Research Progress on the Role and Potential of N6-Methyladenosine in Gastric Cancer Treatment

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Abstract: N6-methyladenosine (m6A) is the most prevalent RNA modification, playing a crucial role in RNA metabolism, including stability, splicing, translation, and degradation. Dysregulation of m6A is involved in gastric cancer (GC), affecting tumorigenesis, epithelial-mesenchymal transition(EMT), and chemotherapy resistance. In GC, m6A modification promotes oncogene translation and alters non-coding RNA (ncRNA) interactions, contributing to tumor proliferation, invasion, and therapy resistance. Overexpression of METTL3 and YTHDF1 enhances m6A methylation which leads to MYC upregulation and EMT progression, while FTO depletion stabilizes E-cadherin, suppressing tumor metastasis. Moreover, ncRNAs are transcriptional modulators significantly affected by m6A modifications, influencing tumor growth and drug resistance. Additionally, m6A regulates various forms of programmed cell death, including pyroptosis, ferroptosis, autophagy, and cuproptosis, which indicates potential therapeutic target. Emerging strategies, such as CRISPR-Cas9 and epigenetic modulation, offer new approaches for targeting m6A-related pathways. Combining m6A-targeted therapies with conventional treatments may enhance GC outcomes, improving patient quality of life and survival.

1 INTRODUCTION

N6-methyladenosine (m6A) is the most well-known post-transcriptional RNA modification in mRNA and non-coding RNAs. It plays an important role in regulating RNA metabolism, including splicing, stability, translation, and degradation. m6A is dynamically formed by methyltransferases (writers), removed by demethylases (erasers), and recognized by binding proteins (readers). This modification influences gene expression and has been implicated in various physiological processes, including embryonic development, immune regulation, and tumor progression. In cancer, m6A dysregulation changes oncogene and tumor suppressor gene expression, affecting proliferation, apoptosis, metastasis, and therapy resistance. As a result, m6A is considered as a potential therapeutic target in multiple cancers, including gastric cancer. Gastric cancer (GC), also known as stomach cancer, is a malignant tumor that originates from the lining of the stomach. It is one of the most common cancers around the world. Gastric cancer is classified into different subtypes based on histology, molecular characteristics, and location within the stomach. The most common type is adenocarcinoma, which accounts for more than 90% of cases. The primary risk factors for gastric cancer include: Helicobacter pylori (H. pylori) infection, a major cause of chronic inflammation and lesions; unhealthy diet, such as high salt intake, smoked foods, and low vegetable consumption; lifestyle factors like smoking and alcohol abuse; chronic gastritis and gastric ulcers, which may lead to intestinal metaplasia and dysplasia. Genetic factors also distribute to gastric tumorigenesis. It is often diagnosed at an advanced stage due to vague early symptoms, such as indigestion, mild abdominal pain, or loss of appetite. This late detection contributes to high mortality rates.

Gastric cancer is the fifth most common cancer worldwide and the fourth leading cause of cancer-related death. According to global cancer statistics, it accounts for approximately one million new cases and 770,000 deaths annually. The prognosis varies based on the stage at diagnosis. Early-stage gastric cancer has a five-year survival rate of over 90% when treated with surgery; locally advanced gastric cancer (spread to nearby lymph nodes) has a five-year survival rate of 30–50%. Metastatic gastric

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cancer (stage IV) has a five-year survival rate below 5–10%, since treatment options are limited. Treatment for gastric cancer depends on the stage, location, and molecular characteristics of the tumor. For advanced and metastatic cases, systemic therapy is required. First line treatment include chemotherapy, basically platinum-based chemotherapy combined with fluoropyrimidines. Targeted Therapy are specially for HER2-positive gastric cancer, and during this kind of therapy, trastuzumab (Herceptin) is added to chemotherapy. PD-1 inhibitors like pembrolizumab or nivolumab are considered with chemotherapy for certain patients with high PD-L1 expression. Second-Line Chemotherapy is usually for those patients who had worsened after first-line therapy, and taxane-based (paclitaxel or docetaxel) or irinotecan-based drugs are used. Ramucirumab (VEGFR-2 inhibitor), either alone or with paclitaxel, improves survival in second-line settings. Despite treatment advances, chemotherapy resistance is still a major challenge, highlighting the need for novel molecular-targeted therapies, including those new findings on m6A regulation.

2 THE MODIFICATIONS INVOLVING M6A

m6A modification is dynamically regulated by three groups of proteins: writers, erasers, and readers. The initiation of m6A is mediated by the methyltransferase complex, primarily composed of METTL3 (methyltransferase-like 3) and METTL14, along with accessory proteins such as WTAP (Wilms tumor 1-associated protein), KIAA1429 (VIRMA), RBM15, and ZC3H13. This complex catalyzes the transfer of a methyl group to adenosine residues in RNA, typically occurring within the RRACH consensus motif (R = A/G, and H = A/C/U). Thanks to the action of demethylases such as FTO (fat mass and obesity-associated protein) and ALKBH5 (alkB homolog 5), the activitiy of m6A could be altered (Jiang et al. 2021, Hu et al. 2022). These enzymes remove m6A marks, allowing for regulation of RNA degradation and function. The biological effects of m6A are mediated by reader proteins, which recognize and bind to m6A-modified RNAs. The YTH domain-containing family (YTHDF1, YTHDF2, YTHDF3, and YTHDC1) determines the fate of m6A-marked transcripts. Other readers, such as IGF2BP1-3 (insulin-like growth factor 2 mRNA-binding proteins) modulate RNA stability, translation efficiency, and localization (Jiang et al. 2021, An & Duan 2022).

The m6A modification impacts many aspects of RNA metabolism: By recruiting the YTHDF2 protein, which promotes transcript decay through interactions with the RNA decay machiner, m6A promotes RNA degradation. m6A enhances translation efficiency by recruiting initiation factors such as eIF3 or promoting ribosome engagement via YTHDF1.m6A could affect RNA splicing by modulating interactions between splicing factors and pre-mRNA, thereby affecting the selection of exons (Jiang et al. 2021, An & Duan 2022). m6A modification is also responsible to nuclear export of transcripts, ensuring their proper localization inside the cell. Regulating specific gene expressions, m6A could mediate various kinds of physiological functions, such as neuron differentiation, embryo development and cancer formation. Dysregulation of m6A modification has been associated with various diseases, particularly cancer. Abnormal m6A levels is associated to oncogenesis by altering mRNA stability and expression of tumor suppressor genes or oncogenes. Additionally, m6A modifications influence other diseases such as immune responses and metabolic disorders. As a newly found promising therapeutic target, M6A has significant clinical potential. Now researchers are focused in exploring small-molecule inhibitors and epigenetic editing techniques to modulate m6A-related pathways.

3 THE DYSREGULATION OF M6A FUNCTION IN GASTRIC CARCINOGENESIS

METTL3,a crucial transmethylase, is widely known because it is associated to tumor cell proliferation and migration. Previous researches have found that METTL3 is overly expressed in cancer cells. By enhancing m6A methylation, MYC translation could increase, leading to cancer cell proliferation. Increased METTL3 levels indicate higher N-cadherin/ Vimentin levels and lower E-cadherin levels. The loss of E-cadherin shows the progression of EMT, which is considered as a molecular marker in cancer studies (Zeng et al. 2020, Wang et al. 2020). Enhanced expression of HOXA10 caused by excessive m6A methylation can also promote tumor cell migration. Absence of FTO expression results in the increase of E-cadherin and the decrease of

vimentin. This indicates that FTO is related to stabilization and expression in EMT related genes. In the specific case of gastric cancer, higher EMT expression levels could lead the transformation from epilethial cells to mesenchymal cells (Wu et al. 2024). By modulating the stability of mRNA, WTAP could increase anaerobic glycolysis, which is a crucial energy supply to cancer cells, since usually there are less oxygen and higher temperature inside the tumor. Over-expression of YTHDF1 is often found in gastric cancer tissue In cases of resistance toward chemotherapy drugs (Wu et al. 2024).

The demethylase, ALKBH5, specifically targets the m6A modification on the mRNA of PKMYT1, a protein kinase involved in cell cycle regulation. The researchers demonstrated that its expression was significantly lowered in gastric cancer tissues, and low ALKBH5 levels correlated with poor prognosis and increased cancer metastasis. This means that ALKBH5 could be a potential suppressor of gastric cancer metastasis. Through a series of experiments, the study found that ALKBH5 directly interacts with the m6A modification site on the PKMYT1 mRNA. ALKBH5's demethylase activity could remove the m6A modification from PKMYT1, thereby stabilizing its mRNA and reducing its translation. When overexpressed, PKMYT1 promotes cell cycle. It has been linked to the increased motility and invasion of cancer cells. The inhibition of PKMYT1 expression by ALKBH5 limits the metastasis of gastric cancer cells (Hu et al. 2022). The researchers further corroborated this finding by demonstrating that overexpressing ALKBH5 in gastric cancer cells reduced cell invasion and migration, while silencing ALKBH5 enhanced the cells' invasive behavior. Additionally, they observed that restoring PKMYT1 expression in ALKBH5-overexpressing cells could partially reverse the inhibition of cell invasion, so PKMYT1 is very probable to be a key mediator of ALKBH5. These findings show the importance of the interaction between ALKBH5 and PKMYT1 in regulating the invasiveness of gastric cancer cells.

4 THE RELATIONSHIP BETWEEN NCRNA AND M6A

There are mainly 3 types of noncoding RNA that interact with m6A, including lncRNA, miRNA and circRNA.

Long noncoding RNAs (lncRNA) are usually described as RNA fragments longer than 200 bases and they don't have the ability to produce proteins, but recent studies show that some of them do encode microproteins that is essential in physiological activities (Jin & Fan 2024). Dysregulation of m6A could change the amount and types of lncRNA, which may affect cell proliferation, apoptosis and metastasis, eventually leading to gastric cancer. Chemotherapy, the first line medication for gastric cancer, faces a major problem of drug resistance. Researchers found that lncRNA-CBSLR could help tumor cells evade from ferroptosis, protecting tumor cells in gastric cancer. This results in chemoresistance. Another lncRNA, ARHGAP5-AS1 is highly expressed in cancer cells, and knocking down it could reverse this kind of drug resistance. Also, high expression rate of LNC942 is a signal of chemoresistant tumor cells in gastric cancer. LNC942 can stabilize Myc mRNA, and the upregulation of Myc would cause unlimited proliferation of gastric cancer cells (Yang et al. 2021, Jin & Fan 2024).

MicroRNAs (miRNA) are small singular strands of RNA. They consist of about 22 nucleotides. Normally, miRNA acts as a transcription modulator by binding base pairs with mRNA to interfere its translation and promote degradation. Adenosine in miRNAs could be modified as m6A, and research shows that m6a plays an important role in processing primary miRNA. The methylation of specific sites within the pri-miRNA can promote or inhibit the recognition of the transcript by Drosha, an RNA enzyme which cuts unnecessary fragments of primary miRNA. This regulation can determine the levels of mature miRNAs suitable for post transcriptional regulation. Some studies have shown that METTL3, which adds m6A modifications to RNA strands, can enhance or suppress the maturation of certain pri-miRNAs, thus modulating the expression of downstream target genes that are involved in tumorigenesis. Other numerous studies have shown miRNAs can suppress the expression of m6A regulators, resulting in alterations in m6A levels (Feng et al. 2023, Jayasree et al. 2024). In the cytoplasm, mature miRNAs associate with RISC complexes to silence the expression of target mRNAs. m6A modifications on miRNAs can also influence their interaction with RISC and the stability of the miRNA-RISC complex. m6A-modified miRNAs may change binding affinities for their target mRNAs, affecting the efficiency of gene silencing.

This mechanism has been linked to the regulation of key genes involved in cancer progression. For example, m6A modifications on the miRNA miR-21, an oncogenic miRNA overexpressed in many cancers, modulates its activity and influences the expression of tumor suppressor genes such as PTEN. This interaction between m6A and miRNA regulation contributes to the complex regulation of cancer cell behavior.

Circular RNAs (circRNA) are generated via mRNA splicing and most of them are found in cytoplasm. circRNA could act like a sponge to absorb miRNA by competing binding sites with mRNA, promoting specific gene expression. It could also affect gene expression at the transcriptional level, regulate variable splicing, and participate in epigenetic regulations (Lin et al. 2022, Qin et al. 2021). While the functional role of circRNAs in cancer has been widely studied, the regulation of circRNAs by m6A modifications is a relatively new area of research. m6A modification affects the circularization of pre-mRNAs and can impact the stability and translation of the resulting circRNAs. In some cancers, m6A-modified circRNAs may promote oncogenesis by stabilizing certain transcripts, while in others, they may function as tumor suppressors. These observations suggest that the interaction between m6A and circRNAs is highly variable and could be a critical factor of cancer cell behavior. circRNAs are associated with chemoresistance. circRNA could regulate the expression of ABC transporters, which pumps chemotherapy drugs out of cancer cells, and it may be modified by m6A to enhance their stability and promote drug resistance. Similarly, circRNAs in the regulation of apoptosis and autophagy can also be modulated by m6A to gain resistance to chemotherapy induced cell death (Qin et al. 2021).

5 THE POTENTIAL OF M6A AS A THERAPEUTIC TARGET IN GASTRIC CANCER

Pyroptosis is a special form of cell death driven by gasdermin-mediated pore formation. When inflammatory signals show pathogens or danger, caspase-1 will be activated to lyse gasdermin, and the product on the N terminal could perforate the cell membrane, causing the cell to lyse. It has been shown to be influenced by m6A modification. Dysregulation of m6A regulators can alter pyroptotic signals in tumor cells. Increased m6A methylation of specific long noncoding RNAs may downregulate inflammasome components, inhibiting pyroptosis and favoring cancer cell survival. Therapeutic interventions that upregulate m6A levels could promote pyroptosis, and part of normal function of cancer cells could be restored (Yang et al. 2023).

Autophagy is a cellular recycling process that is associated with two aspects of cancer -- survival under stress or cell death. In gastric cancer, m6A modifications have been linked to the regulation of autophagy-related genes (ATGs). Overexpression of m6A writers such as METTL3 has been associated with enhanced autophagy that supports tumor cell survival and increases the possibility of chemotherapy resistance. Conversely, inhibition of specific m6A modifiers can disrupt overly active autophagy, making cancer cells more sensitive to conventional therapies (Wang et al. 2020, Yang et al. 2023). When the ROS reach lethal levels and the iron ion is imbalanced in the cell, ferroptosis will start. This is because glutathione peroxidase 4 (GPX4), which is important for reducing peroxidized membrane lipid, is inhibited and iron accelerates peroxidation of lipid. m6A modification affects the stability and translation of mRNAs encoding key ferroptosis regulators, such as lncRNA-CBSLR, SLC7A11 and GPX4. Modulating these targets, m6A regulators can tip the balance between survival and ferroptosis. Targeting the m6A machinery to induce ferroptosis could be a novel approach to combat chemoresistance in gastric cancer (Yang et al. 2021, Yang et al. 2023).

More recent researches found the cell death, cuproptosis, is induced by overload copper ions that blocks TCA enzymes, causing loss of Fe-S clusters, mitochondrial metabolism failure and proteotoxic stress. m6A modifications can influence the expression of cuproptosis related genes such as FDX1, which are critical for copper induced toxicity. Since gastric tumors often exhibit irregular copper metabolism, targeting m6A pathways to promote cuproptosis may provide a new strategy to kill tumor cells which are resistant to other forms of cell death (Yang et al. 2023).

Gene therapy could also help in treating gastric cancer involving m6A. Advancements in CRISPR-Cas9 gene editing have made precise manipulation of m6A regulators easier and more precise. By selectively knocking out or modulating m6A writers, erasers or readers, researchers can analyse the roles of these proteins in gastric tumor development. CRISPR

screens have identified key m6A regulators whose loss decreases tumor cell survival, finding new and hopeful therapeutic targets (Kordyś et al. 2022, Tong et al. 2021). Such approaches not only facilitate functional studies but also provide a framework for the development of gene therapies aimed at balancing m6A levels. In epigenetics, m6A represents a reversible mark that bridges genetic information and post-transcriptional regulation. Specific m6A patterns can lead to sustained oncogenic signaling and contribute to the epigenetic plasticity of cancer cells (Cusenza et al. 2023, Yue et al. 2023). Therapeutic strategies that target m6A modifications can reverse epigenetic deviations and restore normal gene expression profiles. The integration of m6A targeted drugs with epigenetic therapies could make gastric cancer treatments more efficient.

6 CONCLUSION

Evidence shows the significance of m6A modification in gastric cancer, influencing multiple aspects of tumorigenesis, progression, and therapeutic resistance. By modulating RNA stability, translation, and interaction with non-coding RNAs (lncRNA,miRNA and circRNA), m6A dynamically shapes the cellular landscape of gastric tumors. Dysregulation of m6A regulators can significantly affect oncogene expression and tumor-suppressive pathways, making it a promising target for novel cancer therapies. Modulation of m6A levels could enhance the effectiveness of existing treatments, particularly by sensitizing cancer cells to chemotherapy, regulating apoptosis, and inducing various forms of programmed cell death, including pyroptosis, ferroptosis, and cuproptosis. This could be realized by the integration of m6A-targeted therapies with CRISPR-based gene editing and epigenetic modulators. In conclusion, targeting m6A modification represents a novel and promising strategy for gastric cancer therapy. Continued research about the molecular mechanisms of m6A and the development of specific inhibitors or activators will be crucial in releasing its full therapeutic potential. By integrating m6A-targeted approaches with existing treatment modalities, the future of gastric cancer management may gain significant advancements, leading to improved patient outcomes and higher survival rates.

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