficient mice displayed more severe inflammation of the intestine and increased susceptibility to bacteria-induced colitis^[37]. This finding demonstrates that GPR65 deficiency can negatively affect autophagy and markedly increase the susceptibility to IBD. Furthermore, a recent study identified a putative risk polymorphism in TDAG8 (rs8005161) and claimed that it might lead to a severe disease course in patients with IBD^[39]. Thus, TDAG8 plays an important role not only in disease susceptibility but also in the disease course of IBD. Associations between TDAG8 and disease phenotypes, disease activity and disease prognosis merit further investigation.

Important contributions of TDAG8 to the regulation of cytokine production and intestinal epithelial barrier, and the maintenance of lysosome function make it an attractive target for the treatment of IBD. Other promising roles, such as participation in the activation-induced cell death, T cell differentiation, and collagen synthesis, have further made GPR65 a good candidate target in the development of novel therapeutic interventions for patients with immune-mediated diseases and collagen-associated diseases^[38,44]. Recently, Onozawa *et al.*^[44] observed that mice lacking TDAG8 presented with aggravated collagen-induced arthritis and anti-type II collagen antibody-induced arthritis compared to wild-type mice. This finding not only offered valuable insights into the pathogenesis of the aforementioned diseases, but also provided a new direction for researchers to study the roles of TDAG8 in the intestinal fibrosis (collagen deposition) of patients with IBD. However, there are few studies demonstrating its contribution in intestinal fibrosis. There is still a lack of studies elaborating the functional importance of TDAG8 in other cells, such as neutrophils, lymphocytes and dendritic cells. Future work is needed to clarify these issues. Considering that autophagy is one of the newly discovered and crucial contributors to IBD pathogenesis, the development of treatment targeting autophagy is potentially rewarding. However, it is important to emphasize that, autophagy has bi-directional modulatory effects on intestinal inflammation. On the one hand, autophagy can decrease inflammatory responses by down-regulating the production of proinflammatory cytokines and accelerating the clearance of pathogens. On the other hand, it can also aggravate inflammatory responses by inducing endoplasmic

reticulum stress and increasing the activation of inflammasomes^[45]. Simply augmenting autophagy processes might result in acute inflammatory responses that would exacerbate the disease. Thus, enhancing or restricting autophagy to a controllable degree and developing novel chemical compounds that create an equilibrium between autophagy and inflammation have recently become a pressing matter.

GPR132 (G2A): GPR132 (G2A) was initially found to be an antiproliferative cell cycle regulator. It can induce cell cycle arrest at the G2/M stage, resulting in G2 accumulation (G2A), delayed mitosis, and decreased transformation potential of BCR-ABL^[46]. It is highly expressed in lymphoid tissues and macrophages, and plays a vital role in regulating innate and adaptive immunity^[46,47]. Available evidence suggests that G2A has pH-sensing ability, similar to other proton-sensing GPCRs, including GPR4, GPR68 and GPR65^[27]. In contrast, G2A has a lower proton sensitivity compared with other G protein family members in terms of intracellular IP and cAMP accumulation^[27]. In addition to its contributions to the cell cycle, oncogenesis and immunity, G2A is also implicated in the modulation of inflammation and oxidative stress, by stimulating diverse signaling pathways such as the PLC/Ca²⁺, G13/Rho and Ras/ERK transduction pathway^[28,48] (Figure 1).

With regard to the roles of G2A in inflammation, existing evidence has shown controversial results. Some studies indicate that G2A exhibits a proinflammatory role in the inflammatory processes by inducing calcium mobilization and stimulating proinflammatory cytokine (IL-6 and IL-8) secretion^[49]. However, others have claimed that it might attenuate inflammation and autoimmunity by affecting the chemotaxis of monocytes and phagocyte chemotactic responses^[19,50]. A recent study further demonstrated that, at the site of inflammation, G2A can indirectly promote macrophage polarization toward M1-like phenotypes (proinflammation) by positioning macrophages in the proinflammatory microenvironment^[51]. On the other hand, in a tumor environment, activated G2A also can directly promote the polarization toward the anti-inflammatory M2 phenotypes in macrophages^[52]. The opposing roles of G2A in inflammation regulation have made it a popular research topic. Recently, Frasci *et al.*^[53] discovered that G2A-knockout mice with DSS-induced colitis exhibited more severe colitis compared to the wild-type mice. Additionally, the concentrations of proinflammatory monocytes, eosinophils and IL-5 were increased, and the levels of IFN- γ were decreased in comparison with control mice. More importantly, in a surprising finding, the administration of IFN- γ can alleviate colitis severity and decrease the levels of IL-5 and eosinophils. As a result, monocytes in colonic tissues tend to mature to anti-inflammatory ones and eosinophil-induced injury of colonic tissues is diminished. All these results suggest that G2A might exert anti-inflammatory effects in the colon by increasing the production of IFN- γ , which is a well-established anti-inflammatory cytokine associated with IBD. G2A indeed affects inflammatory responses, with opposite effects (proinflammatory and anti-inflammatory effects) in different microenvironments. Given that IBD is considered a result of the disequilibrium between proinflammatory and anti-inflammatory responses, exploring the roles of G2A in IBD may hold the key to knowledge innovation in IBD pathogenesis and treatment. However, it is not yet clear how G2A affects the functions of other cell types in different microenvironments. Regarding the tumor microenvironment, clarification of the contributions of G2A in IBD-associated colorectal cancer (CRC) is an important research area as it may broaden the understanding of IBD-associated CRC, and help us develop novel therapeutic strategies for patients with CRC. In addition, more studies are required to replicate these findings in larger sample sizes, and to explore the roles of G2A in other models of IBD.

G2A may be highly valuable in the field of immunoregulation, cancer therapy, and inflammatory disease treatment, considering its multifaceted roles in these processes. Recent progress in the development of molecule modulators targeting G2A for the treatment of transfusion-related acute lung injury has provided therapeutic avenues for other diseases that share the same signaling pathways^[54]. To date, no pharmaceutical drug targeting G2A for the treatment of IBD has been produced. Identification of the exact roles of G2A in intestinal inflammation and immunity is an essential prerequisite for embarking on a G2A-based therapy. Drawing on the experience using other G protein family members in disease treatment, researchers may make new developments in pharmaceutical research and thereby revolutionize therapy for IBD.

Cannabinoid receptors

The traditional endocannabinoid system (ECS) is composed of cannabinoid receptors, endogenous ligands, and enzymes for endogenous cannabinoids metabolism^[55].

Anandamide, 2-arachidonoylglycerol and Δ^9 -tetrahydrocannabinol are classic ligands for cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2)^[56]. In recent years, some noncannabinoid receptors, such as GPR55, CPR119 and peroxisome proliferator-activated receptors, and atypical ligands, such as O-1602, oleoylethanolamide and palmitoylethanolamide, have been claimed to be constituents of the ECS^[57,58]. The ECS is involved in various mechanisms in the GI tract, including intestinal motility and secretion, as well as epithelial barrier integrity, intestinal inflammation and immune modulation through the Gi/AC/cAMP, Gi/phosphatidylinositol 3 kinase (PI3K)/Akt, ERK/p38MAPK signaling pathway, *etc.*^[59,60] (Figure 1). Previous studies have revealed that cannabinoids can protect individuals from intestinal inflammation and CRC, and exert palliative effects on abdominal pain and diarrhea in patients with IBD^[61]. However, contrary to these findings, some clinical studies have demonstrated that cannabinoids are detrimental to patients by increasing the likelihood of surgery for patients with IBD^[61]. These opposing findings have spurred considerable interest in the study of the relationship between IBD and the ECS (Table 1).

CB1 and CB2: CB1 and CB2 are the two classic cannabinoid receptors belonging to the GPCR family. They are widely expressed in the brain, neuronal tissues, GI tract and immune system and are involved in neurotransmitter release, intestinal motility, immune cell migration and inflammatory responses^[55,59,62]. Extensive studies have suggested the involvement of CB1 and CB2 receptors in colitis, which indicates a novel therapeutic option for patients with IBD.

The roles of CB1 and CB2 in colitis have been explored mostly through animal experiments. Existing evidence shows that CB1-deficient mice experience more severe colonic colitis than their wild-type littermates after administration of 2,4-dinitrobenzene sulfonic acid (DNBS) and DSS^[63]. For wild-type mice, the administration of specific CB1/CB2 antagonists markedly aggravated intestinal inflammation, while activation of CB1/CB2 receptors by agonists conferred a protective effect on the experimental mice with induced colitis^[63,64]. Furthermore, histological evidence also proved that the expression levels of CB1 and CB2 receptors, along with the percentage of myenteric neurons expressing CB1 receptors, were significantly elevated in the inflamed gut after DNBS or DSS administration, indicating the involvement of CB1 and CB2 receptors in the anti-inflammatory processes^[63,64]. With regard to patients with IBD, immunostaining for CB receptors in colonic tissues revealed that epithelial CB1 and CB2 immunoreactivity was evident in the acute phase. It is important to note that normal human colonic epithelium also demonstrates intense CB1 immunoreactivity, whereas CB2 receptor immunoreactivity is faintly detected^[55,64]. This finding implied that the CB2 receptor might play a more critical role in disease activity. A recent finding from an Italian study showed that a functional variant of CB2 (Q63R) contributed to an increased risk of pediatric IBD, which further confirmed the vital role of CB2 in the pathogenesis of IBD^[65]. In addition, when compared with control patients, the patients carrying the RR risk genotype were at a higher risk of suffering moderate-to-severe disease activity at the time of diagnosis (for patients with CD or UC) and an earlier clinical relapse (for patients with UC)^[65]. From this perspective, CB2 may be a valuable indicator of active disease and a poor disease course, providing a promising tool for disease monitoring and prediction. However, a Turkish study of 202 patients with IBD failed to replicate these findings. These inconsistent results may be attributed to the different allele frequencies and genotype distributions between the different races^[65,66]. Collectively, these studies provided novel insights into the complicated roles of CB receptors in the pathogenesis of IBD. However, further efforts are warranted to validate these findings in a larger cohort with different ethnic groups.

In addition to IBD, the ECS has also been implicated in other diseases, including celiac disease, hepatitis, Parkinson's disease, RA, myocardial infarction, obesity, *etc.* Therefore, regulating the activity of CB receptors holds significant therapeutic promise. Sativex, an agonist of CB receptors, has been approved in Canada, the United Kingdom, and Spain for the treatment of neuropathic pain associated with multiple sclerosis (MS). Another CB1 receptor antagonist, rimonabant, has been made available to patients with metabolic syndrome^[63]. Other drugs targeting the ECS, such as ajulemic acid for relieving pain, Epidiolex for tuberous sclerosis, and anabasum for systematic sclerosis and dermatomyositis, are at the stage of clinical trials^[67,68]. With regard to patients with IBD, a pilot prospective study of 13 patients with long-standing IBD claimed that cannabis treatment had beneficial effects on disease activity index, indicating a reduction in symptoms and an improvement in general health status^[69]. In addition, a famous pharmaceutical company has claimed that a prodrug of cannabinoid can display a favorable therapeutic effectiveness in IBD. Related clinical trials are in progress. Although rapid advancements have been made in the development of drugs targeting the ECS, the cannabis-like psychotropic adverse

effects are the main obstacle for wide application in clinical practice. Developing techniques for ensuring the localized activation of cannabinoid receptors may further widen its clinical utility.

GPR55: GPR55 is regarded as a constituent of the ECS. Although it exhibits an affinity for cannabinoids, it shares a low amino acid sequence homology with CB1 and CB2 receptors and lacks classic cannabinoid binding sites, making it an abnormal cannabidiol receptor^[70]. GPR55 is widely expressed in the central nervous system, adrenal gland and the GI tract. CB1 receptors and GPR55 are both highly expressed in brain tissues, but the expression level of GPR55 is significantly lower than that of CB1 receptors^[71]. Furthermore, CB1 and CB2 receptors are mainly coupled to Gi, leading to the reduction of cAMP^[59]. However, GPR55 is primarily coupled to G13 and Gq, resulting in activation of the RhoA/ROCK and PLC/Ca²⁺ signaling pathway, respectively^[72] (Figure 1). Its association with different transduction pathways implies that GPR55 might be involved in distinct cellular responses compared with CB1 and CB2 receptors.

In terms of the pathophysiological roles of GPR55 in the GI tract, existing evidence suggests that it mediates the activation of enteric neurons and the release of proinflammatory cytokines, thereby modulating gut motility and the pain associated with neuropathy and inflammation^[73,74]. A previous animal experiment revealed that treatment with lipopolysaccharide increased the mRNA and protein expression levels of GPR55 in the inflammatory intestine of rats, inferring that GPR55 might play a role in inducing intestinal inflammation^[73]. Further evidence has shown that the application of CID16020046 (a GPR55 antagonist) could significantly suppress the expression levels of inflammatory cytokines, including TNF- α , IL-1 β and IL-6, and inhibit leukocyte migration and activation^[75]. Moreover, in the DSS model, GPR55-deficient mice showed less severe intestinal inflammation than wild-type mice, indicating a proinflammatory role of GPR55 in intestinal inflammation. It is well known that leukocyte migration, accumulation and activation are pathological hallmarks of IBD. Taking these results into consideration, it is possible that pharmacologically blocking GPR55 might delay the development and progression of IBD. A Polish study of 37 patients with IBD and 13 patients without IBD analyzed the colonic expression of GPR55^[76]. The data showed that patients with IBD, especially patients with CD, had a higher mRNA level of GPR55 than healthy controls. Moreover, the GPR55 concentration was also elevated in inflamed colonic tissues in comparison with noninflamed tissues, further indicating its proinflammatory role in the intestine^[76]. However, a recent report claimed that GPR55 was downregulated in DNBS colitis models^[77]. In addition, Schicho *et al*^[78] suggested that the atypical cannabinoid O-1602 (an agonist of GPR55) could inhibit neutrophil recruitment, alleviate disease severity, and protect against experimental colitis in mouse models of colitis. Such an anti-inflammatory effect has also been observed in mice with acute pancreatitis^[79]. Interestingly, the anti-inflammatory effects of O-1602 were present in CB1/CB2-deficient mice and even in mice lacking GPR55^[78]. Such confusing results merit further study. Collectively, these results demonstrate the involvement of GPR55 in the pathophysiology of intestinal inflammation. Considering this point of view, it may be an attractive target for the treatment of IBD. However, the indefinite roles of GPR55 (proinflammatory and/or anti-inflammatory effects) in intestinal inflammation make it difficult for researchers to perform therapeutic translation work. In addition, there is still a lack of knowledge on the downstream effectors and pathways of GPR55 during inflammatory processes. A recent study has reported that GPR55 could form CB2-GPR55 heteromers, regulate CB receptor signaling, and modify antitumor effects^[75,80]. Thus, the identification of interactions between GPR55 and CB receptors during intestinal inflammation may provide new ideas for therapeutic intervention in IBD and even IBD-associated CRC.

Ongoing clinical trials have indicated that GPR55 is potentially an antispasmodic target for the treatment of epilepsy, and other therapeutic indications, such as for MS and pancreatic cancer, have also been proposed, although related signaling pathways have not been clearly identified^[81,82]. Surprisingly, a prospective placebo-controlled study has demonstrated that cannabis could induce a clinical response in patients with CD, indicating the possibility of developing cannabinoid-based pharmacotherapy for CD^[83]. However, to date, no commercially available formulation targeting GPR55 for IBD has been reported, and no agents are reportedly in clinical trials. The ability of GPCR-directed pharmacotherapy in treating other diseases might provide an avenue for therapeutic translation in IBD.

Autonomic nervous system GPCRs

The autonomic nervous system, consisting of the sympathetic and parasympathetic

nervous system, plays an important role in regulating mood, gastrointestinal motility, secretion and absorption, as well as the intestinal immune responses and epithelial barrier function^[84]. Norepinephrine (NE), the main neurotransmitter of the sympathetic nervous system (SNS), is coupled to the α - and β -adrenergic receptors (AR, GPCRs) and modulates the inflammatory processes of a broad array of diseases including IBD, myocarditis and heart failure^[84-86]. Acetylcholine (ACh), the most prominent neurotransmitter of the parasympathetic nervous system, binds to the muscarinic cholinergic receptors (GPCRs) and nicotinic cholinergic receptors, and is then involved in the maintenance of intestinal homeostasis^[84,87]. Considerable evidence suggests that a disturbance in the autonomic nervous system contributes to the complicated pathogenesis of IBD, which could be accounted as aberrations within the brain-gut axis. The brain-gut axis directly or indirectly links the GI with the nervous system, and shows bi-directional effects in GI disorders such as IBD^[88]. The nervous system conveys extrinsic and intrinsic messages to the gut mainly by interacting with adrenergic and cholinergic receptors. The gut can also respond to signaling molecules by adrenergic and cholinergic receptors, and secretes neuroactive molecules, thereby influencing the function of the nervous system^[89]. Available data demonstrate that the co-morbidity with psychological diseases (anxiety and depression) in patients with IBD is up to 35%^[90]. Psychological disorders may have deleterious effects on disease activity and disease severity of IBD, and the inflammatory activity of IBD also worsens psychologic health and is associated with an increased risk of developing new psychological diseases^[88,91]. Thus, it is of utmost importance to explore the roles of the nervous system, especially of adrenergic and cholinergic receptors in the pathogenesis of IBD. In this review, we mainly focus on the roles of autonomic nervous system GPCRs in IBD (Table 1).

Muscarinic cholinergic receptors: There are five subtypes of muscarinic cholinergic receptors (M1R-M5R), with different tissue distribution patterns and signaling pathways. Type 1 muscarinic receptor (M1R) and type 3 muscarinic receptor (M3R) are the main muscarinic cholinergic receptors in the GI tract, accounting for approximately 80% and 20%, respectively^[92]. Although M3R is considered to be the pivotal functioning subtype in the GI tract, the role of M1R in maintaining intestinal structure and function is also important. They are primarily involved in the Gq/PLC signaling pathway, and are implicated in inflammatory responses, mucus secretion, pathogen clearance and intestinal barrier maintenance (Figure 1).

It is well documented that the vagus nerve (VN) exerts dual anti-inflammatory effects either *via* vagal afferents, activating the hypothalamic-pituitary-adrenal (HPA) axis, or *via* vagal efferents, mediating the cholinergic anti-inflammatory pathway (CAIP)^[93]. Existing evidence has indicated that the M1R agonist (McNA343) can activate the CAIP. Administration of McNA343 to DSS- and DNBS-induced colitis models significantly decreased the levels of pro-inflammatory cytokines and ameliorated the disease activity index. In mice with vagotomy, its anti-inflammatory efficacy was abolished^[94]. In addition to influencing the levels of inflammatory cytokines, M1R is also implicated in modulation of the secretory function of the gut^[92]. A Japanese research team claimed that the M1 subtype could negatively modulate secretion in the colonic epithelium by regulating the ERK1/2 and p38MAPK pathways, but M3R was demonstrated to be a positive regulator of secretory function^[92]. It was found that the density of M1R was greatly reduced after the induction of colitis, whilst abundance of the M3 subtype remained almost the same^[92]. This result indicated that M1R is more susceptible to intestinal inflammation than M3R. M3R is another subtype of muscarinic cholinergic receptors expressed in different types of cells including goblet cells, smooth muscle cells, enteric neurons and macrophages^[95]. It is not only involved in mucus production and secretion, but also in pathogen clearance, intestinal epithelial proliferation and intestinal barrier maintenance^[96,97]. McLean *et al*^[97] discovered that the clearance of *Citrobacter rodentium* (bacteria) in M3R-deficient mice was delayed, which could be explained by the extended adherence of *Citrobacter rodentium* to intestinal mucosa, and a decrease in goblet cell number and mucin production. It is noteworthy that the activation of M3R also exerts proinflammatory effects by promoting macrophages toward a M1 phenotype and stimulating proinflammatory cytokine production and release^[97]. This is in opposition to the anti-inflammatory effects mediated by $\alpha 7$ nicotinic receptors ($\alpha 7$ NR)^[98]. Subsequent studies conducted by McLean *et al*^[99] further reported impaired clearance of *Nippostrongylus brasiliensis* (nematode) in M3R-deficient mice, and positive roles in maintaining epithelial barrier function and promoting M1 polarization. With respect to the roles of muscarinic cholinergic receptors in modulation of intestinal permeability, a New Zealand research team further clarified the molecular mechanisms, and proved that under inflammatory conditions, activation of muscarinic cholinergic receptors by ACh could attenuate the destructive

effects of IL-1 β on the epithelial barrier by increasing the expression levels of tight junction (TJ) proteins (occludin and ZO-1) and reducing phosphorylation of myosin light chain (MLC) *via* a NF- κ B independent pathway^[100]. In addition, an animal experiment demonstrated that in DSS models, M3R-deficient mice had faster weight loss and more severe colitis in comparison to wild-type mice, indicating the protective role of M3R in colitis^[101]. It is noteworthy that different muscarinic cholinergic receptors might show different pro- and anti-inflammatory functions across different tissue types^[97]. The underlying mechanisms involved require further investigation. Collectively, all of these studies provided new insights into the intricate roles of muscarinic cholinergic receptors in the pathogenesis of IBD. Considering that the microbiome plays a critical role in IBD and the microbiota-gut-brain axis has been proved to be a key contributor to the pathogenesis of IBD, further large-scale studies are warranted to elaborate the effects of the microbiome on muscarinic cholinergic receptors, and the interplay between them. Moreover, it is well established that muscarinic cholinergic receptors were expressed in various cell types; therefore, identifying the roles of these receptors in different cell types is also warranted.

It is known that following vagus nerve stimulation (VNS), ACh can be released and binds to muscarinic and nicotinic cholinergic receptors, thereby regulating inflammatory and immune responses. In colitis models, VNS substantially reduces disease activity and improves the disease outcome. In colitis models with vagotomy, clinical symptoms of colitis deteriorated and the disease activity index increased^[84]. Based on these findings, Bonaz *et al.*^[102] performed VNS (VNS device implantation) in seven patients with CD, and demonstrated that five of seven patients achieved clinical, biological and endoscopic remission at 6 months of follow-up. Thus, VNS serves as a valuable treatment strategy for patients with CD. In the field of bioelectronics, bioelectronic medicine such as VNS may provide new and promising strategies for IBD treatment, especially in patients with drug intolerance, poor compliance and difficult economic conditions. It should be noted that patient numbers were relatively small in this study, highlighting the need to validate these findings in a larger cohort. Although VNS has been approved by the United States Food and Drug Administration (FDA) to treat drug-refractory epilepsy and drug-refractory depression, VNS for CD is at the stage of clinical trials^[103]. With regard to drugs targeting muscarinic cholinergic receptors, limited evidence has been demonstrated in patients with IBD. On the contrary, therapeutics targeting α 7nAChR such as galantamine, GTS-21 and AR-R17779 are at the stage of animal experiments^[93]. Therefore, further efforts are warranted to develop muscarinic receptor-targeted drugs for patients with IBD, and facilitate clinical translational research.

Adrenergic receptors: Adrenergic receptors (ARs) are divided into two groups: α - and β -ARs. α -ARs are subdivided as α 1- and α 2-AR, involved in Gq/PLC/Ca²⁺ signaling pathways and Gi/AC/cAMP signaling pathways, respectively. β 1-, β 2- and β 3-AR are the main subtypes of β -ARs, implicated in Gs/AC/cAMP signaling pathways^[86] (Figure 1). Accumulated evidence has proven the critical roles of ARs in the inflammatory processes and immune responses.

β -ARs are the most commonly studied in this field. Existing data indicated that activation of β -ARs by NE could markedly suppress the secretion of TNF and IL-6, inhibit the expression of MHC class II, and promote T cell differentiation into anti-inflammatory T cell phenotypes, thereby regulating inflammatory responses^[104-106]. A Dutch study, which included 250 patients with IBD, suggested that patients using β -blockers were at a higher risk of relapse compared to those not using β -blockers, indicating its anti-inflammatory role in IBD^[85]. In 2002, Magro *et al.*^[107] found that NE tissue levels in inflamed mucosa of patients with IBD were significantly lower in comparison with those in control subjects. Moreover, several studies also observed that sympathetic innervation was obviously decreased both in inflamed intestinal tissues of patients with IBD and DSS-induced colitis^[104,108]. Decreased sympathetic innervation may lead to diminished concentrations of anti-inflammatory neurotransmitters such as NE, endogenous opioids and substance P, thereby exacerbating inflammatory responses. It is worth noting that sympathetic innervation is bimodal. Straub *et al.*^[108] claimed that sympathectomy alleviated disease activity in acute DSS colitis, while in chronic DSS colitis, sympathectomized mice had more severe colitis and increased inflammatory activity compared with control mice. Similarly, in arthritis research, the SNS also has a proinflammatory role during the early phases of inflammation, and exerts anti-inflammatory effects in the chronic stage of inflammation^[109]. It should be emphasized that NE also exerts proinflammatory effects at low concentrations by binding to α -ARs. Thus, Straub *et al.*^[110] concluded that the levels of neurotransmitters and neuropeptides, the number and availability of receptors, the receptor affinity, and the timing of sympathetic activity considerably affect the proinflammatory and anti-inflammatory activity of the

SNS. Further efforts are still warranted to explore the underlying mechanisms of this difference.

Given the substantial effects of the SNS and ARs on inflammatory responses, AR-targeted agents may provide an alternative approach to disease treatment. However, their antagonistic roles in inflammatory processes also make it difficult to develop new therapeutics targeting the SNS and ARs. Therefore, there is definitely a pressing need to elucidate the detailed mechanisms, and then accelerate AR-targeted drug discovery in IBD.

Estrogen-related GPCRs

It is apparent that estrogen, produced in endocrine organs and the reproductive system, is important to human health and disease. Estrogen exerts anti-inflammatory, antiatherogenic and antioxidant effects across various diseases such as hypertension, coronary heart disease, breast cancer and IBD^[4]. Although previous studies have claimed that these effects are mediated by classic nuclear estrogen receptors (ERs), including ER α and ER β , recent studies have demonstrated that G protein-coupled receptor 30 (GPR30), a novel estrogen-related receptor, also plays a critical role in estrogen-related biological processes, such as inflammation, proliferation and immunity^[111,112]. Increasing evidence indicates that oral contraceptive use, menopause, and sex hormone replacement therapy greatly affect the susceptibility to and the disease activity of IBD. However, the roles of estrogen in IBD are still controversial. Some researchers have claimed that elevated estrogen exerts protective effects in IBD, in view of the fact that women are at a lower risk of disease recurrence during pregnancy and sex hormone replacement therapy decreases disease severity in postmenopausal women with IBD^[113,114]. However, others have suggested that it has a detrimental role in IBD, and cited the association of oral contraceptive use with an increased risk of developing IBD and the palliative effect of discontinued use of oral contraceptive on disease severity^[115,116]. The inconsistent roles of estrogen in IBD might be due to different receptor distributions, distinct receptor-ligand interactions, and diverse signaling pathways behind them. Therefore, investigating the roles of GPR30 in IBD has become an emerging area, as it holds promise for an enhanced understanding of the pathogenesis of IBD and better disease assessment in patients with IBD (Table 1).

GPR30 (GPER1): GPR30, also known as G protein-coupled estrogen receptor 1 (GPER1), is widely located in the GI tract. The GPR30 ligands are 17 β -estradiol (E2), 17 α -estradiol (E2 α), estrone (E1) and estriol (E3)^[117]. Available data show that GPR30, along with ER α and ER β , is actively involved in neuron-induced contraction of the GI tract in a sex-dependent manner^[118]. GPR30 can activate various downstream transduction pathways (AC/cAMP, PI3K/Akt and Src/ERK signaling pathways) and therefore plays a fundamental role in numerous biological processes^[4] (Figure 1). Marked associations between GPR30 and breast cancer, prostate cancer, ischemic stroke and IBD, have been reported in several studies.

A previous study showed that activation of GPR30 exerted anti-inflammatory effects in regulating endothelial inflammatory responses. GPR30 is able to blunt the TNF-mediated upregulation of adhesion molecules (ICAM-1 and VCAM-1), thereby causing decreased interaction between leukocytes and ECs and suppressing endothelial inflammation^[112]. A subsequent study further demonstrated that the cross-talk between an ER α 36 splice variant and GPR30 mediated the attenuation of IL-6 and TNF- α , and was involved in the inhibition of NF- κ B transcriptional activity, further supporting its anti-inflammatory role in inflammatory responses^[119]. However, conflicting results have been reported that the concomitant activation of GPR30 and classic ERs (either ER α or ER β) blocked the inhibitory effects of GPR30 on inflammation^[112]. Thus, the sophisticated relationship between ERs and GPR30 in inflammation regulation merits further investigation. In 2017, a preliminary study of fifty-seven patients provided evidence that the GPR30 protein levels were markedly reduced in the inflamed tissues of patients with CD compared with those in noninflamed tissues, hinting at the possibility that GPR30 can be used as a marker to monitor the disease activity of IBD^[120]. It is worth noting that no significant difference in GPR30 protein levels was observed between the inflamed and noninflamed tissues of patients with UC^[120]. The different signaling pathways and distinct receptor distributions of CD and UC might partly explain the difference, and other basic mechanisms need to be further explored. Increasing evidence has emphasized the important roles of GPR30 in the pathogenesis of IBD, but little is known about the relationship between GPR30 and disease phenotypes, disease prognosis, or therapeutic responsiveness. Moreover, the interactions between GPR30 and classic ERs, and the roles of GPR30 in different cell types remain largely unknown. Studies on GPR30 in IBD are still in the primary stages, but a rapid improvement has been

made in breast cancer research. Exploring the overlapping transduction pathways and susceptibility loci between IBD and breast cancer might improve our understanding of GPR30 in IBD and possibly help us to manage patients with IBD more efficiently and precisely.

The associations between GPR30 signaling pathways and inflammation have made GPR30 a potential target for disease treatment. Accumulated research data have proven its promising role in the treatment of breast cancer, castration-resistant prostate cancer, MS, cardiovascular disease and obesity^[114,115,117,120]. Specifically, GPR30 antagonists have displayed favorable therapeutic effectiveness in cancer patients who respond poorly to conventional therapy. For patients with IBD, oral contraceptive use, reproductive factors, and hormone replacement therapy have been claimed to contribute to disease susceptibility and activity, suggesting the possibility of designing novel therapeutics targeting GPR30 for patients with IBD^[114,115]. However, the complex roles of estrogens and the intricate interplay between GPR30 and classic ERs pose a challenge for researchers to conduct drug discovery and clinical trials. More efforts need to be made with regard to this topic in the future.

DRUG DISCOVERY AND GPCRs

As the largest membrane protein family, GPCRs are involved in many cellular responses in human pathophysiology, making GPCRs among the most studied pharmacological targets^[3]. According to statistics, the number of drugs targeting GPCRs that have been approved by the FDA has surged to more than 475 in July 2017, accounting for nearly 34% of all the FDA-approved drugs^[81]. Among the world's top 20 bestselling drugs, as many as 12 target GPCRs. Moreover, recent years have witnessed an explosion of interest in developing drugs targeting new potential GPCR targets, and these new drugs account for approximately 19% of the 321 agents targeting GPCRs in clinical trials^[81]. These data suggest that rapid progress has been made in GPCR drug discovery. On the other hand, most of the approved drugs share the same GPCR targets, accounting for only 27% of the human nonolfactory GPCRs, indicating that more efforts are required to explore new drug receptors for novel therapeutics^[81]. Sufficient evidence has demonstrated that GPCRs are involved in sophisticated signaling networks and exert multifarious effects on cellular processes, causing some inappropriate responses through undesired pathways. Side effects associated with inappropriate cellular responses limit the clinical application of GPCR-targeting drugs to some extent. However, recent advances in the development of biased ligands (which preferentially activate specific pathways) have provided a new direction for drug discovery^[121]. Moreover, breakthroughs in the identification of crystal structures and allosteric modulators of GPCRs, as well as discoveries on the interactions between GPCRs and extracellular vesicles, and the cross-talk between arrestins and GPCRs have provided new avenues for GPCR drug development^[122-125]. Although central nervous system diseases (Alzheimer's disease, Huntington's disease, MS, *etc.*) remain the most common indications for GPCR-targeted drugs, other disorders such as diabetes, obesity, cancer and short bowel syndrome have also been added to the expanding disease indications for these drugs in recent years^[81]. It is noteworthy that some patients benefited greatly from GPCR-targeted agents, while many other patients had unfavorable response rates and suffered severe adverse events^[126]. Exploring the pharmacogenomics of GPCR-targeted drugs might help explain the difference in responsiveness and assist physicians in managing patients more cost-effectively, reasonably and precisely.

With regard to drug discovery in IBD, great efforts have been made, especially in the field of biological agents. Monoclonal antibodies targeting TNF- α (infliximab and adalimumab), $\alpha 4\beta 7$ integrin (vedolizumab), and IL-12/23 (ustekinumab) have been approved for the treatment of IBD and have displayed favorable therapeutic effects. Although GPCRs are promising therapeutic targets as they play a critical role in the regulation of inflammatory mediators, intestinal barrier and autophagy, and the modulation of intestinal fibrosis and leukocyte adhesion, no GPCR-targeted therapeutics have been approved for IBD^[127]. Research efforts are warranted to further accelerate GPCR-targeted drug discovery. Moreover, it is of great importance for researchers to translate basic research findings into clinical and pharmaceutical practice. Pharmaco-economic analysis of approved drugs should also be considered to lessen the economic burden on patients.

CONCLUSION

IBD is a strikingly complex disease with an unclear pathogenesis. With an in-depth understanding of the physiology and pathophysiology of GPCRs, increasing evidence has demonstrated a close association between IBD and GPCRs. Recent advances in exploring the roles of GPCRs in IBD have become a driving force to elucidate the complex pathogenesis of IBD. Available data have indicated that GPCRs are involved in a wide range of IBD-associated pathophysiological processes, including inflammatory cytokine production, leukocyte adhesion and activation, cell junction (intestinal barrier maintenance), bacterial defense and autophagy, suggesting that GPCRs are excellent pharmacological targets for IBD treatment. In addition, correlations between GPCRs and disease activity, disease severity and disease phenotypes provide the possibility of using GPCR markers to diagnose and monitor patients with IBD. However, there is still a lack of studies investigating the associations between GPCRs and disease course, disease prognosis and therapeutic responsiveness, as well as the contributions of GPCRs in different cell types and disease subtypes; therefore, additional efforts should be made to fill these gaps. Furthermore, it must be noted that significant achievements have been made in GPCR drug research for other diseases; however, GPCR-targeted drug discovery for IBD treatments is still in its infancy. Given that the proposed "precision medicine initiative" calls for researchers and physicians to develop targeted drugs and carry out targeted therapies for patients, more efforts should be made to unveil the molecular basis of IBD and develop targeted therapeutics for patients with IBD^[128]. Improved experimental technologies, drug biotechnologies, and translational studies are warranted to build momentum for GPCR studies. There is also a pressing need for close collaboration between basic researchers, drug developers, and physicians to accelerate the progress of drug discovery, disease treatment, and disease surveillance in IBD.

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