Journal of Inflammation Research Dovepress

Open Access Full Text Article REVIEW

The Role of the TRPV4 Channel in Intestinal Physiology and Pathology

Dandan Liu[1,*], Mingli Mao[1,*], Wenjia Liu[1], Lihua Xie[1], Xiaolin Zhong[1], Wenyu Cao[2], Ling Chen[1]

[1]Department of Metabolism and Endocrinology, The First Affiliated Hospital of University of South China, Hengyang Medical School, University of South China, Hengyang, Hunan, 421001, People's Republic of China; [2]Clinical Anatomy & Reproductive Medicine Application Institute, Hengyang Medical School, University of South China, Hengyang, Hunan, 421001, People's Republic of China

*These authors contributed equally to this work

Correspondence: Ling Chen, The First Affiliated Hospital of University of South China, Department of Endocrinology and Metabolism, Hengyang Medical School, University of South China, Hengyang, Hunan, 421001, People's Republic of China, Email lingchen-cl@outlook.com

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] OTRPC4[1] TRP12,[3] and VRL-2.[4] After decades of research, TRPV4 is found to be activated by different stimuli, including physical (cell swelling, innoxious heat, mechanical stress) and chemical (arachidonic acid, synthetic ligand 4αPDD 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] pancreas[13] 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 al[16] 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]

Received: 19 June 2024
Accepted: 6 November 2024
Published: 21 November 2024

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	4αPDD-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]
	CD45 positive cell	Human	IBD	N/D	D'Aldebert et al 2011[20]
Nerve tissue	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.

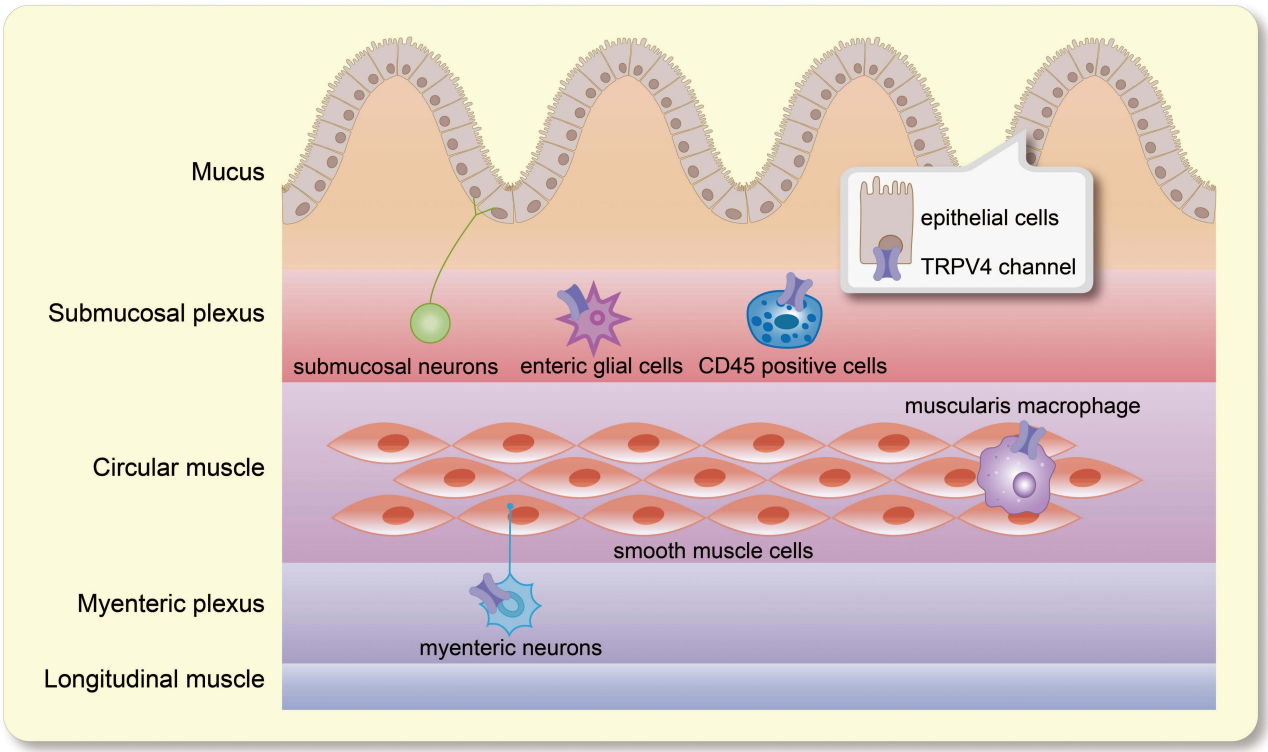

Figure 1 Distribution of TRPV4 in intestinal cells.

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 Ca^{2+} 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 al[37] 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 al[26] found that acid-induced expression of TRPV4 was higher in dyspeptics than controls. Moreover, a recent study[38] 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 al[20] researched that the activation of TRPV4 in the gastrointestinal tract activated transcription factors NF-kB 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 al[45] 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 al[24] demonstrated that mouse myenteric neurons functionally expressed TRPV4, and TRPV4 activation inhibited gastrointestinal motility by reducing NO-dependent Ca^{2+} 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 al[23] 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 4αPDD 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 al[55] demonstrated that histamine-mediated TRPV4 sensitization in IBS via histamine 1 receptor activation. Further, Cenac et al[15] 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 al[57] 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 al[16] 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 Na^+-K^+-$2Cl^-$ 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 4α-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 al[18] 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 al[64] 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

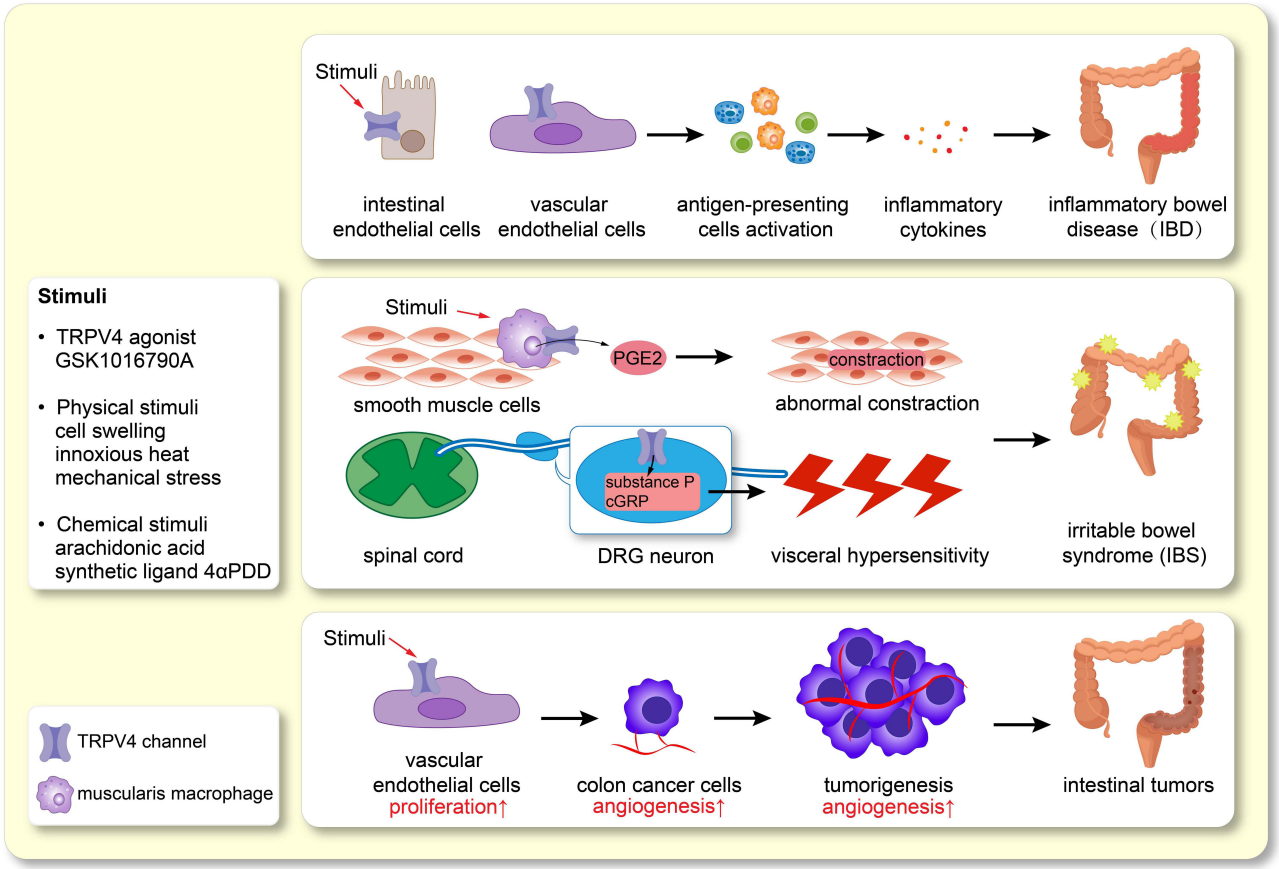

Figure 2 Role of TRPV4 in intestinal diseases.

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 channe, 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 al[72] 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/α2A 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 al[24] 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 deceased 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] pyroptosis[71] and differentiation[79] 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-angiogenetic 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 al[83] 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 al[88] 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 al[89]

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 TRPV 4 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.

Funding

This work was supported by grants from the National Natural Science Foundation of China (82100537) and the Natural Science Foundation of Hunan Province (2023JJ30537).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Strotmann R, Harteneck C, Nunnenmacher K, Schultz G, Plant TD. OTRPC4, a nonselective cation channel that confers sensitivity to extracellular osmolarity. *Nat Cell Biol*. 2000;2(10):695–702. doi:10.1038/35036318
2. Liedtke W, Choe Y, Martí-Renom MA, et al. Vanilloid receptor–related osmotically activated channel (VR-OAC), a candidate vertebrate osmoreceptor. *Cell*. 2000;103(3):525–535. doi:10.1016/S0092-8674(00)00143-4
3. Wissenbach U, Bödding M, Freichel M, Flockerzi V. Trp12, a novel Trp related protein from kidney. *FEBS Lett*. 2000;485(2–3):127–134. doi:10.1016/S0014-5793(00)02212-2

4. Delany NS, Hurle M, Facer P, et al. Identification and characterization of a novel human vanilloid receptor-like protein, VRL-2. *Physiol Genom*. 2001;4(3):165–174. doi:10.1152/physiolgenomics.2001.4.3.165
5. Watanabe H, Vriens J, Prenen J, Droogmans G, Voets T, Nilius B. Anandamide and arachidonic acid use epoxyeicosatrienoic acids to activate TRPV4 channels. *Nature*. 2003;424:(6947):434–438. doi:10.1038/nature01807
6. Vriens J, Watanabe H, Janssens A, Droogmans G, Voets T, Nilius B. Cell swelling, heat, and chemical agonists use distinct pathways for the activation of the cation channel TRPV4. *Proc Natl Acad Sci USA*. 2004;101(1):396–401. doi:10.1073/pnas.0303329101
7. Suzuki M, Mizuno A, Kodaira K, Imai M. Impaired pressure sensation in mice lacking TRPV4. *J Biol Chem*. 2003;278(25):22664–22668. doi:10.1074/jbc.M302561200
8. Kollmann P, Elfers K, Maurer S, Klingenspor M, Schemann M, Mazzuoli-Weber G. Submucosal enteric neurons of the cavine distal colon are sensitive to hypoosmolar stimuli. *J Physiol*. 2020;598(23):5317–5332. doi:10.1113/JP280309
9. Adapala RK, Kanugula AK, Paruchuri S, Chilian WM, Thodeti CK. TRPV4 deletion protects heart from myocardial infarction-induced adverse remodeling via modulation of cardiac fibroblast differentiation. *Basic Res Cardiol*. 2020;115(2):14. doi:10.1007/s00395-020-0775-5
10. Yang P, Lu P, Luo J, et al. Transient stimulation of TRPV4-expressing keratinocytes promotes hair follicle regeneration in mice. *Br J Pharmacol*. 2020;177(18):4181–4192. doi:10.1111/bph.15161
11. Aghazadeh A, Feizi MAH, Fanid LM, Ghanbari M, Roshangar L. Effects of hyperthermia on TRPV1 and TRPV4 channels expression and oxidative markers in mouse brain. *Cell Mol Neurobiol*. 2021;41(7):1453–1465. doi:10.1007/s10571-020-00909-z
12. Mihara H, Suzuki N, Boudaka AA, et al. Transient receptor potential vanilloid 4-dependent calcium influx and ATP release in mouse and rat gastric epithelia. *WJG*. 2016;22(24):5512. doi:10.3748/wjg.v22.i24.5512
13. Ceppa E, Cattaruzza F, Lyo V, et al. Transient receptor potential ion channels V4 and A1 contribute to pancreatitis pain in mice. *Am J Physiol Gastrointest Liver Physiol*. 2010;299(3):G556–G571. doi:10.1152/ajpgi.00433.2009
14. Wan H, Chen XY, Zhang F, et al. Capsaicin inhibits intestinal Cl- secretion and promotes Na+ absorption by blocking TRPV4 channels in healthy and colitic mice. *J Biol Chem*. 2022;298(5):101847. doi:10.1016/j.jbc.2022.101847
15. Cenac N, Bautzova T, Le Faouder P, et al. Quantification and potential functions of endogenous agonists of transient receptor potential channels in patients with irritable bowel syndrome. *Gastroenterology*. 2015;149(2):433–444.e7. doi:10.1053/j.gastro.2015.04.011
16. Cheng L, Luo QQ, Chen SL. Expression of TRP channels in colonic mucosa of IBS-D patients and its correlation with the severity of the disease. *Gastroenterol Res Pract*. 2022;2022:1–7. doi:10.1155/2022/7294775
17. Toledo Mauriño JJ, Fonseca-Camarillo G, Furuzawa-Carballeda J, et al. TRPV subfamily (TRPV2, TRPV3, TRPV4, TRPV5, and TRPV6) gene and protein expression in patients with ulcerative colitis. *J Immunol Res*. 2020;2020:1–11. doi:10.1155/2020/2906845
18. Matsumoto K, Yamaba R, Inoue K, et al. Transient receptor potential vanilloid 4 channel regulates vascular endothelial permeability during colonic inflammation in dextran sulphate sodium-induced murine colitis. *Br J Pharmacol*. 2018;175(1):84–99. doi:10.1111/bph.14072
19. Zhang LP, Kline RH, Deevska G, Ma F, Nikolova-Karakashian M, Westlund KN. Alcohol and high fat induced chronic pancreatitis: TRPV4 antagonist reduces hypersensitivity. *Neuroscience*. 2015;311:166–179. doi:10.1016/j.neuroscience.2015.10.028
20. D'Aldebert E, Cenac N, Rousset P, et al. Transient receptor potential vanilloid 4 activated inflammatory signals by intestinal epithelial cells and colitis in mice. *Gastroenterology*. 2011;140(1):275–285.e3. doi:10.1053/j.gastro.2010.09.045
21. Rizopoulos T, Papadaki-Petrou H, Assimakopoulou M. Expression profiling of the transient receptor potential vanilloid (TRPV) channels 1, 2, 3 and 4 in mucosal epithelium of human ulcerative colitis. *Cells*. 2018;7(6):61. doi:10.3390/cells7060061
22. Yamawaki H, Mihara H, Suzuki N, et al. Role of transient receptor potential vanilloid 4 activation in indomethacin-induced intestinal damage. *Am J Physiol Gastrointest Liver Physiol*. 2014;307(1):G33–G40. doi:10.1152/ajpgi.00105.2013
23. Luo J, Qian A, Oetjen LK, et al. TRPV4 channel signaling in macrophages promotes gastrointestinal motility via direct effects on smooth muscle cells. *Immunity*. 2018;49(1):107–119.e4. doi:10.1016/j.immuni.2018.04.021
24. Fichna J, Poole DP, Veldhuis N, et al. Transient receptor potential vanilloid 4 inhibits mouse colonic motility by activating NO-dependent enteric neurotransmission. *J Mol Med*. 2015;93(12):1297–1309. doi:10.1007/s00109-015-1336-5
25. Brierley SM, Page AJ, Hughes PA, et al. Selective role for TRPV4 ion channels in visceral sensory pathways. *Gastroenterology*. 2008;134 (7):2059–2069. doi:10.1053/j.gastro.2008.01.074
26. Sarnelli G, Pesce M, Seguella L, et al. Impaired duodenal palmitoylethanolamide release underlies acid-induced mast cell activation in functional dyspepsia. *CMGH*. 2021;11(3):841–855. doi:10.1016/j.jcmgh.2020.10.001
27. Johansson MEV, Ambort D, Pelaseyed T, et al. Composition and functional role of the mucus layers in the intestine. *Cell Mol Life Sci*. 2011;68 (22):3635–3641. doi:10.1007/s00018-011-0822-3
28. Mukherjee S, Hooper LV. Antimicrobial defense of the intestine. *Immunity*. 2015;42(1):28–39. doi:10.1016/j.immuni.2014.12.028
29. Sánchez De Medina F, Romero-Calvo I, Mascaraque C, Martínez-Augustin O. Intestinal inflammation and mucosal barrier function. *Inflamm Bowel Dis*. 2014;20(12):2394–2404. doi:10.1097/MIB.0000000000000204
30. Buckley A, Turner JR. Cell biology of tight junction barrier regulation and mucosal disease. *Cold Spring Harb Perspect Biol*. 2018;10(1):a029314. doi:10.1101/cshperspect.a029314
31. Turner JR. Intestinal mucosal barrier function in health and disease. *Nat Rev Immunol*. 2009;9(11):799–809. doi:10.1038/nri2653
32. An J, Liu Y, Wang Y, et al. The role of intestinal mucosal barrier in autoimmune disease: a potential target. *Front Immunol*. 2022;13:871713. doi:10.3389/fimmu.2022.871713
33. Huang YY, Li J, Zhang HR, et al. The effect of transient receptor potential vanilloid 4 on the intestinal epithelial barrier and human colonic cells was affected by tyrosine-phosphorylated claudin-7. *Biomed Pharmacother*. 2020;122:109697. doi:10.1016/j.biopha.2019.109697
34. Xie L, Chen T, Li H, et al. An exopolysaccharide from genistein-stimulated Monascus purpureus: structural characterization and protective effects against DSS-induced intestinal barrier injury associated with the gut microbiota-modulated short-chain fatty acid-TLR4/MAPK/NF-κB cascade response. *J Agric Food Chem*. 2024;72(13):7476–7496. doi:10.1021/acs.jafc.3c09290
35. Johansson MEV, Phillipson M, Petersson J, Velcich A, Holm L, Hansson GC. The inner of the two Muc2 mucin-dependent mucus layers in colon is devoid of bacteria. *Proc Natl Acad Sci USA*. 2008;105(39):15064–15069. doi:10.1073/pnas.0803124105
36. Kayama H, Okumura R, Takeda K. Interaction between the microbiota, epithelia, and immune cells in the intestine. *Annu Rev Immunol*. 2020;38 (1):23–48. doi:10.1146/annurev-immunol-070119-115104

37. Duan J, Xie J, Deng T, et al. Exposure to both formaldehyde and high relative humidity exacerbates allergic asthma by activating the TRPV4-p38 MAPK pathway in Balb/c mice. *Environ Pollut*. 2020;256:113375. doi:10.1016/j.envpol.2019.113375
38. Li Q, Kresge C, Boggs K, Scott J, Feranchak A. Mechanosensor transient receptor potential vanilloid member 4 (TRPV4) regulates mouse cholangiocyte secretion and bile formation. *Am J Physiol Gastrointest Liver Physiol*. 2020;318(2):G277–G287. doi:10.1152/ajpgi.00176.2019
39. Yan L, Yang C, Tang J. Disruption of the intestinal mucosal barrier in Candida albicans infections. *Microbiol Res*. 2013;168(7):389–395. doi:10.1016/j.micres.2013.02.008
40. Groschwitz KR, Hogan SP. Intestinal barrier function: molecular regulation and disease pathogenesis. *J Allergy Clin Immunol*. 2009;124(1):3–20. doi:10.1016/j.jaci.2009.05.038
41. Prakash T, Janadri S. Anti-inflammatory effect of wedelolactone on DSS induced colitis in rats: IL-6/STAT3 signaling pathway. *J Ayurveda Integr Med*. 2023;14(2):100544. doi:10.1016/j.jaim.2022.100544
42. Ma YY, Huo HR, Li CH, et al. Effects of cinnamaldehyde on PGE_2 release and TRPV4 expression in mouse cerebral microvascular endothelial cells induced by interleukin-1β *Biological &*. *Pharm Bull*. 2008;31(3):426–430. doi:10.1248/bpb.31.426
43. Lu Y, Zhang Z, Tong L, et al. Mechanisms underlying the promotion of 5-hydroxytryptamine secretion in enterochromaffin cells of constipation mice by *Bifidobacterium* and *Lactobacillus*. *Neurogastroenterology Motil*. 2021;33(7):e14082. doi:10.1111/nmo.14082
44. Distrutti E, Cipriani S, Mencarelli A, Renga B, Fiorucci S. Probiotics VSL#3 protect against development of visceral pain in murine model of irritable bowel syndrome. *PLoS One*. 2013;8(5):e63893. doi:10.1371/journal.pone.0063893
45. Aguilera M, Vergara P, Martínez V. Environment-related adaptive changes of gut commensal microbiota do not alter colonic toll-like receptors but modulate the local expression of sensory-related systems in rats. *Microb Ecol*. 2013;66(1):232–243. doi:10.1007/s00248-013-0241-0
46. Kunze WAA, Furness JB. The enteric nervous system and regulation of intestinal motility. *Annu Rev Physiol*. 1999;61(1):117–142. doi:10.1146/annurev.physiol.61.1.117
47. Sanders KM, Koh SD, Ro S, Ward SM. Regulation of gastrointestinal motility—insights from smooth muscle biology. *Nat Rev Gastroenterol Hepatol*. 2012;9(11):633–645. doi:10.1038/nrgastro.2012.168
48. Grant AD, Cottrell GS, Amadesi S, et al. Protease-activated receptor 2 sensitizes the transient receptor potential vanilloid 4 ion channel to cause mechanical hyperalgesia in mice. *J Physiol*. 2007;578(3):715–733. doi:10.1113/jphysiol.2006.121111
49. Spencer NJ, Hu H. Enteric nervous system: sensory transduction, neural circuits and gastrointestinal motility. *Nat Rev Gastroenterol Hepatol*. 2020;17(6):338–351. doi:10.1038/s41575-020-0271-2
50. Cenac N, Altier C, Chapman K, Liedtke W, Zamponi G, Vergnolle N. Transient receptor potential vanilloid-4 has a major role in visceral hypersensitivity symptoms. *Gastroenterology*. 2008;135(3):937–946.e2. doi:10.1053/j.gastro.2008.05.024
51. Cenac N, Altier C, Motta JP, et al. Potentiation of TRPV4 signalling by histamine and serotonin: an important mechanism for visceral hypersensitivity. *Gut*. 2010;59(4):481–488. doi:10.1136/gut.2009.192567
52. Poole DP, Amadesi S, Veldhuis NA, et al. Protease-activated receptor 2 (PAR2) protein and transient receptor potential vanilloid 4 (TRPV4) protein coupling is required for sustained inflammatory signaling*. *J Biol Chem*. 2013;288(8):5790–5802. doi:10.1074/jbc.M112.438184
53. Zhao P, Lieu T, Barlow N, et al. Neutrophil elastase activates protease-activated receptor-2 (PAR2) and transient receptor potential vanilloid 4 (TRPV4) to cause inflammation and pain. *J Biol Chem*. 2015;290(22):13875–13887. doi:10.1074/jbc.M115.642736
54. Zhao P, Lieu T, Barlow N, et al. Cathepsin S causes inflammatory pain via biased agonism of PAR2 and TRPV4. *J Biol Chem*. 2014;289(39):27215–27234. doi:10.1074/jbc.M114.599712
55. Balemans D, Aguilera-Lizarraga J, Florens MV, et al. Histamine-mediated potentiation of transient receptor potential (TRP) ankyrin 1 and TRP vanilloid 4 signaling in submucosal neurons in patients with irritable bowel syndrome. *Am J Physiol Gastrointest Liver Physiol*. 2019;316(3):G338–G349. doi:10.1152/ajpgi.00116.2018
56. Grace MS, Lieu T, Darby B, et al. The tyrosine kinase inhibitor bafetinib inhibits PAR 2-induced activation of TRPV 4 channels *in vitro* and pain *in vivo*. *Br J Pharmacol*. 2014;171(16):3881–3894. doi:10.1111/bph.12750
57. Park SJ, Yu Y, Beyak MJ. Effect of high-fat diet on mechanosensitive transient receptor potential channel activation in vagal afferent neurons. *Can J Physiol Pharmacol*. 2021;99(6):660–666. doi:10.1139/cjpp-2020-0306
58. Jung J, Lee MG. Role of calcium signaling in epithelial bicarbonate secretion. *Cell Calcium*. 2014;55(6):376–384. doi:10.1016/j.ceca.2014.02.002
59. Yang X, Wen G, Tuo B, et al. Molecular mechanisms of calcium signaling in the modulation of small intestinal ion transports and bicarbonate secretion. *Oncotarget*. 2018;9(3):3727–3740. doi:10.18632/oncotarget.23197
60. Cui Y, Chu F, Yin K, et al. Role of serosal TRPV4-constituted SOCE mechanism in secretagogues-stimulated intestinal epithelial anion secretion. *Front Pharmacol*. 2021;12:684538. doi:10.3389/fphar.2021.684538
61. Musch MW, Clarke LL, Mamah D, et al. T cell activation causes diarrhea by increasing intestinal permeability and inhibiting epithelial Na+/K+-ATPase. *J Clin Invest*. 2002;110(11):1739–1747. doi:10.1172/JCI0215695
62. Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature*. 2007;448:(7152):427–434. doi:10.1038/nature06005
63. Morita T, Mitsuyama K, Yamasaki H, et al. Gene expression of transient receptor potential channels in peripheral blood mononuclear cells of inflammatory bowel disease patients. *JCM*. 2020;9(8):2643. doi:10.3390/jcm9082643
64. Fichna J, Mokrowiecka A, Cygankiewicz AI, et al. Transient receptor potential vanilloid 4 blockade protects against experimental colitis in mice: a new strategy for inflammatory bowel diseases treatment? *Neurogastroenterology Motil*. 2012;24(11). doi:10.1111/j.1365-2982.2012.01999.x
65. Kobayashi K, Ashina K, Derouiche S, et al. 5,6-dihydroxy-8Z,11Z,14Z,17Z-eicosatetraenoic acid accelerates the healing of colitis by inhibiting transient receptor potential vanilloid 4-mediated signaling. *FASEB J*. 2021;35(4):e21238. doi:10.1096/fj.201903207RRR
66. Dalsgaard T, Sonkusare SK, Teuscher C, Poynter ME, Nelson MT. Pharmacological inhibitors of TRPV4 channels reduce cytokine production, restore endothelial function and increase survival in septic mice. *Sci Rep*. 2016;6:33841. doi:10.1038/srep33841
67. Peng S, Grace MS, Gondin AB, et al. The transient receptor potential vanilloid 4 (TRPV4) ion channel mediates protease activated receptor 1 (PAR1)-induced vascular hyperpermeability. *Lab Invest*. 2020;100(8):1057–1067. doi:10.1038/s41374-020-0430-7
68. Barbara G, Wang B, Stanghellini V, et al. Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome. *Gastroenterology*. 2007;132(1):26–37. doi:10.1053/j.gastro.2006.11.039
69. Öhman L, Simrén M. Pathogenesis of IBS: role of inflammation, immunity and neuroimmune interactions. *Nat Rev Gastroenterol Hepatol*. 2010;7(3):163–173. doi:10.1038/nrgastro.2010.4

70. Shi HL. Alterations in serotonin, transient receptor potential channels and protease-activated receptors in rats with irritable bowel syndrome attenuated by Shugan decoction. *WJG*. 2015;21(16):4852. doi:10.3748/wjg.v21.i16.4852
71. Chen L, Mao M, Liu D, et al. HC067047 as a potent TRPV4 inhibitor repairs endotoxemia colonic injury. *Int Immunopharmacol*. 2023;116:109648. doi:10.1016/j.intimp.2022.109648
72. Kanju P, Chen Y, Lee W, et al. Small molecule dual-inhibitors of TRPV4 and TRPA1 for attenuation of inflammation and pain. *Sci Rep*. 2016;6:26894. doi:10.1038/srep26894
73. Kassinen A, Krogius-Kurikka L, Mäkivuokko H, et al. The fecal microbiota of irritable bowel syndrome patients differs significantly from that of healthy subjects. *Gastroenterology*. 2007;133(1):24–33. doi:10.1053/j.gastro.2007.04.005
74. Dunlop SP, Jenkins D, Neal KR, Spiller RC. Relative importance of enterochromaffin cell hyperplasia, anxiety, and depression in postinfectious IBS. *Gastroenterology*. 2003;125(6):1651–1659. doi:10.1053/j.gastro.2003.09.028
75. Rajasekhar P, Carbone SE, Johnston ST, et al. TRPV4 is expressed by enteric glia and muscularis macrophages of the colon but does not play a prominent role in colonic motility. *bioRxiv*. 2024. doi:10.1101/2024.01.09.574831
76. Lee WH, Choong LY, Jin TH, et al. TRPV4 plays a role in breast cancer cell migration via Ca2+-dependent activation of AKT and downregulation of E-cadherin cell cortex protein. *Oncogenesis*. 2017;6(5):e338–e338. doi:10.1038/oncsis.2017.39
77. Thoppil RJ, Adapala RK, Cappelli HC, et al. TRPV4 channel activation selectively inhibits tumor endothelial cell proliferation. *Sci Rep*. 2015;5(1):14257. doi:10.1038/srep14257
78. Peters AA, Jamaludin SYN, Yapa KTDS, et al. Oncosis and apoptosis induction by activation of an overexpressed ion channel in breast cancer cells. *Oncogene*. 2017;36(46):6490–6500. doi:10.1038/onc.2017.234
79. Nayak PS, Wang Y, Najrana T, et al. Mechanotransduction via TRPV4 regulates inflammation and differentiation in fetal mouse distal lung epithelial cells. *Respir Res*. 2015;16(1):60. doi:10.1186/s12931-015-0224-4
80. Fiorio Pla A, Ong HL, Cheng KT, et al. TRPV4 mediates tumor-derived endothelial cell migration via arachidonic acid-activated actin remodeling. *Oncogene*. 2012;31(2):200–212. doi:10.1038/onc.2011.231
81. Matsumoto K, Deguchi A, Motoyoshi A, et al. Role of transient receptor potential vanilloid subtype 4 in the regulation of azoymethane/dextran sulphate sodium-induced colitis-associated cancer in mice. *Eur J Pharmacol*. 2020;867:172853. doi:10.1016/j.ejphar.2019.172853
82. Sozucan Y, Kalender ME, Sari I, et al. TRP genes family expression in colorectal cancer. *Exp Oncol*. 2015;37(3):208–212. doi:10.31768/2312-8852.2015.37(3):208-212
83. Liu X, Zhang P, Xie C, et al. Activation of PTEN by inhibition of TRPV4 suppresses colon cancer development. *Cell Death Dis*. 2019;10(6):460. doi:10.1038/s41419-019-1700-4
84. Wauters L, Talley NJ, Walker MM, Tack J, Vanuytsel T. Novel concepts in the pathophysiology and treatment of functional dyspepsia. *Gut*. 2020;69(3):591–600. doi:10.1136/gutjnl-2019-318536
85. Wauters L, Ceulemans M, Frings D, et al. Proton pump inhibitors reduce duodenal eosinophilia, mast cells, and permeability in patients with functional dyspepsia. *Gastroenterology*. 2021;160(5):1521–1531.e9. doi:10.1053/j.gastro.2020.12.016
86. Mihara H, Suzuki N, Muhammad JS, et al. Transient receptor potential vanilloid 4 (TRPV4) silencing in Helicobacter pylori-infected human gastric epithelium. *Helicobacter*. 2017;22(2):e12361. doi:10.1111/hel.12361
87. Li C, Cheng R, Li L, Chen M, Wu C. Role of TRPV4 in the diagnosis and treatment of helicobacter pylori infection in children with duodenal ulcers. *Biomed Res Int*. 2022;2022:2777882. doi:10.1155/2022/2777882
88. Zheng Y, Zuo W, Shen D, et al. Mechanosensitive TRPV4 channel-induced extracellular ATP accumulation at the acupoint mediates acupuncture analgesia of ankle arthritis in rats. *Life*. 2021;11(6):513. doi:10.3390/life11060513
89. Goyal N, Skrdla P, Schroyer R, Kumar S. Clinical pharmacokinetics, safety, and tolerability of a novel, first-in-class TRPV4 ion channel inhibitor, GSK2798745, in healthy and heart failure subjects. *Am J Cardiovasc Drugs*. 2019;19(3):335–342. doi:10.1007/s40256-018-00320-6