



Epitranscriptomic Regulation via m⁶A: The Roles of METTL3 and YTHDF1 in Cervical Cancer Progression and Prognosis



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ABSTRACT

Background: Cervical cancer is a leading cause of female morbidity and mortality globally, with the greatest burden in low- and middle-income countries. The limitations of conventional biomarkers in reflecting tumor molecular dynamics drive the search for more precise prognostic biomarkers. Epitranscriptomic modification of N6-methyladenosine (m⁶A) is a promising molecular approach in uncovering post-transcriptional regulation of RNAs that play an important role in cancer progression.

Objective: This article aims to explore the role of METTL3 and YTHDF1, two key components in the m⁶A system as prognostic and predictive biomarkers in cervical cancer.

Methods: This review utilized a narrative and structured literature review approach. Literature was obtained from scientific databases such as PubMed, ScienceDirect, SpringerLink, and Google Scholar, with inclusion criteria including articles within the last 10 years relevant to METTL3, YTHDF1, m⁶A, and cervical cancer.

Results: METTL3 acts as a major m⁶A writer that enhances the stability and translation of oncogenic mRNAs, and activates proliferative and EMT pathways, thus enhancing tumor aggressiveness. Meanwhile, YTHDF1 as an m⁶A reader facilitates the translation of pro-tumor proteins and immunosuppressive factors that suppress antitumor immune responses. Co-expression of METTL3 and YTHDF1 showed significant correlation with tumor progression, therapy resistance, and decreased patient survival.

Conclusion: Epitranscriptomic regulation through m⁶A modification mediated by METTL3 and YTHDF1 plays an important role in cervical cancer progression with cancer cell proliferation and invasion. Elevated levels of METTL3 and YTHDF1 lead to poor prognosis in cervical cancer

Keywords: METTL3, YTHDF1, m⁶A, Epitranscriptomics, Cervical Cancer.

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INTRODUCTION

Cervical cancer remains one of the leading causes of morbidity and mortality among women, accounting for 20% of the global cancer burden. Worldwide, it ranks as the fourth most common cancer in women, with an estimated 660,000 new cases in 2022. In the same year, approximately 94% of the 350,000 deaths due to this disease occurred in low- and middle-income countries.¹ The majority of cases are diagnosed at advanced stages (IIB to IV) due to delayed detection, resulting in reduced chances of curative treatment.² Despite widespread implementation of cytology-based screening programs, HPV DNA detection, and vaccination, challenges persist because of biological variability among patients and the lack

of sensitive molecular indicators to accurately assess disease progression and prognosis.³ Currently, clinical prognosis assessment still relies on conventional parameters such as FIGO stage, tumor size, and lymph node involvement.⁴ However, these parameters do not always accurately reflect the molecular dynamics of the tumor. Therefore, there is an urgent need to identify precise, prognostic molecular biomarkers that better represent the biological aggressiveness of cervical cancer.

One rapidly evolving molecular approach is the study of epitranscriptomics, which focuses on chemical post-transcriptional modifications of RNA that do not alter nucleotide sequences but significantly affect gene expression.⁵ The

most common and significant modification is N6-methyladenosine (m⁶A), which involves the addition of a methyl group to the nitrogen-6 position of adenosine in mRNA.⁶⁻⁸ The m⁶A modification is dynamic and reversible, playing a critical role in regulating mRNA fate, including stability, translation efficiency, alternative splicing, and degradation.⁹⁻¹¹ Dysregulation of the m⁶A system has been linked to various pathological processes, including carcinogenesis and tumor progression.^{12,13}

Within the m⁶A regulatory system, three main groups of proteins exist: writers, erasers, and readers.^{14,15} Among the writers, methyltransferase-like 3 (METTL3) is the primary catalyst for adding m⁶A marks to target mRNAs.¹⁶

METTL3 has been reported to act as an oncogene in multiple cancer types, including cervical cancer, by enhancing methylation of oncogenic mRNAs such as MYC, CCND1, and SOX2.^{17–19} METTL3 overexpression is known to promote cancer cell proliferation, invasion, and resistance to apoptosis through activation of the PI3K/AKT and Wnt/ β -catenin pathways, making it a promising candidate as a prognostic biomarker and molecular therapeutic target.^{20–22}

Conversely, YTH N6-methyladenosine RNA binding protein 1 (YTHDF1) is one of the main readers in the m⁶A system, recognizing and binding mRNAs methylated by METTL3 and enhancing their translation efficiency.^{23–25} YTHDF1 contributes to increased expression of pro-tumor proteins, including Snail, eIF3C, and VEGF-A, which are involved in proliferation, angiogenesis, and immunosuppression.^{26–29} High YTHDF1 expression correlates with tumor aggressiveness, poor therapeutic response, and lower survival in various cancers, including cervical cancer.³⁰

Given the synergistic mechanism between m⁶A writers and readers, co-expression of METTL3 and YTHDF1 shows great potential as a combined biomarker for cervical cancer prognosis. They not only reflect the molecular status of aggressive tumors but also may predict disease progression, clinical risk stratification, and response to molecular or immunotherapy. Exploring METTL3 and YTHDF1 as epitranscriptomic biomarkers offers a novel approach to precision oncology-based management of cervical cancer.

METHOD

This article was written using a narrative and structured literature review approach. Literature searches were systematically conducted using Boolean logical operators “OR” and “AND” to combine relevant keywords, including: “METTL3,” “YTHDF1,” “m⁶A,” “N6-methyladenosine,” “cervical cancer,” “epitranscriptomic regulation,” “tumor progression,” and “prognosis.” Some keyword combinations used in the searches included (“METTL3” OR “YTHDF1”), (“m⁶A” AND “cervical cancer”), and

(“epitranscriptomic regulation” AND “prognosis”). Literature was retrieved from reputable scientific databases such as PubMed, ScienceDirect, SpringerLink, and Google Scholar to ensure quality and relevance of sources for discussion.

Inclusion criteria were established based on the PICO framework, comprising: population of cervical cancer patients; intervention involving investigation of METTL3 and YTHDF1 roles in epitranscriptomic regulation via m⁶A modification; comparison against other biomarkers or differences in expression and functionality within cancer tissue; and outcomes regarding the impact of m⁶A regulation on tumor progression and clinical prognosis. References were limited to articles published within the last ten years (2015–2025), available in English and sourced from indexed, peer-reviewed scientific journals.

Exclusion criteria included non-peer-reviewed literature (such as opinion pieces or case reports without in-depth analysis), articles published before 2015, and publications that did not explicitly address the roles of METTL3, YTHDF1, or m⁶A regulation in the context of cervical cancer. Applying these selection criteria ensured the included sources had high scientific validity and relevance to the review topic, while minimizing selection bias in the literature analysis.

RESULT AND DISCUSSION

Mechanism of m⁶A and Epitranscriptomic Regulation

N6-methyladenosine (m⁶A) epitranscriptomic modification is the most abundant RNA modification in eukaryotic mRNA and plays a critical role in dynamically and reversibly regulating post-transcriptional gene expression.^{31,32} m⁶A occurs through methylation at the nitrogen-6 position of adenosine and functionally influences various aspects of RNA metabolism, including processing, splicing, nuclear export, translation, and degradation.³³ This modification adds an additional layer of rapid and flexible genetic regulation, enabling efficient responses to physiological and pathological signals, such as stress adaptation, differentiation, and disease progression including cancer.³⁴

The fundamental m⁶A mechanism

is governed by three main groups of proteins known as “writers,” “erasers,” and “readers.”^{35,36} Writers are enzymatic complexes responsible for adding methyl groups to adenosine. This complex is centrally led by METTL3 (methyltransferase-like 3), together with METTL14 and adaptor components such as WTAP (Wilms’ tumor 1-associating protein).³⁷ Writers specifically act on the consensus motif RRACH (R = A/G, H = A/C/U) located mainly in the 3’ UTR and near stop codons, critical regions for protein expression regulation.³⁸ Meanwhile, eraser proteins like FTO (fat mass and obesity-associated protein) and ALKBH5 (alkB homolog 5) remove m⁶A modifications, indicating that this process is reversible and modulated in response to changes in the microenvironment or cellular stress.^{39,40} This highlights m⁶A’s dynamic nature as a modifiable epigenetic signal. The final component, the reader proteins, recognize and bind m⁶A sites, translating the chemical mark into biological outcomes. YTH domain-containing family proteins (e.g., YTHDF1, YTHDF2, YTHDC1) are the main readers involved in mRNA translation and stability.⁴¹ For instance, YTHDF1 facilitates the translation of m⁶A-marked mRNA by enhancing ribosome interaction, whereas YTHDF2 primarily promotes the accelerated degradation of modified mRNA. Thus, m⁶A signaling directs distinct transcript fates, either promoting translation or controlling mRNA turnover.⁴²

In the context of cancer, including cervical cancer, dysregulation of m⁶A mechanisms and its components has been shown to contribute to proliferation, invasion, metastasis, and therapy resistance. Liang et al. (2022) reported a correlation between elevated m⁶A levels and enhanced metastatic potential of cancer cells. Their study revealed that circCCDC134, stabilized by m⁶A modification via ALKBH5 and YTHDF2, promotes cervical cancer proliferation and metastasis by recruiting p65 and inhibiting miR-503-5p, making it a potential therapeutic target.⁴³ Lin et al. (2022) demonstrated that m⁶A modification mediated by ZC3H13 enhances CENPK mRNA stability,

whose expression correlates with cancer stemness and chemoresistance in cervical cancer. CENPK activates the Wnt/ β -catenin pathway and suppresses p53, thereby strengthening tumorigenic traits, worsening prognosis, and serving as a promising therapeutic target and prognostic biomarker.⁴⁴ Du et al. (2023) found that m⁶A modification increases RAD51D translation via activation of the HNF1 α /YTHDF3 axis, significantly enhancing DNA repair and inducing radioresistance in cervical cancer. HNF1 α expression was elevated in radioresistant cervical cancer tissues, and its overexpression enhanced post-irradiation cell viability both in vitro and in vivo, while its knockdown reduced resistance ($P < 0.01$), highlighting this axis as a potential target to overcome radiotherapy failure.⁴⁵

METTL3 as an m⁶A Writer Promoting Cervical Cancer Cell Proliferation and Invasiveness

METTL3, the catalytic core of the m⁶A writer complex, cooperates with METTL14 and WTAP to add methyl groups to target mRNAs.⁴⁶ Its epitranscriptomic regulatory role has been linked to the development of various cancers, including cervical cancer. Guo et al. (2024) reported significantly elevated METTL3 expression in cervical cancer tissues compared to normal tissues based on TCGA-CESC, GSE63514, and GSE52903 database analyses, validated by qRT-PCR and immunohistochemistry (IHC) on 22 cervical cancer and 11 normal tissue samples. High METTL3 expression correlated significantly with FIGO stage ($P=0.004$), lymphovascular space invasion (LVSI) ($P=0.049$), lymph node metastasis ($P=0.013$), and reduced overall survival (OS) in Kaplan-Meier analysis.⁴⁷ This upregulation associates with aggressive clinical features including increased proliferation, invasion, and metastasis. METTL3 exerts its oncogenic role mainly by stabilizing and enhancing translation of oncogenic mRNAs such as MYC, SOX2, and EZH2.⁴⁸ The m⁶A marks installed by METTL3 are recognized by reader proteins like IGF2BP1/2/3, which protect mRNAs from degradation and boost translation efficiency, promoting oncogenic protein expression and tumor growth.⁴⁹

Additionally, METTL3 contributes to cell cycle deregulation by upregulating mRNAs of genes like CCND1 and CDK2, accelerating G1 to S phase transition and increasing cervical cancer cell proliferation. METTL3 also enhances invasiveness by activating epithelial-mesenchymal transition (EMT).⁵⁰ Hua et al. (2018) showed METTL3 induces EMT by increasing EMT transcription factors ZEB1, SNAIL, and VIMENTIN expression, while reducing E-cadherin levels by up to 50%. The study reported approximately 2-3-fold increases in ZEB1 and SNAIL, resulting in loss of cell-cell adhesion and 2.5-fold increased cancer cell motility, thus accelerating progression and metastasis.⁵¹ METTL3 also influences oncogenic signaling pathways such as PI3K/AKT and Wnt/ β -catenin by stabilizing mRNAs encoding pathway components, strengthening proliferative and pro-survival signals.⁵²

Knockdown of METTL3 reduces proliferation, migration, and invasion in cervical cancer cell lines. Guo et al. (2024) demonstrated that siRNA-mediated METTL3 knockdown in HeLa and SiHa cells significantly decreased cell viability by 30–50% (CCK-8 assay), reduced colony formation by up to 60%, and lowered proliferation activity by 40–60% (EdU assay). Transwell migration and wound healing assays showed 50–70% reductions in migration and invasion, while flow cytometry revealed increased apoptosis and G1 phase cell cycle arrest.⁵³ Su et al. (2022) further confirmed that METTL3 inhibition significantly suppressed tumor growth in vivo in a cervical cancer xenograft model. Subcutaneous injection of AGS cervical cancer cells with shRNA-mediated METTL3 knockdown into nude mice resulted in significantly smaller tumors after 21 days compared to controls (average tumor volume: 0.45 cm³ vs. 0.85 cm³, $p < 0.001$). Tumor weight was also reduced (0.35 g vs. 0.65 g, $p < 0.001$). METTL3 downregulation correlated with decreased Ki-67 proliferation marker and increased apoptotic markers Bax and Caspase 3, indicating enhanced tumor cell apoptosis.⁵⁴ These results establish METTL3 as a crucial epitranscriptomic regulator in cervical cancer progression.

YTHDF1 as an m⁶A Reader Enhancing Pro-Tumor Protein Translation and Immunosuppression

YTHDF1 is an m⁶A reader protein that plays a vital role in enhancing the translation efficiency of m⁶A-modified mRNAs. By binding m⁶A sites on specific mRNAs, YTHDF1 boosts translational output without altering transcript abundance.⁵⁵ Shi et al. (2025) reported that YTHDF1 knockdown in prostate cancer cells reduced RNF7 expression by 60%, increased p27 levels, and decreased proliferation by 45%. Loss of YTHDF1 also sensitized cells to cisplatin by 2.3-fold, highlighting its central role in translating pro-tumor proteins that support proliferation, invasion, and apoptosis resistance. This activity enhances tumor aggressiveness and disease severity.⁵⁶ Wang et al. (2021) found significantly elevated YTHDF1 expression in cervical cancer tissues compared to normal cervical epithelium. Data from cBioPortal and GEO datasets (GSE63514, GSE52904) identified YTHDF1 as the most upregulated m⁶A regulator in cervical cancer. Immunohistochemistry of 10 paired samples confirmed higher YTHDF1 protein levels in cancerous tissue, with elevated expression correlating with poor prognosis.⁵⁷

Beyond supporting intrinsic pro-tumor phenotypes, YTHDF1 modulates the tumor immune microenvironment by enhancing translation of immunosuppressive proteins.⁵⁸ YTHDF1 promotes expression of immune checkpoint molecules such as PD-L1 and factors that inhibit anti-tumor T cell activation and efficacy, thus suppressing host immune responses. Lin et al. (2023) showed that YTHDF1 significantly increased translation of lysosomal proteins accelerating MHC-I degradation, reducing antigen presentation by 60%, and decreasing CD8⁺ T cell infiltration by 50% within tumors. CRISPR/Cas9-mediated YTHDF1 suppression doubled T cell infiltration and reduced tumor growth by 70%, underscoring its crucial role in tumor immune evasion and immunotherapy resistance.⁵⁹ Jang et al. (2025) demonstrated YTHDF1's role in creating an immunosuppressive tumor microenvironment by enhancing

translation of IRF1 mRNA, resulting in over 50% decreased IRF1 protein expression in gastric cancer models. YTHDF1 knockdown increased CD8+ T cell infiltration 2.5-fold, indicating its function in suppressing anti-tumor immunity and facilitating immune escape.⁶⁰

METTL3–YTHDF1 Axis: Synergistic Epitranscriptomic Interaction and Potential as Prognostic Biomarkers and Predictors of Therapeutic Response in Cervical Cancer

The interaction between the writer METTL3 and the reader YTHDF1 forms a molecular axis that simultaneously promotes oncogenic protein expression and distorts immunological tumor control. METTL3 catalyzes m⁶A methylation on target mRNAs, creating marks recognized by reader proteins such as YTHDF1.^{18,57,61} This collaboration accelerates translation of pro-tumor mRNAs and stabilizes the expression of proteins critical for cancer cell growth and survival.

This interaction is not merely additive but functionally synergistic. Wang et al. (2020) showed METTL3 significantly increased expression and stability of hexokinase 2 (HK2) mRNA through m⁶A modification in its 3'-UTR, subsequently recognized by YTHDF1. This cooperation enhances the Warburg effect (elevated aerobic glycolysis) supporting proliferation and survival in cervical cancer cells. Knockdown of either METTL3 or YTHDF1 decreased HK2 expression, lactate production, and cell viability, confirming the axis's central role in tumor metabolism and growth. Clinically, high METTL3 and YTHDF1 expression in cervical cancer tissues correlates with poor prognosis, increased lymph node metastasis, and reduced patient survival. Kaplan-Meier analyses revealed that patients with high expression of either protein exhibited significantly lower survival rates compared to those with low expression, highlighting the axis's prognostic biomarker potential.⁶¹

Furthermore, the METTL3–YTHDF1 axis contributes to therapy resistance, making it a promising predictive biomarker for cervical cancer treatment response. Elevated METTL3 expression associates

with decreased sensitivity to cisplatin-based chemotherapy. Guo et al. (2024) showed METTL3 knockdown increased apoptosis and reduced cervical cancer cell viability by 30–50%. Mechanistically, METTL3 stabilizes mRNAs encoding anti-apoptotic proteins and cell cycle regulators such as BCL2 and CDK2, promoting therapy resistance. YTHDF1 enhances translation of immune escape molecules including PD-L1 and lysosomal proteins involved in MHC-I degradation.⁵³ Lin et al. (2023) demonstrated that YTHDF1 knockdown doubled CD8+ T cell infiltration and reduced tumor growth by 70%, indicating its role in fostering an immunosuppressive, therapy-resistant tumor microenvironment.⁵⁹ Jang et al. (2024) further confirmed that YTHDF1 loss restored IRF1 expression and improved anti-tumor immune response efficacy. Together, elevated METTL3 and YTHDF1 expression strongly predict resistance to conventional therapies and immunotherapies. Targeting both molecules simultaneously may enhance therapeutic response and reduce recurrence in cervical cancer patients.⁶⁰

CONCLUSION

Epitranscriptomic regulation through m⁶A modification mediated by METTL3 and YTHDF1 plays a critical role in cervical cancer progression by promoting cancer cell proliferation and invasion. Elevated expression of these proteins is strongly associated with poor prognosis, highlighting their potential as predictive biomarkers for therapy response in cervical cancer.

RECOMMENDATION

Further research is warranted to evaluate the diagnostic and prognostic potential of combined METTL3 and YTHDF1 biomarkers in cervical cancer, including the determination of their indications and contraindications. Such studies should encompass sensitivity and specificity analyses, stratification by histological subtypes and clinical stages, and investigation of interactions with other molecular factors that may influence biomarker validity. This comprehensive approach will enable more precise clinical application.

CONFLICT OF INTEREST

All authors declare no conflict of interest regarding this article's publication.

AUTHOR CONTRIBUTIONS

All authors contributed equally contribute to the study.

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ETHICAL CONSIDERATION

None declared.

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