Pathology and physiology of acid-sensitive ion channels in the digestive system (Review)

LI ZHANG, LIMING ZHENG, XINGYUE YANG, SHUN YAO, HUI WANG,
JIAXING AN, HAI JIN, GUORONG WEN and BIGUANG TUO

Department of Gastroenterology, Digestive Disease Hospital, Affiliated Hospital of
Zunyi Medical University, Zunyi, Guizhou 563003, P.R. China

Abstract. As a major proton-gated cation channel, acid-sensitive ion channels (ASICs) can perceive large extracellular pH changes. ASICs play an important role in the occurrence and development of diseases of various organs and tissues including in the heart, brain, and gastrointestinal tract, as well as in tumor proliferation, invasion, and metastasis in acidosis and regulation of an acidic microenvironment. The permeability of ASICs to sodium and calcium ions is the basis of their physiological and pathological roles in the body. This review summarizes the physiological and pathological mechanisms of ASICs in digestive system diseases, which plays an important role in the early diagnosis, treatment, and prognosis of digestive system diseases related to ASIC expression.

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1. Introduction

Maintaining normal proton concentrations inside and outside the cell is essential for the normal physiological functioning of numerous processes throughout the body (1). Acid-sensitive ion channels (ASICs) as effective proton sensors are sensitive to extracellular acidification (2). ASICs are widely expressed throughout the nervous system (2). Relatively more recently, they were discovered to be expressed in non-excitable tissues, such as in taste bud cells in the tongue contour nipple, human bone cells, vascular smooth muscle cells, lung epithelial cells, inner ear, and cochlear hair cells, among others (Fig. 1) (3). The function of ASICs in the nervous system has been widely studied (4), but there are considerably fewer studies assessing their roles in other systems of the body. Recent studies have found that ASICs are closely related to the physiological function and pathological development of diseases of the digestive system. In the digestive system, ASICs are involved in normal physiological functions such as gastrointestinal mechanical sensation and duodenal bicarbonate secretion (5,6). ASICs also underlie the development of gastrointestinal pains, gastrointestinal cancer, and other pathological processes that involve a dysregulated acidic microenvironment or acidosis (7,8). This article reviews the research progress concerning ASICs in the digestive system.

2. Structure and function of ASICs

Molecular and structural characteristics of ASICs. In 1980, Krishtal and Pidoplichko (9) first recorded the cation currents triggered by a decrease in pH on the neuronal membrane. In 1997, Waldmann *et al* (10) first cloned H$^+$-gated sensory neurons and named them ASICs. ASICs belong to the voltage-insensitive, amiloride-sensitive epithelial sodium channel (ENaC)/degenerin (DEG) channel family, which is a group of distantly related, non-voltage-gated Na$^+$ channels found in animals. The epithelial channel ENaC in vertebrates has highly Na$^+$-selectivity and low single-channel conductance, which can be blocked by the potassium retention diuretic, amiloride (11-14). At present, four subunits encoded by ASIC functional genes in humans and rodents have been identified; namely ASIC1a, ASIC1b, ASIC2a, ASIC2b, ASIC3, and ASIC4, where the a and b are subunits derived from the same respective gene but are different splice variants) (2,15,16). The spatial conformation of each subunit is similar to a 'clenched fist', with six domains: Wrist, finger, β-ball, thumb, joint, and a palm domain in the extracellular loop (15,17) (Fig. 2). The β-ball is the main region involved in sensing external protons and is termed the acidic pocket (2). Functional ASICs are aggregated by three homologous or heterologous subunits (18,19). Each ASIC subunit is composed of two hydrophobic transmembrane domains (TM1 and TM2),

a large cysteine-rich extracellular loop, and a short conserved amino acid sequence at the C-terminal and N-terminal of the cell (10,17,20). Different subunits of ASICs have different properties, and the functional channels of the same trimer or heterotrimer are combined according to their own structural characteristics. The polymerization between different subunits allows for differing pH sensitivities, desensitization kinetics, and ion selectivity in the different ASICs (21). Due to these different electrophysiological properties, ASICs have a wide range of functions. Among the ASIC subunits, ASIC1a, ASIC1b, ASIC2a, and ASIC3 are directly controlled by protons, whereas ASIC2b and ASIC4 generally do not exhibit a functional role alone, and most ASIC2b and ASIC4 are auxiliary or regulatory subunits. ASIC2b and ASIC4 form oligomers with other subunits to allow them to exhibit their functional channel role (22). For example, ASIC2b mostly forms a heterotrimer with ASIC3 (23,24), and also forms a functional channel with ASIC1a during ischemic brain injury (25).

ASIC biological functions and features. Waldman and Lazdunski (12) recorded that when the extracellular pH dropped rapidly from 7.4 to <6.9, the proton concentration gradient on both sides of the channel changed, and the ASICs were activated. The activated ASICs showed permeability to cations and could allow the passage of sodium ions, calcium ions, and potassium ions (permeability index, sodium ions > calcium ions > potassium ions). ASICs generate characteristic instantaneous currents following proton-induced activation, and the current persistence is acid-dependent, thus the activated ASICs are rapidly deactivated (9,10,26). Therefore, ASICs, as a major proton-gated cation channel, are generally activated when the environmental pH drops. In recent years, significant progress has been made in the understanding of the structure and function of ASICs. ASICs have also been found to be activated by aprotic ligands (e.g., 2-guanidin-4-methylquin-azoline) (27) at a normal physiological pH and this has been shown to be related to pain (21). Regarding the pH sensitivity of ASIC subunits, different subunits have different pH sensitivity ranges. Slight extracellular acidosis can activate ASIC1 and ASIC3 channels, whereas ASIC2a requires strong acidic conditions for activation. The pH-sensitive range of ASIC1a is 6.2-6.8, 5.1-6.2 for ASIC1b, 6.2-6.7 for ASIC3, and 4.1-5.0 for ASIC2a (28). Their pH sensitivity is related to His-72 and Gly-430 residues in the extracellular loop of ASIC protein (29). Therefore, in general, ASICs can perceive a large pH range. After activation of ASICs, Na^+ and Ca^{2+} enters the cells, activating a series of pathophysiological processes (26). ASICs are widely expressed in various organs and tissues throughout the human body (Table I) (5,10,28,30-68). Thus far, ASICs have been found to be involved in various physiological processes such as in tactility (69), pain (3,70), olfaction (71), retinal integrity (48,72), learning and memory (73,74), fear (30,75), and anxiety (76). They are involved in the pathological process of various diseases in the human heart (77), brain (78), bone (79), gastrointestinal tract (80), and other organs and tissues.

3. Related physiology of ASICs in the digestive system

ASICs and gastrointestinal acid-sensitive neurons. The stomach contains an abundance of glands, and the high concentration of HCl produced plays an important role in the normal digestive process (81); however, the strongly acidic environment is also a factor leading to certain gastrointestinal diseases (82). The erosion of the gastric mucosa by the excessively high concentration of gastric acid can cause a series of digestive symptoms (22). To enable gastric acid to play a physiological role without damaging the gastrointestinal mucosa, a cell capable of sensing acid is needed for fine regulation of the pH, in which epithelial cells and acid-sensitive neurons play a special role (22). Previous studies suggested that the vagus nerve pathway mainly regulates autonomic function, but recent studies have shown that the vagus nerve pathway may contribute to acid-sensing. Molecular and electrophysiological studies have shown that vagal sensory neurons projected to the proximal gastrointestinal tract express proton-gated ion channels (83,84). Krishtal and Pidoplichko (85) observed that sensory neurons could respond to protons nearby. Later, a large number of experimental studies confirmed this finding and indicated that acids could stimulate primary afferent neurons. Proton-gated ASICs are highly sensitive acid sensors. Although ASICs are rapidly deactivated after activation, they can still monitor long-term acidosis. This plays an important role in the gastrointestinal tract, which is rich in gastric acid. Whole-cell voltage-clamp recordings of dorsal root ganglia (DRG) and nodular ganglia (NG) neurons showed that proton-gated currents are related to ASICs (84). ASICs in the gastrointestinal tract primarily occur in the peripheral fibers of exogenous primary afferent neurons derived from the DRG and NG, and studies have shown that NG and DRG neurons in rats express ASIC3 (22,86). ASIC1, ASIC2, and ASIC3 are expressed in the DRG of thoracolumbar vertebrae that project into the colons of mice (87). When the *ASIC3* gene was knocked out in mice, acid-induced excitability of gastric and esophageal vagus nerve fibers decreased (85). ASIC-mediated currents can be recorded from DRG neurons (88). ASICs are widely present in the digestive tract where they act as acid sensors and play an important role in acid monitoring of the gastrointestinal tract (2). During this process, ASICs perceive a decrease in extracellular PH, which stimulates acid-sensitive neurons and excites acid-sensitive neurons, thereby initiating the body's acid balance regulation system to maintain normal physiological functions (22).

ASICs and gastrointestinal mechanical sensation. Two major groups of mechanoreceptors in the vagus nerves of the stomach and esophagus of mice elicit signals of muscle stretching and mucosal touch (89), while two major groups in the innervation of the colon of mice elicit signals of serosal and mesenteric deformation (90). These mechanosensitive groups not only play a role in food intake and pain, but also in the regulation of digestive reflexes. On the basis of this experimental conclusion, Page *et al* (5) determined the expression of ASIC1a, 2, and 3 in the vagus nerve and DRG of mice using *ASIC* gene knockout mice, and proved that ASICs were involved in gastrointestinal mechanoreception. Their further studies have shown that ASIC1a contributes to gastroesophageal and colonic afferent mechanotransduction, and increased sensitivity to all afferent mechanotransduction sites of visceral colonic afferent and vagus nerves after ASIC1a destruction. Conversely, in ASIC-deficient mice, except for gastroesophageal mucosal
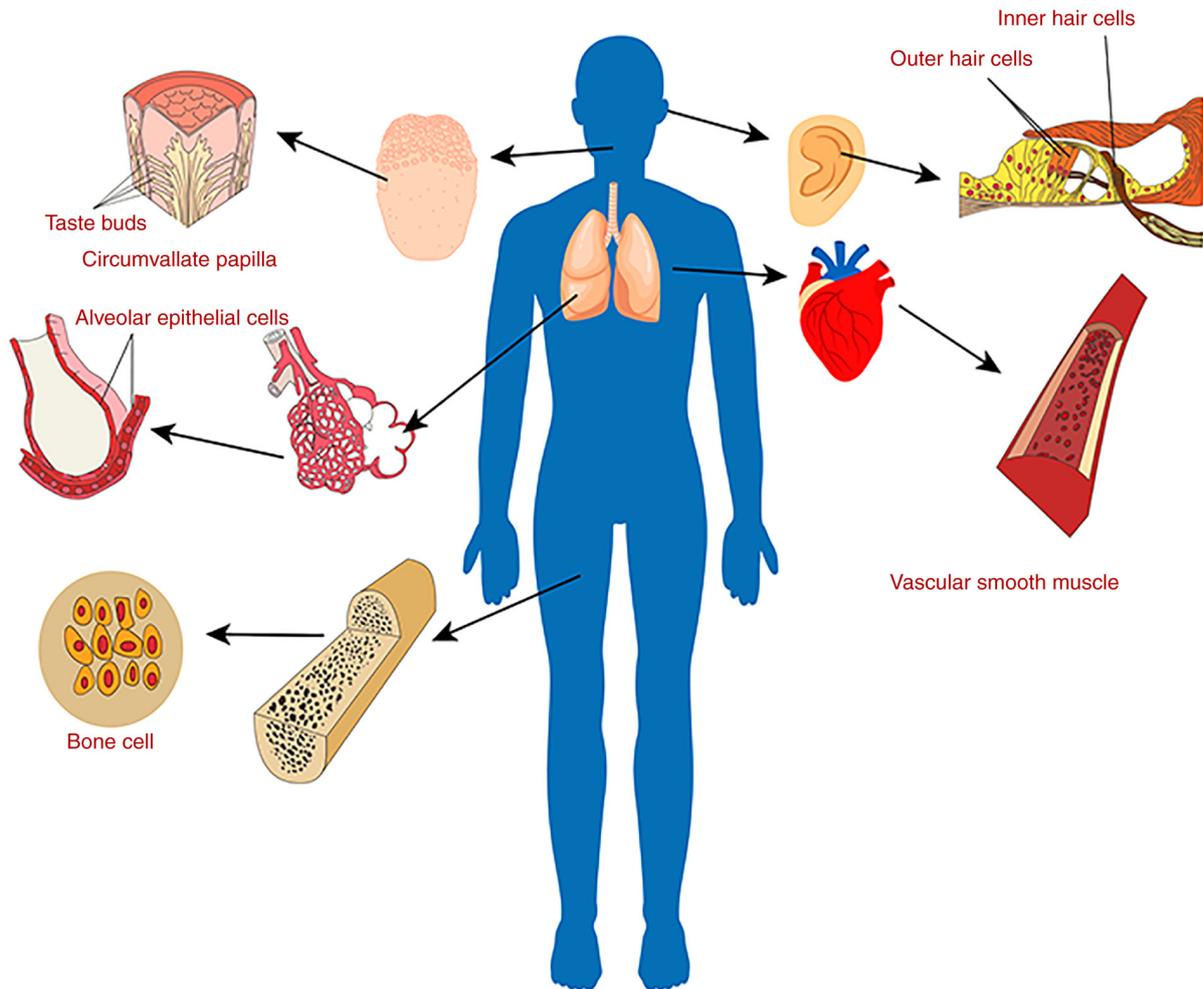
Figure 1. ASICs are expressed in the contour papilla, cochlear hair cells, lung epithelial cells, vascular smooth muscle, and bone cells. They are involved in maintaining the normal physiological functions of taste buds, the cardiovascular system, lung, inner ear and human bone cells. ASIC, acid-sensitive ion channel.
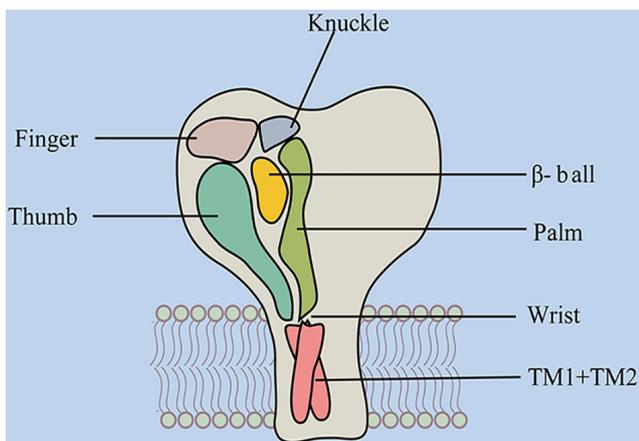

Figure 2. Spatial structure of ASIC subunits. The spatial conformation of each subunit is similar to a 'clenched fist' with six domains: Wrist, finger, β-ball, thumb, joint, and palm domain in the extracellular loop. ASIC, acid-sensitive ion channel.

destroyed, the stomach showed an increase in the mechanical sensitivity of the gastroesophageal mucosal endings and a decrease in the gastroesophageal tension receptor, whereas, for the colon, it showed an increase in the colonic serous endings and no change in the colonic mesenteric endings (5). This indicates that ASIC subtypes have different effects on gastrointestinal mechanical receptors. These *ASIC* gene knockout experiments affected mechanical conduction, and this resulted in a change in the gastrointestinal 'emptying mode' and affected food digestion.

The above studies show that ASICs are an important target for regulating gastrointestinal mechanical sensation. Several gastrointestinal diseases involving mechanical sensation can be treated by inhibiting or enhancing ASICs. For example, in irritable bowel syndrome, the stronger the expansion of the colon and rectum, the stronger the intestinal mechanical sensory signal, and the higher the perceived pain (91). If the expression of ASICs is weakened, the colorectal mechanical sensation signal is also weakened, and the pain will also be reduced. Similarly, in gastroesophageal reflux disease, if the expression of ASICs in the proximal stomach is lower, the proximal gastric mechanical sensory signal is reduced, the trigger of lower esophageal sphincter relaxation is weakened, and the reflux is also reduced (91).

receptors, the mechanical sensitivity of all afferent classes was significantly reduced. For ASIC2, there was a notable difference in the different afferent subtypes. After ASIC2 was

Table I. Distribution of the expression of ASICs in tissues.

ASICs	Expression	$PH_{0.5 \text{ activation}}$	(Refs.)
ASIC1a	Rat, mouse and human brain	6.2-6.8	(10,28,30,31)
	Rat, mouse and human spinal cord		(31-33)
	Human lung epithelial cells		(34)
	Human bone cells		(35)
	Rat and mouse taste receptor cells		(36)
	Rat cultured vascular smooth muscle cells		(37)
	Human gliomas		(38)
ASIC1b	Rat and mouse DRG	5.1-6.2	(28,31,39,40)
	Rat taste receptor cells		(41)
	Rat carotid body		(42)
	Mouse cochlear hair cells		(43)
ASIC2a	Rat, mouse and human brain	4.1-5.0	(28,31,44,45)
	Rat, mouse and guinea pig DRG and NG		(45-47)
	Rat and mouse spinal cord		(31-33)
	Rat, mouse and rabbit retina		(48-50)
	Mice spiral ganglion in the cochlea		(51)
	Rat astrocytes		(52)
	Rat microglia		(53)
	Human bone cells		(35-48)
	Human lung epithelial cells		(34)
	Rat cultured vascular smooth muscle cells		(37)
	Rat carotid body		(42)
	Human gliomas		(38)
	Rat taste receptor cell		(36,54)
ASIC2b	Rat and human brain	NA	(45,55)
	Rat and mouse spinal cord		(32,33)
	Rat and mouse DRG		(56,57)
	Guinea pig NG and JG		(58)
	Rat and mouse retina		(48,49)
	Rat taste receptor cells		(54)
ASIC3	Rat, mouse and human DRG, TG and NG	6.2-6.7	(5,28,31,39)
	Human brain, spinal cord, testis		(55,59)
	Rat and guinea pig vagal and glossopharyngeal ganglia		(58)
	Rat, mouse and rabbit retina		(49,50,60)
	Mouse chondrocytes and synoviocytes		(61,62)
	Rat brain		(63)
	Rat astrocytes		(52)
	Rat microglia		(53)
	Mouse adipocytes		(64)
	Human lung epithelial cells		(34)
	Human bone, cartilage and teeth		(35,65)
	Rat cultured vascular smooth muscle cells		(35,37)
	Rat and mouse taste receptor cells		(36,61)
	Mouse inner ear		(66)
	Rat carotid body		(42)
ASIC4	Mouse brain and spinal cord	NA	(31)
	Human brain, inner ear and pituitary gland		(67)
	Mouse immune cells		(68)
	Rat and rabbit retina		(49,50)

ASICs, acid-sensitive ion channels; DRG, dorsal root ganglia; TG, trigeminal ganglia; JG, jugular ganglia; NG, nodular ganglia; NA, not available.

ASICs and bicarbonate secretion in the duodenal mucosa. Through RT-PCR analysis, Dong *et al* (6) detected *ASIC1a* mRNA expression in the mouse duodenal epithelium and in the HT29 human intestinal epithelial cell line, and *ASIC1a* gene expression in mouse and human intestinal epithelial cells was confirmed. ASIC1a has notable permeability to extracellular calcium, and the lower the pH value of the solution is, the greater its permeability to calcium ions is. However, after the use of amiloride, an ASIC blocker, the increase in Ca^{2+} mobilization induced by acidosis was significantly weakened, indicating that the Ca^{2+} mobilization induced by acidosis was exerted via ASIC1a and ASIC1a played an important role in Ca^{2+} homeostasis in human intestinal epithelial cells. In their further research, they used acid as a physiological stimulus for duodenal lumen perfusion and compared amiloride to stimulation of the secretion of bicarbonate in the duodenal mucosa. According to the amount of bicarbonate secretion (DMBS) in the duodenal mucosa, it was concluded that acid may stimulate DMBS in mice *in vivo* by acting on duodenal ASIC1a. DMBS can maintain the weak alkaline environment of the digestive tract, provide a suitable pH environment for the activities of various digestive enzymes, neutralize gastric acid, and protect the intestinal mucosa. The experimental conclusion that acid promotes the secretion of bicarbonate in duodenal mucosa through ASICs may bring novel therapeutic targets for gastrointestinal diseases caused by increased acid.

For example, in duodenal ulcers, by enhancing the expression of ASICs, the secretion of duodenal bicarbonate also increases, which is beneficial to the improvement of symptoms in patients with duodenal ulcers.

4. Pathology of ASICs in the digestive system

ASICs and gastrointestinal pain. It has been well studied that central and peripheral nervous systems can regulate pain through ASICs (23,31,70,92,93). It has been found that ASICs are also associated with non-nerve associated pains. A decreased extracellular pH and inflammation are stimuli for pain. Local tissue acidification is also involved in the production of pain under pathological conditions. It may be that the acidic substances produced during inflammation reduce extracellular pH, activate proton-sensitive receptors/channels, regulate the function of pain-sensing neurons, and induce inflammatory pain allergy. Stimulating the gastric cavity of rats or mice with HCl concentrations exceeding physiological levels caused a visceral motor response, indicative of pain (94). Wultsch *et al* (95) eliminated the effects of *ASIC3* gene disruption on the expression of c-Fos after gastric acid-induced neuronal excitability under gastric inflammation, whereas *ASIC2* gene knockout did not alter the inflammatory hyperresponsiveness. Therefore, ASIC3 plays a role in the inflammatory hyperresponsiveness of gastric acid, which may also be related to ASIC3 leading to gastroesophageal reflux disease related to gastric acid reflux. Several studies have shown that primary neurons that dominate the small intestine and large intestine express acidic sensors such as ASICs (47,96). Previous experiments have shown that ASIC3 and TRPV1 contribute to the common functional visceral hypersensitivity in irritable bowel syndrome (7). After intracolonic injection of butyric acid (97), the colon of rats expanded

without any inflammatory characteristics. Injection of the ASIC1a specific antagonist PcTx1 completely prevented the occurrence of colonic hypersensitivity (98), indicating that ASIC1 and ASIC3 were associated with the resultant colonic hypersensitivity. The more sensitive the colon expansion, the stronger the pain. A related study also confirmed that the high reactivity of colon dilatation was related to the upregulation of ASIC1a in colon DRG neurons and in the spinal cord (96,98). This established a novel direction for the treatment of patients with irritable bowel disease; reducing pain by weakening the expression of ASICs. Together, these studies suggest that ASICs play an important role in colonic hypersensitivity and hyperalgesia in irritable bowel patients.

ASICs and gastroesophageal reflux disease. As the symptoms of gastroesophageal reflux disease are closely related to acid reflux, the role of ASICs in the esophagus has attracted considerable attention. Studies have shown that ASIC1, ASIC2, and ASIC3 are expressed in the esophagus and its innervated nerves (5). The expression and function of each subtype of ASIC differ in the esophagus. ASIC1 mainly mediates the inhibitory response to acid and mechanical stimulation in the esophagus, whereas ASIC3 is expressed in esophageal spine cells and the mucosal muscle layer mediates high sensitivity to acid and inflammatory responses following acid stimulation and stimulation by strong mechanical expansion (99). Inflammatory mediators in the esophageal mucosa of gastroesophageal reflux disease patients can reduce the signal transduction threshold of ASICs, thereby mediating peripheral sensitization (100). Previous studies have shown that ASIC3 is closely related to the perception of pain, and more recent studies have found that they are also related to pain sensitivity. ASIC3 persistent expression in DRG neurons is involved in the formation of pain. With a decrease in the pain threshold and the emergence of pain sensitivity, ASIC3 expression is significantly upregulated (101,102). Inhibitors of ASICs can inhibit the pain allergy caused by peripheral acidification in rats and the pain caused by acidification in the human body (29), which further indicates the role of ASICs in pain sensitization. Although the pathogenesis of gastroesophageal reflux disease is complex, through in-depth studies of gastroesophageal reflux disease, it has been shown that visceral hypersensitivity and inflammation play an important role in the pathogenesis of gastroesophageal reflux disease (103). Recent studies have demonstrated that the upregulation of ASIC1 and ASIC3 expression is a possible cause of esophageal hypersensitivity to gastroesophageal reflux disease, providing a potential therapeutic target for patients with gastroesophageal reflux disease who do not respond to proton pump inhibitors (104). A gastroesophageal reflux disease rat model study found that during inflammation, the expression of ASIC1 and ASIC3 subunits was increased in the rat DRG (5). The above experiments show that ASICs are involved in gastroesophageal reflux disease caused by visceral hypersensitivity and inflammation. This discovery has provided a novel direction for the development of ASIC-related therapeutics for the management of gastroesophageal reflux disease.

ASICs and gastric cancer. Tumor tissues generally grow faster and metabolize vigorously, so local hypoxia and acidification
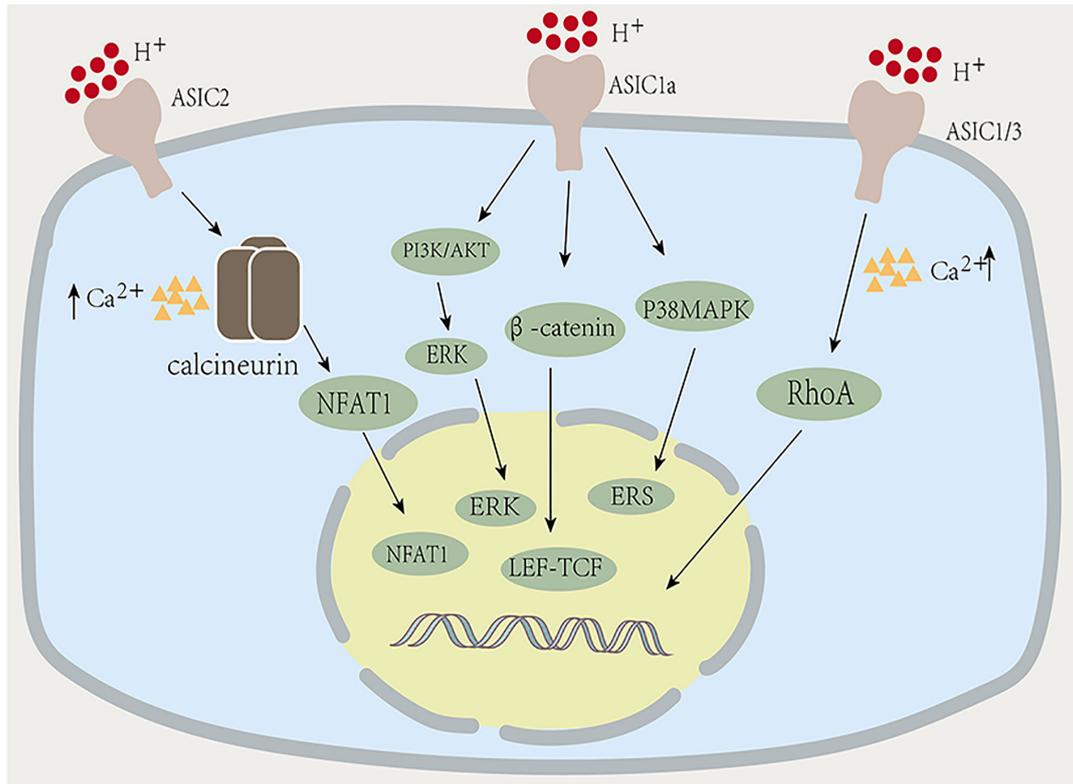
Figure 3. ASICs are involved in the formation of liver, colorectal and pancreatic diseases through dysregulation of the acidic environment. ASIC, acid-sensitive ion channel; NFAT, T nuclear factor; LEF, lymphoid enhancer factor; TCF, T cell enhancer factor; ERS, endoplasmic reticulum stress.

of solid tumors are common phenomena and pathological features. An acidic microenvironment is an intrinsic feature of a tumor, and it promotes tumor invasion and metastasis (105). Several cancers are associated with the expression of ASICs, such as liver cancer, breast cancer, and glioma; ASIC expression in liver cancer is associated with its clinical stage (106,107). This suggests that ASICs are involved in the process of various tumor diseases. After activation of ASICs, extracellular signals can be introduced into cells, thereby regulating the expression of specific proteins in tumor cells. As mentioned above, there is an abundance of ASICs in the gastrointestinal tract, thus it is reasonable to speculate that the occurrence and development of gastric cancer may be related to ASICs. Chen *et al* (8) found that the expression of ASIC1a at the protein and mRNA level in gastric cancer tissues was higher than that in normal tissues, and that the upregulation of ASIC1a expression was positively correlated with advanced gastric cancer metastasis. ASIC silencing significantly inhibited the proliferation, migration, and invasion of gastric cancer cells *in vitro*, and the inhibition was affected by the acidity in the cell microenvironment, suggesting that a change in acidity could alter the tumorigenicity of cancer cells *in vivo*. This study also showed that ASIC1a was involved in the occurrence of gastric cancer, and that ASIC1a expression could affect the tumorigenicity of gastric cancer cells. Knockdown of ASIC1a in gastric cancer cells reduced the invasion and metastasis of gastric cancer. ASICs have been reported to activate autophagy (108,109). Zhang *et al* (110) found that ASIC1 and autophagy-associated protein 5 (ATG5) were expressed in the gastric cancer cell line SGC-7901. Downregulation of ATG5 or ASIC1 was able to inhibit the growth of gastric cancer cells,

and ASIC1 also upregulated autophagy by activating ATG5 in gastric cancer cells. At the same time, it was found in the *ASIC1*-knockout mouse model that the downregulation of ASIC1 slowed down the growth of tumors and increased the survival time of mice. Although the current research on ASICs and gastric cancer is still in its infancy, these data show that inhibition of ASIC1 expression or inhibition of autophagy signaling pathways may serve as a novel means of targeted therapy for gastric cancer. At the same time, it may also play such a role in other types of cancers, thus highlighting novel avenues for the treatment of other types of cancer as well.

ASICs, liver fibrosis, and hepatolenticular degeneration. When inflammation is stimulated, oxidative stress and lipid peroxidation damage occur in the liver, leading to an imbalance in extracellular matrix (ECM) synthesis and degradation, and excessive ECM deposition in the liver tissue resulting in the formation of fibrosis (111).

The formation of hepatic fibrosis is related to the activation of hepatic stellate cells (112). ASIC1a is expressed in rat hepatic stellate cells, suggesting that the formation of liver fibrosis is related to ASIC1a (112). Zhu *et al* (113) found that ASIC1a expression was significantly increased in liver fibrosis, and miR-350 was involved in the formation of liver fibrosis regulated by ASIC1a and activation of stellate cells. Further analysis proved that the mechanism of hepatic fibrosis caused by ASIC1a was via ASIC1a-mediated regulation of m6A to affect the processing and modification of miR-350, and participate in hepatic fibrosis through modulation of the PI3K/AKT and ERK pathways (Fig. 3). This provided

powerful insights into the potential treatment of liver fibrosis, highlighting the potential value of antagonists of PI3K/AKT and ERK signaling pathways to prevent and treat liver fibrosis. The early stages of hepatolenticular degeneration are the same as those for hepatic fibrosis, which is characterized by fibrosis of stellate cells. It was hypothesized that hepatolenticular degeneration may also be related to ASIC1a. Hepatolenticular degeneration is a disorder of copper metabolism. The disease is caused by a gene mutation of copper to Golgi body in the transfer cells, which leads to a disorder of copper metabolism. Excessive copper accumulates in the liver and brain, causing the corresponding systemic abnormalities (114). A large amount of copper accumulates in liver cells and this is toxic, leading to liver cell necrosis, inflammation, and activation of hepatic stellate cells to secrete ECM. Therefore, the early occurrence of hepatolenticular degeneration is the same as that of liver fibrosis. Kong *et al* (115) induced HSC-T6 activation with $CuSO_4$, and found that ASIC1a was highly expressed in activated HSC-T6 cells. They speculated that ASIC1a played a role in promoting the process of hepatolenticular degeneration fibrosis. They also found high expression levels of ASIC1a in liver tissues of copper-loaded rats in animal experiments. Further analysis showed that ASIC1a in $CuSO_4$-induced HSC-T6 cells may have regulated endoplasmic reticulum stress (ERS) via the P38MAPK pathway, thereby affecting hepatolenticular degeneration fibrosis and copper transport. Inhibition of ASIC1a-mediated ERS can improve copper transport, and the accumulation of copper in the liver and the degree of fibrosis in rats can be alleviated, which has a protective effect on Wilson's disease fibrosis. In summary, the above studies showed that liver fibrosis and hepatolenticular degeneration fibrosis are related to the activation of ASIC1a in an acidic environment, and the inhibition of ASIC1a may serve as a means of treatment of liver fibrosis.

ASICs and liver cancer. Hepatocellular carcinoma (HCC) mortality ranks third in global cancer mortality rates (116). β-catenin expression is common in cancer cells due to its ability to bind to intracellular surface cadherins to regulate cell adhesion. In cancer cells, the β-catenin/lymphoid enhancer factor (LEF)/T cell enhancer factor (TCF) axis is readily activated, leading to cancer cell proliferation (107). Jin *et al* (107) showed that ASIC1a could promote the excessive proliferation of liver cancer *in vitro* and *in vivo* through β-catenin activation and nuclear accumulation in an acidic environment. Knockdown/knockout of ASIC1a can inhibit the growth of liver cancer cells *in vivo* and *in vitro*, induce apoptosis of liver cancer cells, and induce cell cycle arrest of liver cancer by inhibiting LEF-TCF activity. This suggested that the mechanism by which ASIC1a resulted in the pathogenesis of liver cancer involved the activation of the β-catenin/LEF-TCF pathway to induce excessive proliferation of liver cancer cells. This finding provides a potential druggable target for the treatment of liver cancer. Quantitative studies have shown that an acidic microenvironment promotes cancer cell proliferation and migration (117). Jin *et al* (106) showed that the expression of ASIC1a in tumor tissues was significantly higher than that in non-tumor tissues based on immunohistochemical analysis, and that the expression in liver cancer tissues that exhibited postoperative metastasis was higher than that in liver cancer tissues without metastasis. Transwell assays showed that the mRNA and protein expression levels of ASIC1a in SMMC-7721 cells were significantly higher than those at pH 7.4 and 6.0 in a moderately acidic environment at pH 6.5, while the migration and invasion of SMMC-7721 cells were significantly inhibited after knockdown of ASIC1a. Additionally, in the same study, in 90 patients with liver cancer, it was found that ASIC1a expression in these patients was upregulated and was significantly correlated with a later clinical stage and a poorer prognosis. The above studies show that ASIC1a is significantly correlated with the migration and invasion of HCC, as well as a later clinical stage and a poorer prognosis. The higher the expression of ASIC1a in a moderately acidic environment, the more obvious the liver cancer symptoms were. Therefore, ASIC1a may serve as a marker for the diagnosis and prognosis of HCC. The inhibition of ASIC1a expression may highlight a novel direction for the treatment of liver cancer.

ASICs and pancreatic cancer. Pancreatic cancer is a common malignant epithelial tumor of the digestive system, with strong invasive properties. Epithelial-mesenchymal transition (EMT) plays an important role in tumor invasion and metastasis. In recent years, several studies have shown that the occurrence, development, invasion, and metastasis of pancreatic cancer show active EMT (118-120), but the specific mechanism of EMT in pancreatic cancer has not been elucidated. It has been previously reported that melanoma cells in acidic environments exhibit significant EMT-like characteristics *in vitro* and *in vivo* (121).

An acidic microenvironment induces EMT in pancreatic cancer cells by regulating the miR-652/ZEB1 pathway (122). An acidic microenvironment is also associated with ASICs, thus the relationship between ASICs and pancreatic cancer has attracted attention. Zhu *et al* (123) confirmed that ASIC1 and ASIC3 proteins are expressed in pancreatic cancer cell lines where they have a regulatory effect on pancreatic cancer cells in an acidic environment. In further experiments, they knocked out both ASIC1/ASIC3 and used amiloride to inhibit ASICs to reverse EMT of pancreatic cancer cells in an acidic environment, indicating that ASICs were involved in the process of EMT-induced pancreatic cancer. Calcium, as a second messenger in cells, is widely involved in various signaling pathways and plays an important role in regulating the invasion and migration of tumor cells (124). It was confirmed that ASIC1 and ASIC3 regulate EMT induced by an acidic environment via an increase in the intracellular Ca^{2+} concentration. RhoA is a member of the Rho family of small GTPases and plays a key role in cell invasion and metastasis (125). Ca^{2+} can regulate cytoskeletal remodeling by activating RhoA, thus playing a role in cell migration (126,127). Based on this theory, they showed that RhoA was activated by an ASIC1/ASIC3-$[Ca^{2+}]_i$ pathway in an acidic environment to promote EMT of pancreatic cancer cells. In addition, stable knockdown of ASIC1 and ASIC3 in a nude mouse subcutaneously implanted tumor model significantly inhibited the invasion and metastasis of pancreatic cancer. In conclusion, they elucidated the complete signaling pathway of ASIC-induced pancreatic cancer; that is, an acidic environment induces EMT of pancreatic cancer cells through an ASIC1/3-$[Ca^{2+}]_i$-RhoA signaling pathway, resulting in increased invasion and metastasis of pancreatic cancer cells. The inhibition of ASIC1/3 can

delay the progression of pancreatic cancer. It can also be used to manage pancreatic cancer by decreasing the Ca^{2+} concentration or inhibiting the RhoA protein.

ASICs and colorectal cancer (CRC). An acidic extracellular microenvironment, namely acidosis caused by the Warburg effect (aerobic glycolysis) and a poor vasculature, is a biochemical feature of cancer (128). Acidosis changes the transcriptome characteristics of tumor cells, resulting in tumor cells suitable for survival, growth, and even metastasis in acidic environments (129). An increasing number of studies have shown that acidosis affects cancer progression by promoting tumor cell migration, invasion, metastasis, and angiogenesis (130-132). Previous studies have shown that acidosis promotes the invasion of CRC cells (131). On this basis, it is speculated that CRC may be related to ASICs. Zhou *et al* (80) verified the conjecture that ASIC2 promotes the invasion of CRC cells during acidosis. In further experiments, it was found that the average weight of tumors expressing ASIC2 was significantly higher than that of tumors in which ASIC2 expression was knocked down, indicating that ASIC2 promoted the proliferation of CRC cells *in vitro* and *in vivo*. At the same time, ASIC2 was also found to promote liver metastasis of CRC cells *in vivo*. Calcineurin is a Ca^{2+}-dependent serine/threonine phosphatase with the immune central function that promotes the development of intestinal tumors by regulating the function of mouse tumor stem cells (133). When activated by intracellular Ca^{2+}, calcineurin dephosphorylates the activated T nuclear factor (NFAT) protein, leading to nuclear translocation of NFAT (133). The transcription factors of the NFAT family play a key role in T-cell activation (134). The expression of IL-6 in NFAT1-deficient mice was significantly decreased, resulting in the occurrence and development of CRC (135,136). The results showed that ASIC2 overexpression significantly increased NFAT1 nuclear translocation induced by acidosis, while *ASIC2* gene knockout had the opposite effect. In addition, CsA (a calcineurin inhibitor) inhibited calcineurin/NFAT signaling in a dose-dependent manner, which significantly reduced the invasion of SW480 cells induced by ASIC2 acidosis, and NFAT1 knockdown also inhibited the invasion of CRC cells. These results suggest that NFAT1 plays an important role in the invasion, migration, and metastasis of CRC by regulating gene transcription. Based on the above experimental results, ASIC2 promotes the invasion of CRC cells by activating the calcineurin/NFAT1 signaling pathway under acidosis. Further studies also showed that ASIC2 expression is related to CRC recurrence, tumor staging, distant metastasis, a poorer prognosis, and NFAT1 expression. If ASIC2 expression is inhibited, CRC can be delayed to a certain extent, highlighting a novel direction for the treatment of CRC. In summary, ASICs are associated with the occurrence, development, invasion, and metastasis of several digestive system tumors in acidosis, and this may underlie treatments for the prevention and treatment of digestive system tumors, and also open up avenues for novel research directions for tumors of other systems.

5. Conclusions

ASICs are widely distributed throughout the body where they function as acid sensors, widely involved in a variety of pathophysiological processes that involve acidosis. This review provides a basic and systematic summary of the physiological and pathological roles of ASICs in the digestive system, and shows that different subtypes of ASICs participate in the occurrence, development, invasion, and metastasis of digestive diseases and tumors in the acidic microenvironments, which is of great significance for further exploring the physiological role of ASICs in the body and developing targeted ASIC drug therapies. However, the extensive physiological and pathological mechanisms of ASICs in the human body have not been elucidated and require further study. The physiological and pathological significance of ASICs in the digestive system should be further studied and their relevance as molecular markers for the diagnosis and treatment of human-related diseases should be assessed.

Availability of data and materials

Not applicable.

Authors' contributions

LZ and LZ made substantial contributions to the conception and design of the article. XY, SY, HW, JA, HJ, GW, and BT were involved in revising the manuscript critically for important intellectual content. Data authentication is not applicable. All authors read and approved the final manuscript for publication.

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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