

The Role of the TRPV4 Channel in Intestinal Physiology and Pathology

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Abstract: The transient receptor potential vanilloid 4 channel (TRPV4) is an important member of the TRP superfamily of cation channels. The channel can be activated by different physical and chemical stimuli, such as heat, osmotic, and mechanical stress. It regulates the release of nociceptive peptides (substance P and calcitonin gene-related peptide), and mediates neurogenic inflammation, which indicates the involvement of TRPV4 as a nociceptor. Previous studies show that TRPV4 regulates the contraction of intestinal smooth muscle, mucosal barrier permeability, intestinal ion transport, activation of submucosal enteric neurons, and generation of immune cells. TRPV4 is involved in various pathophysiological activities, and altered TRPV4 expression has been detected in some intestinal diseases (IBD, IBS, intestinal tumors, etc). Evidence indicates that TRPV4 plays a noxious role in intestinal barrier function when the intestine is damaged. This review focuses on the role of the TRPV4 channel in the physiological and pathological functions of the intestine, and evaluates the potential clinical significance to target TRPV4 channel in the treatment of intestinal diseases.

Plain Language Summary: TRPV4 is expressed in the intestine and regulates intestinal functions, such as intestinal barrier function, gastrointestinal motility, sensory transduction, and intestinal ion transport. It is upregulated in most intestinal disease models and participates as a negative regulator. TRPV4 inhibition is a potential treatment for intestinal diseases. TRPV4 antagonists also show a positive protective effect on intestinal related diseases. The activation or inhibition of TRPV4 in the treatment of different intestinal diseases has put forward a feasible research direction in the future.

Keywords: TRPV4, intestinal diseases, gastrointestinal motility, sensory transduction

Introduction

The transient receptor potential vanilloid type 4 (TRPV4), is a mammalian TRP channel that forms Ca^{2+} -permeable, nonselective cation channels.¹ TRPV4 was previously named VR-OAC,² OTRPC4¹ TRP12,³ and VRL-2.⁴ After decades of research, TRPV4 is found to be activated by different stimuli, including physical (cell swelling, innocuous heat, mechanical stress) and chemical (arachidonic acid, synthetic ligand 4 α PDD and GSK1016790A) stimuli.⁵⁻⁷ The absence or dysfunction of this ion channel is closely related to the occurrence and development of intestinal diseases such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) and intestinal tumors.

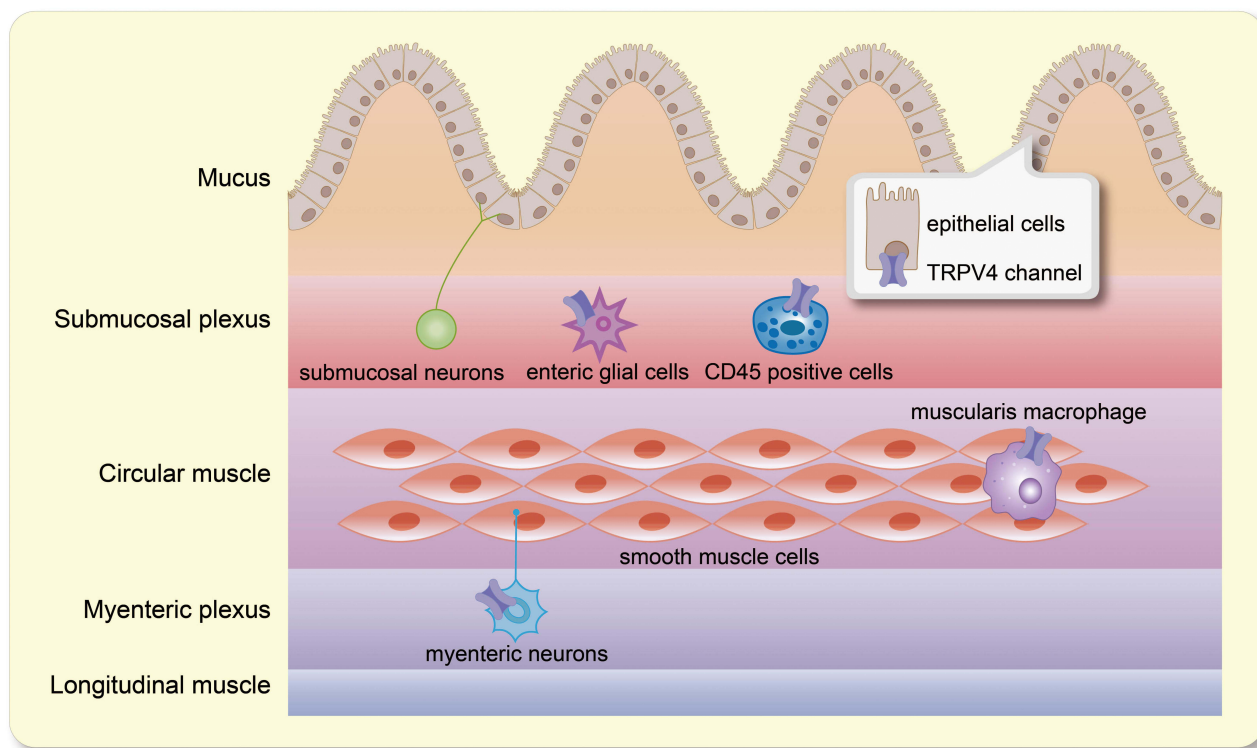
TRPV4 is expressed in the airway, kidney epithelia, autonomic nervous system,^{4,8} heart,⁹ skin,¹⁰ brain,¹¹ stomach,¹² pancreas¹³ and intestine.¹⁴ In irritable bowel syndrome (IBS), the visceral reaction induced by proteinase-activated receptor 2 (PAR2) is closely related to inflammatory reaction and depends on the activation of TRPV4. Moreover, other members of the TRP family TRPV1 and TRPA1 are closely related to visceral hypersensitivity.¹⁵ Recently, Cheng et al¹⁶ found the expression levels of TRPV1, TRPV4 and TRPA1 in intestinal mucosa of IBS patients can be significantly increased. In addition, the levels of TRPV 4 and TRPV 6 in the colon of patients with ulcerative colitis (UC) are evidently higher than those of normal people.¹⁷

Table 1 Distribution and Functions of TRPV4 in the Intestine

Cell Type	Cell Names	Species	Disease Models	Functions	Ref.
Epithelial cell	Caco-2 and T84 cells	Mice, Human	4 α PDD-induced colitis	TRPV4 activation caused the elevation of intracellular calcium concentrations, release of cytokines and chemokines, and colitis formation	D'Aldebert et al 2011 ²⁰
	N/D	Human	Ulcerative colitis	N/D	Rizopoulos et al 2018 ²¹
	IEC-6 cells	Rat	NSAID-induced intestinal damage	TRPV4 activation and indomethacin caused epithelial hyperpermeability	Yamawaki et al 2014 ²²
Immune cell	Muscularis macrophages	Mice	Chemotherapy-associated gastrointestinal dysmotility	TRPV4 promoted the release of prostaglandin E2 and elicited colon contraction	Luo et al 2018 ²³
Nerve tissue	CD45 positive cell	Human	IBD	N/D	D'Aldebert et al 2011 ²⁰
	Myenteric neuron	Mice	Gastrointestinal transit	TRPV4 activation reduced gastrointestinal motility and reduced stool production	Fichna et al 2015 ²⁴
	Nerve fiber	Human, Mice	TRPV4+/+ and -/-	Deletion of TRPV4 reduced the mechanosensory responses	Brierley et al 2008 ²⁵
	Nerve fiber	Human	dyspeptic	TRPV4 upregulation increased the acid-induced mast cells infiltration	Sarnelli et al 2021 ²⁶
	Enteric glial cells	Human	IBD	N/D	D'Aldebert et al 2011 ²⁰

Abbreviations: IBD, inflammatory bowel disease; IEC, intestinal epithelial cell; N/D, not determined.

Many studies show that TRPV4 is involved in pan pathophysiological activities in the intestine. For example, GSK1016790A, a TRPV4 agonist, exacerbated the severity of dextran sodium sulfate (DSS)-induced colitis.¹⁸ Furthermore, the pain-related behaviors in rats with pancreatitis were effectively alleviated by the TRPV4 antagonist, HC067047.¹⁹ Recent findings about the distribution of TRPV4 in the intestine were summarized in Table 1 and Figure 1. We reviewed the researches to explore the role and important mechanisms of TRPV4 in the intestine and evaluate the potential use of TRPV4 as a therapeutic target for intestinal diseases.

**Figure 1** Distribution of TRPV4 in intestinal cells.

TRPV4 channels are expressed on different parts of intestinal epithelium, submucosa and muscle layer (Figure 1). The distribution of TRPV4 channels in the intestine includes the following aspects: (1) TRPV4 channels are expressed in intestinal epithelial cells and affect the intestinal barrier function by regulating calcium release; (2) Myenteric neurons express TRPV4, and activation of TRPV4 inhibits gastrointestinal motility; (3) TRPV4, as an osmotic receptor, can sense and respond to osmotic pressure in the submucosal plexuses; (4) Expression of TRPV4 channels in muscle macrophages can directly regulate the colon contraction by regulating the release of prostaglandin E₂; (5) TRPV4 acts as a visceral nociceptor and mediates the PAR2-induced Ca²⁺ signals in DRG neurons; (6) TRPV4 regulates intestinal Na⁺ absorption and Cl⁻ secretion.

Distribution and Functions of TRPV4 in the Intestine

The intestine is the largest digestive organ of the human body, which undertakes the important task of digesting food and absorbing nutrition and, in the meantime, preventing harmful substances from invading the organism in the intestinal lumen.^{27,28} Defects in mucosal barrier function can lead to bacterial translocation and exacerbate systemic inflammatory responses.²⁹ Here, we summarize the intestinal distribution and functions of TRPV4. In addition to being expressed in intestinal epithelial cells, TRPV4 is also expressed in immune cells and nerve tissue of the intestine to take effects (Table 1).

TRPV4 and Intestinal Barrier Function

The intestinal mucosal barrier is the main line of defense against potentially harmful substances and infectious substances, and it consists of physical barrier, chemical barrier, immune barrier, and microbial barrier.^{30–32} As we know, TRPV4 is detected in mice colonic tissues and human intestinal cell lines, and is expressed on the basolateral side of epithelial cells.^{20,22,33} 4αPDD as a specific agonist of TRPV4 can significantly increase colonic permeability in mice and human,²⁰ which indicates the negative role of TRPV4 in intestinal mechanical barrier.

The intestinal chemical barrier consists of gastric acid, bile, various digestive enzymes, lysozyme, mucopolysaccharide and other components secreted by the digestive tract.³⁴ The intestinal chemical barrier plays an important role in maintaining intestinal microecological balance and protects the intestinal mucosa from erosion due to enzymes and acidic and alkali conditions. It is essential to emphasize that these chemicals must be confined in the undisturbed mucus layer. If the mucus layer is broken, these chemicals can be turned into destroyers to cause further damage to the intestine.^{35,36} Duan et al³⁷ reported that the activation of the TRPV4 ion channel in the lung exacerbates inflammation and hypersecretion of mucus in the airways. And TRPV4 also responded significantly to low pH and citrate.⁷ Sarnelli et al²⁶ found that acid-induced expression of TRPV4 was higher in dyspeptics than controls. Moreover, a recent study³⁸ showed that bile flow increased significantly in mice after intravenous administration of the TRPV4 agonist glycogen synthase kinase (GSK). Therefore, the activation of TRPV 4 may disturb the chemical barrier and further aggravate digestive system diseases.

The intestinal immune barrier refers to antibacterial substances (mucins and AMPs), gut-associated lymphoid tissues (mainly Peyer's patches and mesenteric lymph nodes). The effector site is represented by intestinal lamina propria, which consists of antigen-presenting cells.^{39,40} Indeed, IL-1β, which has been shown to be up-regulated in the DSS-induced colitis model,^{41,42} is able to cause an increase in TRPV4 mRNA expression in mice microvascular endothelial cells.⁴² Considering the strong expression of TRPV4 in intestinal epithelial cells, upregulation of TRPV4 expression in this cell type in response to inflammatory mediators could also occur, at least in mice colon. D'Aldebert et al²⁰ researched that the activation of TRPV4 in the gastrointestinal tract activated transcription factors NF-κB and AP-1 which mediate immune inflammatory reaction, thus promoting the production of inflammatory factors IL-8 and even colitis. These indicated that the immune barrier function of intestinal mucosa was impaired. So, TRPV4 agonists were considered as an activator to induce classic proinflammatory signaling pathways in intestinal epithelial cells.

The gut is the largest organ to accommodate the external microbes. Normal intestinal flora (gut microbiota, especially *Bifidobacterium* and *Lactobacillus* species) constituted the intestinal biological barrier.^{39,43} The TRPV4 gene expression was downregulated by Probiotics (*VSL#3*) in neonatal maternal separation (NMS)-induced visceral hyperalgesia rat

model.⁴⁴ However, Aguilera et al⁴⁵ reported that environment-related adaptive changes in gut commensal microbiota modulated the expression of markers (MOR, TRPV3, PAR-2, and CB2) but did not alter the expression of TRPV4.

In short, the above data support that TRPV4 affects the intestinal mucosal barrier function, and TRPV4 agonist increases intestinal permeability and induces the release of inflammatory factors which leads to impaired intestinal mucosal barrier.

TRPV4 and Gastrointestinal Motility

Gastrointestinal motility is a complex physiological process that refers to the coordinated contractions of the tunica muscularis. Studies have shown that the enteric nervous system, interstitial cells of Cajal (ICC) and smooth muscle cells (SMC) form a network that participates in the regulation of gastrointestinal motility.^{46,47} Several studies indicated that TRPV4 was expressed in colonic sensory neurons.^{15,25,48} Furthermore, Fichna et al²⁴ demonstrated that mouse myenteric neurons functionally expressed TRPV4, and TRPV4 activation inhibited gastrointestinal motility by reducing NO-dependent Ca²⁺ release. It was known that the ICCs generated the slow waves in the gastrointestinal tract and then transmitted this electrical activity to SMCs, which regulated smooth muscle contraction.⁴⁷ However, it was interesting that Luo et al²³ provided an additional pathway that TRPV4 channel signaling in muscularis macrophages mediated colon contraction by directly effecting smooth muscle cells, and TRPV4 expressed specifically on muscularis macrophages which was required for this process. However, TRPV4 was not present in other contractile apparatus components, including ICCs and SMCs.²³ TRPV4 could be detected in the submucous plexus, which may sense and respond to osmotic shifts,⁸ and was reported as an osmoreceptor involved in regulating systemic osmotic pressure,² which suggested a possible involvement of TRPV4 in the pathophysiology of secretory diarrhea. However, it is noteworthy that the exclusive expression of TRPV4 by muscularis macrophages is inconsistent with the expression of TRPV4 by vascular endothelial and other cell types as outlined.

The above data support that the activation or inhibition of TRPV4 may provide a new therapeutic strategy for improving constipation or diarrhea by controlling gastrointestinal motility.

TRPV4 and Sensory Transduction

TRPV4 expression in intrinsic enteric neurons mainly regulates the gastrointestinal motility. The gastrointestinal tract is also innervated by extrinsic neurons from dorsal root ganglia (DRG).⁴⁹ The visceral afferents expressed TRPV4 more abundantly than the general population of neurons in their respective ganglia. Previous studies identified that colonic neurons within thoracolumbar DRG TRPV4 showed the highest levels, it is several times higher than DRG in other parts, and it colocalized with the sensory neuropeptide calcitonin gene-related peptide (CGRP) in colonic nerve fibers in mice.²⁵ TRPV4 agonist 4 α PDD specifically activated the calcium influx in isolated colonic DRG neurons and caused visceral hypersensitivity.⁵⁰ The mechanosensory responses of splanchnic colonic and pelvic colonic afferents were reduced in TRPV4^{-/-} mice.²⁵ These functional evidences were correlated with the enrichment of TRPV4 expression in colonic sensory neurons.

Previous studies identified that PAR2 could directly activate sensory neurons, and TRPV4 was not only a downstream signal of the PAR2 but was also composed of a common mechanism to other mediators including histamine and serotonin (released by visceral hypersensitivity).^{48,51–54} Balemans et al⁵⁵ demonstrated that histamine-mediated TRPV4 sensitization in IBS via histamine 1 receptor activation. Further, Cenac et al¹⁵ demonstrated that PAR2-agonist peptide could induce 5,6-EET (TRPV4 agonist) synthesis in sensory neurons. TRPV4 was co-expressed with substance P and CGRP in DRG neurons. Activation of TRPV4 promoted the release of substance P and CGRP and induced mechanical hyperalgesia.⁴⁸ Therefore, inhibition of TRPV4 prevented the release of TRPV4-dependent nociceptive peptides and relieved pain.⁵⁰ In addition, bafetinib (a tyrosine kinase inhibitor) was found to block PAR2-TRPV4 coupling and to inhibit mechanical hyperalgesia.⁵⁶ The authors further showed that mechanosensory responses were dramatically reduced in mice with a targeted disruption of TRPV4.²⁵ Park et al⁵⁷ found that diet-induced obesity disrupts the activation of TRPV4 and TRPA1 and further suggested that TRPV4 may participate partly in vagal afferent satiety signaling. Moreover, some of the reports described a decreasing response to noxious mechanical stimulation in TRPV4^{-/-} mice lacking the channel, which confirmed the selective role of TRPV4 in afferents to be visceral nociceptors.⁷ So, TRPV4 may present a selective novel target for the reduction of visceral pain.

TRPV4 and Intestinal Ion Transport

TRPV4 could be detected in the submucous plexus, which may sense and respond to osmotic shifts, and was reported as an osmoreceptor involved in regulating systemic osmotic pressure.⁷ The TRPV4 channel is a tetrameric protein localized in the plasma membranes of different cells, where it regulates ion fluxes, particularly Ca^{2+} , in response to several stimuli. Ca^{2+} is considered to be an important regulator of intestinal ion transport in epithelial cells.⁵⁸ Ca^{2+} signaling mediated duodenal Cl^- and HCO_3^- secretion in mice.⁵⁹ TRPV4 is a nonselective cation channel with higher permeability for Ca^{2+} and is widely expressed in the intestinal epithelium.^{1,20} The authors further demonstrated that TRPV4 was involved in the molecular composition of store-operated Ca^{2+} entry (SOCE). Furthermore, Ca^{2+} influx via TRPV4 was required for cholinergic signaling-mediated intestinal anion secretion, which was indirectly inhibited by capsaicin.^{14,60} The reduction of Na^+ absorption would cause diarrhea.⁶¹ Cheng et al¹⁶ showed that TRPV4 in the colonic mucosa was enhanced in IBS-diarrhea patients. In support, suppressing the activation of epithelial TRPV4 channels could increase intestinal Na^+ absorption but reduce Cl^- secretion, thereby leading to a decrease in colitis diarrhea.¹⁴ The role of TRPV4 in regulating intestinal Na^+ absorption and Cl^- secretion means that TRPV4 antagonism may have the potential to reverse diarrhea.

However, it is not clear how the manipulation of $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ cotransporter and Ca^{2+} changes the function of TRPV4 in intestinal ion transport. But this may be an effective drug target for treating intestinal-related diseases.

The Role and Clinical Significance of TRPV4 in Intestinal Diseases TRPV4 and IBD

IBD consists of two primary diseases: UC and Crohn's disease (CD). Many studies supported the concept that IBD was resulted from a dysregulation of the mucosal immune system in response to the microbiota that resides in the intestinal lumen.⁶² TRPV4 is expressed and functional in human intestinal cell lines, where it causes the release of proinflammatory cytokines. Of note, TRPV4 was co-localized with CD45-positive cells infiltrating inflamed colon.²⁰ TRPV4 agonists, such as 4 α -PDD and GSK1016790A, activated classic proinflammatory signaling pathways in intestinal epithelial cells and exacerbated the severity of colitis.^{18,20} Studies indicated that high expression of TRPV4 was observed in the intestinal tissues and peripheral blood mononuclear cells of UC and CD patients.^{17,20,63} Besides, Matsumoto et al¹⁸ showed that TRPV4 expression was increased in endothelial cells in DSS-treated mice, which was consistent with the results in the colonic epithelium of ulcerative colitis patients.²¹ They further performed bone marrow transplantation experiments in the DSS model and showed that TRPV4 in non-hematopoietic cells (endothelial cells, sensory neurons, and epithelial cells) played a dominant role in DSS-induced colitis. These mean that TRPV4 antagonism may potentially protect intestinal mucosal barrier function and help the treatment of IBD. Indeed, Fichna et al⁶⁴ found that RN1734 (TRPV4-selective antagonist) alleviated colitis and the pain associated with intestinal inflammation. In support, indomethacin-induced intestinal injury in WT mice was partially reduced by the specific TRPV4 antagonist HC067047 or the epoxygenase inhibitor MS-PPOH.²² In addition, in TRPV4^{-/-} mice, indomethacin-induced intestinal damage was significantly reduced compared to WT mice.²² 5,6-dihydroxy-8Z,11Z,14Z,17Z-eicosatetraenoic acid (5,6-DiHETE) as another novel endogenous TRPV4 antagonist could also repair edema and leukocyte infiltration in DSS-induced colitis.⁶⁵ The activation of TRPV4 in vascular endothelium can enhance the influx of calcium ions, promote vascular relaxation and increase blood perfusion.⁶⁶ Besides, TRPV4 ion channel mediates protease activated receptor 1 (PAR1)-induced vascular hyperpermeability and promotes the release of edema and inflammatory reaction.⁶⁷ Up-regulation of TRPV4 expression in vascular endothelial cells contributes to the progression of colonic inflammation via the activation of vascular permeability, and TRPV4 further decreased the expression of the major endothelial adhesion molecule vascular E-cadherin in mouse aortic endothelial cells and the colon.¹⁸ These data indicate that TRPV4 antagonists may provide promising means for the treatment of colitis progression (Figure 2).

TRPV4 and IBS

IBS is a chronic gastrointestinal disorder characterized by abdominal pain and disturbed bowel habits. In the absence of detectable organic cause, visceral hypersensitivity and gastrointestinal dysmotility were two primary characteristics of IBS.^{68,69} TRPV4 agonist (RN1747) decreased the pain pressure threshold in the IBS rat model induced by chronic water

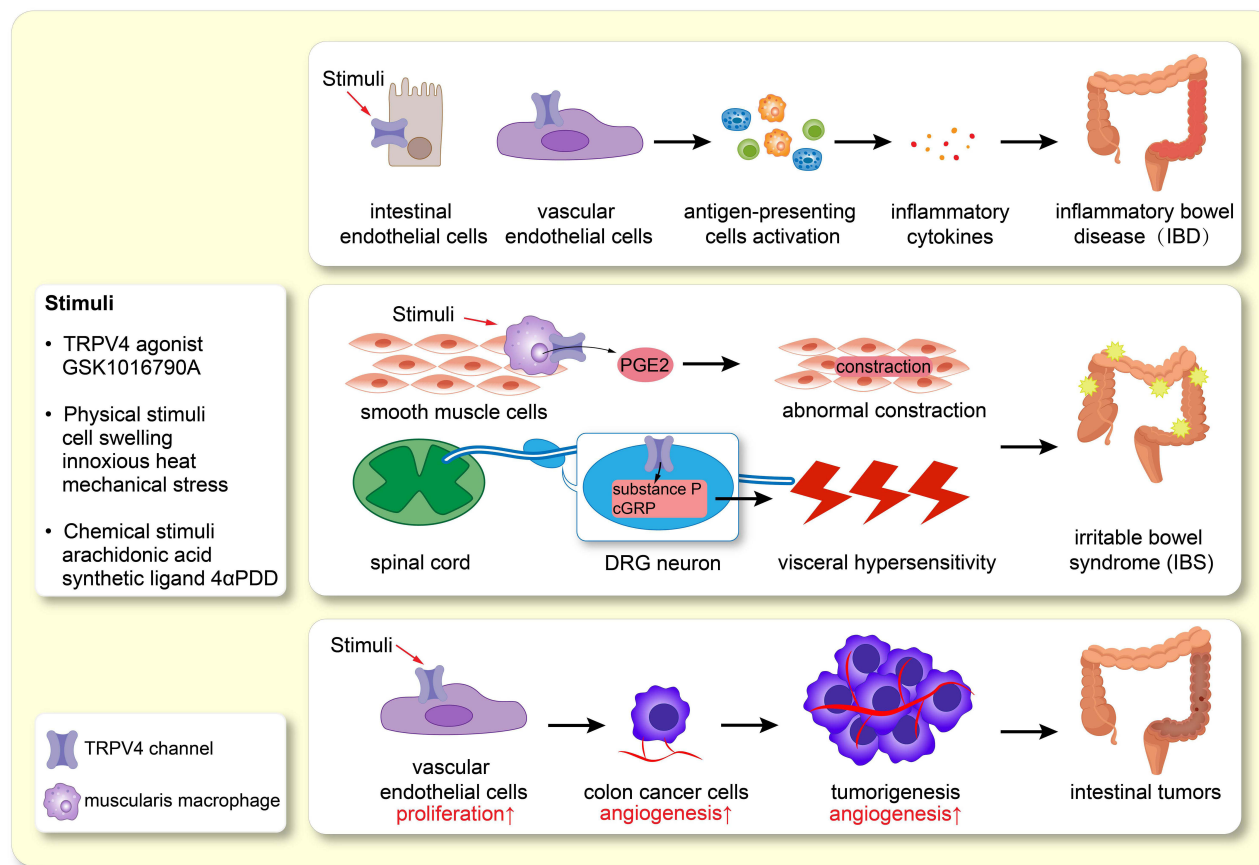


Figure 2 Role of TRPV4 in intestinal diseases.

avoidance stress, suggesting that TRPV4 played a vital role in visceral hypersensitivity. Correspondingly, a Chinese traditional medicine named *Shugan decoction* was reported to effectively improve the abnormal colonic motility by inhibiting the activation of TRPV1, TRPV4, TRPA1 and PAR2.⁷⁰ In addition, TRPV4 inhibitors can affect visceral hypersensitivity in other models. As an inhibitor of the calcium permeant cation channel, HC067047 restores LPS-induced endotoxemia colons against oxidative stress, mitophagy, inflammatory pyroptosis, and colonic barrier dysfunction.⁷¹ HC067047 restores endotoxemia colons against oxidative stress, mitophagy, inflammatory pyroptosis, and colonic barrier dysfunction. TRPV4 antagonist HC067047 was reported to effectively alleviate visceral hypersensitivity and pain-related behaviors in a rat chronic pancreatitis model.¹⁹ Besides, Kanju et al⁷² developed novel compounds that inhibited both TRPV4 and TRPA1 to effectively attenuate inflammation and pain-associated behavior in a model of acute pancreatitis. Reports above indicated the potential functions of TRPV4 in regulating visceral hypersensitivity and gastrointestinal dysmotility in IBS.

Increasing studies were focused on the role of gut microbiota alterations in IBS patients.⁷³ The probiotic *VSL#3* reversed both allodynia and hyperalgesia in the IBS-NMS rat model, wherein the expression of TRPV4 was indirectly down-regulated under the probiotic intervention.⁴⁴ It was also found that *Bifidobacterium animalis* F1-7 (F1-7) and *Lactobacillus paracasei* F34-3 (F343) promoted 5-hydroxytryptamine (5-HT) secretion in enterochromaffin cells (EC) of constipation mice by activating the chromogranin A/ α 2A adrenoreceptor cascade signal and downregulated the expression of TRPV4.⁴³ Wherein, approximately 90% of 5-HT which can effectively relieve constipation was synthesized and distributed in ECs.⁷⁴ TRPV4 channels may constitute SOCE to contribute to prostaglandin E2 and 5-HT-induced Ca^{2+} -dependent duodenal anion secretion,⁶⁰ and these strains above can be well colonized in the large intestine of mice. Thus, probiotic colonization may affect TRPV4 to provide an effective treatment for IBS.

Constipation was the most common gastrointestinal motility disorder in the clinic. In acute colitis, the calcium signaling pathway is inhibited; meanwhile, the glial signal coordinating GSK 1016790 a response is also destroyed.⁷⁵ Moreover, Fichna et al²⁴ found that TRPV4 activation in vivo reduced gastrointestinal motility and stool production and the TRPV4 agonist GSK1016790A reduced colonic contractility. Their studies also showed a significant decreased TRPV4 mRNA expression in colon biopsies from IBS-Constipation patients, and TRPV4 antagonist RN1734 increased the stool production in the mice model of hypomotility. However, if TRPV4 in macrophages can also promote gastrointestinal motility,²³ then this would most likely reverse constipation. Therefore, in the treatment of constipation and IBS, it is a question worth pondering whether to choose the antagonist or agonist of TRPV4.

Together, TRPV4 could be significant in visceral nociception, the development of hypersensitivity and constipation in IBS (Figure 2).

TRPV4 and Intestinal Tumors

TRPV4 was reported to induce cell migration,⁷⁶ proliferation,⁷⁷ apoptosis,⁷⁸ pyroptosis⁷¹ and differentiation⁷⁹ in multiple processes of tumor progression and was also contributed to angiogenesis migration of tumor-derived endothelial cells in breast cancer.⁸⁰ However, the role of TRPV4 in intestinal tumors has not yet been sufficiently identified.

Recent researches showed that the expression of TRPV4 was upregulated in vascular endothelial cells in the colon of DSS-induced colitis mice model.¹⁸ The authors further demonstrated that TRPV4 activation enhanced the proliferation of neovascular endothelial cells in the intestine, contributing to the progression of colitis-associated cancer.⁸¹ Therefore, antagonists of the TRPV4 channel are expected to be a molecular intervention for anti-angiogenic treatment in colorectal cancer (CRC).

CRC is one of the most common cancers in the gastrointestinal tract. TRPV4 expression in CRC patients was revealed to be lower in tumor tissues than in normal tissue.⁸² However, Liu et al⁸³ showed that TRPV4 expression was higher in CRC when compared to adjacent normal tissues. These observations indicated that TRPV4 expression in the colon may be altered with gender difference. They further demonstrated that upregulated TRPV4 was associated with poor prognosis and the PTEN pathway contributed to TRPV4 mediated cell growth. Colitis-associated cancer is a tumor that develops in chronic inflammation and is considered as the most severe complication of IBD. Blockade of TRPV4 inhibited chronic intestinal inflammation and subsequent tumor formation, and TRPV4 expressed in bone marrow-derived macrophages played a significant role in colitis-associated tumorigenesis.⁸¹

Taken together, TRPV4 drives the intestinal deterioration from inflammation to carcinogenesis, and plays a key role in the progression from colitis to CRC. More studies are still needed to determine the potential role of TRPV4 in intestinal tumors (Figure 2).

TRPV4 and Other Intestinal Diseases

Duodenal mucosal hyperpermeability and low-grade duodenal inflammation are pathophysiological conditions that are associated with functional dyspepsia (FD). Excessive acid secretion is prevalent in many FD patients. Thus, acid suppressive therapy is the first-line treatment in FD, however the pathophysiology remains incompletely understood.^{84,85} Study indicated that following acid exposure, the expression of TRPV4 was higher in duodenum than controls.²⁶ In addition, the acid exposure initiated over-expression of TRPV4 was mostly located on submucosal nerve endings, thus indicating that TRPV4 may be a regulator of pathological acid activation in the nervous system.

Helicobacter pylori infection has been recognized as a major etiology for the development of duodenal ulcer (DU). TRPV4 expression is directly suppressed by DNA methylation silencing with *Helicobacter pylori* infection in gastric epithelium.⁸⁶ However, another study found that TRPV4 was significantly highly expressed in the tissues of children with DU (with *Helicobacter pylori* infection), and animal experiments have proved that TRPV4 can enhance intestinal permeability, thereby promoting further infiltration of inflammatory factors.⁸⁷ There is still a need to explore detailed mechanism that how TRPV4 functions in DU.

TRPV4 was reported sensitive to noxious mechanical stimulation. Zheng et al⁸⁸ found that acupuncture analgesia effect was suppressed by the inhibitor of TRPV4 channel. Therefore, TRPV4 is a candidate to being activated by acupuncture. Additionally, a few studies so far have explored the clinical trial for TRPV4 antagonists. Goyal et al⁸⁹

observed that GSK2798745 was well tolerated in healthy volunteers and patients with stable heart failure. In IBS patients, the increased polyunsaturated fatty acid stimulated sensory neurons from mice and generate visceral hypersensitivity via activation of TRPV4.¹⁵ As a result, aiming at the TRPV4 antagonists should be taken into account as the promising and fascinating strategy.

Conclusion

In relation to the physiological functions of TRPV4, we speculate that endothelial TRPV4 is activated to show negative effects by intrinsic ligands under inflammatory conditions. TRPV4 agonist did not affect vascular permeability in normal mice. But in colitis mice, TRPV4 could promote the release of inflammatory factors. In IBS patients, the increased polyunsaturated fatty acid stimulated sensory neurons from mice and generate visceral hypersensitivity via activation of TRPV4. Moreover, TRPV4 can promote the formation of intestinal neovascular, thereby inducing the progression of colitis-associated cancer as an inflammation-related cancer. The intestine has been considered as the motor of multiple organ dysfunction syndromes (MODS). Further, the inhibition of TRPV4 reduced mortality and maintained vascular endothelial functions in a lipopolysaccharide-induced murine septic model, but the observation was not focused on the intestine. Also, rare data existed on the function of TRPV4 in acute enteritis. This truth is frequently a source of frustration for patients and clinicians alike. We need to further study the role of TRPV4 in acute intestinal injury, so as to provide more effective treatment for clinical treatment.

As we described before, TRPV4 participated in most intestinal disease models as a negative regulator, it is more clinically significant to study the effects of TRPV4 deficiency. No other signs of changes in behavior or conscious sensory capacity in TRPV4 null-mutants. TRPV4^{-/-} mice were protected against DSS-induced weight loss, leukocyte infiltration, colon shortening, diarrhoea, occult fecal blood, and histological damage. In a colitis-associated cancer mice model, about 40% of WT mice died at the end of the treatment of AOM/DSS, but all TRPV4^{-/-} mice survived during the treatment. Application of antagonists alone did not affect the integrity and permeability of the epithelial. Therefore, we consider that specific TRPV4 inhibition shows positively protective effects but fewer side effects, and the TRPV4 antagonists can be potential in clinical application for the treatment of intestinal inflammation-related diseases.

Nowadays, the treatment of intestinal diseases has changed from traditional medication to new immunotherapy, targeted therapy and ion channel therapy. With the rapid development of medical research related to TRPV4 channel, the treatment of various intestinal diseases based on TRPV4 channel has aroused great concern. A crucial challenge is that the activation or inhibition of TRPV4 has different effects on intestinal diseases. After activation, constipation may be solved for patients with low intestinal peristalsis, but it may be unfavorable for diarrhea patients. An in-depth understanding of TRPV4 in human and animal studies will further advance the field of clinical application of TRPV4 agonists or antagonists. In summary, we need to better understand the role of TRPV4 in intestinal functions and intestinal diseases, which may provide clinicians with important evidence and new therapeutic targets for treating intestinal diseases.

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Disclosure

The authors report no conflicts of interest in this work.

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