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Clinical Application of M6A in Cervical Cancer and Precancerous Lesions

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Abstract: N6-methyladenosine (m6A) is a key epigenetic modification in eukaryotic RNA. Studies in cervical cancer reveal that m6A levels and its modifying enzymes may serve as promising molecular markers for tumor progression monitoring and precision diagnosis. This paper aims to explore the relationship between Writer (methyltransferase), ERASERS (desmethyltransferase), Readers (recognition proteins) and cervical cancer cell molecules In m6A methylation modification, which are the regulators of m6A methylation modification, to provide new perspectives and strategies for the clinical diagnosis and treatment of pre-cancerous cervical lesions and cervical cancer. Modulating its expression *in vivo* may enhance cervical cancer cells' radiotherapy sensitivity, potentially addressing chemotherapy resistance and improving therapeutic outcomes for advanced-stage cases.

Keywords: Cervical cancer; m6A; Methylation; Precancerous lesion

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1. Introduction

According to research data, cervical cancer (CC) is the 4th most prevalent malignant tumor among women worldwide [1]. In 2020, WHO launched the Cervical Cancer Elimination Initiative, aiming to reduce global incidence below 4 cases per 100,000 women-years by 2030. The initiative's 90–70–90 targets require: 90% HPV vaccination coverage for girls by age 15, 70% high-performance screening for women by age 45, and 90% treatment for those with cervical precancer or cancer [2]. In order to achieve this goal, the WHO has taken active measures: on the one hand, vigorously promote human papillomavirus (HPV) vaccination to radically reduce the incidence of cervical cancer. On the other hand, strengthen the early screening of cervical cancer, through cervical cytology or HPV testing and other means, to timely detect and deal with pre-cancerous cervical lesions, to prevent further malignant changes.

Cervical cancer is mainly attributed to the persistent infection of high-risk HPV, and its pathogenesis has not been clarified after extensive research. While the underlying mechanisms of cervical cancer remain incompletely understood despite decades of study, emerging evidence identifies RNA modification as a critical mechanism in gene regulation. Among over 170 identified RNA epigenetic modifications, N6-methyladenosine (m6A) has emerged as a focus due to its reduced levels being closely linked to cervical cancer initiation and progression, positioning m6A as a potential diagnostic and therapeutic target [3,4]. m6A is co-regulated by Writers (methyltransferases), ERASERS (demethyltransferases) and Readers (recognition proteins) [5]. Studies have shown that this methylation modification plays a crucial role in regulating tumorigenesis and progression [6]. After an in-depth analysis of the literature, we found that many m6A regulators play important roles in cervical cancer, such as METTL3, METTL14, WTAP, FTO, ALKBH5, and so on. Therefore, the role of m6A modification regulators may be a very promising target for the prediction, diagnosis and prognosis of cervical cancer.

2. Overview of m6A methylation

The m6A modification refers to the methylation of the sixth N atom of adenine in adenine nucleotides in RNA molecules and is an important part of RNA regulation [7]. N6-methyladenosine (m6A), first identified in 1974, is the most prevalent RNA epigenetic modification and the predominant internal RNA structural alteration in eukaryotic cells [8,9], which is closely associated with cervical carcinogenesis, progression, immune invasion, drug sensitivity and prognosis [10]. m6A writers, erasers, and readers collaboratively drive tumor progression through regulation of RNA stability, nuclear export, translation efficiency, and degradation [11]. They affect different pathways, which in turn affect various life activities of the organism.

2.1. m6A-related regulatory factors

2.1.1. m6A methylase (Writers)

Writers are enzymes responsible for adding m6A methylation to RNA molecules, and the major m6A writer enzymes include METTL3, METTL14 and WTAP.METTL3 usually forms a complex with METTL14 protein and participates in the m6A methylation process together [12–15]. METTL14 regulates the substrate specificity of METTL3 through its RNA-binding domain, which results in the synergistic catalytic methylation reaction of METTL3, enhanced catalytic activity and has a certain effect on the localization of m6A modification [13,16]. Knockdown of METTL14 by SiRNA attenuated the proliferation, migration and invasion of cervical cancer cells [17,18]. WTAP, a key cofactor in the m6A writers complex, precisely regulates the catalytic activity of the complex on RNA by modulating the nuclear localization of METTL3-METTL14. The RNA-binding ability of METTL3 was significantly decreased in the absence of WTAP, a finding that implies the role of WTAP in regulating the recruitment of the m6A methyltransferase complex to mRNA targets [19]. The presence of WTAP not only enhanced the activity of the METTL3-METTL14 complex but also increased the efficiency of m6A modification. This finding is crucial for understanding the role of m6A methyl modification in tumor biology, and in particular provides a plausible explanation for the influence of m6A modification on the occurrence and development of gynecological tumors such as cervical cancer.

2.1.2. m6A demethyltransferases (Erasers)

In the regulatory network of m6A methylation, Erasers-particularly FTO and ALKBH5-play crucial roles. FTO has

been implicated in human obesity and energy homeostasis, acting as an eraser in the regulation of m6A to mediate methylation reversal [20]. As demethylases, they regulate a variety of biological processes, including nuclear RNA export, RNA metabolism, and gene expression by eliminating m6A modifications on RNA. It was shown that knockdown of FTO using siRNA technology resulted in an increase in m6A content in mRNA, while overexpression of FTO resulted in a decrease in m6A content in human cells. This finding confirms that FTO regulates RNA m6A levels through its oxidative demethylation activity [21,22]. ALKBH5, a key m6A demethylase, enzymatically removes mRNA methylation modifications. This activity is critical for maintaining nuclear speckle integrity, regulating mRNA export and metabolism, and ensuring proper assembly of RNA processing machinery [23].

2.1.3. m6A recognition proteins (Readers)

The m6A methylated reading proteins (Readers) are a unique class of molecules that play a central role in cell biology by recognizing m6A marks on RNAs and participating in mRNA degradation, stability maintenance, and translation processes. Among many Readers, YTHDF1-3, YTHDC1-2, HNRNP, eIF3 and IGF2BP1 are of particular interest [24,25]. In particular, IGF2BP1 stabilizes RNA and boosts translation by recruiting RNA-binding proteins (ELAVL1, MATR3, PABPC1) to safeguard mRNA pools. Clinically, its overexpression correlates with poor cancer prognosis, while reduced levels disrupt cell cycle dynamics and suppress tumor progression. Experimental studies confirm that IGF2BP1 upregulation drives cellular proliferation, whereas its knockdown exerts inhibitory effects [26]. In addition to IGF2BP1, YTHDF1 is also a research hotspot.YTHDF1 promotes the translation and overall translation efficiency of EIF3C by binding to m6A-modified EIF3C mRNA, which in turn promotes tumor formation and metastasis and the up-regulation of its expression correlates with the poor prognosis of the patients. At the same time, the increase in protein expression of EIF3C is positively correlated with the protein expression of YTHDF1. suggesting that the modification of EIF3C mRNA has an important impact on its role in cancer [27].

These findings provide important clues to our understanding of the function of m6A methylation in tumor biology. By deeply investigating the mechanism of action of these Reader proteins, we are expected to find new cancer treatment strategies and bring a better prognosis to cancer patients (**Figure 1**).

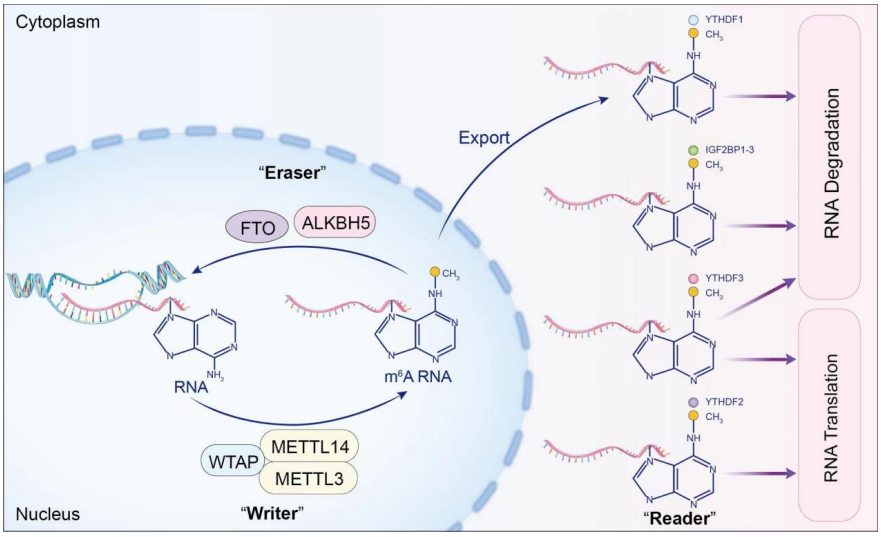

Figure 1. The m6A modification is a process that is both dynamic and reversible. It can be added to RNA by "writer"

proteins such as METTL3/14, WTAP, removed by “eraser” proteins like FTO and ALKBH5, and its function is regulated by “reader” proteins including YTHDF1-3, IGF2BP1-3, eIF3.

3. m6A regulation and prediction of cervical pre-cancerous lesions

Currently, research on RNA methylation in the field of precancerous cervical lesion prediction is still in its early stages and has not yet established a comprehensive and in-depth systematic research framework. Although the importance of RNA methylation in gene regulation and biological processes is increasingly recognized, its application value and mechanisms of action in predicting precancerous cervical lesions require further research. Existing studies mainly focus on descriptive analysis and preliminary functional validation, lacking large-scale clinical samples and in-depth mechanism research, which limits their extensive application and accuracy in prediction. Cervical cancer research is most extensively studied in terms of host cell modifications involving DNA methylation [28]. DNA methylation is found in both HPV and host cell genomes across all stages of cervical cancer development. Currently, analyzing host cell DNA methylation is primarily used to screen hrHPV-positive women for identifying cervical cancer and advanced CIN [29]. A study has shown that DNA methylation testing has high diagnostic accuracy and specificity for CIN2+ lesions, indicating its promise as a screening tool for hrHPV-positive women and even as an independent method for precancerous cervical lesions [30]. The level of DNA methylation of CADM1 (a tumor suppressor gene) increases with the severity of cytological abnormalities, with a significant increase of 3.37 times compared to NILM, and CADM1 methylation performs well in distinguishing histologically HSIL+ from negative/LSIL, with an area under the ROC curve of 0.684 [31]. DNA methylation shows significant value in detecting precancerous cervical lesions and assessing progression risks. Currently, DNA methylation test kits are used clinically to screen for low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL) [32]. Through these examples, we can imagine that during the development of cervical cancer, m6A methylation may also play a hidden but crucial role. It may affect the growth and spread of tumors through specific molecular mechanisms. A study detected two different m6A modification patterns in 306 cervical cancer patients, named m6Acluster A and B, respectively, and the results showed that these two patterns have different immune cell infiltration characteristics and biological behaviors, which may be related to the immune monitoring of precancerous lesions [33]. In summary, m6A methylation has the potential to become a powerful predictive tool, providing key clues for the early detection and intervention of cervical cancer. More research is needed in the future to fill the gaps in this field and establish a systematic research system from molecular mechanisms to clinical applications.

4. m6A regulation in cervical cancer diagnosis prospects

Research has found that the degree of methylation is consistent with the progression of cervical cancer. As the degree of the lesion increases, the degree of methylation also increases accordingly [34]. Ao *et al.* found that the expression of mortalin (heat shock protein (HSPA9)) was up-regulated in plasma isolated from patients with cervical cancer, and in addition, through the methylation of m6A in the 3′UTR of HSPA9 mRNA, mortalin gained higher mRNA stability and higher translational efficiency, this study demonstrated that METTL3-mediated mortalin has a role in the malignant transformation and cellular senescence inhibition in cervical cancer [33,35]. Mortalin shows promise as a latent-stage cervical cancer diagnostic biomarker. CircRNA profiling identified circCCDC134 (derived from

CCDC134) as overexpressed in cervical cancer. Its stability and upregulated expression are controlled through YTHDF2-dependent, ALKBH5-mediated m6A modification, highlighting its role in metastatic dysregulation [36], the ALKBH5-driven m6A dynamics of circCCDC134 position it as a novel molecular target for cervical cancer management.

In summary, m6A modification is critical in the progression, development, and spread of cervical cancer. Further exploration of its regulatory mechanisms and functional roles in cervical cancer could drive the development of novel diagnostic tools and therapeutic approaches, ultimately enhancing outcomes for patients with cervical cancer.

5. m6A regulation and cervical cancer treatment

IGF2BP1, an oncofetal protein in the m6A methylated reading protein family and expressed in various cancers, when inhibited, reduces tumorigenicity, promotes myeloid differentiation, increases cell death, enhances chemosensitivity, and affects leukemia cell proliferation by regulating HOXB4, MYB, and ALDH1A1 expression. Research indicates that IGF2BP1 maintains leukemia stem cell properties by modulating multiple stemness pathways through transcriptional and metabolic factors [37]. The small molecule ALKBH5 inhibitor ALK04, along with METTL3 and METTL14 inhibitors, has been shown to significantly enhance the efficacy of immunotherapy and immune checkpoint inhibitors [38]. Tumors' m6A expression profiles hold significant potential for differentiating immune profiles, which supports personalized immunotherapy approaches for cancer patients [39]. Studies have shown that FOXD2-AS1 is significantly elevated in cervical cancer cells and tissues and is closely linked to poor prognosis. It accelerates cervical cancer progression by enhancing stability via METTL3 and attracting lysine-specific demethylase 1 (LSD1) to the p21 promoter, thereby reducing p21 expression. [40]. Overall, these findings provide new insights into the therapeutic strategy of m6A in cervical cancer.

Tumor microenvironment (TME) directly determines patient prognosis and treatment efficiency, and m6A modifications play an important role in the formation of TME diversity and complexity. Evaluating m6A modification patterns will help enhance our knowledge of TME infiltrate characterization and guide more effective immunotherapy strategies [41]. In the treatment of highly aggressive cancers, targeting tumor cells alone may have a limited effect because tumors have adapted to their microenvironment. According to studies, modulation of m6A has an important role in influencing the tumor immune microenvironment and secretion by tumor mesenchymal stromal cells, suggesting that intervening in the tumor microenvironment may provide additional therapeutic benefits [42]. This suggests that modulating m6A has great application prospects in the intervention of tumor microenvironment. Thus, exploring TME in cervical cancer could help to find key subpopulations associated with tumor immune responses and provide clues for optimizing treatment regimens. However, studies investigating the association between m6A and TME with cervical cancer are still at an early stage. Other studies have indicated that TME is linked to m6A methylation regulators, and variations in their copy number dynamically influence the number of immune cells infiltrating the tumor [43,44].

The Warburg effect, also known as aerobic glycolysis, is a defining feature of cancer metabolism [45]. The Warburg effect, or aerobic glycolysis, is a key feature of cancer metabolism. Despite sufficient cellular oxygenation, tumor cells do not use mitochondrial oxidative phosphorylation but aerobic glycolysis to produce energy [46]. METTL3 plays a key role in cancer development by targeting the 3'-untranslated region (3'-UTR) of hexokinase 2 (HK2) mRNA and recruiting the m6A reader YTHDF1 to enhance the stability of HK2, which promotes the Warburg effect and proliferation of cancer cells, This newly discovered mechanism provides new insights and potential

therapeutic strategies for understanding and treating cervical cancer [47]. The high expression of METTL3 indicates poor prognosis, and METTL3 enhances HK2 (hexokinase 2) stability through recruitment of YTHDF1, promoting proliferation and the Warburg effect in CC cells [48]. The m6A-modified HK2 mRNA is enhanced in stability by the YTHDF1 reader protein. Studies have shown that the HPVE6/E7/IGF2BP2/m6A-MYC/glycolysis axis is closely related to the development and progression of cervical cancer. E6/E7 proteins regulate the m6A modification of MYC mRNA through IGF2BP2 to promote aerobic glycolysis, proliferation and metastasis of cervical cancer cells, and IGF2BP2 expression in cervical cancer tissues is positively correlated with tumor stage [49].

Secondly, Yang *et al.* [47] found that ZFAS1 was significantly up-regulated in cervical cancer tissues by qRT-PCR, and the survival of patients with high expression was worse compared with those with low expression, and functional experiments showed that ZFAS1 promoted the proliferation, migration, and invasion of cervical cancer cells, and the mechanistic study showed that the interaction between ZFAS1 and miR-647 was regulated by METLL3-mediated m6A. These findings suggest that ZFAS1 may be an oncogene in cervical cancer and serve as a potential therapeutic target [47]. Taken together, m6A modification provides a new perspective on the regulation of the Warburg effect by regulating the stability of key metabolic enzyme mRNAs and the expression of genes that are closely related to the development of cervical cancer, for example, through the E6/E7 proteins and ZFAS1, which may provide novel strategies for the treatment of cervical cancer.

These findings enhance our insights into m6A methylation and its regulatory mechanisms, while also identifying novel targets for cervical cancer diagnosis and treatment, offering hope for more effective treatment strategies.

6. m6A detection of cervical cancer prognosis and recurrence

Numerous studies have shown that m6A RNA modifications are associated with the development of cervical cancer, but strong support is lacking in determining recurrence and prognosis. HPV infection is highly correlated with the development of cervical cancer [50]. HPV E6/7 proteins influence m6A modification, with E7 specifically boosting ALKBH5 expression, which is up-regulated in cervical cancer. ALKBH5 promotes cancer cell malignancy, playing a key role in cervical cancer progression [51]. Therefore, m6A demethylase ALKBH5 can be used as a prognostic biomarker for cervical cancer patients. Ji *et al.* [39] using The Cancer Genome Atlas (TCGA) and Genotype Tissue Expression (GTEx) databases, identified a strong predictive signature based on m6A RNA methylation regulators, which showed that PD-L1 expression was significantly increased in cervical cancer tissues, and that METTL16, YTHDF1, and ZC3H13 were independent prognostic indicators for cervical cancer. Some studies suggest that METTL3 may be a potential prognostic biomarker for cervical cancer [52]. Studies show that METTL3 drives the malignant progression of cervical cancer by regulating TXNDC5 expression.METTL3 was significantly up-regulated in cervical cancer tissues and cells, which was strongly associated with lymph node metastasis and poor prognosis of patients with cervical cancer. METTL3 recruited YTHDF1 to regulate the stability of HK2 mRNA, accelerated glycolysis through the YTHDF1/HK2 axis, and contributed to the development of cervical cancer. glycolysis, providing a potential biomarker for cervical cancer prognosis [47]. The m6A “reader” is the m6A “reader” YTHDF1 promotes proliferation, migration and invasion of cervical cancer cells. RANBP2 was identified as a key YTHDF1 target in cervical cancer cells by analyzing the combined online data of RIP-seq, meRIP-seq and Ribo-seq after YTHDF1 knockdown. target, YTHDF1 regulates RANBP2 translation in an m6A-dependent manner and plays an important role in cervical cancer, and YTHDF1 may be a potential target for cervical cancer therapy . The eukaryotic translation initiation factor 3 (eIF3) is the largest eukaryotic translation initiation factor (eIF) discovered to date.

Among them, eIF3b, as a key subunit, is highly expressed in various human malignant tumors and can be connected through m6A mediation. A retrospective study of 187 patients with cervical squamous cell carcinoma who underwent tumor resection and immunohistochemistry found higher EIF3B expression in tumor tissues than in adjacent tissues (45.5% vs. 32.1%, P=0.015). EIF3B overexpression was linked to higher FIGO stages in these patients. Stage, lymph node metastasis and unfavorable survival in cervical cancer patients. In summary, m6A RNA methylation regulators are key players in the malignant progression of cervical cancer and have a potential role in postoperative recurrence and prognosis.

7. Summary and outlook

Cervical cancer, a gynecological malignancy with high incidence and mortality, has long posed a threat to women's health. As research into m6A methylation's role in tumors deepens, its close link to cervical cancer has become apparent. m6A methylation plays a significant role in cervical cancer's development and progression, and detecting its expression levels offers a new approach for early diagnosis. Moreover, the mechanism of m6A methylation modification holds promise as a potential therapeutic target for cervical cancer. By regulating its expression level in the human body, it is expected to improve the sensitivity of cervical cancer cells to radiotherapy, providing new possibilities for solving the problem of chemotherapy resistance as well as the treatment of advanced cervical cancer. This discovery brings light to the treatment of cervical cancer. However, despite the great potential of m6A methylation in cervical cancer, its application in large-scale clinical practice is still in its infancy. Further research and validation are needed to ensure its safety and efficacy. In the future, we should continue to carry out relevant studies in large-scale populations to apply m6A methylation more widely in the early detection, diagnosis and prognostic assessment of cervical cancer. With the continuous progress of medical scientific research, we expect that m6A methylation will bring a revolutionary change to the clinical treatment of cervical cancer in the near future. Through early detection and effective treatment, we expect to delay the occurrence and recurrence of cervical cancer and provide patients with more opportunities for treatment, thereby reducing the national healthcare burden and bringing health to more women. If cervical cancer can be controlled at the pre-cancerous stage (cervical high-grade lesion stage) through m6A methylation testing, and patients can receive timely intervention and treatment, the desire to reduce or even eliminate cervical cancer globally is within reach.

Disclosure statement

The author declares no conflict of interest.

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