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Research Progress on the Role of M6A Methylation Modification in the Genesis and Development of GC

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Abstract: Modification of M6A RNA methylation is the most prevalent form of RNA editing in eukaryotic organisms. The m6A-methylated regulatory protein is intimately associated with biological processes, including GC proliferation, invasion, and metastasis. This protein is anticipated to serve as a target for the clinical treatment of GC in the future. This comprehensive review delineates the most recent advancements and clinical implications of m6A aberrant modification in GC, aiming to furnish a novel research avenue for the exploration of GC's future direction.

Keywords: GC; m6A; ALKBH5; Epigenetics

Introduction

The term gastric cancer (GC) refers to a malignant tumor that develops within the digestive system. As per the Global Cancer Statistics Report in 2020, GC ranks as the fifth most prevalent cancer globally and stands fourth in terms of cancer-related mortality. Annually, more than one million new cases are reported[1]. The early signs of GC are subtle and often overlooked, resulting in a majority of diagnoses occurring in the middle to late stages. This delays the initiation of optimal treatment, placing patients at a higher risk of missing the best therapeutic window or experiencing intolerable systemic toxic reactions due to chemotherapy drugs. Consequently, the prognosis for these patients is generally unfavorable[2]. The development of GC can be influenced by numerous unmodifiable risk factors, such as advancing age[3], being male[4],and inheritable genetic factors[5],among others. Additionally, there are several modifiable pathogenic factors that can contribute to the onset of GC, including Helicobacter pylori infection[6],EB virus infection[7],and the presence of GC stem cells[8].

Precise epigenetic factors significantly contribute to the genesis and progression of tumors. The ever-expanding scope of epigenetic research has revealed a potential link between the invasive and metastatic capabilities of GC cells and epigenetics[9]. Among the various aspects, the investigation of the interaction mechanism between m6A RNA methylation and its regulatory molecules has emerged as a prominent research hotspot[10]. Modification of m6A RNA is intimately associated with the incidence, progression, prognosis, and drug responsiveness of GC. Consequently, targeting abnormal m6A modifications holds great. The present article reviews the current advancements in research and clinical application of m6A aberrant modification in GC, aiming to inspire the exploration of novel therapeutic targets for this malignancy.

1. Overview of M6A RNA Methylation

The term "m6A RNA methylation" refers to the modification of base A at its sixth nitrogen atom through methylation. This modification, known as m6A, is the most prevalent form of RNA modification and is widely observed in the mRNAs and lncRNAs of eukaryotes[11]. The regulation of m6A modification encompasses a wide range of RNA metabolic activities, including but not limited to RNA maturation, cleavage, transportation, degradation, and translation. The m6A modification, similar to DNA methylation or histone methylation, is a dynamic and reversible process primarily mediated by methyltransferase enzymes, demethylase enzymes, and RNA methylation-binding proteins[12].

The methylation of the sixth nitrogen atom in RNA adenine is catalyzed by methyltransferase, which primarily consists of methyltransferase-like protein 3 (METTL3), methyltransferase-like protein 14 (METTL14), and Wilms tumor 1 associated protein 1-associated protein (WTAP) et al. [13]. The demethylation of RNA is primarily catalyzed by two demethylases, namely fat mass and obesity-associated protein

(FTO) and alpha-ketoglutarate-dependent dioxygenase homolog 5 (ALKBH5) [14]. The methylated reading protein is capable of recognizing and binding the M6A-modified base, thereby recruiting the RNA into a specialized protein complex. This process influences the metabolic pathway of RNA and regulates the expression of target genes. The previously identified m6A recognition protein harbors the YT521-B homology (YTH) domain, encompassing YTHDF1, YTHDF2, YTHDF3, YTHDC1, and YTHDC2. These proteins play a pivotal role in facilitating mRNA degradation. The insulin-like growth factor 2 mRNA binding protein (IGF2BP), including IGF2BP-1, IGF2BP-2, and IGF2BP-3, is also a methylated RNA-binding protein. In contrast to the YTH domain family proteins, IGF2BP enhances mRNA stability and promotes protein translation[15].The present article provides a comprehensive review on the pivotal role of m6A-modified proteins in the initiation and progression of GC.

2. Research Progress of M6A Methylation and GC

With the continuous advancement of science and technology, our comprehension of m6A methylation modification has progressively deepened. Through intricate mechanisms, m6A modification exerts a certain impact on the occurrence and progression of GC.

2.1 M6A Methyltransferase and GC

The role of ADAMTS9 as a downstream regulator of METTL3 in GC has been demonstrated by multiple studies, highlighting its ability to activate the PI3K/AKT pathway and drive the progression of GC[16]. METTL3-mediated m6A modification of lncRNA SNHG3 accelerates GC progression by regulating the miR-186-5p/cyclinD2 axis[17]. The miR-181-5p/KLHL5 complex facilitates the proliferation, migration, and invasion of GC cells by modulating METTL3 to activate the m6A process[18]. The WTAP-mediated FAM83H-AS1 facilitates GC development through m6A modification, thereby offering a novel biomarker for the diagnosis and targeted therapy of GC[19]. The oncogenic role of KIAA1429 in GC is mediated by its ability to stabilize c-Jun mRNA, independent of m6A modification[20]. Studies have demonstrated that METTL16 can contribute to the promotion of GC by augmenting the stability of cyclin D1 mRNA[21]. These findings suggest that certain m6A methyltransferases play a role in promoting the initiation and progression of GC, thus necessitating further investigation into their mechanisms of action within this context.

The expression of METTL14 led to an increase in the m6A methylation level of circORC5 and a subsequent inhibition of its expression. This resulted in the up-regulation of miR-30c-2-3p and down-regulation of AKT1S1 and EIF4AB, ultimately leading to the suppression of GC progression[22]. The METTL14 protein serves as a prominent regulator of aberrant m6A modification in GC, exerting its tumor suppressor role by deactivating the PI3K/AKT/mTOR pathway and modulating the EMT pathway, thereby impeding GC cell progression and invasion[23]. The findings suggest that the m6A methyltransferase METTL14 exerts inhibitory effects on GC, indicating its potential as a promising biological target with significant implications in GC.

2.2 M6A Demethylase and GC

The M6A demethylase FTO has the ability to enhance PI3K/AKT signal transduction, thereby facilitating GC progression. Consequently, FTO serves as a valuable prognostic biomarker for GC[24]. The FTO enzyme also facilitates caveolin-1 mRNA degradation through demethylation, regulates mitochondrial fission/fusion and metabolism, and enhances GC proliferation and metastasis[25]. According to Hu et al., PKMYT1 is identified as the downstream target gene of ALKBH5, which undergoes m6A modification and can subsequently be recognized and bound by the “reader” protein IGF2BP3. This interaction leads to enhanced mRNA stability and increased expression levels of PKMYT1, ultimately resulting in a significant promotion of GC metastasis[26]. The diverse findings imply the necessity for further investigation into the mechanisms of various m6A demethylases in GC, aiming to offer novel insights and targets for clinical management of stomach malignancies.

2.3 M6A Reading Protein and GC

Chen et al. discovered that PLAGL2 enhances the expression of Snail and promotes GC progression through the UCA1/miR-145-

5p/YTHDF1 pathway, indicating that targeting PLAGL2 could be a potential therapeutic strategy for GC therapy[27]. The overexpression of YTHDF1 in GC is associated with a pro-tumor role. Loss of YTHDF1 leads to the upregulation of IFNGR1 and activation of JAK1/2-STAT1 pathways in tumor cells, potentially restoring sensitivity to anti-tumor immune responses. Targeting YTHDF1 can enhance adaptive anti-tumor immunity, thereby facilitating effective immunotherapy for GC[28]. The study conducted by Shen et al. demonstrated that YTHDF2 exerts inhibitory effects on the growth of GC cells through negative regulation of FOXC2, thus suggesting its potential as a prognostic marker for GC[29]. The m6A reader IGF2BP2 binds to and stabilizes CSF2 mRNA in GC MSCs, while CSF2 induces Notch1 ubiquitination for the reprogramming of MSCs[30].

3. Progress in the Clinical Treatment of M6A Methylation and GC

Chemotherapy plays a pivotal role as a non-surgical therapeutic modality for patients diagnosed with GC. Current research endeavors in the field of m6A modification in GC predominantly revolve around unraveling mechanisms underlying chemotherapy resistance. Wang et al.'s study demonstrated that knockdown of METTL3 induced apoptosis in oxaliplatin (OXA)-resistant GC cells and significantly inhibited the DNA repair pathway. Therefore, targeting METTL3 could potentially enhance the efficacy of oxaliplatin in treating GC[31]. The promotion of KIAA1429 enhances the resistance of GC cells to OXA by facilitating the stabilization of FOXM1 mRNA[32]. Zhu et al. discovered that KIAA1429 was upregulated in cisplatin-resistant GC cells, and its regulation of GC cell sensitivity to cisplatin was mediated through the stabilization of FOXM1 mRNA, providing supporting evidence for potential therapeutic strategies[33]. Liu et al. discovered that WTAP plays a crucial role in accelerating TGF-β signaling, thereby promoting the epithelial mesenchymal transition (EMT) of GC cells and conferring enhanced resistance to chemoradiotherapy. Consequently, WTAP exhibits promising potential as a predictive biomarker for GC[34].

4. Summary and Prospect

Currently, numerous studies have demonstrated the dual regulatory role of m6A modification in GC. The modulation of m6A modification levels can either facilitate or impede the progression of GC. The m6A modification system, comprising a diverse array of regulatory proteins, is intricately associated with GC. Although significant advancements have been made in current research, there remains a substantial gap in fully elucidating the complete picture, warranting further investigation.

In conclusion, the investigation of m6A modification and regulatory proteins presents a novel concept for the diagnosis, prognosis, and treatment of GC, thereby paving the way for exploring its underlying mechanisms. Anticipated advancements in clinical studies are expected to facilitate its application in medical practice, benefiting a substantial number of patients with GC.

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Conflict Of Interest

The researchers affirm that the study was carried out without any affiliations or financial associations that could be interpreted as a possible source of conflict of interest.

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