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WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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EDITORIAL

Targeting methyltransferase-like 5-mediated sphingomyelin metabolism: A novel therapeutic approach in gastric cancer

Jin-Juan Zhang, Chang Yuan, Sheng-Chun Dang

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Abstract

Gastric cancer (GC) is a global health problem and a leading cause of cancer-related deaths, with its mortality rate ranking third among all cancers. The etiology and progression of GC are characterized by a complex interplay of genetic and epigenetic changes, which present challenges for its early diagnosis and effective treatment. Elucidating the mechanisms underlying the occurrence and development of GC and identifying novel biomarkers for early detection and prognosis are crucial to improving patient outcomes. This editorial examines the role of methyltransferase-like 5 (METTL5) in the progression of GC through sphingomyelin metabolism by considering an article published by Zhang *et al* in the *World Journal of Gastrointestinal Oncology* in 2024, which is entitled "METTL5 promotes GC progression *via* sphingomyelin metabolism". These authors investigated the biological behavior of METTL5 in GC by examining its expression patterns, clinical relevance, functional effect, and potential mechanisms, as well as its response to chemotherapy. This editorial provides valuable insights into the role of METTL5 in the progression of GC and its potential as a therapeutic target.

Key Words: Gastric cancer; Methyltransferase-like 5; Sphingomyelin metabolism; Biomarkers; Chemotherapy response

Core Tip: This study comprehensively analyzes the role of methyltransferase-like 5 (METTL5) in the progression of gastric cancer (GC), highlighting its potential as a new therapeutic target and prognostic biomarker. However, further research is needed to fully understand the functional mechanism of METTL5 in GC and translate these insights into clinical applications. Targeting METTL5-mediated sphingomyelin metabolism is a novel therapeutic approach in GC.

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INTRODUCTION

Gastric cancer (GC) is one of the most prevalent malignancies worldwide, and its mortality rate is the second highest among all malignancies[1]. The etiology and progression of GC involve a multitude of genetic and epigenetic alterations, contributing to its complex nature[2]. A lack of early detection methods and suboptimal prognostic predictions are the main reasons for unfavorable outcomes in patients with GC. Therefore, elucidating the mechanisms underlying the occurrence and development of GC and identifying novel biomarkers for risk assessment and prognosis are essential for improving the early diagnosis and therapeutic management of this malignancy.

TARGETING METTL5-MEDIATED SPHINGOMYELIN METABOLISM: A NOVEL THERAPEUTIC APPROACH IN GASTRIC CANCER

This editorial examines the role of methyltransferase-like 5 (METTL5) in the progression of GC through sphingomyelin metabolism by considering an article published by Zhang *et al*[3] in the *World Journal of Gastrointestinal Oncology* in 2024, which is entitled "METTL5 promotes GC progression *via* sphingomyelin metabolism". These authors investigated the role of METTL5 and its potential mechanisms in the development of GC by examining its expression patterns and clinical significance, performing functional analyses (through knockdown and overexpression experiments), and studying the role of sphingophospholipid metabolism. Additionally, Zhang *et al*[3] conducted *in vivo* experiments and studied the responses of METTL5 to chemotherapy, offering a comprehensive insight into the function of METTL5 in GC. They also evaluated the effects of METTL5 on tumor growth *in vivo* and studied the response of GC cells to chemotherapy, especially cisplatin.

METTL5 is a protein-encoding gene that encodes an enzyme involved in RNA modification, and it has received increasing attention in recent years for its potential role in tumorigenesis[4]. METTL5 can influence tumor proliferation, invasion, and metastasis, immunotherapy resistance, and metabolic reprogramming in tumor cells[5]. Furthermore, METTL5 may contribute to tumor development by modulating the expression of specific genes.

As a human 18S rRNA-specific M6A methyltransferase, METTL5 has been the focus of numerous recent studies that underscore its various roles in biological processes. The exact interplay between METTL5 and tumor development remains an area of active investigation, and future research is likely to elucidate its precise mechanisms. Van Tran *et al*[6] reported that METTL5 forms a heterodimeric complex with TRMT112, a methyltransferase activator that is crucial for metabolic stability in cells. This interaction is hypothesized to facilitate the extrusion of adenosine from double-stranded nucleic acids, thereby influencing cellular functions[6].

Dysregulation of METTL5 expression is associated with several human malignant tumors, with hepatocellular carcinoma (HCC) currently being the most extensively studied topic. Qi *et al*[5] demonstrated that METTL5 plays a crucial role in the tumorigenesis of HCC *in vitro* and in mouse models. Research on METTL5-dependent fatty acid metabolism has revealed a new mechanism for regulating mRNA translation and HCC development through lipid metabolism, laying a molecular foundation for the development of targeted HCC therapy[4].

Xia *et al*[7] explored the role of METTL5 in HCC development and its association with the Warburg effect. They discovered that METTL5 regulates c-Myc ubiquitination, affecting glucose metabolism and tumor growth[7]. Wang *et al*[8] reported that increased METTL5 expression in HCC is linked to immune microenvironment factors, including immune modulators, chemokines, and chemokine receptors[8]. Peng *et al*[9] demonstrated the critical role of METTL5 in HCC tumorigenesis. METTL5 depletion impairs 80S ribosome assembly and diminishes the translation of mRNAs involved in fatty acid metabolism[9].

Additionally, Xu *et al*[10] discovered that the suppression of METTL5 reduced PD-L1 expression and mitigated the malignant behavior of HCC cells; this effect was counteracted by the overexpression of c-Myc, indicating that METTL5 modulates HCC *via* the Myc pathway[10]. They found that the loss of 18S RNA m6A modification mediated by the methyltransferase METTL5 can inhibit the assembly and aggregation of 80S ribosomes, thereby reducing the translation of mRNAs related to fatty acid metabolism, including acetyl-CoA synthase family members (ACSLs). However, ACSL4 can also affect the function of METTL5 by regulating the metabolism of fatty acids. Targeting ACSL4 and METTL5 *in vivo* can inhibit the occurrence and development of liver cancer[9]. Furthermore, investigations into databases such as the

Cancer Genome Atlas (TCGA) have implicated METTL5 in the pathogenesis and progression of lung adenocarcinoma (LUAD), identifying it as a potential biomarker for early detection and prognostic monitoring, potentially improving outcomes for patients with LUAD[11,12].

Although research on the association of METTL5 with the metabolism of sphingophospholipids is still in its infancy, preliminary findings have indicated a possible link. METTL5 may influence the metabolism of sphingolipids that are integral to cell membrane structure and function, opening a new avenue for exploring the role of sphingolipids in cellular processes. Evidence from several studies has indicated that METTL5 potentially influences the synthesis and metabolism of sphingophospholipids by modulating the expression of key genes and RNA modification processes.

Such interactions can alter the composition and characteristics of cell membranes, consequently affecting cellular functions and metabolic pathways. Although the precise mechanisms by which METTL5 influences the metabolism of sphingophospholipids remain to be fully elucidated, ongoing research is progressively shedding light on this topic. Future studies are anticipated to reveal the specific role of METTL5 in the metabolism of sphingophospholipids, offering novel insights and directions for research into cell membrane biology and associated diseases.

Despite the incomplete understanding of the role of METTL5 in the progression of GC, ongoing research continues to elucidate its underlying mechanisms. It is anticipated that future studies will elucidate the precise functions of METTL5 in the pathogenesis of GC, revealing novel therapeutic and preventive strategies for this disease.

The expression of METTL5 and its correlation with clinicopathological characteristics were analyzed using a dataset from TCGA. The *in vivo* role of METTL5 in tumor progression was evaluated using a xenograft tumor model. The EpiQuik m6A RNA Methylation Quantification Kit was used to quantify m6A levels, and the association between METTL5 and sphingomyelin metabolism was assessed using liquid chromatography-mass spectrometry. The study found that METTL5 was substantially upregulated in GC cells, which is associated with poor prognosis, distant lymph node metastasis, advanced cancer stage, and higher pathological grade. Increased METTL5 expression correlates with higher m6A methylation levels. METTL5 significantly promotes the proliferation, migration, and invasion of GC cells *in vitro* and also enhances the growth of GC cells in animal models. Knockdown of METTL5 leads to significant changes in sphingomyelin metabolism, suggesting that METTL5 may influence the development of GC through this metabolic pathway. Additionally, high METTL5 expression is linked to cisplatin resistance[3].

Wang *et al*[13] investigated the expression and prognostic implications of METTL5 in the context of GC. Patients with high METTL5 expression have a better prognosis than those with low METTL5 expression, and METTL5 expression is mainly related to oxidative phosphorylation, nucleotide excision repair, and mismatch repair. METTL5 expression is correlated with improved patient prognosis. These findings contrast with those reported in a previous study[13].

This study provides comprehensive insights into the role of METTL5 in the progression of GC, addressing a gap in current research. Furthermore, this study experimentally validated the effect of METTL5 on the proliferation, migration, and invasion of GC cells, underscoring its oncogenic potential. Additionally, the exploration of the link between METTL5 and sphingophospholipid metabolism offers novel perspectives on its contribution to cancer development. These findings also shed light on the influence of METTL5 on the chemosensitivity of GC cells to cisplatin, which could inform future therapeutic approaches[3].

Despite these strengths, this study has several limitations, including a small clinical sample size, which may affect the generalizability of the findings. Therefore, a large number of clinical samples should be included in future studies to confirm the associations between METTL5 expression and various clinical variables such as tumor-node-metastasis stage, pathological stage, lymph node metastasis, and prognosis. Since the current study did not sufficiently explore the correlation between METTL5 and sphingomyelin levels in clinical samples, future studies should verify this relationship in a clinical context. The exact mechanism by which METTL5 affects sphingomyelin metabolism remains unclear. This study hypothesized that METTL5 is involved in the synthesis of enzymes related to sphingomyelin metabolism, but this requires further investigation.

We used the TCGA visualization tool GEPIA[14] to analyze METTL5 expression and clinical outcomes in patients with GC but did not obtain consistent results. Further validation using more databases is needed. Sharing raw data and experimental protocols is essential for transparency and enables the independent verification and replication of results, thereby maintaining the integrity of scientific research.

CONCLUSION

In summary, this study comprehensively analyzed the role of METTL5 in the progression of GC, highlighting its potential as a new therapeutic target and prognostic biomarker. However, further research is needed to fully understand the functional mechanism of METTL5 in GC and translate these insights into clinical applications.

FOOTNOTES

Author contributions: Zhang JJ, Yuan C, and Dang SC wrote the manuscript; all authors have read and approved the final manuscript.

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