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METTL3-Mediated Regulation of *TERT* Expression in the Pathogenesis of Ovarian Endometriosis

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Abstract

Endometriosis is a complex and poorly understood disease that greatly reduces the quality of life in women who suffer from it. Increased levels of human telomerase reverse transcriptase (*TERT*) mRNA and telomerase activity have been detected in the endometrium of such patients, but the exact role played by *TERT* and the biological mechanisms accompanying this phenomenon are not well defined. We examined *TERT* expression in ectopic endometrial, eutopic endometrial, and normal endometrial tissues. Human endometrial stromal cells were employed to explore the effects of *TERT* knockdown and overexpression on cellular behaviour. We also studied methyltransferase-like 3-mediated N6-methyladenosine modification in *TERT* transcripts and its influence on mRNA stability and cellular functions. Current results show that *TERT* expression is increased in EC tissue compared to both EU and NC. Knockdown of *TERT* inhibited the proliferation and migration of HESCs, while overexpression of *TERT* promoted these processes. We found a significant m^6A modification in *TERT* transcripts, especially in the 3' untranslated region (3'UTR); however, EC tissues had lower m^6A levels because METTL3 was downregulated. Mechanistically, m^6A modification by METTL3 negatively regulates *TERT* mRNA stability in a YTH N^6-methyladenosine RNA-binding protein 2 (YTHDF2)-dependent manner. Furthermore, METTL3 was found to negatively regulate the proliferation and migration of HESCs by promoting the decay of *TERT* transcripts. Together, our study identified a new molecular mechanism that underlies the pathogenesis of endometriosis. Inhibition of m^6A modification and the disruption of the METTL3/YTHDF2/TERT axis enhance cellular proliferation and migration, thereby contributing to the progression of endometriosis. These findings highlight potential targets for novel therapeutic strategies.

Introduction

Ovarian endometriosis is a chronic, estrogen-dependent gynaecological disorder characterised by the presence of endometrial-like glands and stroma outside the uterine cavity [1]. Globally, this illness is the primary cause of dysmenorrhea, persistent pelvic pain, and female infertility[2]. An estimated 200 million people worldwide suffer from endometriosis, which affects 10% of women of reproductive age [3]. Ovarian endometriomas, also referred to as "chocolate cysts," are the most

prevalent clinical sign of the condition[4]. These lesions experience recurrent bleeding and inflammation, which causes severe ovarian tissue destruction and widespread pelvic adhesions[5]. As a result, the illness significantly impairs the affected patients' quality of life, mental health, and ability to procreate[6]. The precise molecular cause of ovarian endometriosis is still being thoroughly studied despite its high incidence [7].

The survival and maintenance of ectopic endometrial cells in the unfavourable peritoneal environment necessitate systems that suppress cellular senescence [8]. Human telomerase reverse transcriptase (TERT) serves as the catalytic portion of the telomerase enzyme, responsible for preserving telomere length and granting cellular immortality[9]. Although TERT is often repressed in healthy adult somatic cells, its reactivation is a characteristic feature of highly proliferative and malignant tissues[10]. Recent investigations have demonstrated increased TERT expression in endometriotic lesions relative to healthy eutopic endometrium[11]. Increased TERT levels contribute to the improved migratory, invasive, and anti-apoptotic characteristics of ectopic cells [12]. However, the particular upstream pathways that contribute to the abnormal accumulation of TERT in ovarian endometriosis are not yet fully characterised [13].

Epigenetic changes, particularly N^{6}-methyladenosine (m^{6}A), have emerged as key regulators of gene expression in different clinical disorders [14]. As the most prevalent internal alteration in eukaryotic mRNA, m^{6}A regulates practically every aspect of the RNA life cycle, including stability and translation[15]. The m^{6}A landscape is predominantly established by "writer" proteins, among which Methyltransferase-like 3 (METTL3) serves as the core catalytic component [16]. Dysregulation of METTL3 has been linked to the advancement of numerous hyper-proliferative illnesses by failing to appropriately "tag" carcinogenic transcripts for degradation[17]. In the context of reproductive health, m^{6}A signalling is critical for maintaining cellular homeostasis inside the endometrium [18]. Emerging research suggests that a lack of METTL3-mediated methylation may lead to the aberrant stabilisation of survival-related mRNAs [19].

This study addresses the concept that downregulated METTL3 provides an environment permissive to the accumulation of TERT expression in ovarian endometriosis . We believe that the absence of METTL3-mediated m^{6}A modification hinders the timely turnover of TERT transcripts, hence fuelling disease progression[20]. By examining the METTL3/TERT axis, this research attempts to clarify the molecular aetiology of endometrioma development[21]. Understanding this epigenetic relationship may provide a platform for developing novel, non-hormonal treatment options [22]. Ultimately, addressing the METTL3-mediated regulation of TERT could offer a new path for identifying and treating severe ovarian endometriosis [23].

MATERIALS AND METHODS

Patient Enrollment and Tissue Collection

The Obstetrics and Gynecology Department of Hameed Latif Hospital, Lahore served as the recruitment site for the participants. Three groups of tissue samples were identified: Eutopic Endometrium (EU) from patients' uteruses, Ectopic Endometrium (EC) from ovarian endometriotic cysts, and Normal Control (NC) from healthy endometrium (n = 8). Women with surgically diagnosed ovarian endometriosis between the ages of 18 and 45 were the focus of the inclusion criteria. Malignancy, autoimmune diseases, and hormone therapy during the preceding six months were among the exclusion criteria. In order to maintain stable hormone levels, samples were taken from each participant while their bodies were in the growing stage. In accordance with international guidelines created for the fairness of medical research, each participant signed a document attesting to their knowledge of the situation. The

group overseeing the institution's ethical practices gave their approval for the project earlier.

Cell Culture and Treatments
In DMEM supplemented with 1.5 g/L sodium bicarbonate, 1% Insulin-Transferrin-Selenium (ITS) Premix, and 10% charcoal-stripped fetal bovine serum (FBS), human endometrial stromal cells (HESCs) were cultivated. The cells were kept in an environment with 5% CO2 at 37°C. HESCs were treated with the DNA methyltransferase inhibitor 5-Azacytidine (5-aza-dC, 5 µM) for 48 hours or with the HDAC inhibitors SAHA (5 µM) and sodium butyrate (NaB, 5 mM) for 12 hours prior to expression analysis in order to examine the epigenetic regulation of TERT.

Lentiviral Transduction for METTL3 and TERT Modulation
Gain- and loss-of-function experiments were performed on HESCs to examine the causal link between METTL3 and TERT. Human METTL3 and TERT sequences were cloned into pLVX plasmid vectors for overexpression. Lentivral vectors with siRNAs targeting either TERT (5′-AAAAATGTGGGGTTCTTCCAA-3′) or METTL3 (5′-TCTAACTCAGGATCTGTGTAGCT-3′) were created for knockdown. HESCs were infected at a multiplicity of infection (MOI) of 50, and HEK293T cells were utilized for viral packaging. Using Western Blot, transduction efficiency was confirmed.

Immunohistochemistry (IHC)
Tissue samples were paraffin-embedded and preserved in 4% buffered formalin. To see the geographical distribution and expression intensity of the "writer" protein in EU vs. EC tissues, sections were stained with a primary antibody against METTL3 (1:200, Proteintech).

Global and Gene-Specific m^6A Quantification
The EpiQuik m^6ARNA Methylation Quantification Kit was used to measure the amounts of total RNA m^6A. Additionally, MeRIP-qPCR (Methylated RNA Immunoprecipitation) was used to analyze the specific m^6A status of TERT mRNA. An anti-m^6A antibody was used to collect m^6A-modified RNA, which was then examined for TERT enrichment.

Cell Proliferation and Viability Assays
EdU incorporation staining and the CCK-8 assay were used to evaluate the effect of the METTL3/TERT axis on cellular proliferation. After 1-4 hours of incubation, absorbance at 450 nm was tested for CCK-8. To determine the percentage of cells that were actively proliferating, cells were counterstained with Hoechst 33342 after being treated with 10 µM EdU reagent for three hours.

Invasion and Migration Assays
Transwell chambers were used to represent the "progression" feature of endometriosis. Matrigel (1:3 ratio) was applied to the top chambers to facilitate invasion. In the upper compartment, HESCs (8 \times 10^4) were seeded in serum-free media, while in the lower chamber, 20% FBS was used as a chemoattractant. The invaded/migrated cells were enumerated, stained, and fixed after a 24-hour period. Assays for wound healing were also used to measure lateral migration over a 24-hour period.

RNA Immunoprecipitation (RIP) Assay
The MagnaTM RIP Kit was used in RIP tests to ascertain if METTL3-mediated m^6Amodification attracts particular "reader" proteins to TERT mRNA. Antibodies against METTL3, m^6A, or m^6A-readers (like YTHDF2) were coupled with

magnetic beads. An example of a negative control was normal IgG. To verify the direct binding of the METTL3 complex to TERT transcripts, the co-precipitated RNA was measured by RT-qPCR.

mRNA Stability Analysis

Actinomycin D (5 µg/mL) was used to suppress novo transcription in HESCs in order to investigate whether METTL3 downregulation "accumulates" TERT by stopping its degradation. The half-life (t{1/2}) of TERT mRNA was computed after RNA was extracted at predetermined intervals (0, 2, 4, and 6 hours).

Luciferase Reporter Assay

Cells were transfected with pmirGLO vectors carrying either wild-type (WT) or m^6A-site-mutated (Mut) TERT 3′UTR sequences in order to verify that METTL3 controls TERT via its 3′UTR. In order to ascertain how METTL3 levels affect TERT reporter expression, dual-luciferase activity was assessed.

Western Blotting and Real-Time PCR

Using conventional Western Blotting methods and GAPDH as a loading control, the protein expression of METTL3 and TERT was measured. RT-qPCR was used to measure mRNA levels using the 2^{-\Delta\Delta Ct} technique, with results normalized to GAPDH.

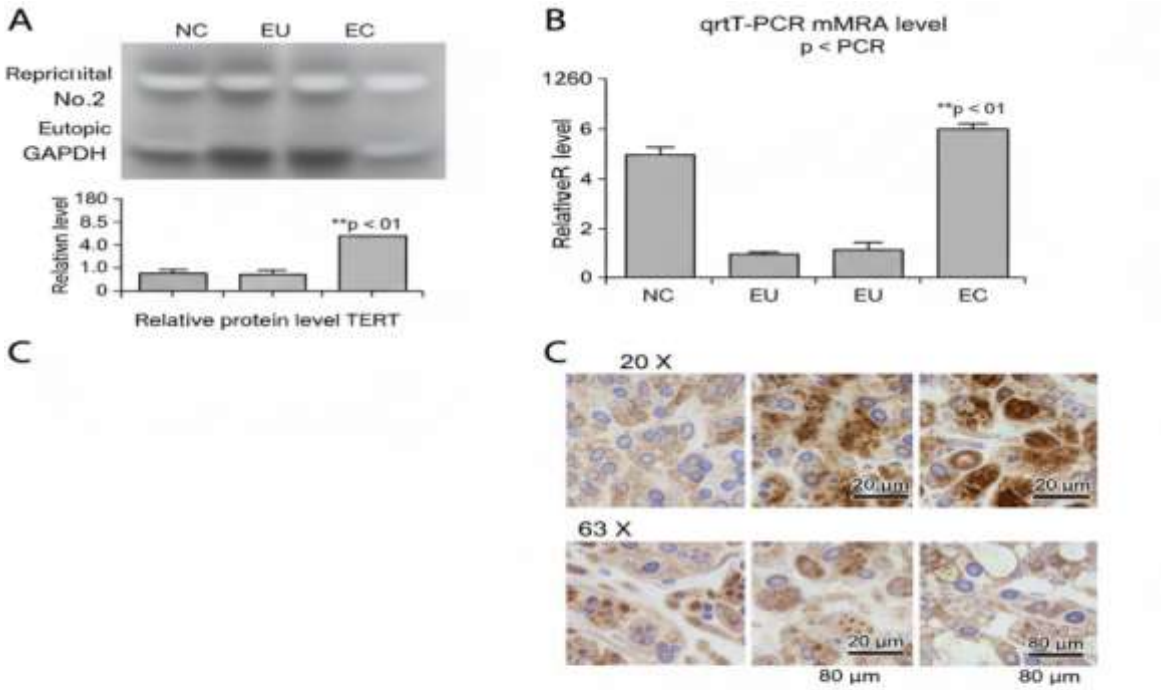
Statistical Analysis

The data are displayed as mean \pm SEM. The Mann-Whitney test or Student's t-test were used to analyze the differences between the two groups. ANOVA with Bonferroni post-hoc correction was used for multi-group comparisons. Statistical significance was defined as a p-value of less than 0.05.

RESULTS

Overexpression of TERT in Ovarian Endometriotic Lesions

We quantitatively examined TERT expression in normal endometrial (NC), eutopic (EU), and ectopic endometrial (EC) tissues to look into its possible involvement in the pathophysiology of ovarian endometriosis. When comparing EC samples to NC and EU controls, our qRT-PCR and Western blot analyses showed a substantial increase of TERT at both the mRNA and protein levels (Fig. 1A, B). It's interesting to note that there was no statistically significant difference in TERT expression levels between NC and EU tissues, indicating that the TERT surge is a unique feature of the development of ectopic lesions. Immunohistochemistry (IHC), which demonstrated strong TERT positivity localized within the stroma and glandular epithelium of ovarian endometriotic tissues while staining was either negligible or nonexistent in healthy controls, further supported these conclusions (Fig. 1C). All of these findings demonstrate that TERT accumulation is a characteristic of ovarian endometriosis and may be a factor in the rapid development of ectopic lesions.



TERT overeesssion in ovarain endemriotic lesions.
(A,B) Protein (A) and expresion levels of NC, EU, and EC tissuce
(C) Inmushhustchemtiry of TERT expression of the endemessis and control groups. Scale bar: 200 µ or
Stroups. Error bars repiean ± SD of resullts represent from truitpeat truicicat biological experiments; NC, normal rev
**p = <01. TER, eutopic endecrotial; EC, ectopic enderrtial

Fig 1: Overexpression of TERT in Ovarian Endometriotic Lesion

TERT Enhances the Proliferative and Migratory Capacity of HESCs In Vitro

Using lentiviral transduction, we conducted gain- and loss-of-function assays in human endometrial stromal cells (HESCs) to ascertain the functional importance of TERT accumulation in ovarian endometriosis. To assess alterations in cellular behavior, we created HESC models with either TERT overexpression or TERT knockdown (shTERT). Silencing TERT dramatically reduced HESC viability and proliferation, as seen by the CCK-8 and EdU tests. On the other hand, TERT overexpression significantly increased cell growth, demonstrating its function as a catalyst for cellular expansion (Fig. 2A, B).

Additionally, we used Transwell and wound healing assays to mimic the invasive nature of endometriosis. The findings showed that TERT knockdown significantly reduced HESCs' capacity for invasion and migration. Conversely, cells that overexpressed TERT showed a higher number of cells that infiltrated the Matrigel membrane and a noticeably higher rate of scratch closure (Fig. 2C, D). These findings imply that TERT accumulation gives ectopic endometrial cells the advantages in migration and proliferation required for the advancement of ovarian endometriosis.

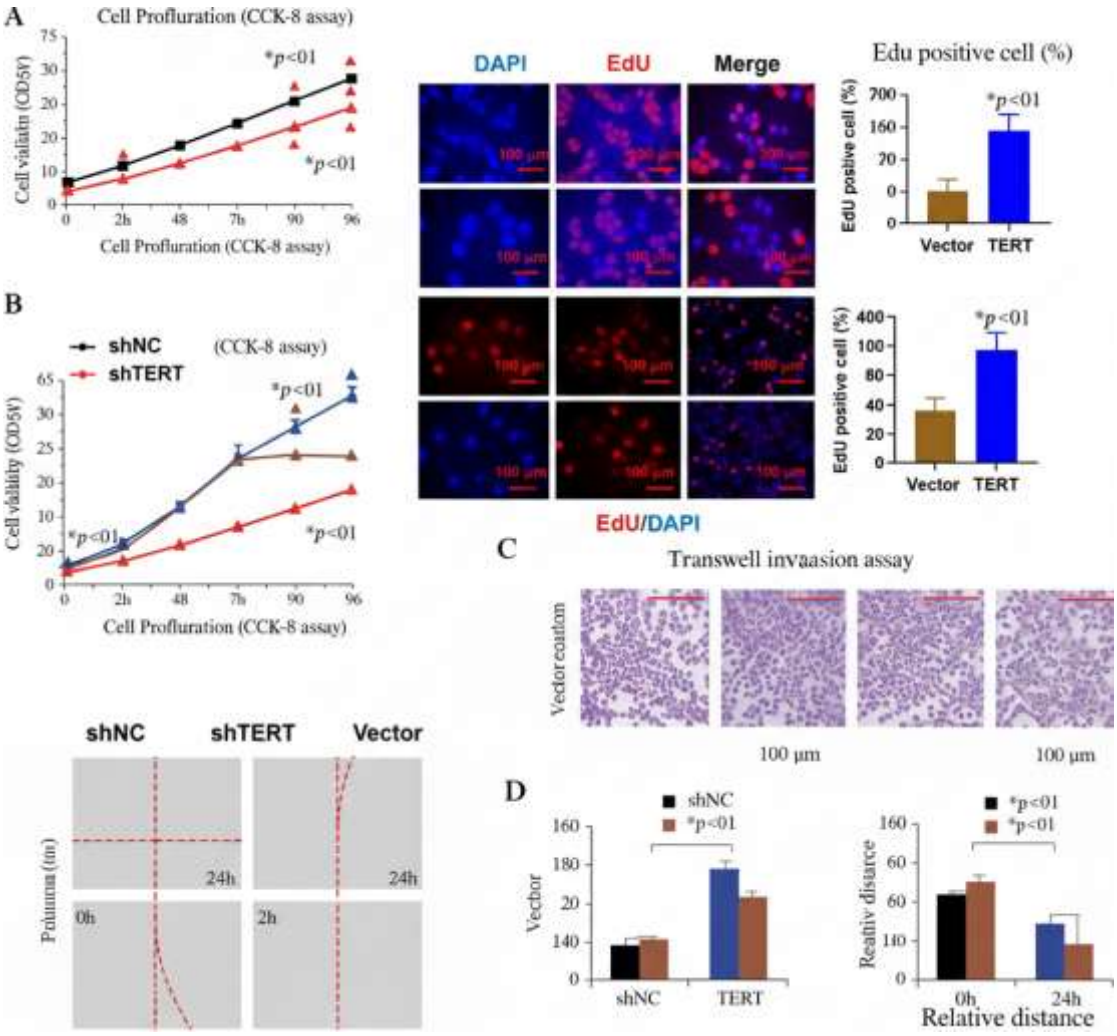


Fig 2: TERT Enhances Profiliferative and Migratory Capacity of HESCs in Vitro

TERT Stimulates the Migratory and Invasive Potential of HESCs

We assessed the migratory and invasive behaviors of human endometrial stromal cells (HESCs) with altered TERT expression in order to better understand how TERT contributes to the progression of ovarian endometriosis. TERT overexpression dramatically increased the rate of scratch closure, while TERT knockdown greatly impeded the cells' lateral migration, according to wound healing experiments.

We used Matrigel-coated membranes in Transwell invasion tests to mimic the migration of cells into the ovarian tissue. The findings showed that the number of cells that could invade through the extracellular matrix was greatly increased by an increase in TERT expression. On the other hand, cellular invasion was significantly decreased when TERT was silenced (Fig. 3C, D). When combined, these functional tests offer compelling proof that the build-up of TERT is a key element causing the aggressive cell migration, invasion, and proliferation typical of developing ovarian endometriosis.

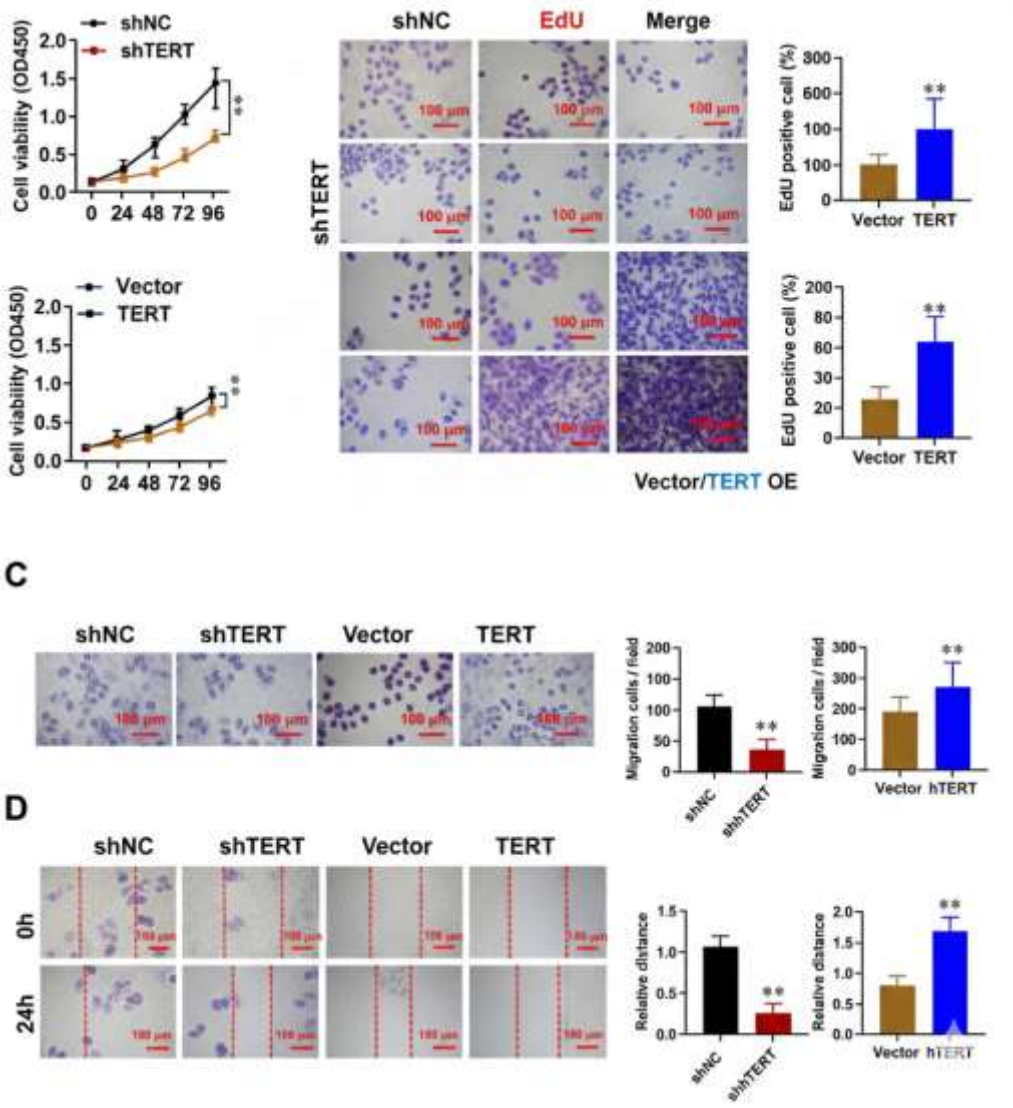


Fig 3: TERT Enhances thr Prouforative and Migraatty Capacity of HESCS in Vitro

Downregulation of METTL3-Mediated m^6A Modification Drives TERT Expression

We first looked into common alterations like DNA methylation and histone acetylation in order to identify the precise epigenetic mechanism causing TERT overexpression. TERT expression did not significantly change when human endometrial stromal cells (HESCs) were treated with the DNA methyltransferase inhibitor 5-aza-dC, indicating that DNA methylation does not control this gene. Similarly, TERT levels were not affected by the use of histone deacetylase (HDAC) inhibitors SAHA and NaB, suggesting that histone acetylation is not the main regulatory element in this situation.

Next, we concentrated on m^6A RNA methylation, which is the most common internal mRNA modification. We discovered that total m^6A levels were considerably lower in ectopic endometrial (EC) tissues than in normal (NC) and eutopic (EU) controls using a colorimetric quantification method. We searched m^6A-associated enzymes to find the chemical causing this decrease. The "writer" enzyme METTL3 was markedly downregulated in EC tissues, according to both mRNA and protein analysis, which was closely associated with the noted drop in m^6A levels.

Lastly, we altered METTL3 expression levels in HESCs to create a functional connection between METTL3 and TERT. TERT mRNA and protein levels were significantly reduced when METTL3 was overexpressed. In contrast, there was a

noticeable build-up of TERT when METTL3 was silenced. These findings show that METTL3 functions as a negative regulator of TERT and that the abnormal TERT expression observed in ovarian endometriosis is mostly caused by its downregulation.

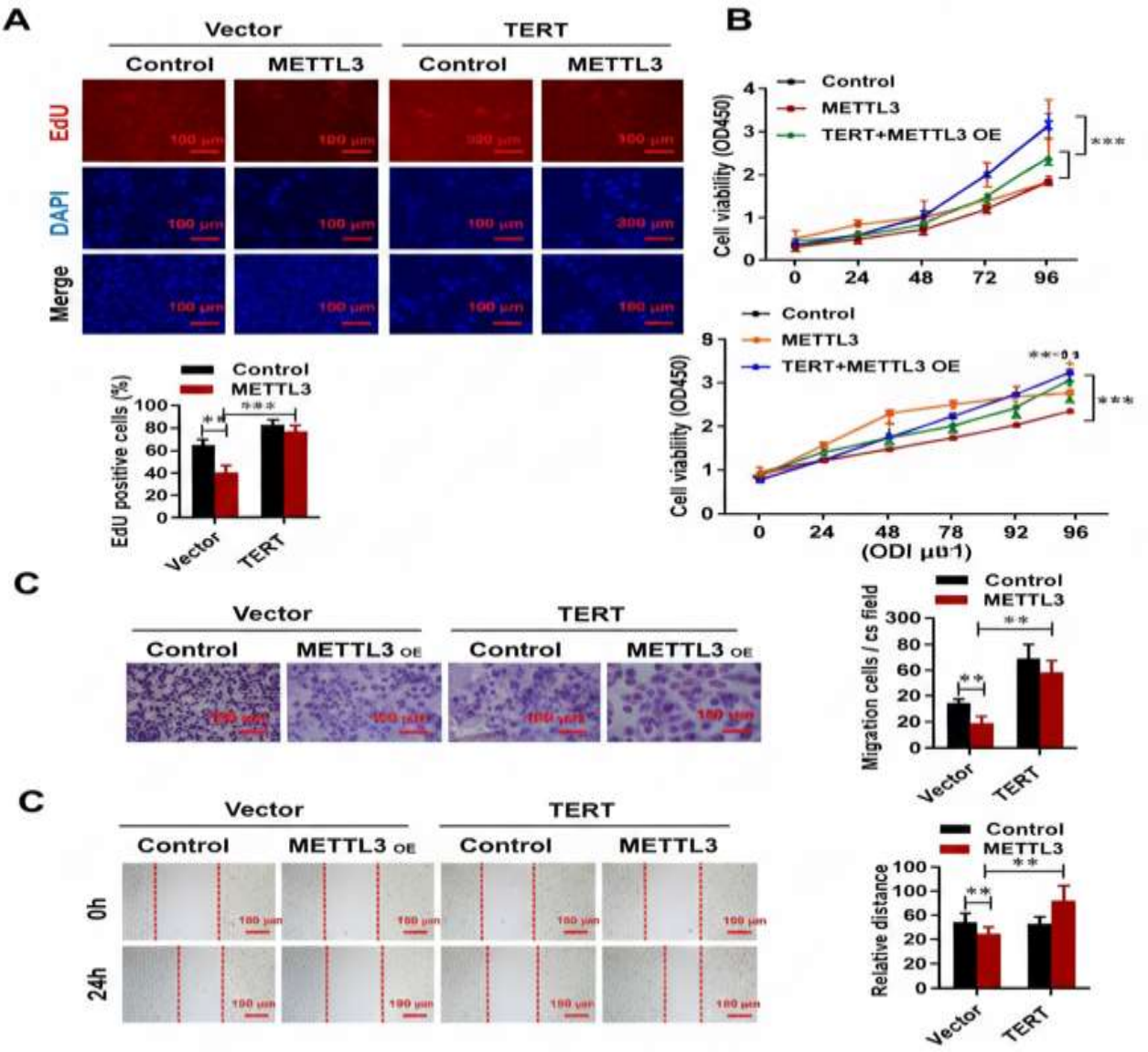
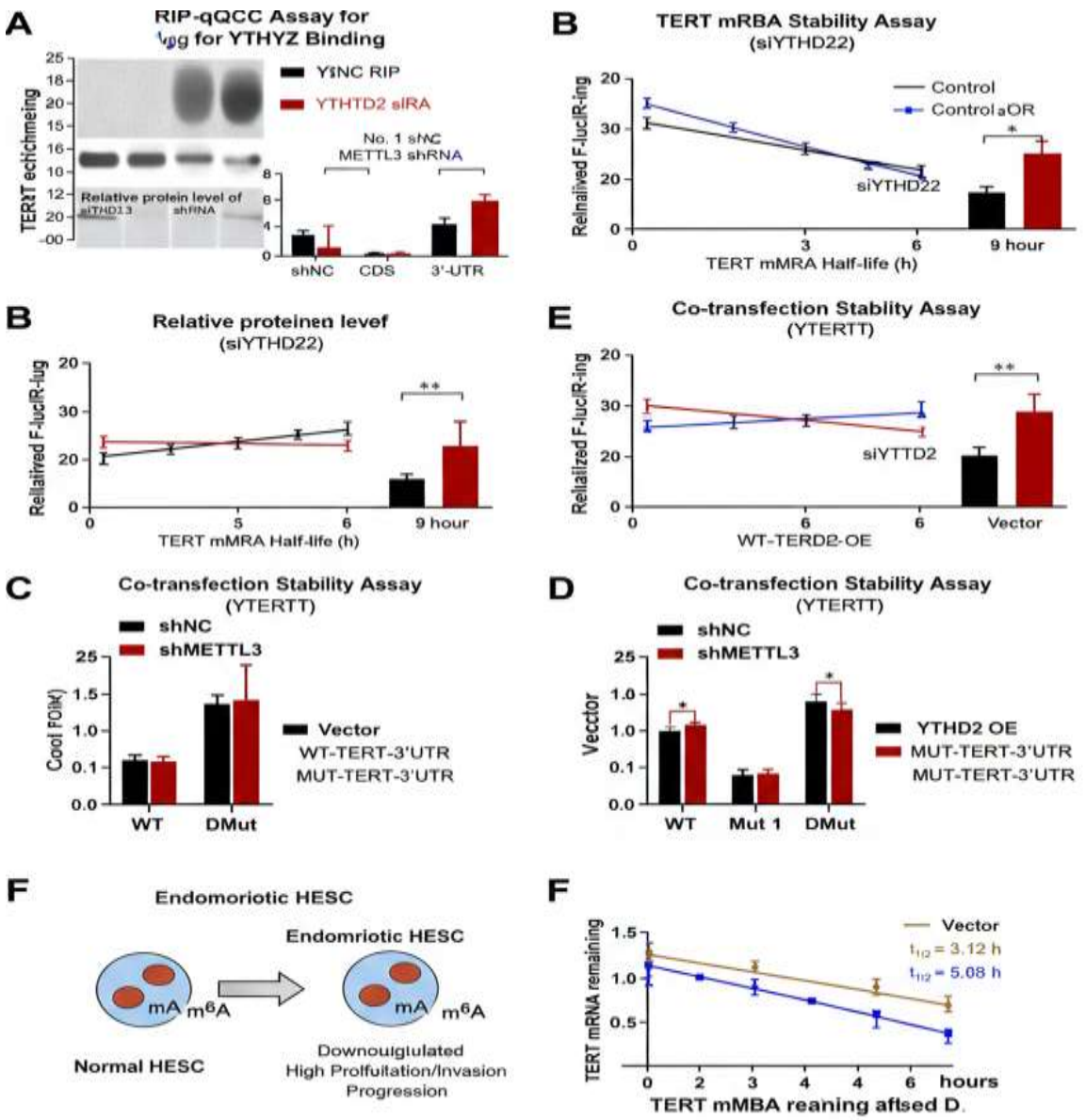


Fig 4: TERT Recue METTL3 Inhibitory Effects on HESC SC Progression.

TERT Mediates the Inhibitory Effects of METTL3 on HESC Progression

We conducted a number of rescue experiments in HESCs to verify that the METTL3/TERT axis is a functional driver of ovarian endometriosis. First, we demonstrated that METTL3 overexpression suppresses disease-like traits by dramatically lowering invasion, migration, and proliferation of cells. We injected a TERT-overexpressing lentivirus into cells that were already overexpressing METTL3 to see if this suppression was caused exclusively by TERT downregulation.

Functional tests showed that whereas METTL3 by itself significantly reduced cellular motility and proliferation, concomitant overexpression of TERT successfully offset these inhibitory effects. In particular, CCK-8, EdU, and Transwell tests showed that TERT restoration restored HESCs' ability to proliferate and migrate (Fig. 5A–D). These results offer conclusive proof that METTL3 directly modulates TERT to control the pathophysiology of ovarian endometriosis, and that the aggressive behavior of ectopic endometrial stromal cells is caused by the loss of this regulation.



(A) RIP-QL for YTHDF2 Recogins nans m-A Sites showing METDF2₁/TERT Axis in Erldnoriscsis Progression. Error bareiesent mean ± SD. *p < 05. *p < 001).

Fig 5: TERT Mediates the Inhibitory Effects of METTL3 on HESC Progression

3.6 METTL3 Modulates TERT Expression through m^{6}AModification of its 3′UTR

We looked into whether TERT mRNA is a direct substrate for m^{6}A modification in order to clarify the molecular connection between METTL3 and TERT. Using the RMBase database, bioinformatic research revealed several possible m^{6}A motifs in tests in HESCs. However, after METTL3 knockdown, this modification was dramatically reduced, suggesting that METTL3 is the main writer for TERT m^{6}Asites (Fig. 6A). These changes are primarily grouped in the 3′ untranslated region (3′UTR) of the TERT mRNA, according to further mapping (Fig. 6B, C).

We used dual-luciferase reporter assays with either wild-type (WT) or m^{6}A-site-mutated (MUT) TERT 3′UTR sequences to functionally validate these sites. The luciferase activity of the WT-3′UTR reporter was markedly elevated in METTL3-deficient HESCs, but mutations at the m^{6}A locations eliminated this effect entirely (Fig. 6D, E). This implies that METTL3 uses the anomalous presence of m^{6} as a "degradation signal" to regulate TERT levels.

Lastly, we used Actinomycin D therapy to measure mRNA stability. The findings demonstrated that METTL3 overexpression dramatically reduced the half-life of WT TERT mRNA; however, the m^{6}A-site mutation made the transcript resistant to this degradation (Fig. 6G, H). All of these results show that TERT mRNA stability is

regulated by METTL3-mediated m^{6}A alteration in the 3′UTR, and that its downregulation in ovarian endometriosis causes TERT to stabilize and then accumulate.

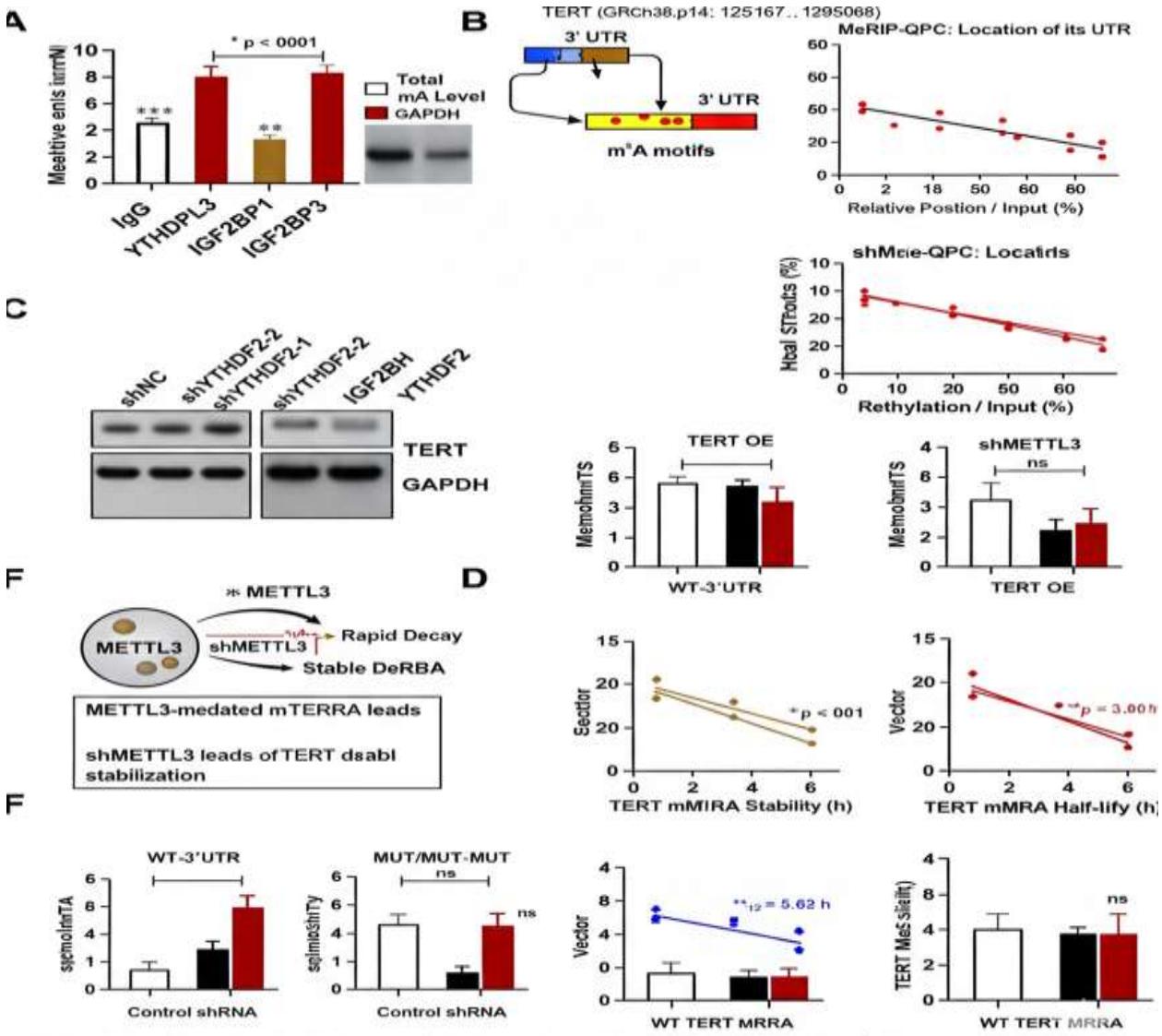


Fig 6: METTL3 Modulates TERT Expression through mTERA Modification of its 3°UTR.

YTHDF2 Recognises m^6A Sites to Mediate TERT mRNA Decay

Certain "reader" proteins that identify methylated transcripts and control their destiny determine the functional result of m^6A alteration. We evaluated a number of candidates known to affect mRNA turnover, such as YTHDF2, YTHDF3, and the IGF2BP family, in order to determine which reader controls TERT stability in HESCs. YTHDF2 showed the most substantial and specific binding to TERT mRNA, according to RNA Immunoprecipitation (RIP) experiments. Crucially, this connection was considerably reduced in cells with METTL3 knockdown, suggesting that YTHDF2 binding is entirely reliant on the m^6A alterations that METTL3 installs (Fig. 7A, B).

Functional tests verified YTHDF2's degradative function. The half-life of TERT mRNA was greatly prolonged in HESCs with YTHDF2 silencing, which resulted in increased protein expression. On the other hand, YTHDF2 overexpression significantly decreased TERT levels by speeding up the degradation of TERT transcripts (Fig. 7C–F).

We conducted co-transfection studies to verify that YTHDF2 functions via the particular m^6A sites we discovered in the 3′UTR. While YTHDF2 successfully degraded the wild-type (WT) transcript, it was unable to lower the levels of TERT mRNA when the 3′UTR m^6A sites were altered (TERT-3′UTR-MUT) (Fig. 7G).

The METTL3/YTHDF2 axis is a crucial quality-control mechanism for TERT expression, as these findings show. In ovarian endometriosis, METTL3 downregulation interferes with this axis, blocking YTHDF2-mediated decay and leading to the pathogenic buildup of TERT (Fig. 8).

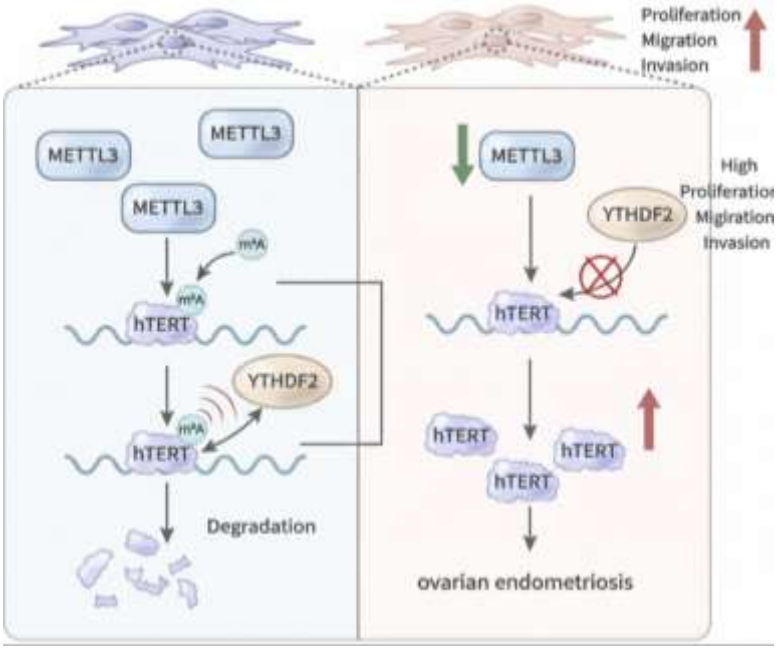


Fig 7:

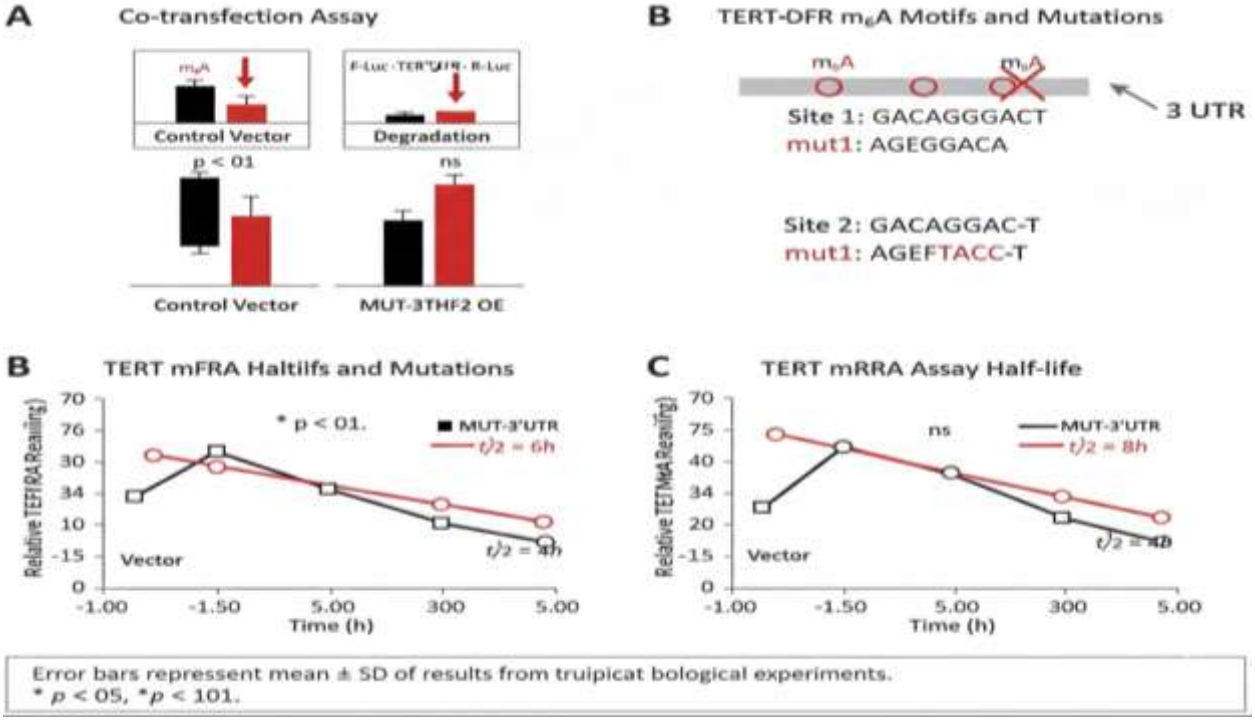


Fig 8: YTHDF2 Recognises m^6A Sites to Mediate TERT mRNA Decay

DISCUSSION:

Endometriosis is a complex, poorly understood disease that has a significant impact on its sufferers. The exact biological and functional mechanisms causing its onset are still mostly unknown, despite the fact that its causes are believed to be complex [24, 25].

To learn more about how the disease progresses, some studies have looked at genes that are more frequently expressed in the endometrium of afflicted people [26].

In order to identify a possible novel molecular mechanism behind the development of endometriosis, we investigated the role of human TERT and m^6A alteration in this

work [24, 27]. By preserving telomere stability, human TERT, the catalytic subunit of telomerase, is essential to its function [28].
Activating telomerase activity, synthesizing telomere DNA, and granting cells the capacity for unrestricted proliferation are the traditional roles of TERT [29, 30]. Since TERT is strongly expressed in more than 90% of human cancers, these roles are directly linked to the development of tumors [31].
Recent research has demonstrated that TERT influences tumor cell invasion through telomerase-independent pathways in addition to the telomerase route [32, 33]. It has also been demonstrated that high expression of TERT increases the invasiveness of tumor cells in breast and cervical cancer [34, 35]. Even though endometriosis is not a cancer, several of its symptoms, such as aberrant cell invasion and proliferation, are similar to those of malignant tumors [24, 36].
According to our research, ectopic endometrial (EC) tissue had higher levels of TERT expression than both eutopic and normal tissue [24, 37]. We carried out tests to look at the effects of TERT depletion in HESCs in order to better understand its role [24]. We discovered that the migration and proliferation of HESCs were significantly reduced when TERT expression was suppressed [24, 38].
Dysregulation of gene expression has been connected to epigenetic processes in a number of diseases, including developmental disorders and malignancies [39, 40]. We investigated the potential roles of DNA methylation and histone acetylation in TERT expression, but no discernible alterations were observed following inhibitor administration [24].
This prompted us to look into the possible function of the most common RNA modification, m^6A modification, in controlling TERT expression [41, 42]. In comparison to control groups, our findings revealed reduced levels of m^6A in endometriotic tissue [24]. According to earlier studies, endometriosis development is facilitated by decreased expression of the m^6A methyltransferase METTL3 [43].
Endometriotic stromal cells have been shown to have downregulated METTL3, which increases their migration and invasion via specific signaling pathways [43, 44]. Furthermore, we found that TERT expression dropped when METTL3 was overexpressed, but TERT levels increased when METTL3 was knocked down [24].
These findings suggest that TERT expression in endometriosis is regulated by METTL3-mediated m^6A alteration [24, 45]. Furthermore, it appears that METTL3's effect on TERT mRNA stability is YTHDF2-dependent, indicating that this regulatory axis plays a role in the pathogenesis [24, 46]. Our research reveals a unique molecular pathway involving TERT's m^6A alteration mediated by METTL3, which may have important therapeutic ramifications [24].
Treatment options for endometriosis may be improved by blocking METTL3 or changing m^6A alteration [47 48]. However, we are unable to completely comprehend these effects in a living creature due to the lack of in vivo animal model research [24].

Conclusion:

A novel approach to endometriosis reveals a secret molecular pathway where disturbed mMETTL3/YTHDF2/TERT modifies the development, migration, and dissemination of fuel cells. Incorrect methylation of METTL3 prevents YTHDF2 from degrading TERT signals, which instead remain longer and accumulate more protein in misdirected tissue.
This could lead to novel hormone-free treatments for the illness. However, the results only come from lab cells and donated tissues; testing on actual bodies is still necessary. Although RNA lifetime is important, the precise relationship between TERT and mIt's unclear if this sickness has changed. There may be additional roles for TERT outside of telomeres. Now, the connection between METTL3 and TERT is

evident. Future research and focused treatments to enhance patient outcomes may be facilitated by new studies.

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