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Editorial

Bile Acids and Gastric Intestinal Metaplasia: Exploring a New Feedback Loop

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See "GATA4 Forms a Positive Feedback Loop with CDX2 to Transactivate MUC2 in Bile Acids-Induced Gastric Intestinal Metaplasia" by Xiaofang Yang, et al. on page 414, Vol. 18, No. 3, 2024

Gastric cancer, also known as stomach cancer, is characterized by abnormal cell growth in the stomach lining, ranking as the fourth leading cause of cancer-related mortality globally.[1] The development of gastric cancer is often preceded by gastric intestinal metaplasia (GIM), a precancerous condition where the normal stomach lining transforms into intestinal-type cells, significantly increasing the risk of progressing to gastric cancer.[2] Intestinal metaplasia (IM) is classified into stages of low-grade dysplasia and high-grade dysplasia, with higher grades indicating a closer association with cancer. Understanding this transition from GIM to gastric cancer is crucial for early detection and effective intervention strategies. While the global prevalence of GIM remains largely uncertain, it has been observed to correlate positively, though not causatively, with regional rates of gastric cancer incidence.

Certain factors contribute to the progression of IM, including conditions like esophagitis, chronic gastritis or gastric atrophy, *Helicobacter pylori* infection, acid reflux, bile reflux, and alcoholism, with bile acid reflux being a significant underlying cause.[3] Duodenogastric reflux refers to the backward flow of bile and other duodenal contents into the stomach. This reflux exposes the stomach lining to bile acids, which play a critical role in triggering IM.[4] The impact of bile acids causes normal gastric epithelial cells to transform into cells resembling intestinal epithelium, highlighting the intricate interaction between environmental factors and cellular responses that drive the progression of gastric mucosal changes towards malignancy.

The mucin gene family, which includes MUC2, plays a critical role in protecting the mucosal surface. MUC2, typically expressed in intestinal epithelial cells, is upregulated during IM, a precursor to gastric cancer. In gastric cancer, increased MUC2 expression is associated with intestinal-type tumors.[5] Notably, MUC2 can also be detected in gastric epithelium, particularly in cases of IM and gastric cancer. This upregulation of MUC2 is believed to contribute to the formation of IM, a recognized precursor to gastric cancer. Furthermore, reports suggest that bile acids can induce the upregulation of CDX2 and MUC2 in normal gastric epithelial cells through the farnesoid X receptor (FXR) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) signaling pathways. Therefore, MUC2 expression serves as a marker of gastric mucosal changes and a potential indicator of gastric cancer risk.

In the latest issue of *Gut and Liver*, Yang *et al.*[6] conducted comprehensive studies to explore the intricate mechanisms by which GATA4 participates in the activation of MUC2 through a positive feedback loop with CDX2 in GIM. Their investigation began by examining the expression of GATA4 in both human tissue samples and a GES-1 cell model induced by bile acids, where they observed a significant increase in GATA4 levels. By identifying GATA4's binding site on the MUC2 promoter region, they established its critical role in transcriptional activation.

Furthermore, their analysis of GIM tissues revealed a notable positive correlation between GATA4 and MUC2 expression, providing additional support for their initial findings. Using a bile acid-induced GIM cell model, the researchers discovered that activation of NF-κB signaling is

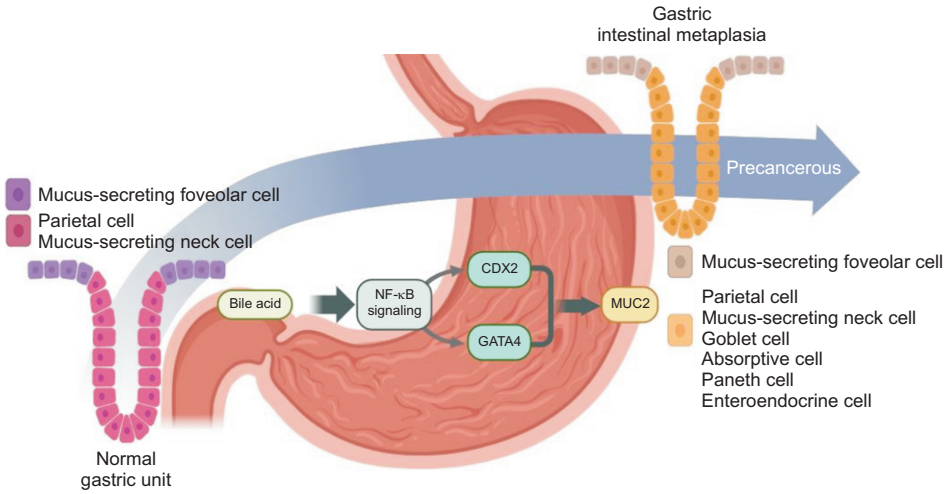

Fig. 1. A schematic model illustrating how bile acid-induced NF-κB signaling drives the expression of GATA4 and CDX2, leading to MUC2 transactivation in gastric epithelial cells and contributing to gastric intestinal metaplasia, a precancerous lesion of gastric cancer.

essential for upregulating both GATA4 and MUC2. Moreover, they demonstrated a reciprocal regulatory relationship between CDX2 and GATA4, driving the transcription of MUC2.

These findings were further substantiated through *in vivo* mouse studies, where chenodeoxycholic acid-treated mice exhibited elevated levels of MUC2, CDX2, GATA4, and components of the NF-κB pathway (p50 and p65) in the gastric mucosa, providing compelling evidence of their discoveries in an animal model. Nevertheless, the roles of GATA4, CDX2, and MUC2 in GIM pathogenesis are complex and require further investigation. Continued research in this area not only promises advancements in GIM treatment but also holds potential for preventing the progression to gastric cancer, emphasizing the significance of understanding these molecular interactions.

Based on extensive research findings, CDX2 is recognized as a specific marker of the intestinal mucosa and is extensively utilized as a highly specific and sensitive diagnostic marker for colorectal adenocarcinoma.[7-9] Its role as a biomarker, especially in the context of metastatic colorectal cancer, has been the subject of numerous studies. Similarly, GATA4, characterized as an intestinal transcription factor implicated in the carcinogenesis of gastric cancer, is generally observed to be highly expressed in pancreatic cancer, where it has been associated with cell proliferation and differentiation processes.[10] The correlation between CDX2 and GATA4 induced by NF-kB activation across different types of cancer, as discussed in this paper, suggests a potential avenue for therapeutic intervention (Fig. 1). By leveraging this correlation, it is conceivable that therapeutic strategies targeting MUC2 and other related factors could be developed with greater efficacy and broader applicability compared to current approaches. This approach underscores the importance of exploring molecular mechanisms and interrelationships among transcription factors and signaling pathways to advance precision medicine strategies in cancer treatment.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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