The function of chloride channels in digestive system disease (Review)

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Received December 16, 2024; Accepted March 11, 2025

DOI: 10.3892/ijmm.2025.5540

Abstract. Cation channels have been extensively studied in the context of digestive disorders, but comparatively little attention has been given to anions and their associated channels. Chloride ions, the most abundant anions in the human body, act as signaling molecules, modulating cellular behavior and playing a key role in regulating multiorgan physiological and pathophysiological mechanisms. The intra- and extracellular distributions of chloride ions are primarily controlled by various chloride channels and transporters. Currently, these chloride channels are classified into several groups: The chloride channels family, cystic fibrosis transmembrane conductance regulator, calcium-activated chloride channels, volume-regulated anion channels, proton-activated chloride channels and ligand-gated anion channels. This review aims to summarize the roles of chloride ion channels and transporter proteins in digestive system diseases, providing a theoretical basis for future research and offering potential new strategies for disease treatment.

Contents

1. Introduction

Ion channels are a major class of membrane proteins that are sensitive to a variety of stimuli, including changes in membrane potential, ligand binding, temperature fluctuations and mechanical forces (1). These stimuli trigger conformational changes in the protein, leading to the formation of gated ion-permeable pores in biological membranes, which facilitate the passive diffusion of ions along their respective electrochemical gradients both across the cell membrane and between intracellular compartments. Ion channels contribute to the regulation of various processes, such as the maintenance of cellular osmotic pressure and membrane potential, motility (through interactions with the cytoskeleton), invasion, signal transduction, transcriptional activity and cell cycle progression, all of which can lead to tumor progression and metastasis (2). Their central role in intracellular and intercellular signaling also facilitates the coupling of extracellular events to cellular responses (3).

Over the past decade, interest in the study of ion channels in digestive disorders has increased. The literature suggests that dysregulated ion channel activity plays a pathogenic role in various digestive diseases, including cancer. For instance, dysfunction of ion channels and transporter proteins can lead to gastrointestinal mucosal damage, such as disruption of the bicarbonate and mucosal layers (4-7), loss of epithelial cells (8,9), atrophy of glandular mucosa (10), loss of tight junction (TJ) proteins (11-13), imbalances in the gut flora (14) and changes in mucosal blood flow (15). These alterations contribute to gastrointestinal mucosal diseases, including gastritis, ulcers, inflammatory bowel disease and gastrointestinal cancers (16).

Ion channels and transporter proteins have been reported to be crucial for maintaining both the exocrine and endocrine functions of the pancreas. They facilitate enzymatic reactions necessary for the digestion of fats and proteins in the intestines, while also facilitating the secretion of bicarbonate-rich fluids (17,18). Pancreatic islet β-cells express a variety of ion channels located in lipid membranes or subcellular organelles, which are collectively involved in glucose-dependent insulin secretion. Consequently, dysfunction of these ion channels and transporter proteins can result in pancreatic injury, potentially leading to conditions such as pancreatitis, diabetes mellitus, pancreatic cystic fibrosis (CF) and an increased risk of pancreatic cancer (19,20).

In addition, the role of ion channels and transporter proteins in liver diseases has garnered considerable attention. For instance, dysfunction of various calcium channels can disrupt intra- and extracellular calcium homeostasis, leading to endoplasmic reticulum stress, mitochondrial dysfunction and the inhibition of autophagy in hepatocytes, all of which contribute to the development of nonalcoholic fatty liver

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Key words: chloride channel, ClC, CFTR, CaCCs, VRACs

disease (NAFLD) (21). Ion channels intersect with multiple signaling pathways, promoting hepatocellular carcinoma (HCC) cell invasion and metastasis by modulating gene expression, regulating cell proliferation and triggering epithelial-mesenchymal transition (22). In addition, ion channels and transporter proteins also regulate the growth and invasion of esophageal cancer (EC) (23-25).

As mentioned above, ion channels and transporter proteins play critical roles in regulating pathophysiological processes in various organs of the digestive system. While numerous studies have extensively investigated the role of cation channels, particularly calcium channels (26-32), sodium channels (33-36) and potassium channels (37-39), anion channels have received comparatively less attention. Anion channels (40,41) have been identified as important molecules with aberrant expression, activity and localization in various pathological conditions, including cardiovascular diseases, neurological disorders, metabolic diseases and cancer.

As the primary anion in the human body, intracellular chloride concentrations are dynamically regulated (42) and play a crucial role in maintaining intracellular and osmotic homeostasis, primarily through transmembrane transport and ion channels (43). Chloride channels have been implicated in a variety of pathological diseases (44). These channels and transport proteins are located both in the plasma membrane and intracellular membranes, with functions ranging from ion homeostasis and cell volume regulation to transepithelial transport and electrical excitability regulation (45). Chloride ions are regulated by chloride channels for their intra- and extracellular distribution and transport. Chloride channels are currently classified into several groups (Fig. 1), including the chloride channel (ClC) family, CF transmembrane conductance regulator (CFTR), calcium-activated chloride channels (CaCCs), volume-regulated anion channels (VRACs), proton-activated chloride channels (PACs) (46) and ligand-gated anion channels (47). Chloride channels have undergone significant functional differentiation and diversification during evolution and are distributed from prokaryotes to higher vertebrates (Fig. 2). The ClC family is one of the evolutionarily oldest classes of chloride channels and is widespread in prokaryotes and eukaryotes (48). During evolution, the ClC family differentiated into voltage-gated chloride channels and chloride/proton exchangers. In vertebrates, the ClC family has further differentiated into several isoforms (e.g., ClC-1 to -7), which are involved in the regulation of cell membrane potential or chloride homeostasis of intracellular organelles (49). Among CaCCs, anoctamin (ANO)1 has been extensively studied. ANO1 [transmembrane protein (TMEM)16A] belongs to the anoctamin family and is found in both invertebrates and vertebrates (50). ANO1 may have initially evolved as a lipid scramblase, and subsequently gained calcium-activated chloride channel function. In mammals, ANO1 is expressed in a variety of tissues and is involved in secretion, smooth muscle contraction and signaling (51). CFTR belongs to the ATP-binding cassette (ABC) superfamily of transporter proteins and is a vertebrate-specific chloride channel (52). CFTR has evolved to acquire a unique regulatory domain (R-domain) that allows it to be activated by cAMP-dependent phosphorylation (53). PACs/TMEM206 belongs to a family of transmembrane proteins, TMEM, that are highly conserved in vertebrates. No direct homologs have been identified in invertebrates, but functionally similar channels may exist in some lower organisms. In mammals, PACs are expressed in a variety of tissues, particularly in the brain, lungs and kidneys, and may be associated with pathological processes related to acidosis. PACs may have evolved as an adaptive mechanism for cells to cope with acidic environments, and are involved in maintaining intracellular pH homeostasis (54). Ligand-gated anion channels belong to the Cys-loop ligand-gated ion channel superfamily and share a common ancestor with related channels in invertebrates, such as glutamate-gated chloride channels (55). In vertebrates, gamma-aminobutyric acid type A receptor (GABA-A) and glycine receptor (GlyR) mediate inhibitory neurotransmission (56) (Fig. 2). Of note, in a study investigating chloride channels in an *in vivo* porcine model of esophageal acid damage, ClC-2 was found to localize to the basal epithelium of the porcine esophageal mucosa and esophageal submucosal glands. Chloride intracellular channel protein 1 recruited phosphatidylinositol 4-phosphate 5-kinases to lipid membranes, which, in turn, regulate cell-matrix adhesion and membrane protrusion, contributing to tumor aggressiveness, metastasis and a poor prognosis (57).

To date, there has been no comprehensive review of the role of chloride ion channels in digestive system diseases. Therefore, the aim of this review was to compile and summarize the physiopathological roles of chloride channels and transporter proteins in digestive system diseases, with the goal of providing a solid theoretical foundation for future research and offering new perspectives for the treatment of these diseases.

2. Chloride channels and digestive system diseases

The ClC family and digestive system diseases. The ClC channel exists as a dimer, with each monomer forming a separate ion-conducting pore, and each monomer contains 18 alpha helices, some of which form ion-conducting pores (49). The ClC family comprises ClC-0, ClC-1, ClC-2, ClC-Ka, ClC-Kb, ClC-3, ClC-4, ClC-5, ClC-6 and ClC-7. On the basis of their distribution, ClC-0, ClC-1, ClC-2, ClC-Ka and ClC-Kb are plasma membrane channels, whereas the others are intracellular membrane channels. Functionally, ClC-1, ClC-2, ClC-Ka and ClC-Kb are voltage-gated chloride channels, whereas the remaining members act as Cl^-/H^+ exchangers. The ClC family is involved in several key functions, including volume regulation, ion dynamic homeostasis, transepithelial transport and the regulation of electrical excitability. ClC-2, a voltage-gated chloride channel composed of 907 amino acids with a molecular weight of 99 kDa, features a two-pore homodimeric structure (58,59). Its activity is regulated by changes in the extracellular pH, displaying a biphasic response. ClC-2 is activated by moderate acidification but abruptly shuts down when the pH drops below ~7.

ClC-2 mRNA levels are significantly elevated in patients with nonalcoholic steatohepatitis and mice lacking ClC-2 exhibit a beneficial metabolic phenotype, suggesting that reducing or knocking down ClC-2 may be a potential strategy for treating NAFLD and further research revealed that ClC-2 downregulated the activation of IRS-1/Akt/mTOR signaling (60) (Fig. 3).

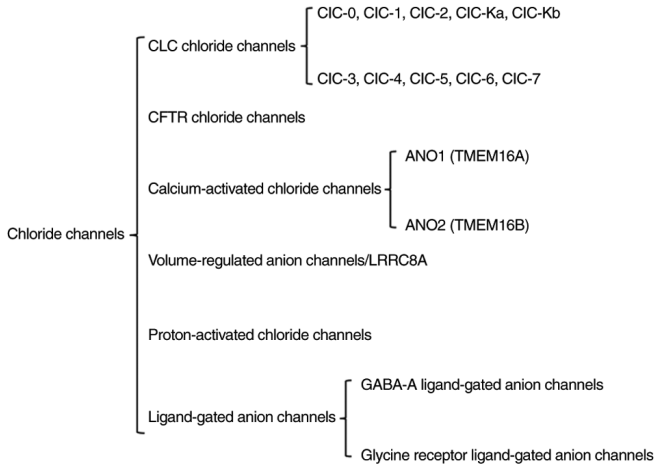

Figure 1. The classification of chloride channels. Chloride channels are divided into six classes. The ClC family is divided into ClC-0 through ClC-7, ClC-Ka and ClC-Kb. CaCCs are divided into ANO1 and ANO2. Ligand-gated anion channels are divided into GABA-A and glycine receptor channels. ClC-0, chloride channel-0; ClC-Ka, chloride channel-Ka; CaCCs, calcium-activated chloride channels; ANO1, anoctamin 1; GABA-A, gamma-aminobutyric acid type A receptor.

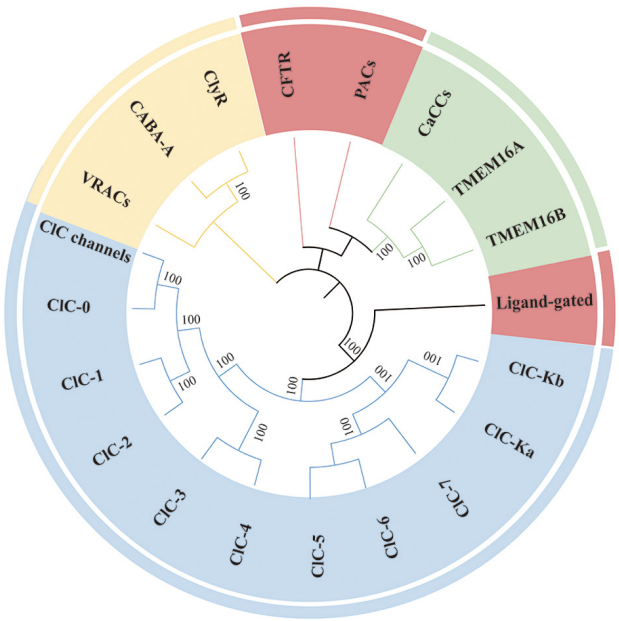

Figure 2. The phylogenetic tree of humans based on chloride ion channel genes. The branches of the phylogenetic tree illustrate the evolutionary relationships among different ion channels. Pink areas represent ligand-gated anion channels, CFTR and PACs. Green areas represent TMEM16A, TMEM16B and CaCCs. Yellow areas represent VRACs, GABA-A and GlyR ligand-gated anion channels. Blue areas represent ClC-0-7, ClC-Ka and ClC-Kb. The '100' labeled on the branch represents the bootstrap value, which is used to assess the reliability of the branches in the phylogenetic tree. This value ranges from 0 to 100, with higher numbers indicating greater stability of the branch in repeated resampling analyses, and thus higher confidence in the corresponding evolutionary relationship. VRACs, volume-regulated anion channels; CFTR, cystic fibrosis transmembrane conductance regulator; PACs, proton-activated chloride channels; CaCCs, calcium-activated chloride channels; ClC-Ka, chloride channel-Ka. GABA-A, gamma-aminobutyric acid type A receptor; GlyR, glycine receptor.

Chloride channels also play a critical role in intestinal diseases. The intestinal barrier, which is essential for nutrient absorption and preventing the entry of harmful substances, consists of epithelial cells connected by apical junction complexes, comprising TJs and adherens junctions (AJs) (61,62). In a ClC-2 knockout mouse model, the absence of ClC-2 delayed recovery of intestinal barrier function after ischemic injury, possibly because ClC-2 anchors the TJ structure following injury (63). Additionally, disruption of AJs affected colon homeostasis and differentiation, promoting tumorigenicity through the regulation of β-catenin signaling (64). Furthermore, genetic inactivation variants in the ClC-Ka and ClC-Kb genes have been associated with renal salt-losing nephropathies, with or without deafness, including the rare Bartter's syndrome (BS) (65), highlighting the crucial role of the ClC-Ka and ClC-Kb genes in renal and inner ear chloride processing (66); however, to the best of our knowledge, no studies to date have explored the role of these chloride channels in digestive diseases.

ClC-3 plays an important role in cancer regulation as a volume-regulated anion channel that also controls the cell cycle and is overexpressed in various cancers. ClC-3 can promote the development and metastasis of colorectal cancer (CRC) through the Wnt/β-catenin signaling pathway (67) (Fig. 3). In a study on prognostic biomarkers in gastric cancer (GC), high expression of ClC-3 was associated with deeper tumor invasion and increased lymph node metastasis, with overexpression of ClC-3 being regulated by x-ray repair cross complementing 5 (68). ClC-3 is also significantly overexpressed in HCC, and its upregulation is associated with tumor size and overall prognosis, suggesting that ClC-3 expression may serve as a predictor of tumor size and overall prognosis in HCC (69). Furthermore, ClC-3 has been reported to be expressed in intestinal tissues and to be involved in the regulation of intestinal inflammation (70). ClC-3 deficiency may exacerbate inflammatory bowel disease (IBD) by promoting the apoptosis of intestinal epithelial cells and causing Paneth cell deficiency (Fig. 3), indicating that modulating ClC-3 expression could be a novel therapeutic strategy for treating IBD (71).

ClC-3 to ClC-7 are located primarily in intracellular organelles, particularly along the endosome-lysosome pathway, and are distributed differentially across compartments (43,72-74). ClC-4 localizes to various endosomal clusters, whereas ClC-5 is predominantly expressed in the kidney, where it localizes to early endosomes and participates in endocytic uptake in the proximal tubule. Both ClC-3 and ClC-4 are widely expressed and found in various endosomal populations. ClC-6 is expressed primarily in neurons and localizes to late endosomes, whereas ClC-7, along with its β-subunit osteopetrosis-associated transmembrane protein 1, localizes to lysosomes in all cell types and is also found at the ruffled borders of bone-resorbing osteoclasts. Dysfunction of ClC-3, ClC-4, ClC-6 and ClC-7 has been linked to intellectual disability, epilepsy, lysosomal storage disorders and neurodegeneration, respectively (75-77). However, to the best of our knowledge, their roles in digestive disorders have not yet been reported.

CFTR and digestive system diseases. CFTR is a member of the ABC transporter protein superfamily (78) and functions as an anion channel. The anion-selective pore of CFTR is formed by two transmembrane domains (TMDs) regulated by

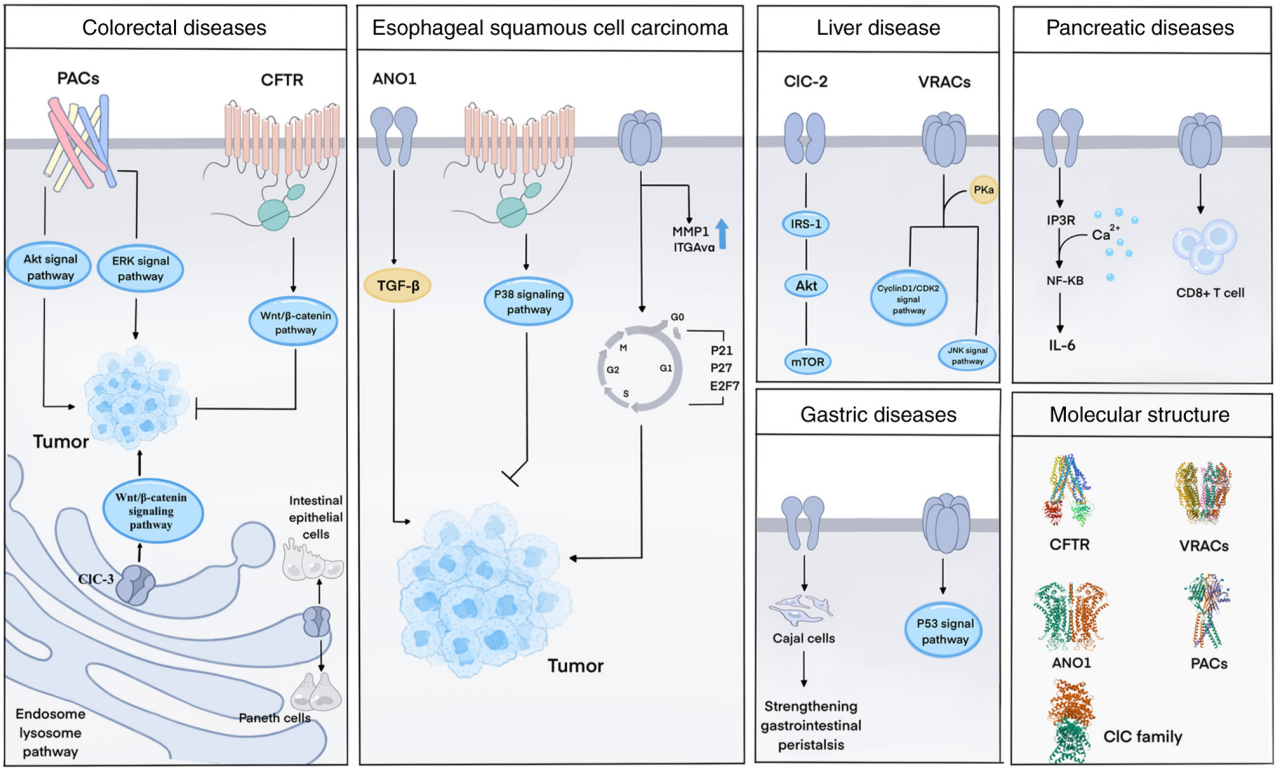

Figure 3. Mechanisms of chloride channel regulation in human diseases. This figure shows ClC-2 activates IRS-1/Akt/mTOR signaling upon downregulation in NAFLD. ClC-3 promotes CRC development and metastasis through the Wnt/β-catenin signaling pathway in CRC. Defects in ClC-3 promote IBD by facilitating apoptosis of intestinal epithelial cells and Paneth cell deletion. Overexpression of CFTR in ESCC activates the p38 signaling pathway and inhibits CRC tumor growth. ANO1 is overexpressed in ESCC and HCC, and possibly through the TGF-β pathway and MAPK signaling pathway. ANO1 is expressed in Cajal cells and promotes gastrointestinal motility. VRACs affect p53, the JNK signaling pathway, regulate $CD8^+$ T-cell immune infiltration and modulate the expression of genes associated with the G1/S checkpoint regulatory pathway, including p21, p27, E2F7, MMP1 and ITGAvα in ESCC. VRAC activates the cyclinD1/CDK2 pathway after linkage to PKCα in HCC. PACs promote the interaction between AKT and ERK signaling pathways for CRC development. ClC-2, chloride channel-2; CFTR, cystic fibrosis transmembrane conductance regulator; ANO1, anoctamin 1; VRACs, volume-regulated anion channels; PACs, proton-activated chloride channels; NAFLD, non-alcoholic fatty liver disease; IBD, inflammatory bowel disease; ESCC, esophageal squamous cell carcinoma; CRC, colorectal cancer; HCC, hepatocellular carcinoma; CDK2, cyclin-dependent kinase 2; ITGAvα, integrin αV.

cytoplasmic domains, which include two nucleotide-binding domains (NBDs) and a regulatory (R) domain. Channel activation requires cAMP-dependent protein kinase phosphorylation of the R domain, and the opening and closing (gating) of phosphorylated channels is driven by ATP binding and hydrolysis at NBDs (79).

Mutations in the CFTR gene lead to CF due to CFTR dysfunction. This gene encodes an anion channel that mediates the transport of chloride (Cl^-) and bicarbonate (HCO_3^-) across epithelial surfaces, which is crucial for osmotic homeostasis and the maintenance of normal electrolyte transport in the lungs, upper respiratory tract, pancreas, liver, gallbladder, intestine and other exocrine glands on the apical surface of epithelial cells (80). While the CFTR protein is located primarily in the plasma membrane, increasing evidence suggests its presence in intracellular organelles such as endosomes, lysosomes, phagosomes and mitochondria. Dysfunction of CFTR not only impairs ion transport across epithelial tissues but also disrupts the normal functioning of these organelles (81).

CFTR and esophageal diseases. Following CFTR dysfunction, bicarbonate ion transport is inhibited, disrupting the pH balance of the esophageal epithelium. This imbalance can result in cellular stress, DNA damage and increased susceptibility to carcinogenesis. In esophageal squamous cell carcinoma (ESCC), overexpression of CFTR was found to activate the p38 signaling pathway, which inhibits cell proliferation, migration and invasion; induces apoptosis; and is associated with a favorable patient prognosis (82). In esophageal cancer, gamma-aminobutyric acid receptor subunit pi(GABRP) promoted CFTR expression, and CFTR knockdown significantly counteracted the inhibitory effects of GABRP overexpression on EC cell proliferation, migration and invasion. These findings suggest that GABRP overexpression inhibits EC progression by increasing CFTR expression (83). Therefore, CFTR may act as a mediator and/or biomarker for ESCC (82). In addition, CFTR has been shown to inhibit the growth and migration of ESCC by downregulating NF-κB protein expression (23). CFTR modulators improve gastroesophageal reflux disease symptoms in patients with advanced CF (84). One of the specific reasons for this is that CFTR modulators improve gastroduodenal pH (85), in addition, CFTR is expressed in esophageal tissues and CFTR modulators may have a direct effect on esophageal motility and gastric emptying (82).

CFTR and pancreatic diseases. Pancreatitis is a common cause of hospitalization for digestive diseases, with high morbidity and mortality rates (86). It is a complex inflammatory disease of the acinar and ductal epithelium that is often

caused by the premature activation of digestive enzymes (87). There is substantial evidence that CFTR plays a critical role as an anion transporter in maintaining normal pancreatic exocrine function. Dysfunction of CFTR triggers pancreatic disorders, including impaired insulin regulation, pancreatic ductal obstruction, acute and chronic inflammation and carcinogenesis (88,89). However, the specific pathophysiological mechanisms remain to be fully understood.

In the pancreas, digestive enzymes play a well-known role; however, electrolytes are equally important as carriers, helping to transport enzymes to the small intestine, neutralize gastric acid and increase the duodenal pH to the optimal level for enzyme activity (90). In particular, bicarbonate (HCO_3^-) secretion is essential, as it regulates the pH of the ductal epithelium, increases mucin secretion (which acts as an antimicrobial) and prevents the premature activation of pancreatic enzymes (91). CFTR is a key player in HCO_3^- secretion in pancreatic fluid. This secretion involves the coordinated action of ion-transporting proteins located on the basolateral and luminal membranes of pancreatic ductal cells (PDCs). HCO_3^- can accumulate *via* electrogenic sodium-bicarbonate cotransporter 1 (NBCe1), the solute carrier family 4 member 4 (SLC4A4) cotransporter protein, which is produced intracellularly through the carbonic anhydrase-catalyzed reaction of CO_2 and water. It is then secreted into the ductal lumen via the coordinated action of CFTR and SLC26A6 (91,92). CFTR not only functions in conjunction with SLC26A6 but its R domain also binds to the spread through air spaces domain of SLC26A6, further regulating HCO_3^- secretion (93,94).

CFTR channels directly mediate epithelial HCO_3^- transport and selectively secrete HCO_3^- when intracellular Cl^- levels are low and HCO_3^- levels are relatively high (95). The dynamic regulation of CFTR anion conductance is thought to be mediated by With No Lysine Kinase (WNK) (18). WNK1, for example, has been shown to activate oxidative stress-responsive kinase 1 and STE20/SPS1-related proline/alanine-rich kinase (SPAK) at low extracellular Cl^- concentrations, significantly increasing HCO_3^- secretion in CFTR-transfected 293 cells and guinea pig PDCs (96). However, WNK1 and WNK4 can also inhibit CFTR by reducing its level at the cell surface, thus inhibiting CFTR-mediated anion efflux (97). This inhibition is counteracted by the binding of the inositol 1,4,5-trisphosphate (IP3) receptor, with released IP3 antagonizing the WNK/SPAK pathway (98). IRBIT, through its PDZ domain, binds to CFTR and NBCe1 at the apical and basolateral membranes, recruiting protein phosphatase 1 to counteract SPAK-mediated phosphorylation of CFTR and NBCe1 (99).

IRBIT recruitment may involve signaling pathways involving cAMP and Ca^{2+} (100). Furthermore, CFTR is closely linked to the organization of the actin cytoskeleton and the formation of cellular junctions among epithelial cells, which are essential for establishing apical-basolateral polarity and ensuring proper epithelial barrier function. In CF cells, this barrier function is disrupted, suggesting that CF may not only be an ion channel disease but also a disorder of epithelial differentiation (101).

CFTR and gastroduodenal diseases. Studies have reported that *Helicobacter pylori* infection damages duodenal mucosal CFTR, contributing to the development of duodenal ulcers (102). The gastrointestinal tract relies on mucin production, maturation and transport to defend against pathogens and lubricate the epithelium. Research by Reyes *et al* (103) revealed that TNF facilitates ion transport and intestinal luminal flow *via* CFTR and that TNF deficiency leads to increased mucus accumulation in the gastrointestinal tract and reduced intestinal luminal fluid pumping, which slows intestinal transit. These findings suggest the existence of a TNF/CFTR signaling axis in the adult intestine, with epithelial cell-derived TNF identified as an upstream regulator of mucin homeostasis (103).

In addition, patients with CF are at increased risk of developing various types of cancer, particularly gastrointestinal cancers (104). A study involving 1,468 heterozygous germline carriers of the CFTR F508del mutation revealed an increased risk of GC in this population. Another report showed that serum CFTR levels in patients with GC correlated with the expression of the tumor biomarker CA199 (105). A study by Yamada *et al* (106) further highlighted that patients with CF have a significantly increased risk of gastrointestinal cancers, including small bowel cancer, and recommended the development of individualized screening protocols for site-specific gastrointestinal cancers in this population.

CFTR and colorectal diseases. CFTR is expressed throughout the intestine, with a decreasing gradient of expression from the proximal (duodenum) to the distal (ileum) small intestine. In both the small and large intestines, CFTR is most strongly expressed at the base of the crypts and can influence intestinal stem cell function. Studies have demonstrated that CFTR is expressed by intestinal stem cells (107). The transmembrane domains of CFTR form water channels that allow Cl^- and HCO_3^- ions to be secreted from epithelial cells into the intestinal lumen, particularly within the crypts, while simultaneously increasing water secretion in the same direction. This regulates the water homeostasis and pH of the intestine (108). CFTR also influences the composition of the intestinal flora (109,110), the maintenance of the epithelial barrier (111,112), and the balance of innate and adaptive immune responses (113,114). Clinical manifestations of gastrointestinal issues in patients with CF, such as inflammation, chronic abdominal pain and complications such as Crohn's disease and gastroesophageal reflux disease (115,116), are associated with dysregulation of these processes, increasing the risk of cancer. A 20-year epidemiologic study reported that patients with CF have an elevated risk of gastrointestinal cancers with age, particularly a sixfold increase in the risk of Colorectal Cancer (CRC), the most common gastrointestinal malignancy in patients with CF (117).

CFTR deficiency has also been linked to CRC in the general population, with disease-free survival being lower in patients with CRC with reduced CFTR expression in the tumor (118). CFTR-depleted CRC cell lines exhibit enhanced oncogenic features, including increased colony formation, migration and invasion (119). Increased β-catenin activity, associated with increased proliferation, has been observed in CFTR knockout crypt cells and organoids. Although studies on CRC without CF are limited, Palma *et al* (120) reported that CFTR may play a nontumor suppressive role in CRC initiation and progression by enhancing a set of genes associated with cancer stemness in patients without CFTR mutations. Mechanistic studies have shown that

CFTR knockdown or transient inhibition by CFTR (inh)-172 leads to an increase in the intracellular pH of leucine-rich repeat-containing g-protein coupled receptor 5+ stem cells, promoting the binding of dishevelled segment polarity protein 2 (a member of the Wnt/β-catenin signaling pathway) to plasma membrane phospholipids and thereby enhancing Wnt/β-catenin signaling (121).

CFTR expression is downregulated in CRC, potentially due to promoter methylation. Overexpression of CFTR has been shown to inhibit CRC tumor growth by suppressing cell proliferation, migration and invasion. Furthermore, CFTR promoter methylation is significantly correlated with lymph node metastasis, suggesting that CFTR may serve as a potential marker for lymph node metastasis in patients with CRC (122).

CaCCs and digestive system diseases. CaCCs are chloride channels that can be synergistically activated by intracellular calcium and voltage. ANO1/TMEM16A contains 8 transmembrane structural domains (TM1-TM8), of which TM3-TM7 form the ion-conducting pore. The calcium binding site is located on the cytoplasmic side and contains multiple acidic residues responsible for calcium ion binding and channel activation. ANO1 exists as a dimer, with each monomer having a separate ion-conducting pore (123,124). CaCCs are expressed in both invertebrates and mammals, suggesting that they play crucial physiological roles, including regulating epithelial Cl^- secretion, neuronal and cardiomyocyte excitability, smooth muscle contraction and injury perception (125). The main CaCCs identified so far are ANO1, also known as TMEM16A, and ANO2, also known as TMEM16B (126). ANO1 is widely expressed in various cancers, where it controls cancer cell proliferation, survival and migration (127). It also regulates the secretory function of epithelial cells (128) and the electrical pacing activity of interstitial cells of Cajal in gastrointestinal smooth muscle (129). By contrast, ANO2 (TMEM16B), although functioning as a CaCC, is expressed primarily in olfactory sensory neurons (130), hippocampal pyramidal neurons (131) and thalamocortical neurons in the brain (132).

ANO1 (TMEM16A) and esophageal diseases. Vanoni *et al* (133) investigated the relationship between eosinophilic esophagitis (EoE) and ANO1 and reported increased expression of ANO1 in the basal region of the esophagus in both esophageal biopsy samples from patients with EoE and from mice with EoE. This increase was positively correlated with disease severity. ANO1 serves as the primary apical Cl^- transporter induced by IL-13 in the esophageal epithelium and regulates basal cell proliferation, a process linked to the regulation of TP63 expression and phosphorylated cell cycle protein-dependent kinase 2 (p-CDK2) levels (133). Additionally, a genome-wide copy number variation analysis revealed that ANO1 promotes ESCC cell proliferation, migration and invasion by activating the TGF-β pathway (Fig. 3). Knockdown of ANO1 significantly inhibited tumor progression both *in vitro* and *in vivo*, suggesting that ANO1 is a novel oncogene in ESCC and may serve as a prognostic biomarker for this disease (134).

ANO1 (TMEM16A) and gastrointestinal diseases. ANO1 (TMEM16A) is the most well-known CaCC with typical Ca^{2+} and voltage-dependent activation, and it is regulated by phosphatidylinositol 4,5-bisphosphate (135). ANO1 has been associated with various gastrointestinal disorders. The interstitial cells of Cajal (Fig. 3), which act as pacemakers controlling smooth muscle contraction, express TMEM16A. The activation of TMEM16A is thought to promote gastrointestinal muscle contraction. Keratin is a TMEM16A activator that promotes contraction of smooth muscle cells (129), providing a theoretical basis for treating gastrointestinal dysfunction. ANO1 also regulates gastrointestinal motility (136), and mutations in this gene are linked to conditions such as diverticulitis, diverticulosis, congenital megacolon and constipation, likely due to its role in gastrointestinal pacemaker activity (137,138). ANO1 is highly expressed in gastrointestinal cancers and is correlated with tumor-lymph node-metastasis staging in patients with GC. Studies have shown that the knockdown of ANO1 significantly inhibits GC cell migration, invasion and metastasis *in vitro*. This involves a mechanism in which specificity protein 1 increases ANO1 transcription, recruits mixed lineage leukemia protein 1 to the ANO1 promoter region and promotes H3K4 trimethylation, leading to increased ANO1 expression (139). Additionally, opa interacting protein 5 antisense RNA 1 has been identified as a critical regulator of GC pathogenesis, acting as an oncogenic competitive endogenous RNA by binding and sequestering microRNA-422a to increase ANO1 expression (140). STAT6/ANO1 activation has also been shown to reduce the proliferation, migration and invasion of GC cells (141). In CRC, ANO1 expression is upregulated and is associated with the TNM stage, histologic type, pathological differentiation and poor prognosis. Knockdown of endogenous ANO1 inactivates the Wnt/β-catenin signaling pathway by downregulating key components (e.g., Frizzled protein 1 and β-catenin) and upregulating glycogen synthase kinase 3β, suggesting that targeting ANO1 may have therapeutic potential in colon cancer (142).

ANO1 (TMEM16A) and pancreatic diseases. In research on acute pancreatitis (AP), IL-6 was found to promote TMEM16A (ANO1) expression *via* IL-6R/STAT3 signaling activation, and overexpression of TMEM16A further increased IL-6 secretion through the inositol 1,4,5-triphosphate receptor/Ca^{2+}/NF-κB signaling pathway (143). Therefore, inhibiting TMEM16A could represent a novel therapeutic strategy for treating AP. In addition, studies have identified ANO1 as a prognostic factor after radical resection of pancreatic carcinoma, where ANO1 may induce an immunosuppressive tumor microenvironment in a paracrine manner (144), suggesting that ANO1 could be a potential therapeutic target for pancreatic cancer.

ANO1 (TMEM16A) and hepatic diseases. Ion channels have been extensively studied in liver diseases in recent years, but chloride channels, including TMEM16A (ANO1), have been less frequently explored. Studies have shown that TMEM16A expression is elevated in the liver tissues of both mice and patients with NAFLD. Hepatocyte-specific knockdown of TMEM16A in mice improved hepatic glucose metabolism disorders and steatosis. TMEM16A in hepatocytes interacts with vesicle-associated membrane protein 3 (VAMP3), inducing its degradation and inhibiting the formation of VAMP3/synaptobrevin complexes, such as VAMP3/synaptosome-associated protein 23 and VAMP3/syntaxin 4. This interaction disrupts the translocation of hepatic glucose transporter protein 2 (GLUT2), leading to impaired glucose uptake. Notably, VAMP3 overexpression counteracts the

Table I. Roles of chloride channels in digestive system disease.

Author(s), year	Cl^- channel	Organ	Disease	Mechanism	(Refs.)
Blikslager *et al*, 2007; Gehren *et al*, 2015	ClC-2	Esophagus	Gastroesophageal reflux disease	ClC-2 secretion and tight junction remodeling	(61,62)
Fu *et al*, 2018	ClC-2	Liver	NAFLD	ClC-2 downregulated the activation of IRS-1/Akt/mTOR signaling	(60)
Nighot *et al*, 2009	ClC-2	Jejunum	Damage of intestinal barrier	ClC-2 anchors the tight junction structure after ischemic injury	(63)
Gu *et al*, 2018	ClC-3	Stomach	Gastric carcinoma	Overexpression of ClC-3 was regulated by XRCC5	(68)
Mu *et al*, 2020	ClC-3	Colon and rectum	Colorectal cancer	Wnt/β-linker protein signaling pathway	(67)
Huang *et al*, 2014	ClC-3	Colon and rectum	IBD	Promoting apoptosis of intestinal epithelial cells and Paneth cell deficiency	(71)
Cheng *et al*, 2019	ClC-3	Liver	HCC	The specific mechanism remains elusive	(69)
Matsumoto *et al*, 2021; Li, *et al*, 2018	CFTR	Esophagus	Esophagus carcinoma	Activating the p38 signaling pathway/downregulating NF-κB protein expression	(82,23)
Hou *et al*, 2016; Fűr *et al*, 2021	CFTR	Pancreas	Pancreatitis, pancreatic carcinoma	CFTR dysfunction, the specific mechanism remains elusive	(88,89)
Wen *et al*, 2016	CFTR	Duodenal	Duodenal ulcer	*H. pylori* impairs CFTR; the specific mechanism remains elusive	(102)
Reyes *et al*, 2023	CFTR	Gastrointestinal tract	Intestinal motility slows down	TNF facilitates ion transport and intestinal luminal flow via CFTR	(103)
Bhattacharya *et al*, 2022; Liu *et al*, 2014	CFTR	Stomach	Gastric carcinoma	CFTR F508del mutation, CFTR is associated with CA199	(104,105)
Yamada *et al*, 2018	CFTR	Small intestine	Small intestine carcinoma	CFTR dysfunction, the specific mechanism remains elusive	(106)
Palma *et al*, 2021; Strubberg *et al*, 2018; Liu *et al*, 2020	CFTR	Colon and rectum	Colorectal cancer	Active β-catenin increased; Enhanced Wnt/β-catenin; CFTR promoter methylation	(120-122)
Vanoni *et al*, 2020	ANO1 (TMEM16A)	Esophagus	Eosinophilic esophagitis	ANO1/IL-13 induces chloride ion transport mechanism	(133)
Yu *et al*, 2019	ANO1 (TMEM16A)	Esophagus	ESCC	ANO1/TGF-β signaling pathway	(134)
Fairfield *et al*, 2022; Camilleri *et al*, 2020; Schafmayer *et al*, 2019	ANO1 (TMEM16A)	Gastrointestinal tract	Diverticulitis, diverticulosis, congenital megacolon, constipation	ANO1 regulates the activity of Cajal	(136-138)
Zeng *et al*, 2019; Xie *et al*, 2020; Lu *et al*, 2018; Yan *et al*, 2022	ANO1 (TMEM16A)	Stomach	Gastric carcinoma	SP1 increased ANO1 transcription and H3K4 trimethylation, then promoted ANO1 expression; OIP5-AS1/miR- 422a/ANO1, STAT6/ANO1, ANO1/coiled protein 1/β-catenin/GSK3β/Wnt/β-catenin	(139-142)
Wang *et al*, 2020	ANO1 (TMEM16A)	Pancreas	Acute pancreatitis	IL-6R/STAT3/ANO1; ANO1/IP3R/Ca^{2+}/NF-κB/IL-6	(143)

Table I. Continued.

Author(s), year	Cl^- channel	Organ	Disease	Mechanism	(Refs.)
Zhang *et al*, 2024	ANO1 (TMEM16A)	Pancreas	Pancreatic carcinoma	ANO1 and immunization	(144)
Guo *et al*, 2020; Guo *et al*, 2022	ANO1 (TMEM16A)	Liver	NAFLD	TMEM16A/VAMP3/GLUT2	(145,146)
Konishi *et al*, 2019	VRACs (LRRC8A/ SWELL1)	Esophagus	ESCC	LRRC8A/PI3K/AKT/p21, p27, E2F7/MMP1, ITGAvα	(153)
Kurashima *et al*, 2021	VRACs (LRRC8A/ SWELL1)	Stomach	Gastric cancer	LRRC8A/p53 signaling pathway	(154)
Xu *et al*, 2022	VRACs (LRRC8A/ SWELL1)	Pancreatic	Pancreatic carcinoma	LRRC8A/$CD8^+$ T cells	(155)
Lu *et al*, 2019	VRACs (LRRC8A/ SWELL1)	Liver	HCC	SWELL1/PKCa/cyclinD1/ CDK2, SWELL1/JNK	(156)
Zhang *et al*, 2018; Fujii *et al*, 2018	PACs (ASOR/ TMEM206)	Colon and rectum	Colorectal cancer	The expression of LRRC8A was increased; the specific mechanism remains elusive	(157,158)
Zhao *et al*, 2019	PACs (ASOR/ TMEM206)	Colon and rectum	Colorectal cancer	TMEM206/AKT/ERK	(163)
Zhang *et al*, 2020	PACs (ASOR/ TMEM206)	Liver	HCC	The expression of TMEM206 was increased	(164)

This table shows the research of ClC-3 and ClC-2 in ClC Cl^- channel family in gastroesophageal reflux disease, NAFLD intestinal barrier injury, IBD, gastric cancer, colorectal cancer, liver cancer and other diseases, CFTR in esophagus carcinoma pancreatitis, pancreatic carcinoma, duodenal ulcer, intestinal motility slows down, gastric carcinoma, small intestine carcinoma and colorectal cancer, ANO1 in eosinophilic esophagitis, ESCC, diverticulitis, diverticulosis, congenital megacolon, constipation, gastric carcinoma, acute pancreatitis, pancreatic carcinoma and NAFLD, VRACs in ESCC, gastric cancer, pancreatic carcinoma, HCC and colorectal cancer and PACs in colorectal cancer and HCC. NAFLD, non-alcoholic fatty liver disease; IBD, inflammatory bowel disease; HCC, hepatocellular carcinoma; ESCC, esophageal squamous cell carcinoma; ClC-2, chloride channel-2; CFTR, cystic fibrosis transmembrane conductance regulator; ANO1, anoctamin 1; TJ, tight junction; VRACs, volume-regulated anion channels; PACs, proton-activated chloride channels; GSK3β, glycogen synthase kinase 3β.

inhibitory effect of TMEM16A on GLUT2 translocation and helps reduce lipid deposition, insulin resistance and inflammation (145). These findings suggest that inhibiting hepatic TMEM16A or disrupting the TMEM16A/VAMP3 interaction could offer new therapeutic strategies for NAFLD. Guo *et al* (146) reported that the TMEM16A-glutathione peroxidase 4 (GPX4) interaction and GPX4 ubiquitination are essential for TMEM16A-regulated hepatic ischemia/reperfusion injury, suggesting that blockade of the TMEM16A-GPX4 interaction or inhibition of TMEM16A in hepatocytes may represent promising therapeutic strategies for acute liver injury. Kondo *et al* (147) reported that downregulation of TMEM16A expression in cirrhotic portal hypertension-associated portal vein smooth muscle cells reduces Ca^{2+}-activated Cl^- channel activity; it is mediated by the increase in angiotensin II in cirrhosis. In addition, while ANO1 plays a regulatory role in various cancers, its role in HCC has been less studied. TMEM16A is overexpressed in HCC, and the inhibition of TMEM16A suppresses the MAPK signaling pathway (Fig. 3), reducing HCC growth. These findings indicate that TMEM16A may serve as a promising therapeutic target for HCC (148).

VRACs and digestive system diseases. VRACs, also known as volume-sensitive outwardly rectifying channels, regulate vertebrate cell volume by mediating the extrusion of chloride ions and organic osmolytes. VRACs are composed of a heterodimer of leucine-rich repeat-containing 8 (LRRC8) proteins, where LRRC8A (also known as SWELL1) serves as an essential subunit. LRRC8A binds to any of its homologs, such as LRRC8B-E, to form the hexameric VRACs complex, which functions as an anion-selective channel. VRACs are activated either by cellular swelling or by reactive oxygen species, a process dependent on intracellular ATP (149-151). VRACs play a crucial role in various physiological processes, including cell volume regulation, proliferation, migration and apoptosis (152).

VRACs and esophageal diseases. A study by Konishi *et al* (153) revealed that high expression of LRRC8A in ESCC tissues from patients was associated with poor prognosis. LRRC8A mediated the proliferation, survival and migration of ESCC cell lines. It regulates the expression of genes involved in the G1/S cell cycle checkpoint, including p21, p27 and E2F7, as well as genes related to cell migration, such as matrix metalloproteinase 1 and integrin αV. Depletion of LRRC8A reduced cell proliferation and migration and promoted apoptosis, and microarray analysis demonstrated that LRRC8A depletion inhibited the PI3K/AKT signaling pathway in cells (153).

VRACs and GC. LRRC8A has been shown to influence the growth of GC cells, and high expression of LRRC8A was identified as an independent prognostic factor for 5-year survival in patients with GC on the basis of multivariate analysis of clinical samples. Further research revealed that knockdown of LRRC8A inhibited cell proliferation and migration, enhanced apoptosis and affected the expression of genes associated with the p53 signaling pathway, including JNK, p53, p21, Bcl-2 and FAS (154).

VRACs and pancreatic diseases. Pancreatic adenocarcinoma (PAAD) is a highly malignant tumor of the digestive system with increasing morbidity and mortality rates. LRRC8A has been shown to influence the prognosis of PAAD and to be associated with cell proliferation, migration, drug resistance and immune infiltration. Notably, LRRC8A plays a role in the progression and prognosis of patients with PAAD by regulating the immune infiltration of $CD8^+$ T cells (155).

VRACs and hepatic diseases. SWELL1, an integral component of the VRACs, is highly expressed in HCC tissues and is associated with poor prognosis. An *in vitro* study showed that the overexpression of SWELL1 significantly promoted cell proliferation and migration while inhibiting apoptosis. Mechanistically, SWELL1 interacts with protein kinase Cα, activates the cyclin D1/cyclin-dependent kinase 2 pathway to induce cell growth, and regulates cell migration through the JNK pathway (156).

VRACs and colorectal diseases. LRRC8A was found to be elevated in 60% of CRC patient tissues, and patients with high LRRC8A expression had shorter survival times, suggesting that LRRC8A may serve as a novel prognostic biomarker for CRC. Elevated expression of LRRC8A has been linked to enhanced cancer cell growth and metastasis (157), whereas downregulation of VRACs has been shown to inhibit colon cancer cell proliferation (158). Furthermore, one study reported that LRRC8A contributed to oxaliplatin resistance in colon cancer cells (159). Of note, exosomes, which are crucial mediators of intercellular communication in the tumor microenvironment and accelerate colon cancer progression, contain LRRC8A. This protein, which is one of the components of exosomes released from colon cancer HCT116 cells, is responsible for exosome production and is involved in volume regulation (160).

PACs and digestive system diseases. PACs, also known as acid-sensitive outwardly rectifying anion channels (161), are assembled from symmetric trimers of TMEM206. Each subunit consists of a large extracellular domain (ECD), which resides in the lumen of endosomes, and two TMDs with helices (TM1 and TM2) connected by a near-membrane interface that links the ECD to the TMD. Acidic clusters in the ECD serve as primary proton sensors under acidic conditions (162).

Research has reported elevated TMEM206 expression in CRC tissues compared with adjacent noncancer tissues. TMEM206 promotes CRC cell proliferation, invasion and migration by increasing the levels of phosphorylated AKT and downstream signaling components, as well as the level of phosphorylated extracellular signal-regulated kinase (ERK), facilitating interactions between the AKT and ERK pathways (163). Bioinformatics analysis revealed that TMEM206 expression is significantly elevated in CRC, breast cancer, HCC and lymphoma tissues compared with corresponding normal tissues, identifying TMEM206 as a potential prognostic biomarker for HCC (164).

Ligand-gated chloride channels, such as GABA-A and glycine receptor channels, consist of five subunits that form the central ionotropic pore. Each subunit contains a characteristic Cys-loop structural domain involved in ligand binding and channel gating (165). They primarily play roles in the development and function of the nervous system (166). Channelopathies involving these channels have been linked to neurological disorders such as Parkinson's disease, Huntington's disease and Alzheimer's disease (167-169). However, to the best of our knowledge, no studies have explored the role of these channels in digestive disorders.

3. Summary and outlook

Ion channels and transport proteins play crucial roles in regulating pathophysiological processes across various organs of the digestive system. In recent years, sodium, calcium and potassium ion channels have been extensively studied, whereas chloride channels have received comparatively less attention. Chloride, the most abundant anion in the body, is regulated primarily by chloride channels or transporters. Existing studies on chloride channels have demonstrated their significant role in the development of numerous digestive system diseases (Table I), including esophagitis, esophageal cancer, gastrointestinal dyskinesia, gastritis, GC, colonic diverticulitis, diverticulosis, congenital megacolon, colon cancer, pancreatitis, pancreatic cancer, hepatic lipid metabolism disorders and HCC. Although the involvement of chloride channels in the digestive system has been explored, the underlying physiological and pathological mechanisms within various organs have not been thoroughly investigated. Most research to date has focused on verifying the high or low expression of chloride channels in digestive diseases or their involvement in relevant signaling pathways, whereas fewer studies have delved into deeper mechanisms such as transcriptional regulation or posttranslational modifications. Therefore, further investigations into chloride channels constitute an important and promising research area that remains to be fully explored.

Acknowledgements

The authors thank Professor Hui Dong (Department of Medicine, School of Medicine, University of California, San Diego University, San Diego, USA) for providing guidance in the writing of the paper.

Funding

The authors gratefully acknowledge financial support from the National Natural Science Foundation of China (grant no. 81960507), the Basic Research Projects of Science and Technology Department of Guizhou Province (grant code, Qian Ke He-zk[2022]-646) and the 2023 Graduate Research Fund Program B (grant no. ZYK248).

Availability of data and materials

Not applicable.

Authors' contributions

YH wrote the original manuscript and performed the literature review. BT was responsible for the conceptualization and review of the study and provided supervision. Both authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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