Biomedical Research and Reviews

Review Article ISSN: 2515-9186

The role of m6A modification in gastric cancer

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Abstract

m6A modification is one of the most abundant RNA modifications, which is a dynamic and reversible process. Methyltransferase catalyzes the methylation of adenosine acid on mRNA, dimethyl-transferase removes methyl, and m6A methyl binding protein specifically binds to m6A methylation modification of mRNA. m6A modification is involved in all aspects of RNA metabolism, such as RNA processing, splicing, nuclear output, decay, etc. m6A modification provides more possibilities for tumor treatment. In this review, we focus on the mechanism and function of m6A modification in the development of gastric cancer and summarize the application prospect of m6A modification in the treatment of gastric cancer.

Introduction

The latest international cancer data show that the incidence rate and mortality of gastric cancer rank fifth and fourth in the world's total incidence rate and mortality of cancer [1]. At present, the treatment of gastric cancer includes surgery, chemotherapy, radiotherapy, molecular targeted therapy, etc. [2]. These treatment measures provide more choices for patients with gastric cancer at different stages, but the 5-year survival rate of patients with gastric cancer is still not optimistic, only 35.1% [3]. Finding the key target of gastric cancer treatment is an important method to improve the prognosis of gastric cancer. However, the genesis and development mechanism of gastric cancer is a complex process of multifactorial and polygenic regulation, it is an urgent problem to deeply study the mechanism of gastric cancer genesis and development.

In recent years, with the development of high-throughput sequencing technology, the role of m6A modification in the pathophysiology of the body has been widely concerned; m6A modification is mainly composed of methyltransferase (m6A writer), demethyltransferase (m6A eraser) and binding protein (m6A reader). m6A modification regulates the occurrence, development, metastasis, chemotherapy resistance and other malignant biological behaviors of tumors by participating in the whole metabolic process of mRNA, such as splicing, fading and translation. Therefore, this article has clarified the molecular mechanism of gastric cancer from the perspective of m6A modification in the existing literature, aiming to further clarify the mechanism of gastric cancer from the perspective of post transcriptional modification, in order to provide new ideas for exploring potential therapeutic targets of gastric cancer.

Biological characteristics of m6A modification

m6A modification was first discovered in the 1970s [4,5], mainly referring to the methylation modification on the 6th carbon atom of adenine (A) base in RNA [6], which is the most common methylation modification in eukaryotes [7]. Previous studies have shown that it participates in the whole process of RNA, such as RNA translation, splicing, degradation, nuclear output etc. [8]. In recent years, with the rapid development of new technologies, especially the emergence of high-throughput sequencing technology, it has been found that m6A is mainly distributed in the protein coding region, near the terminator and 3' noncoding region [6,8]. With the discovery and further study of m6A demethylase FTO and ALBKH5, researchers found that the function of m6A RNA methylation modification in the body is a reversible and dynamic process. m6A modification consists of methylation catalyzed by methyltransferase, methyl removal by demethylase and specific recognition of m6A by methyl binding protein. Recent studies have found that m6A methylation modification can play an important role in tumor progression by regulating tumor proliferation and differentiation, invasion, metastasis, chemotherapy resistance and other malignant biological phenotypes [9-13].

m6A modification and proliferation of gastric cancer

SOCS2 is a member of the SOCS family that regulates intracellular signaling pathways induced by various cytokines and participates in the regulation of many biological processes, including immune response. METTL3 inhibits the expression of SOCS2 and promotes the proliferation of gastric cancer [14]. METTL16 mediates the expression of cyclin D1, promotes the transformation of cell cycle G1/S, and promotes the proliferation of gastric cancer cells [15]. In gastric cancer cells, IGF2BP3 interacts with CircARID1A to promote gastric cancer proliferation. In mechanism, CircARID1A interacts with IGF2BP3 to promote the up regulation of IGF2BP3 on SLC7A5. SLC7A5 regulates the expression of AKT/mTOR pathway [16]. YTHDF2 is low expressed in gastric cancer and is positively correlated with clinical prognosis. It inhibits the growth of gastric cancer cells by negatively regulating FOXC2 [17].

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Key words: *m6A, gastric cancer, chemotherapy resistance, invasion, metastasis*

Received: December 22, 2022; **Accepted:** January 17, 2023; **Published:** January 25, 2023

m6A modification, invasion and metastasis of gastric cancer

An important reason for poor prognosis of gastric cancer after surgery is metastasis of gastric cancer, especially in advanced gastric cancer, which is often an important reason for failure of surgery or secondary surgery. METTL3 is an important m6A writer, which is highly expressed in gastric cancer and is associated with poor prognosis [18]. ZYM1 is an important target of METTL3. METTL3 enhances its stability by m6A modification of ZYM1 mRNA through reader protein HuR dependent pathway. ZYM1 promotes the metastasis of gastric cancer by recruiting CtBP/LSD1/CoREST complex to bind, mediating the inhibition of E-cadherin promoter [19]. Other studies showed that the expression of METTL3 was regulated by HOXA10, which promoted the progression and metastasis of gastric cancer through HOXA10/TGFB2/Smad/METTL3 signal axis [20]. On the one hand, METTL3 overexpression inhibits the activities of apoptosis related proteins Bax and Caspase-3, on the other hand, it activates the AKT signaling pathway in human gastric cancer cells, including the reduction of AKT phosphorylation level, the expression of downstream effectors p70S6K and Cyclin D1, and the activation of Hippo signaling pathway to promote gastric cancer metastasis [21,22]. The low expression of METTL14 in gastric cancer is a key regulatory factor leading to the decrease of m6A modification level in gastric cancer. The low expression of METTL14 activated PI3K/AKT/mTOR pathway and EMT pathway and promoted the proliferation and invasion of gastric cancer cells [23]. FTO is highly expressed in gastric cancer, especially in liver metastasis. FTO directly targets caveolin-1 mRNA and promotes its degradation. Caveolin-1 can inhibit mitochondrial respiration, leading to a decrease in ATP supplementation, thereby limiting the growth of cancer cells. These results indicate that FTO can promote the proliferation, invasion and metastasis of gastric cancer by regulating mitochondrial division/fusion and metabolism [24]. In addition, FTO can adjust the synthase by reducing the m6A level β1 (ITGB1) to promote GC transfer [25]. Compared with gastric cancer patients without distant metastasis, the expression of ALKBH5 in gastric cancer patients with distant metastasis is reduced. PKMYT1 is the downstream target of ALKBH5. ALKBH5 negatively regulates the expression of PKMYT1 in a m6A dependent manner, thereby promoting gastric cancer metastasis [26]. In addition, ALKBH5 can combine with NEAT1 to affect the expression of EZH2, thereby affecting GC invasion and metastasis [27]. m6A reader YTHDF1 promotes the translation of USP14 protein in a m6A dependent manner, promotes the tumorigenesis and metastasis of GC, and may be a potential target for gastric cancer treatment [28]. MYC is the direct target of IGF2BP3. IGF2BP3 regulates the expression of MYC in a m6A dependent manner, thereby promoting the metastasis of gastric cancer [29].

m6A modification and tumor microenvironment of gastric cancer

The microenvironment of tumor cell growth and survival plays a key role in tumor progression. The TME with low expression of m6A writer KIAA1429 has significantly increased immune cell infiltration, mainly increased dendritic cell infiltration in the tumor microenvironment. In addition, the low expression of KIAA1429 led to an overall increase in the expression of MHC molecules, costimulatory molecules and adhesion molecules. Gastric cancer with low expression of KIAA1429 is significantly enhanced in immune activation pathway, including antigen presentation and presentation pathway, C-type lectin receptor, NOD like receptor, tumor cell receptor, Toll like receptor and NF-κB signal transduction pathway, while the high expression of KIAA1429 shows the opposite effect [9]. METTL3 reduces the infiltration level of follicular helper T cells, memory activated CD4 T cells and M0 macrophages in the immune microenvironment by up regulating the expression of PD-L1, resulting in tumor cells effectively avoiding the immune recognition of the body [30]. The above results indicate that m6A modification achieves anti-tumor immunity by influencing the immune infiltration of gastric cancer microenvironment.

m6A modification and drug resistance of gastric cancer

Heterogeneity of tumor cells is the main reason for failure of chemotherapy, and gastric cancer is a highly heterogeneous tumor. In oxaliplatin resistant gastric cancer tissues, the expression of CD133 is increased. $CD133^+$ gastric cancer cells have the characteristics of tumor stem cells. PARP1 is the central gene of $CD133^+$ cells. PARP1 stabilizes the stability of $CD133^+$ tumor stem cells. PARP1 mediates oxaliplatin resistance through DNA damage repair and BER pathway. m6A writer METTL3 promotes CD133's resistance to oxaliplatin by stabilizing and promoting the expression of PARP1 [31]. KIAA1429 modifies FOXM1 m6A through the m6A modification site on 3′UTR of FOXM1 mRNA to enhance the stability of FOXM1 and mediate the chemoresistance of gastric cancer [32,33]. The high expression of FTO in gastric cancer reduces the m6A level in the CDS region and 3′UTR region of the tumor suppressor gene DDIT3 related to apoptosis downstream of mTORC1 signal transduction and promotes chemotherapy resistance of gastric cancer [34]. YTHDF1 inhibits the recruitment of mature dendritic cells by increasing the infiltration inhibitor of immune cells from bone marrow and inhibits the systemic anti-tumor immune response leading to chemotherapy resistance of gastric cancer [35]. HnRNPA2B1 regulates the expression of cancer stem cell marker CD44 in gastric cancer and affects the phenotypic function of gastric cancer stem cells. HnRNPA2B1 regulates the selective splicing of BIRC5, reduces apoptosis, increases cell migration and chemoresistance [36].

Conclusion and future directions

RNA epigenetics is a research hotspot in recent years. m6A modification is one of the most abundant RNA modifications and affects RNA transcription, splicing and processing. m6A modification is a double-edged sword in cancer. The role of m6A modification in some genes may lead to changes in mRNA behavior and expression and promote tumor development, while the lack of m6A modification in other genes will also lead to tumor progression.

The important role of m6A modification in the occurrence and development of gastric cancer provides a new possibility for the treatment of gastric cancer. Studies have shown that the high expression of METTL3 promotes tumor angiogenesis and glycolysis in gastric cancer. Therefore, targeting METTL3 can inhibit tumor angiogenesis and glycolysis, exacerbating the hypoxia and ATP supply of tumor cells, so as to achieve the purpose of tumor treatment [37]. In addition, it is reported that targeting YTHDF1 small cell vesicles inhibits frizzled7 (FZD7) translation and inactivates Wnt in an m6A dependent manner/β-Catenin pathway effectively reduces YTHDF1 expression and mediates interferon (IFN)- γ Overexpression of receptor 1 (IFNGR1) and enhancement of IFN-γ Response, promote the expression of major histocompatibility complex class I (MHC-I) on tumor cells, so as to realize the self-presentation of immunogenic tumor cells, thus stimulate the response of strong cytotoxic T lymphocytes (CTL), and promote the efficacy of immunotherapy [38].

However, there are still many challenges in the study of m6A modification. At present, the research on modification is still more focused on the mechanism of action and potential molecular markers, while the research on the relationship between m6A modification and gastric cancer from the perspective of targeted therapy is still relatively small. At present, there are still some problems in the research of m6A

modification: the regulatory network of m6A modification in cancer is still unclear; The specificity and sensitivity of m6A modification as a tumor marker have not been verified; The clinical value of m6A modification in tumors has not been studied. It is urgent for researchers to carry out more in-depth research to clarify the precise regulatory network of m6A modification in gastric cancer, to take a significant step forward for human to conquer tumors.

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