Bile reflux and bile acids in the progression of gastric intestinal metaplasia

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Abstract

Gastric intestinal metaplasia (GIM) is a precancerous lesion of gastric cancer (GC) and is considered an irreversible point of progression for GC. *Helicobacter pylori* infection can cause GIM, but its eradication still does not reverse the process. Bile reflux is also a pathogenic factor in GIM and can continuously irritate the gastric mucosa, and bile acids in refluxed fluid have been widely reported to be associated with GIM. This paper reviews in detail the relationship between bile reflux and GIM and the mechanisms by which bile acids induce GIM.

Keywords: Bile acids; Bile reflux; Farnesoid X receptor; Gastric intestinal metaplasia; Hepatocyte nuclear factor 4α; Methylation; Nuclear factor-κB

Introduction

According to the latest epidemiological data, the global incidence and mortality rate of gastric cancer (GC) ranks fifth and third among malignant tumors, posing a serious threat to human health.[1] Histologically, GC can be divided into intestinal-type GC and diffuse-type GC, with the former predominating in the high-risk population.[2-4] It is generally accepted that the development of intestinal GC follows the Correa model: chronic superficial gastritis – chronic atrophic gastritis – intestinal metaplasia – dysplasia – GC.[5]*Helicobacter pylori* (Hp) infection is considered the main trigger for the development of gastric intestinal metaplasia (GIM).[6-8] Although eradication of Hp partially reverses gastric mucosal atrophy and reduces the risk of GC, it is difficult to reverse GIM.[9-12] This suggests the existence of other factors that play an important role in promoting the development of GIM.

Bile acids, products of cholesterol metabolism, are synthesized in the liver (primary bile acids) and then transformed by intestinal bacteria (secondary bile acids).[13-15] The different hydrophobicities of bile acids cause them to exert different biological effects. Normally, hydrophobic bile acids are cytotoxic, while hydrophilic bile acids are cytoprotective.[16-18] Bile acids act as ligands and exert their physiological effects by binding to nuclear membrane receptors, such as farnesoid X receptor (FXR), vitamin D3 receptor, and G protein-coupled bile acid receptor (TGR5).[19-24] Recently, growing evidence has shown that bile reflux, as one of the risk factors for GC, is related to GIM.[25,26] Therefore, understanding the mechanism of action of bile acids, important components of bile, on the gastric mucosa may provide some innovative views into the pathogenesis of GIM and GC. In this review, we summarize the role of bile reflux in GIM and the molecular biological mechanisms of bile acids in promoting GIM [Figure 1, Table 1], providing ideas for finding new treatments for GIM.

GIM

As a precancerous lesion and risk factor for GC, GIM is attributed to the appearance of intestinal lineage cells in the gastric mucosa in response to factors, such as continuous inflammatory stimulation and autoantibodies.[27-29] Histologically, GIM is a pathological condition in which the columnar epithelial cells of the gastric mucosa are replaced by Paneth's cells, goblet cells, and absorptive cells.[30,31] According to the type of intestinal marker enzymes expressed by metaplastic cells, GIM can be divided into complete and incomplete types.[32,33] Complete GIM (type I), characterized by the presence of absorptive cells, Paneth's cells, and goblet cells expressing sialomucins, is phenotypically similar to that of the small intestine. Based on the results of high iron diamine/Alcian

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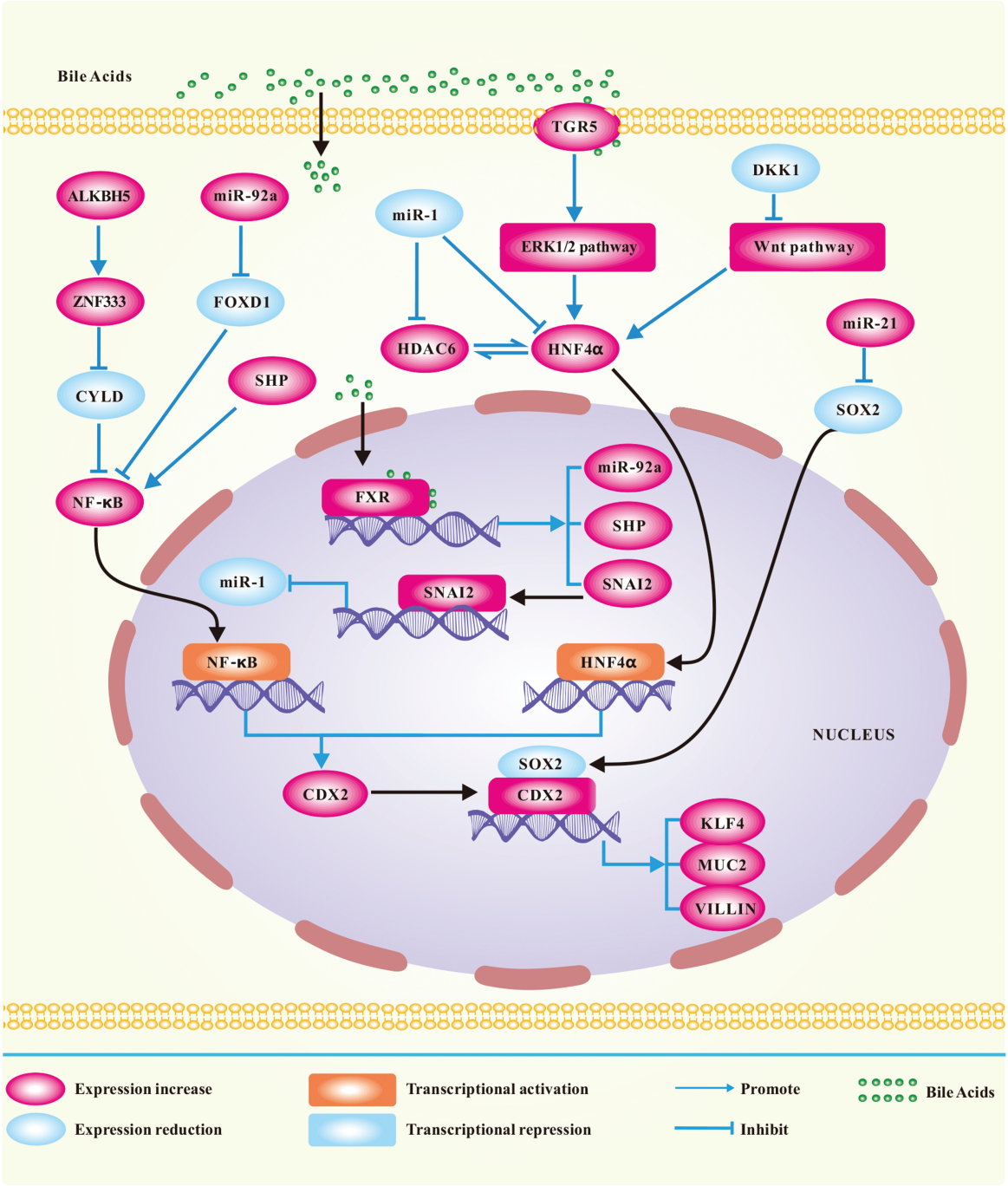

Figure 1: Pathways involved in the induction of GIM by bile acids. ALKBH5: Alkylation repair homolog protein 5; CDX2: Caudal type homeobox 2; CYLD: Cylindromatosis; DKK1: Dickkopf-related protein 1; FOXD1: Forkhead box D1; FXR: Farnesoid X receptor; GIM: Gastric intestinal metaplasia; HDAC6: Histone deacetylase 6; HNF4α: Hepatocyte nuclear factor 4α; KLF4: Krüppel-like factors 4; MUC2: Mucin 2; NF-κB: Nuclear factor-κB; SHP: Small heterodimer partner; SNAI2: Snail family transcriptional repressor 2; SOX2: SRY-box transcription factor 2; TGR5: G protein-coupled bile acid receptor; ZNF333: Zinc finger protein 333.

blue staining, incomplete GIM, which resembles the colonic epithelial phenotype can be divided into type II (characterized by the presence of Paneth cells and secretion of gastric and intestinal mucins) and type III (characterized by the absence of Paneth cells and secretion of sulfomucins).[34-37] You *et al*[38] reported that GIM increased the risk of cancer in patients with chronic gastritis by 17.4- to 29.3-fold and among GIM, incomplete GIM (especially type III) has a higher risk of developing GC.[29,39-42]

Regarding molecular characteristics, GIM is mainly associated with abnormal expression of homeodomain protein CDXs (CDX1 and CDX2), SRY-box transcription factor 2 (SOX2), Krüppel-like factors 4 (KLF4), and Mucin 2 (MUC2). CDX1/2, as intestine-specific transcription factors,[43] play an essential regulatory role in intestinal differentiation and development.[44-46] CDX2 not only directly activates specific genes responsible for regulating epithelial cell function, such as Lactase-phlorizin hydrolase,[47] Calbindin-D9K,[48] and Hephestin[49] but also

Table 1: Molecular mechanism of GIM induction by bile acids.

Key molecule	Bile acid	Mechanism	Reference
FXR	CDCA	FXR/miR-92a-1-5p/FOXD1/NF-κB/CDX2 axis	[69]
	CDCA, DCA	FXR/p65 and p50/CDX2 axis	[74,103]
	CDCA	FXR/SHP/NF-κB/CDX2 axis	[98]
HNF4α	DCA	TGR5/ERK1/2 pathway/HNF4α/CDX2 and KLF4 axis	[109]
	DCA	FXR/SNAI2/miR-1/HNF4α-HDAC6 loop/intestinal marker axis	[110,113]
SOX2	DCA	Reduce the CDX2 promoter DNA methylation level	[64]
	DCA	miR-21/SOX2/CDX2 axis	[70]
DKK1	DCA	DKK1 expression downregulated by promoter methylation	[115]
ALKBH5	CDCA	ALKBH5/ZNF333/CYLD/NF-κB/CDX2 axis	[119]

ALKBH5: Alkylation repair homolog protein 5; CDCA: Chenodeoxycholic acid; CYLD: Cylindromatosis; DCA: Deoxycholic acid; DKK1: Dickkopf-related protein 1; FOXD1: Forkhead box D1; FXR: Farnesoid X receptor; GIM: Gastric intestinal metaplasia; HDAC6: Histone deacetylase 6; HNF4α: Hepatocyte nuclear factor 4α; KLF4: Krüppel-like factors 4; SHP: Small heterodimer partner; SNAI2: Snail family transcriptional repressor 2; SOX2: SRY-box transcription factor 2; TGR5: G protein-coupled bile acid receptor; ZNF333: Zinc finger protein 333.

promotes the intestinal phenotype by regulating the expression of intestine-specific proteins such as sucrase-isomaltase,[50] MUC2,[51] and KLF4.[52] Homozygous CDX2 null mice have been reported to be embryonic lethal, and CDX2$^{\pm}$ mice survive and develop non-cancerous polypoid lesions alongside the intestine.[53] The appearance of intestinal metaplasia induced in both CDX1 and CDX2 transgenic mice confirms that ectopic expression of CDXs leads to GIM.[54-56] Mutoh *et al*[57] found that transgenic CDX2 was able to bind directly to the promoter region of CDX1 to induce endogenous CDX1 expression in mouse intestinal metaplasia tissue, and Eda *et al*[58] revealed that CDX2 expression in GIM precedes CDX1. These results suggest that aberrant CDX2 expression is the activating factor in the development of GIM. In contrast to CDXs, SOX2 mainly appears in organs of foregut origin, such as the pharynx, esophagus, and stomach, and is not expressed in organs of hindgut origin, such as intestinal tissue.[59-61] Francis *et al*[62] found that knockdown of SOX2 in mouse gastric mucosal tissues resulted in the loss of forestomach features, indicating that SOX2 may be involved in regulating forestomach differentiation. In addition, it was shown that elevated CDX2 expression in intestinal metaplasia (IM) tissues was accompanied by a decrease in SOX2,[63] and inhibition of SOX2 expression could promote GIM by promoting CDX2 promoter demethylation.[64] KLF4 is a zinc finger-containing transcription factor that is highly expressed in a variety of human tissues, such as the gut and skin,[65] and it can inhibit cell proliferation and promote cell differentiation.[66,67] Jonathan *et al*[68] found a reduction in colonic goblet cells in KLF4$^{-/-}$ mice, and ultrastructural analysis showed abnormal cupped cell morphology, while other epithelial cell types were unaffected, confirming that KLF4 plays an essential role in colonic epithelial cell differentiation. KLF4 was strongly positively expressed in IM tissues in a bile reflux-induced rat Barrett's esophagus (BE) model and was significantly elevated in a bile acid-induced IM cell model.[69-71] Furthermore, KLF4 induces the expression of MUC2 and reciprocal transcriptional activation with CDX2 to promote IM.[68] MUC2, mainly found in the goblet cells of the intestinal epithelium,[72] is a major component of small and large intestinal mucus and is involved in the maintenance of intestinal homeostasis.[73] *In vitro* results confirmed that the expression level of MUC2 was significantly higher in a bile acid-stimulated IM cell model than in normal cells and that this process was regulated by CDX2.[74] Numerous studies have shown that MUC2 expression levels are significantly elevated in BE and GIM tissues.[75,76] Overall, the aberrant expression of these proteins plays a role in the process of GIM, and CDX2 seems to be more critical among them.

Current studies show that GIM is associated with various factors such as Hp infection,[77] age, sex,[78] family history of GC,[79] and bile acid reflux.[25,26] Recently, an increasing number of studies have been conducted to investigate the mechanism of bile reflux-induced GIM, and these are reviewed in detail as follows.

Cause and effect of bile reflux and bile acids on GIM

Bile reflux, also known as duodenogastric reflux (DGR), is the flow of duodenal contents, including bile, pancreatic juice, and duodenal fluid, back into the stomach. It is usually caused by gastroduodenal motility disorders (primary DGR) or altered gastroduodenal anatomy after surgery (secondary DGR)[80-82] and is considered to be associated with GC and precancerous lesions. As summarized in Table 2, Li *et al*[83] reported that the detection rate of bile reflux increased with the aggravation of mucosal lesions and that the degree of reflux increased. Bile reflux may increase the severity of Hp infection by promoting its colonization and aggravating gastric mucosal lesions.[84] Matsuhisa *et al*[85] found that although bile reflux was not significantly associated with atrophic gastritis, high concentrations of bile acids in the stomach are related to a high risk of GIM. These studies have demonstrated a strong association between bile reflux and GIM, and bile acids, as one of the major components of bile, are thought to play a crucial role in this process. The main physiological functions of bile acids are involved in food digestion and fat solubilization,[86] and can act as signaling molecules participating in the regulation of cellular biological functions, such as epigenetic regulation, nuclear receptor activation, and metabolism,[87] and interact with the intestinal microbiota.[88] As amphiphilic molecules, the biological func-

Table 2: Summary of the clinical research related to bile reflux, bile acids, and GIM.

Author	Year	Research topic	Participant	Testing method	Conclusion	Reference
Matsuhisa *et al*	2013	Bile acid reflux, atrophic gastritis, and intestinal metaplasia	2283	Gastroscopy and enzymatic assay	Bile acid concentration was positively correlated with the degree of GIM	[25]
Tatsugami *et al*	2012	Bile acids, intestinal metaplasia, and gastric carcinogenesis	767	Gastroscopy and enzymatic assay	Bile acid promoted the progression of mucosal atrophy and GIM	[26]
Dan Li *et al*	2020	GC and bile reflux	30,465	Gastroscopy	Bile reflux rate was increased with the aggravation of mucosal lesions	[83]
Matsuhisa *et al*	2011	Bile acid reflux, mucosal atrophy, and intestinal metaplasia	294	Gastroscopy and enzymatic assay	High concentration of bile acids was related to the high risk of GIM	[85]
Nakamura *et al*	2001	Bile acid reflux and intestinal metaplasia	9852	Gastroscopy and enzymatic assay	Bile acid concentration was increased in intestinal metaplasia patients	[91]

GC: Gastric cancer; GIM: Gastric intestinal metaplasia.

tion of bile acids is influenced by their hydrophilicity. Hydrophilic bile acids such as ursodeoxycholic acid are important therapeutic agents for bile acid-related diseases.[89] Hydrophobic bile acids such as chenodeoxycholic acid (CDCA) and deoxycholic acid (DCA), are cytotoxic and can induce oxidative stress and deoxyribonucleic acid (DNA) damage, lyse cell membranes, promote immunosuppression, and induce tissue damage, which are susceptibility factors for cancer.[90] Matsuhisa *et al*[25] collected gastric fluid by gastroscopy followed by an enzymatic assay of bile acid concentration and found that the bile acid concentration was positively correlated with the degree of GIM. The results of Nakamura *et al*[91] also confirmed the strong association between bile acids and GIM. Furthermore, Tatsugami *et al*[26] not only reported that bile acids promoted the progression of mucosal atrophy and GIM, but also revealed that bile acids collaborated with Hp to regulate the expression of CDX2 in gastric cells. Given the close association of bile acids with GIM, Li *et al*[69] stimulated GES-1, a normal gastric epithelial cell, with various bile acids and found that CDCA and DCA were able to significantly upregulate the expression of intestinal markers such as CDX2, KLF4, MUC2, and VILLIN at the mRNA and protein levels, confirming that bile acid stimulation induced a GIM phenotype in gastric epithelial cells. In the animal model of bile acid-induced GIM, after 45 days of bile acid gavage treatment, Yu *et al*[74] found a significant increase in the expression levels of the enteric markers CDX2 and MUC2 in the gastric mucosa of mice exposed to DCA, CDCA, or a mixture of DCA and CDCA, further confirming the important role of bile acid in the induction of GIM.

Therefore, it is particularly important to clarify the detailed molecular mechanisms underlying the bile acid-induced GIM phenotype for the prevention and treatment of GIM.

Molecular mechanism of GIM induction by bile acids

FXR in bile acid-induced GIM

FXR is a transcription factor of the nuclear receptor superfamily and a bile acid-binding receptor.[20,92] It is not only a potent regulator of bile acid homeostasis, lipid metabolism, and the inflammatory response but also plays an important role in immune regulation, cell proliferation, and differentiation,[93,94] and is associated with various cancers and Barrett's esophagus.[95,96] FXR is mainly highly expressed in the liver, intestine, kidney, and adrenal glands, and is less expressed in normal gastric mucosa.[93] Nevertheless, Shi *et al*[97] and Zhou *et al*[98] found that FXR expression was significantly increased in GIM tissues. Recent studies have shown that FXR can be involved in the regulation of bile acid-induced GIM through microRNA (miRNA). miRNAs are endogenous RNAs of approximately 22 nucleotides (nts) that can affect the expression of proteins by directly binding to complementary sequences in the 3'-untranslated regions (3'-UTRs) of target mRNAs, causing degradation or translational repression of the target mRNA.[99] Li *et al*[69] found that the expression of miR-92a-1-5p and CDX2 was upregulated in GIM tissues, whereas the expression of Forkhead box D1 (FOXD1) was downregulated. Given that the miR-17–92 family plays a key role in GC and IM,[100] they treated GES-1 cells with CDCA and GW4064, an agonist of FXR, consistently found significant upregulation of miR-92a-1-5p and CDX2 and downregulation of FOXD1 at the RNA level. miR-92a-1-5p has a binding site in the 3'-UTR of FOXD1, thereby

reducing FOXD1 expression. FOXD1, as a molecule that plays a role in multiple cancers, can inhibit Nuclear factor-κB (NF-κB) activation,[101,102] and CDX2 expression was positively regulated by NF-κB in GIM caused by Hp infection. Li *et al*[69] first validated the mechanism by which the FXR/miR-92a-1-5p/FOXD1/NF-κB/CDX2 axis promotes GIM in a bile acid-induced GIM cell model. Similarly, Yu *et al*[74] and Li *et al*[103] also demonstrated that DCA and CDCA can promote GIM by upregulating the expression of intestinal markers such as CDX2, through the FXR/NF-κB signaling pathway. Zhou *et al*[98] found that FXR could directly induce the expression of a small heterodimer partner (SHP), and the FXR-induced stimulation of CDX2 upregulation is dependent on SHP to promote NF-κB activity.

Hepatocyte nuclear factor 4α (HNF4α) in bile acid-induced GIM

HNF4α, a nuclear transcription factor, is involved in various physiological processes, such as gastrointestinal tract development, hepatocyte differentiation, and glycolipid metabolism.[104] In the gastrointestinal tract, HNF4α is essential for goblet cell maturation and regulation of normal colonic function.[105] Aberrant expression of HNF4α is involved in the progression of colon and GCs.[106,107] HNF4α is normally not expressed in the esophagus but is upregulated in BE and GIM tissues.[108] Ni *et al*[109] found that HNF4α, the intestinal markers CDX2, and KLF4, and the bile acid receptor TGR5 increased in parallel during GIM progression and that the HNF4α positive rate was up to 100% in severe GIM endoscopic biopsy specimens. Luciferase reporter gene analysis and ChIP assays confirmed that HNF4α binds to the promoter regions of CDX2 and KLF4, promoting the expression of both. Upstream, bile acid stimulation can activate the ERK1/2 pathway via TGR5, which in turn induces HNF4α expression. Based on that Ni *et al* demonstrated the important role of HNF4α in bile acid-induced GIM at the cellular level, Wang *et al*[110] further constructed $Rosa26^{Hnf4\alpha}$ transgenic mice and found significant structural abnormalities in gastric tissues and increased mucin in gastric cells in the transgenic mice. Moreover, they identified another aberrantly expressed protein in GIM tissue, Histone deacetylase 6 (HDAC6), which not only modifies histones but also targets a number of non-histone proteins, and has been reported to promote GC progression.[111,112] HDAC6 can be transcriptionally activated by HNF4α and can promote the expression of HNF4α, thus forming an HDAC6/HNF4α loop. miR-1, which was significantly downregulated in GIM tissues, could bind to the 3'-UTR of HDAC6 and HNF4α. In another study by Wang *et al*,[113] it was shown that after DCA stimulation, FXR expression was upregulated and further activated SNAI2 (Snail family transcriptional repressor 2), which transcriptionally repressed miR-1 expression. Eventually, the FXR/SNAI2/miR-1/HNF4α-HDAC6 loop/intestinal marker axis was formed in response to bile acid stimulation.

Methylation in bile acid-induced GIM

DNA methylation plays a vital role in various biological processes, and gene-related DNA methylation can occur in promoters and usually represses gene transcription.[114] Niu *et al*[64] found that reduced SOX2 expression during GIM progression promoted CDX2 expression by reducing the level of DNA methylation in the CDX2 promoter region. Yuan *et al*[70] also demonstrated that miR-21 inhibited SOX2 expression, resulting in the opposite expression patterns of CDX2 and SOX2 in bile acid-stimulated gastric cells. Dickkopf-related protein 1 (DKK1), known as an inhibitor of the Wnt signaling pathway, plays an important role in the progression of GC. Lu *et al*[115] observed that in bile acid-induced GIM, DKK1 expression was reduced and the methylation level of the DKK1 promoter region was increased, resulting in upregulated expression of intestinal markers in GIM tissues.

RNA methylation refers to the addition of methyl groups at different positions in RNA, such as m^6A methylation, which is considered the most common methylation modification occurring on the nucleobase.[116,117] ALKBH5 (Alkylation repair homolog protein 5) is a major demethylase that reverses m^6A methylation modifications, while YTHDF2 (YTH N^6-Methyladenosine RNA binding protein 2) recognizes specific m^6A sites and accelerates the degradation of m^6A-modified RNA.[118] Yue *et al*[119] found that ALKBH5 upregulation increased the expression of ZNF333 (zinc finger protein 333) in GIM tissues as well as in bile acid-treated gastric cell lines by eliminating m^6A-YTHDF2-dependent mRNA degradation. Then, ZNF333 transcriptionally represses Cylindromatosis expression and indirectly activates NF-κB signaling pathway, which in turn promotes CDX2 expression. In addition, p65, a key transcription factor of the NF-κB signaling pathway, promotes ALKBH5 expression by binding to the ALKBH5 promoter, thus forming a feed-forward loop.

Potential therapeutic targets for bile acid-induced GIM

Although bile acids have been shown to play an important role in the induction of GIM, there is a relative lack of research addressing whether key molecules in the mechanism of action of bile acids can serve as therapeutic targets for GIM. Resveratrol is a drug with potential antitumor effects,[120] Lu *et al*[121] found that resveratrol could activate FOXO4 by increasing FOXO4 phosphorylation via the PI3K/AKT pathway, then inhibited CDCA-induced GIM marker expression, and has a potential reversal effect on GIM, especially GIM caused by bile acid reflux. There may be other molecules or signaling pathways in the induction of GIM by bile acids that could be potential targets for the treatment of GIM, but further exploration is needed.

Conclusions and perspectives

As one of the precancerous lesions and risk factors for GC, the relationship between intestinal metaplasia and bile reflux has been widely reported and recognized. We suggest that the role of bile reflux in the GIM process explain why GIM remains difficult to reverse after Hp eradication. Bile reflux-induced GIM is mainly mediated by bile acids and regulated by several critical molecules

and signaling pathways, including FXR, TGR5, HNF4α, microRNAs, methylation modifications, and the NF-κB pathway. However, given that existing studies have only explored the mechanism of single bile acid in the induction of the GIM phenotype, they are also somewhat flawed. Therefore, more in-depth studies should be conducted to determine how the bile acid profile of gastric juice changes in patients with GIM and the role of other bile acids in promoting the process of GIM. Altogether, the study of bile acid-induced GIM is of great significance, not only suggesting the need for special attention to the occurrence of GIM and GC events in patients with bile reflux but also providing many possible therapeutic targets for the treatment of GIM.

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Conflicts of interest

None.

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