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REVIEW ARTICLE OPEN

Roles and action mechanisms of bile acid-induced gastric intestinal metaplasia: a review

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Gastric intestinal metaplasia (IM) is a precancerous lesion that increases the risk of subsequent gastric cancer (GC) development. Therefore, the mechanism of IM has been the focus of basic and clinical research. Helicobacter pylori (H. pylori) infection has been recognized as the main pathogenesis of gastric IM. However, more and more studies have shown that chronic inflammation of gastric mucosa caused by bile reflux is the key pathogenic factor of gastric IM. Bile reflux activates the expression of IM biomarkers via the bile acid receptor. In addition, microRNAs, exosomes, and epigenetics are also involved in the occurrence and development of bile acid-induced gastric IM. Currently, the relevant research is still very few. The molecular mechanism of the phenotypic transformation of gastrointestinal epithelial cells induced by bile acids has not been fully understood. This article mainly reviews the physiology and pathology of bile acid, mechanism of gastric IM induced by bile acid, bile acid receptors, and so on, in order to provide reference for further research.

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FACTS

- Gastric intestinal metaplasia (IM) is a precancerous lesion of gastric cancer (GC), and early diagnosis and treatment is important.
- Accumulative evidence has revealed that bile reflux is associated with gastric IM and even carcinoma.
- Bile reflux into the stomach can not only directly stimulate the gastric mucosal barrier, but also regulate multiple downstream pathways to induce chronic inflammation of the gastric mucosa.

OPEN QUESTIONS

- What is the action mechanism of bile acid-induced gastric IM?
- Is gastric IM reversible?

INTRODUCTION

Gastric cancer (GC) is a common malignant tumor of the digestive system in the world, which ranks fifth in incidence and the fourth leading cause of cancer-related death [1]. Although the treatment has advanced greatly in recent decades, the prognosis for GC patients is still poor, with five-year overall survival rates ranging from 20% to 40%, mainly due to the rapid progress of local recurrences and metastasis [2]. Gastric adenocarcinoma is the most common form of GC, of which there are 2 histologic subtypes: intestinal type and diffuse type. It is generally believed that GC development, especially the intestinal type of noncardia GC, follows the Correa's cancer cascade—a successive progression from chronic nonatrophic gastritis, by way of atrophic gastritis and intestinal metaplasia (IM), to dysplasia [3] (Fig. 1). A study in Japan demonstrated that the presence of gastric IM was the only criteria associated with the development of intestinal-type GC [4]. The relative risk of developing GC is 10 times higher for individuals with IM than for those healthy individuals [5]. Therefore, monitoring gastric IM and reversing it is an important idea to stop the development of GC. Identifying its pathogenesis and taking proper measures may become the key to GC prevention. Increasing evidence has demonstrated that bile reflux is thought to be associated with atrophic gastritis, IM, dysplasia, and even carcinogenesis [6]. However, the mechanism of bile acid-induced gastric IM in the stomach is not clear and needs further research.

DEFINITION, HISTOLOGIC SUBTYPING, AND CANCER RISK OF GASTRIC IM

Definition

Gastric IM, a precancerous histopathological change, is defined as the replacement of gastric columnar cells by cells of intestinal morphology characterized by the presence of mucin-containing goblet, Paneth and absorptive cells, resulting in normal gastric mucosal epithelium and the surrounding glands are replaced by intestinal epithelium and glands [7]. Helicobacter pylori (H. pylori) infection is the most important risk factor for gastric atrophy and

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intestinal metaplasia [8]. In addition, male gender, old age, ethnicity, dietary factors, such as smoked food, high salt intake, pickled vegetables and nitrated meat, bile reflux, smoking, and family history are also associated with gastric IM [9, 10].

Histologic subtyping

Most gastric IM is divided into complete IM and incomplete IM based on hematoxylin and eosin staining. Occasionally, mixed characteristics of complete and incomplete types are observed [11]. The complete type resembles small intestinal epithelium comprising mature absorptive columnar cells, goblet cells, and Paneth cells, with a brush border given by large numbers of apical microvilli. While the incomplete type displays goblet cells of variable size and intervening columnar mucin-secreting cells without a brush border [11]. Another classification system was suggested by pathologists Filipe and Jass based on morphology and classic mucin staining, which divided the gastric IM into three types: type I corresponds to complete gastric IM and types II and III are subclassifications of incomplete gastric IM [12].

Risk of developing cancer

Liming Shao et al. systematically assessed the risk of GC in patients with gastric IM through 21 studies, which showed that incomplete IM but not complete IM was significantly associated with a higher risk of GC [13]. Incomplete IM, considered the most advanced stage of IM, is a valid marker for identifying subjects at high risk of GC [14]. Besides, it appeared that the risk of GC was higher among patients with IM in the corpus than those with IM in the antrum only [15, 16]. In clinical practice, the analysis of gastric IM subtyping using a small number of biopsies for histopathological examination is useful for monitoring the risk of GC.

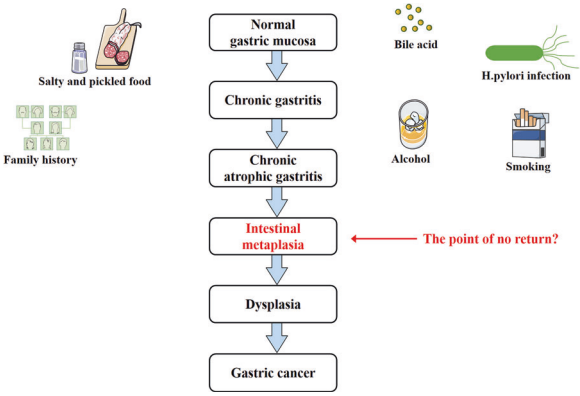

Fig. 1 GC development following the Correa's cancer cascade. Gastric IM is the key point for the development of GC. Whether it can be reversed is a new idea for the treatment of GC.

THE PHYSIOLOGY AND PATHOLOGY OF BILE ACID

Bile acids, a 24-carbon derivative of cholanic acid in structure, primarily synthesized in the liver, are the major components of bile. Primary bile acids of cholic acid (CA) and chenodeoxycholic acid (CDCA) are synthesized from cholesterol in hepatocytes and conjugated with glycine or taurine, secreted into the bile [17]. Postprandial contraction of the gallbladder drains bile acids into the intestine, and conjugated primary bile acids are stripped of glycine and taurine in the terminal ileum and colon, mostly reabsorbed into the blood to the liver [18]. A proportion is not reabsorbed and reaches more distal parts where gut bacteria can dehydroxylate the primary bile acids, forming the secondary bile acids lithocholic acid (LCA), deoxycholic acid (DCA), and their conjugated types, absorbed by passive diffusion in the colon or excreted in stool [19]. The human bile acid pool is 2–4 g, and cycles multiple times daily for a total of up to 30 g/day absorbed, with less than 10% lost in feces [20] (Fig. 2).

Bile reflux, also known as duodenogastric reflux, refers to the backflow of duodenal contents, including bile, pancreatic juice, and duodenal juice, into the stomach [21]. There are many clinical methods to diagnose bile reflux, mainly including endoscopy with

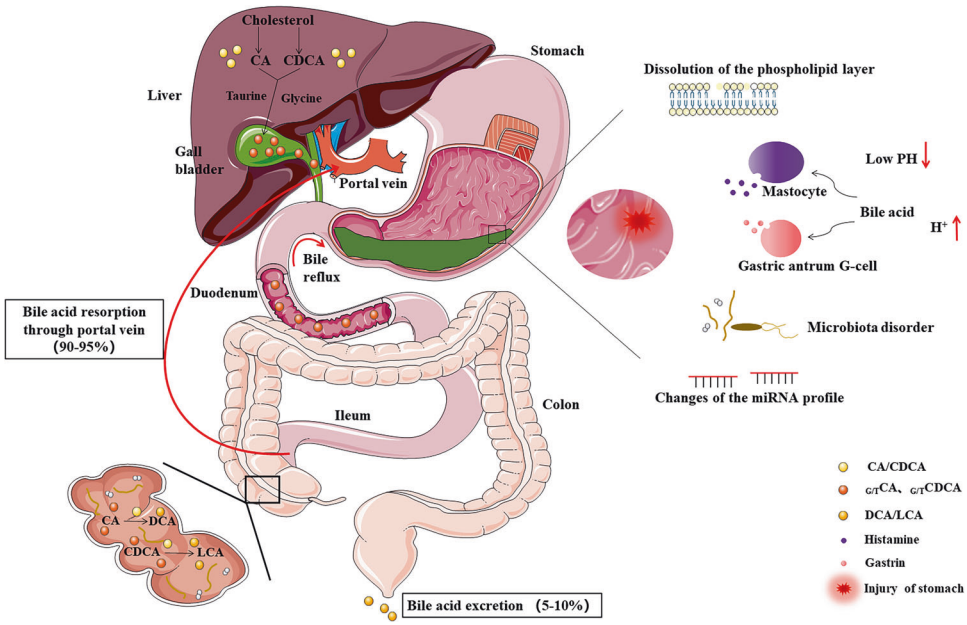

Fig. 2 Bile acid circulation and bile reflux. Primary bile acids (e.g., CA and CDCA) are synthesized by cholesterol mediated. They conjugated with glycine or taurine (G/T), and stored in the gallbladder. The majority (90–95%) of bile acid secreted into the small intestine are reabsorbed in the terminal ileum through portal vein and circulate back to the liver. Gut microbiota contributes to the conversion of CA and CDCA into secondary bile acids through dehydroxylation (e.g., DCA and LCA), which are mostly excreted from feces (5–10% of bile acid). Bile reflux to the stomach can induce mucosal dysfunction through some factors, such as dissolution of the phospholipid layer, low pH, mastocyte-secreting histamine, gastric antrum G-cell-secreting gastrin, microbiota disorder, and changes of the miRNA profile.

histological examination, intragastric pH monitoring, radionuclide scanning, gastric aspiration, and bile detection with special probes. The normal gastric mucosal epithelium is covered with a mucous gel layer and a bicarbonate layer, which blocks the contact of harmful components in the stomach and mucosa. Under normal circumstances, primary bile acids formed in the liver are secreted into the intestine lumen, where they are modified by the intestinal bacteria to produce secondary bile acids [22]. When bile reflux occurs, secondary bile acids and free bile acids are regurgitated into the stomach. Lecithin from bile acids and bile salts is converted to lysolecithin by the action of phospholipase A, which dissolves the phospholipid layer of the epithelial cell membrane of the gastric mucosa, resulting in increased cell permeability. Bile acids inhibit the activity of NO enzyme and the sodium hydrogen exchange of cells, leading to intracellular DNA damage, apoptosis, and mutation. Bile acids can also promote the reverse diffusion of H^+ and stimulate mast cells to release histamine, so as to stimulate gastric acid secretion and further aggravate gastric mucosal injury [23, 24]. Under low-pH conditions, bile acids are converted to nonionic forms, making them more cytotoxic, more likely to penetrate cell membranes, and damage tight intercellular junctions [25]. In addition, bile reflux can stimulate gastrin secretion from G cells, which promotes gastric acid secretion and inhibits pyloric sphincter contraction, further promoting bile reflux and forming a vicious circle. Reflux of alkaline substances from bile into the stomach can cause flora displacement, thus aggravating the inflammatory response of the gastric mucosa [26]. Recent studies have shown that acidic bile acids in gastric juice after successful Hp eradication can also induce mucosal dysfunction with changes in the microRNA (miRNA) profile, which might drive the development of gastric carcinogenesis [27] (Fig. 2).

MECHANISM OF GASTRIC IM INDUCED BY BILE ACID

IM is considered the point of no return in the GC. Investigating bile acid-induced IM is important and necessary for the prevention of GC. Matsuhisa et al. found that high concentrations of bile acid appeared to be associated with an elevated risk of IM, regardless of H. pylori infection [28]. Another study demonstrated that the incidence of GC was at a high rate of 41% in a rat model of bile reflux [27]. In addition, a retrospective cohort study indicated that high concentrations of bile acids in the stomach were associated with a higher incidence of GC [29]. Recent studies have shown that IM biomarkers, microRNAs (miRNAs), exosomes, and epigenetic modifications are associated with gastric IM.

IM biomarkers

Caudal-related homeobox transcription-factor 2 (CDX2), an intestine-specific nuclear transcription factor, plays a critical role in directing intestinal development, differentiation, and maintenance of the intestinal phenotype [14]. Studies have shown that CDX2 is expressed in the intestinal metaplasia of the stomach, while it is not expressed in the normal gastric mucosa [30]. Furthermore, CDX2 transgenic mice developed IM in the stomach with the induction of mucin 2 (MUC2), while knockdown of CDX2 resulted in intestinal malformation and inactivation of the expression of IM-related immunohistochemical marker, suggesting that ectopically expressed CDX2 may play a key role in GC via induction of IM [31].

The transcription-factor sex-determining region Y box2 (SOX2) plays a pivotal role in the regulation of normal gastric phenotype [32, 33]. For example, SOX2 gradually decreased expression in the process of gastric mucosa developing into IM, but there is no expression of SOX2 in small intestinal tissues and large intestinal tissues [34, 35]. The abnormal loss of SOX2 expression is highly correlated with IM of gastric and esophageal mucosa, which can be used as a molecular marker to detect the occurrence of IM [32, 36]. Moreover, SOX2 is negatively correlated with the expression of intestinal-specific molecules such as CDX1 and CDX2 in normal gastric epithelium, atrophic gastritis, and intestinal metaplasia tissues [34, 35]. Yuan et al. found that bile acids induced the expression of miR-21, which could inhibit the expression of SOX2 by directly binding its 3′-UTR and abrogate its suppression on the transcriptional activity of CDX2, thus leading to IM [37].

Hepatocyte nuclear factor-4 alpha (HNF4α) is a ligand-activated nuclear transcription factor, which is widely associated with the transcriptional regulation of hepatocyte genes and plays a role in regulating gene expression relating to drug metabolism, lipid metabolism, cell proliferation, and inflammation [38–40]. In adults, HNF4α is expressed in the colon and small intestine, not in the gastric mucosa, but HNF4α mediated by the P1 promoter can be observed in gastric IM tissues [41]. Zhen et al. found that bile reflux activated the TGR5–ERK1/2 pathway after induction of HNF4α expression, thus upregulating the expression of CDX2 [42]. Wang et al. found that bile acids promoted the development of gastric IM through HNF4a/HDCA6/CDX2 pathway in vivo and in vitro [43].

In addition, IM biomarkers also include mucin 2 (MUC2), Kruppel-like factor 4 (KLF4), villin-1, and cadherin 17, which are downstream of CDX2. Studies have shown that the expression of them is elevated in gastric epithelial cells exposed to bile acids, leading to the genesis of intestinal metaplasia [37, 43].

MiRNAs

MiRNA, a class of small endogenous noncoding RNA molecules, leads to mRNA degradation or translational inhibition of specific target genes by base-pairing to their mRNAs [44]. They can participate in a series of physiological and pathological processes, including development, differentiation, cell proliferation, apoptosis, organogenesis, and homeostasis [45]. Within diverse cancer types, the expression of miRNA is substantially different compared with their normal tissue [46]. Li et al. found that bile acid-stimulated IM induced the upregulation of miR-92a-1–5p [47]. Wang et al. found that DCA inhibited miR-1 in gastric cells to induce high expression of HDAC6 and HNF4α, thereby inhibiting the expression of downstream IM markers [43]. Further studies are needed to confirm the role of miRNA in gastric IM.

Exosomes

Exosomes, a type of membrane vesicles with a diameter of approximately 40–100 nm [48], contain multiple biological molecules, such as proteins, lipids, and mRNAs, and play an important role in regulating tumor development, metastasis, and drug resistance [49, 50]. Xu et al. demonstrated that DCA-activated macrophages could secrete exosomes to carry miR-30a-5 to gastric epithelial cells, thereby promoting gastric IM by targeting FOXD1 [51]. It was found that IM might arise from spasmolytic polypeptide-expressing metaplasia (SPEM) [52]. DCA could promote SPEM by macrophage-derived exosomes [53]. Further studies are needed to explore the role of exosomes in gastric IM.

Epigenetics

Epigenetics is defined as the study of chemical modifications of DNA and histone proteins that alter the structure of chromatin without changes to the underlying nucleotide sequence. N6 methyladenine (m6A) is the most common modification of mRNA in mammals [54]. AlkB homolog 5 (ALKBH5) is one of the currently discovered m6A demethylases, which plays an important role in the dynamic regulation of m6A [55]. Ben et al. demonstrated that ALKBH5 activated CDX2 by targeting the ZNF333/CYLD axis and activating NF-kappaB (NF-κB) signaling [56]. Therefore, targeting ALKBH5 and ZNF333 may be an effective preventive and therapeutic strategy for GIM in patients with bile reflux. Transcription-factor Dickkopf (Dkk) family is a specific antagonist

of the Wnt signaling pathway, which participates in many developmental processes of embryo formation and plays an important role in maintaining adult tissue homeostasis [57, 58]. Studies have shown that enhanced expression of DKK1 has been observed in various cancers, which promotes tumor cell proliferation, invasion, and migration [59]. Lu et al. found that DKK1 was epigenetically downregulated by promoter methylation, thereby inhibiting bile acid-induced gastric IM [60].

BILE ACID RECEPTORS

Bile acid receptors, mainly including G-protein-coupled receptor 5 (TGR5), farnesoid X receptor (FXR), pregnane X receptor (PXR), constitutive androstane receptor (CAR), and vitamin-D receptor (VDR), regulate bile acid metabolism, glucose utilization, fatty acid synthesis and oxidation, energy-homeostasis balance, immune-cell function, nerve activity, and other functions [61, 62]. In gastric IM, FXR and TGR5 are widely studied. Bile acids, acting as signaling molecules, regulate downstream signal-transduction pathways by activating the nuclear receptor FXR or the plasma-membrane receptor TGR5 (Table 1).

FXR

The bile acid-activated nuclear receptor FXR, mainly expressed in the liver and intestine, is a key regulator of signaling pathways and cellular functions, such as bile acid homeostasis, lipid metabolism, and glucose metabolism [63, 64]. Many studies in vitro have shown a rank order for the ability of bile acids to activate FXR: CDCA > DCA > LCA > CA, while this order had differences in mouse [65, 66]. It is generally recognized that unconjugated bile acids have greater potential to activate FXR than conjugated bile acids [67]. A previous study has reported that high expression levels of FXR are associated with the gastric IM formation [68]. Xu et al. first reported that CDCA stimulating the normal gastric epithelial cells of the rat upregulated the expression of CDX2 and MUC2 by activating FXR [69]. Subsequently, Li et al. revealed that DCA activated the FXR/NF-kappaB signaling pathway, thereby upregulating CDX2 and MUC2 expression in normal gastric epithelial cells [70]. Further, Zhou H et al. found that FXR and CDX2 were concomiantly overexpressed and were positively correlated in IM tissues [71]. Recently, more and more studies on the bile acid-induced IM via activating FXR have been reported (Table 1).

TGR5

The bile acid-activated membrane receptor TGR5, widely distributed in the liver, intestine, brown adipose tissue, and immune cells, involves in the regulation of energy metabolism, glucose metabolism, and inflammatory response [72, 73]. Secondary bile acids LCA and DCA are potent agonists for TGR5 [74]. Zhen et al. revealed that DCA treatment induced HNF4α expression via TGR5 and following ERK1/2-pathway activation [42]. Thus, inhibition of the TGR5–HNF4α signaling-cascade response may be a potential therapeutic target to prevent the progression of the Correa cascade and the proceeding of GC. At present, further studies are needed regarding the role played by the bile acid receptor TGR5 in gastric intestinal metaplasia.

MONITOR AND REVERSE GASTRIC IM

Monitor the gastric IM

Gastric IM, a key point in the multistep process of GC, is considered to be an important gastric premalignant lesion. Therefore, endoscopic surveillance of the progression of gastric IM is an effective means of prevention of GC. Operative link for gastric cancer metaplasia assessment (OLGIM) indicates that OLGIM stage III and IV are significantly more likely to develop intraepithelial neoplasia than OLGIM stage 0–II [75]. It is recommended that the patients with OLGIM stage III/IV should

Table 1. The articles on the bile acid-induced gastric IM via receptors of FXR and TGR5.

Bile acid	Receptor	Subjects	Regulatory mechanism	References
CDCA	FXR	cell lines	FXR may cause the ectopic expression of CDX2 and MUC2 in the gastric mucosa, and that CDCA may be a potent activator of the FXR in the stomach.	[69]
DCA	FXR	cell lines	DCA is capable of modulating the expression of CDX2 and the downstream MUC2 via the nuclear receptor FXR-NF-κB activity in normal gastric epithelial cells.	[70]
CDCA	FXR	tissues, cell lines	The activation of FXR and sequential direct transcriptional induction of SHP were involved in the expression of CDX2 induced by bile acid in gastric IM lesions.	[71]
DCA, CDCA	FXR	tissues, animals, cell lines	Bile acids may activate the FXR/NF-κB signaling pathway, thereby upregulating CDX2 and MUC2 expression in normal gastric epithelial cells.	[108]
CDCA	FXR	tissues, cell lines	Bile acid induces upregulation of miR-92a-1–5p through the activation of FXR, leading to a decrease of FOXD1 and a continuous activation of NF-κB pathway, which in turn promotes the transcription of CDX2 and intestinal differentiation.	[47]
DCA	FXR	tissues, cell lines	Under the stimulation of bile acids, enhanced FXR gene expression increases the expression of SNAI2, which in turn decreases the inhibitory effect of miR-1 on HDAC6 and HNF4α expression. Upregulated HDAC6 and HNF4α interact with each other, which further promotes upregulation of CDX2, KLF4 and MUC2, thereby promoting gastric IM development.	[109]
DCA	TGR5	tissues, cell lines	BAs treatment could activate TGR5–ERK1/2 pathway following induction of HNF4α expression, which further promoted metaplasia markers expression through direct regulation of KLF4 and CDX2.	[42]

be followed up with a high-quality endoscopy every 3 years [76]. American Gastroenterological Association recommended that the patients with incidental findings of gastric IM on endoscopy should detect and eradicate H. pylori. Endoscopic surveillance is reasonable for gastric IM patients at high risk of GC, including those with incomplete IM, extensive IM involving the gastric body and sinuses or the gastric horn, and a family history of GC. Routine short-interval repeat endoscopy for the purpose of risk stratification is not recommended for patients with gastric IM [77]. Meanwhile, the application of pigment endoscopy and narrow-band imaging endoscopy improves the detection rate of gastric IM [78, 79]. The confocal laser endomicroscopy has a sensitivity and specificity of 98.13% and 95.33% for the diagnosis of IM, and can also differentiate its subtypes [80].

Long-term exposure to bile acids has been shown to increase the risk of transition from normal mucosa to IM, and eventually leads to the development of GC over many years [81–83]. However, there are no clear studies on whether bile-reflux monitoring can be used to monitor and delay the development of gastric IM. Combining our previous description of bile acid and gastric IM, we may speculate that bile- reflux monitoring will be a possible means for monitoring and delaying the development of gastric IM in the future. Endoscopy may show duodenogastric reflux or the presence of bile in the stomach. Endoscopic findings most often include bile pooling, erythema of the gastric mucosa, thickened gastric folds, erosions, and gastric atrophy [84]. Histologic features include foveolar hyperplasia, edema, acute or chronic inflammation, and IM [84]. These features are not specific to bile reflux, which are similar to those found in some chemical injuries, so it is important to exclude competing etiologies. The aspiration of gastric juice under endoscopy allows chemical analysis of the fluid and determines the presence of bile acids [85]. Modalities for establishing bile reflux also include measurement of bilirubin in the stomach using a fiber-optic spectrophtometer, or biliary radionuclide scanning showing radiotracer in the stomach [86, 87].

The reversal of gastric IM

As a general treatment approach to bile reflux, the first step may be to stop any food or nonessential medications that might cause gastrointestinal motor dysfunction, such as strong tea, coffee, alcohol, and opioids [88]. Proton-pump inhibitors are common, which reduce the secretion of gastric acid and duodenal contents [89]. In addition, it also has a potent anti-inflammatory effect via inhibition of chemokines and adhesion molecules [90, 91]. Gastric mucosal-protective agents with the binding ability of bile acids, such as hydrotalcite, strengthen the gastric mucosal barrier, thereby alleviating gastric mucosal injury caused by bile reflux [92]. Prokinetic agents, such as mosapride and domperidone, can reduce bile reflux [93, 94]. In addition, short-term use of ursodeoxycholic acid (UDCA) may be appropriate. It changes the relative concentrations of lipophilic bile acids with high cytotoxicity, and with time promotes mucosal healing [95, 96]. Combination therapy could be tried if individual therapies are ineffective. Surgical management of bile reflux may be considered in severely symptomatic patients, especially those with reflux caused by previous surgery. The most commonly used operative procedures include the Roux-en-Y procedure, the Braun enteroenterostomy, and Henley jejunal interposition. A Roux-en-Y choledochojejunostomy can be used to divert bile directly from the biliary tree after cholecystectomy [97]. In addition, surgical treatment is also suitable for patients with cancer or poor drug-treatment outcomes. In summary, the symptoms caused by bile reflux can be alleviated by drugs and surgery. However, there are no high-

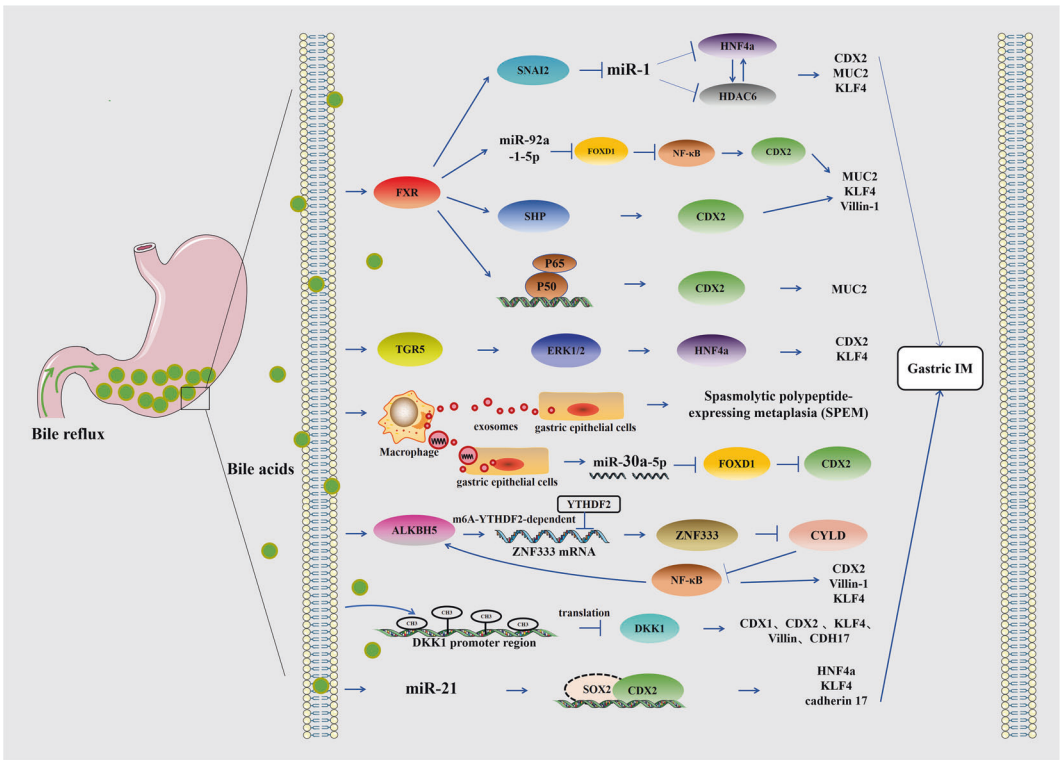

Fig. 3 Mechanism of bile acid-induced gastric IM. Bile acids increase intestinal marker expression via the pathways of FXR/SNAI2/miR-1, FXR/miR-92a-1–5p/FOXD1/NF-κB/CDX2, FXR/SHP/CDX2, FXR/NF-κB/CDX2, TGR5/ERK1/2/HNF4a, miR-21/SOX2/CDX2, and the promoter methylation and downregulation of DKK1 in the stomach. An m6A modification-associated positive feedforward loop between ALKBH5 and NF-kB signaling is involved in generating the IM. Bile acid-induced ALKBH5 enhances ZNF333 levels through an m6A–YTHDF2-dependent manner. In addition, macrophage-derived exosomes facilitate cellular communication between macrophages and gastric epithelial cells in the DCA microenvironment, which promotes the development of SPEM and contributes to gastric IM by transferring miR-30a-5p.

quality studies on whether the treatment of bile reflux can reverse IM.

Currently, there is a controversial debate whether or not gastric IM is reversible. It is generally believed that H. pylori eradication before the occurrence of gastric IM can help control gastritis, while once gastric IM is established, H. pylori eradication cannot reverse gastric IM but can help prevent or delay the progression of gastric IM [98, 99]. However, a meta-analysis showed that H. pylori eradication did not reverse gastric IM and reduce the risk of GC in patients with IM [100]. Therefore, more evidence is needed to determine whether H. pylori eradication can delay and reverse IM. In addition, a clinical study showed that a healthy diet may play a key role in inhibiting IM, which can be used as a primary prevention measure for the disease [101]. Certain vitamins and selenium may reduce the risk of GC [102–104]. For some patients with low folic acid level, appropriate supplementation of folic acid can alleviate progress of precancerous lesions and reduce the incidence of GC [105, 106]. Other studies have shown that endoscopic radiofrequency ablation provides a new direction for delaying gastric mucosal atrophy and IM, but more clinical evidence is still needed. In recent years, traditional Chinese medicine (TCM) in the treatment of gastric IM has highlighted obvious advantages. However, the lack of standardized TCM-syndrome diagnosis and the lack of clinical evidence to support need to be addressed in subsequent studies. It has been reported that resveratrol has a potential reversal effect on bile acid-induced gastric IM via PI3K/AKT/P-FoxO4 signaling pathway [107]. However, more studies are needed to further investigate whether the mechanism of bile reflux can be targeted to reverse IM.

SUMMARY AND PROSPECTS

Gastric IM, an important precancerous lesion of GC, is considered a critical stage in the prevention and control of GC because it provides a wide time window for clinical intervention of GC. Early diagnosis and treatment of gastric IM are of great significance for the prevention of GC. As shown in Fig. 3, bile reflux into the stomach acts as a signaling molecule involved in the development of IM by regulating downstream signaling pathways. Currently, there are few mechanisms for bile acid-induced gastric IM, including activation of bile acid receptors of FXR and TGR5, secretion of exosomes by macrophages acting on gastric epithelial cells, epigenetics, and miRNA involvement, which ultimately lead to the elevation of IM biomarkers. At present, some achievements have been made on the classification, pathogenic factors, and prevention and treatment methods of gastric IM. However, the molecular regulation mechanism of bile acid-induced gastric IM has not been fully clarified, and the related process cannot be fully explained. Therefore, more studies are needed to explore the mechanism of gastric IM and clarify the specific mechanism of intestinal metaplasia induced by bile acid reflux to provide a new plan for the prevention and treatment of early GC.

DATA AVAILABILITY

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

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AUTHOR CONTRIBUTIONS

KJ, JZ, and XC conceived the study and revised the paper; QH and LL wrote and revised the paper; QH and LL constructed and revised the figures; JW, JJ, and ZR revised the paper. All authors approved the final paper and agreed to be responsible for this review.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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