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Review article

The role of m5C RNA modification in cancer development and therapy

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ABSTRACT

RNA modifications have been demonstrated to affect the function, stability, processing, and interactions of RNA, including pseudouridylation, acetylation and methylation. RNA methylation products, such as N6-methyladenosine (m6A), 5-methylcytidine (m5C), N7-methylguanosine (m7G), 2′-O-dimethyladenosine (m6Am), and N1-methyladenosine (m1A), have been reported to participate in tumorigenesis and tumor progression. The role of m6A in carcinogenesis has been well studied and summarized. In this review, we described the biological functions of m5C RNA modifications in tumorigenesis and tumor progression. Moreover, we highlighted the molecular mechanisms of m5C RNA modification in oncogenesis. Furthermore, we discussed whether targeting m5C regulator-associated genes could be a novel strategy for improving therapeutic outcomes in patients with cancer.

1. Introduction

Ribonucleic acid (RNA) modifications are the chemical changes in RNA molecules [1]. These modifications can occur at various positions on the RNA nucleotides and alter the function, stability, processing, and interactions of RNA within cells [2]. Over 170 different types of RNA modifications have been identified in different types of RNA, including messenger RNA (mRNA), transfer RNA (tRNA), ribosomal RNA (rRNA), and non-coding RNAs (ncRNAs) [3]. Common and well-studied RNA modifications include pseudo-uridylation, acetylation, and methylation [4]. Pseudo-uridylation changes the RNA structure and function by converting uridine into pseudouridine. Acetylation may affect the interactions of RNA with other molecules by adding an acetyl group to the nucleotide. Methylation is conducted via the addition of a methyl group (CH3) to bases or the backbone of RNA, including N6-methyladenosine (m6A), N7-methylguanosine (m7G), 5-methylcytidine (m5C), 2′-O-methylation (Nm), 2′-O-dimethyladenosine (m6Am), N1-methyladenosine (m1A) [5].

N6-methyladenosine (m6A) is a common and well-explored chemical modification of RNA, particularly mRNA [6,7]. In this modification, a methyl group is added to the nitrogen atom at the sixth position of the adenine base. m6A is an abundant internal modification in eukaryotic mRNA and is also found in other types of RNA such as rRNA and small nuclear RNA (snRNA) [8–11]. It has

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been well-summarized that m6A plays a crucial role in the regulation of RNA stability, RNA splicing, RNA transport, and translation efficiency [12–15]. m5C methylation is a biochemical process that involves modification of the nucleotide cytidine with RNA. This modification occurs via adding a methyl group to the fifth carbon position of the cytosine ring, which is known as "5-methylcytidine" or "m5C" [16]. The m5C modification has been increasingly explored and appears to be involved in the stability and function of various RNA molecules, such as mRNA and tRNA, by influencing RNA stability and splicing. In recent years, m5C has been demonstrated to be involved in various biological processes and diseases, including cancer [17–20]. Research on RNA modifications is rapidly growing, providing new insights into the regulation and expression of genetic information in cells. Moreover, RNA modification could uncover potential targets for therapeutic intervention in diseases that negatively alter RNA processing [21–26]. In this review, we will discuss the biological and pathological functions of m5C in tumorigenesis and malignancy. Notably, we will describe the molecular mechanisms through which m5C RNA modification regulates carcinogenesis. Modification of m5C regulator-associated genes may be a potential strategy for improving therapeutic efficacy in patients with cancer.

2. Role of m5C in various cancer types

Numerous regulatory factors have been reported to participate in m5C methylation, including writers, erasers, and readers. Writers are methyltransferases that add methyl groups, including NOP2, NSUN1-7, DNMT1, DNMT3A, DNMT3B, and TRDMT1. Readers are proteins that recognize and bind to m5C-modified RNA, such as ALYREF (Aly/REF export factor), YBX1 (Y-box binding protein 1), and

Table 1
The role of NSUN2, NSU3, NSUN5, NSUN6 and ALYREF in various cancer types.

Items	Targets	Mechanism	Functions	Ref
NSUN2	HDGF, RABL6, TK1	Increases RABL6/TK1 mRNAs splicing and stabilization	Enhances tumor malignant and progression in BLCA	[101, 103]
ALYREF	PKM2	Stabilizes PKM2 mRNA and regulates glycolysis	Enhances proliferation in BLCA	[102]
ALYREF	RABL6/TK1	Enhances RABL6/TK1 mRNAs splicing and stabilization	Promotes tumor progression in BLCA	[101]
NSUN2	LRRC8A, KRT13	Induces the m5C methylation of KRT13, increases the stabilization of LRRC8A	Enhances proliferation, migration, invasion of CC cells	[80,81]
NUSN5	GPX4	NSUN5 modifies GPX4 and activates STING	Promotes anticancer immunity in CRC	[32]
NSUN2	SMOX	Promotes YBX1-induced tumor progression by stabilizing SMOX mRNA and activating mTORC1	Enhances cell proliferation and metastasis in ESCC	[123]
NSUN6	CDH1	Influences tRNA m5C modifications; boosts CDH1 mRNA translation efficiency	Reduces tumor progression in ESCC	[124]
NSUN2	GBR2	Enhances m5C modification of GRB2 mRNA and its stability; activates ERK/MAPK, PI3K/AKT	Enhances oncogenesis and progression in ESCC	[125]
NSUN2	LINC00324	Induces LINC00324 stability through m5C modification; decreases CBX3 mRNA degradation; increases VEGFR2 transcription	Facilitates tumor angiogenesis in GEC	[86]
NSUN2	ERK1/2	Increases ERK1/2 phosphorylation; regulates Bcl-2 and Bax	Promotes chemosensitivity in GC	[105]
NSUN2	FOXC2	FOXC2-AS1 facilitates NSUN2 recruitment to FOXC2 mRNA, enhancing its m5C modification and interaction with YBX1	Promotes proliferation, migration, and invasion of GC cells	[112]
NSUN2	NTN1	DIAPH2-AS1 stabilizes NSUN2 and enhances the m5C modification of NTN1	Promotes neural invasion in GC	[108]
NSUN2	ORAI2	Induces ORAI2 m5C methylation; increases E2F1 and AMPK	Facilitates peritoneal metastasis in GC	[107]
NSUN5	ZEED3	Activates Wnt/β-catenin signaling pathway	Promotes proliferation of HCC cells	[54,55]
ALYREF	EGFR	Induces m5C modification and increases the stabilization of EGFR mRNA and pSTAT3 activation.	Facilitates cell proliferation, invasion, and EMT in HCC	[58]
NSUN2	LINC00324	Enhances LINC00324 stability through m5C modification; regulates CBX3 and VEGFR2	Promotes angiogenesis in GECs.	[86]
NSUN5	beta-catenin, RBFOX2	Suppresses β-catenin by facilitating its mRNA breakdown; increases RBFOX2 recruitment to chromatin.	Boosts the phagocytic activity of TAMs in glioma	[82]
NSUN3	M1 infiltration, M2	NSUN3 knockdown increases M1 macrophage infiltration and decreases M2 macrophages	Promotes proliferation and growth of HNSCC cells	[76]
NSUN2	SRSF2	Reduces NSUN2 expression lowers mRNA m5C levels, diminishes SRSF2 binding, and affects RNA splicing.	Increases the development of leukemia	[142]
NSUN6	NH23-H1	Controls NM23-H1 expression by modifying the 3′-UTR of NM23-H1 mRNA using m5C.	Inhibits cell proliferation, migration and EMT in LC	[66]
NSUN2	NRF2	Maintains the expression of NRF2 via YBX1 in NSCLC cells	Governs NRF2-induced ferroptosis resistance in NSCLC	[61]
NSUN2	QSOX1	Regulates YBX1 and QSOX1 in NSCLC	Causes gefitinib resistance and cancer recurrence in NSCLC	[62]
ALYREF	YAP1	Interacts with LINC02159; increase the stability of YAP1 mRNA; activates Hippo and beta-catenin	Enhances tumor progression in NSCLC	[70]
NSUN2	E2F1	Elevates E2F1 mRNA stability via m5C modification of its mRNA; governs MYBL2 and RAD54L expression	Promotes tumor progression in OC	[128]
NSUN2	AR	NSUN2 enhances AR stability through m5C cluster modification.	Increase development of PCa	[46]
NUSN5	ACC1	CDK13 binds to NSUN5, thereby promoting the m5C modification of ACC1 mRNA and increasing ACC1 expression	Increases lipid accumulation in PCa cells	[43]
NSUN2	TIAM2	Induces TIAM2 mRNA expression via reducing TIAM2 mRNA decay via YBX1	Promotes proliferation, migration, invasion and EMT in PC cells	[113]

FMRP (fragile X mental retardation protein). Erasers are enzymes that remove methyl groups, such as TET1-3 and ALKBH1. These regulatory factors dynamically control m5C progression and influence various cellular functions. Dysregulation of m5C can lead to various diseases, including cancer [27]. Using bulk RNA-seq and scRNA-seq analysis, NSUN1 has been identified as a biomarker for cancer diagnosis, prognosis, and therapy in multiple cancer types [28]. In the following sections, we will discuss the role of m5C in the occurrence and progression of cancer (Table 1).

2.1. Colorectal cancer (CRC)

One study conducted a thorough analysis of the predictive value of the 14 m5C RNA methylation regulators in colon cancer. The risk score derived from the three-m5C signature serves as an independent prognostic indicator. Furthermore, the three-m5C signature influences the tumor immune microenvironment (TIME), affecting the presence of tumor-infiltrating immune cells. Notably, these three regulatory factors are associated with the MAPK/p38 signaling pathway [29]. Another study investigated the role of 13 m5C-related regulators in colon cancer and explored their prognostic value using informatics analyses. NSUN6 and ALYREF have been identified as independent prognostic m5C-associated regulators of colon cancer [30]. An integrated analysis of colon cancer was performed to evaluate the role of m6A/m5C/m1A mutations in prognosis and immunotherapy. The immunophenoscore of the low m6A/m5C/m1A score group increased after CTLA-4/PD-1 immunotherapy. Moreover, the expression levels of VIRMA and DNMT3B were elevated in colon cancer samples [31]. Chen et al. reported that glutathione peroxidase 4 (GPX4) was modified by NSUN5 in colon cancer, leading to the promotion of anticancer immunity via the activation of cyclic GMP-AMP synthase (cGAS)-stimulator of interferon (STING) signaling [32]. Moreover, Chen and coworkers explored m5C-related regulators of tumor microenvironment (TME) infiltration in colorectal cancer. The m5C score demonstrated a strong predictive accuracy for prognosis. Additionally, CRC patients with a low m5C score presented a “hot” TME, marked by enhanced infiltration of immune cells and elevated expression of immune checkpoints. Although a high m5C score indicates a non-inflammatory phenotype, patients with CRC with this score showed a high responsiveness to molecular-targeted therapy [33].

2.2. Breast cancer (BC)

Huang et al. reported that most of the 11 m5C RNA methylation regulators showed variable expression levels in TNBC and normal tissue samples. Simultaneously, the increase in NSUN2 expression was associated with pathways involving the spliceosome, RNA degradation, cell cycle, and RNA polymerase. In contrast, decreased NSUN6 expression was linked to interactions with the extracellular matrix receptor, metabolism, and cell adhesion. Prognosis-related genes influenced the TIME, and the types of immune-infiltrating cells varied between those associated with NSUN2 and NSUN6 [34]. Among the 13 m5C regulators, the expression of DNMT3B and ALYREF was upregulated in breast cancer and associated with poor prognosis. Both DNMT3B and ALYREF were effective in differentiating between BC and normal breast tissues [35]. It has been accepted that microRNAs (miRNAs) regulate cancer development via inhibition of its targets [36,37]. Five potential upstream miRNAs, including miR-26a-5p, and miR-26b-5p, miR-29a-3p, miR-195-5p, and let-7b-5p, served as independent prognostic indicators of BC. VEGFA and EZH2 have been identified as the most likely target genes in the ncRNA-mRNA network associated with m5C regulators in BC [35]. One group identified m6A/m5C/m1A/m7G-related long noncoding RNAs (MRlncRNAs) that could be used to predict the prognosis and immunological characteristics of BC [38]. Therefore, m5C RNA modification plays a critical role in breast tumorigenesis and progression. A total of 334 differentially expressed m5C-lncRNAs were identified in BC. A reliable risk model utilizing m5C-lncRNAs linked to cancer metabolism and tumor immune cell infiltration was developed to predict patient survival. Additionally, AP005131.2, AL121832.2, and LINC01152 have shown potential as novel biomarkers and therapeutic targets in BC [39]. Similarly, Xu et al. reported the prognostic value of 11 m5C-related lncRNAs associated with immune cell infiltration in BC [40].

2.3. Prostate cancer (PCa)

Xu et al. investigated the role of m5C RNA modification in the regulation of the TME and the recurrence of PCa. The m5C modification patterns were established. Two distinct patterns emerged, showing significant differences in the biochemical recurrence risk, TME, and immunotherapy responses in PCa. Notably, TET2 is linked to numerous infiltrating immune cells and is highly expressed in the adjacent normal tissues. Therefore, we developed an m5C modification signature for clinical use. The risk score derived from this signature correlated with the T stage, N stage, Gleason score, and likelihood of biochemical recurrence [41]. Yu et al. found that TET3 is upregulated in PCa and is linked to poor prognosis. We created an m5C prognostic model that included NSUN2, TET3, and YBX1. Additionally, significant differences in m5C regulatory gene expression, TME scores, and levels of immune cell infiltration were observed among different risk subgroups. Two distinct m5C gene clusters were correlated with patient prognosis and immune cell infiltration. CTLA4, NSUN6, TET1, and TET3 showed differential expression among various immune subtypes [42]. The upregulation of CDK13 in PCa cells leads to an increase in fatty acyl chains and lipid classes, resulting in lipid accumulation within cells. Lipid deposition is positively associated with ACC1 expression. Mechanistically, CDK13 binds to NSUN5, thereby promoting Ser327 phosphorylation of NSUN5. Phosphorylated NSUN5 enhances the m5C modification of ACC1 mRNA. The m5C-induced ACC1 mRNA subsequently interacts with ALYREF, promoting its stability and facilitating its nuclear export, leading to increased ACC1 expression and further lipid accumulation in PCa cells [43]. Wang et al. identified 17 5 mC-related lncRNAs and determined their recurrent signatures in PCa [44].

Sun et al. used multi-omics analysis to explore the expression and prognosis of NSUN members (NSUN1-7) in PCa. NOP2 and

NSUN2 expression increased in PCa samples. In addition, NSUN2 has been linked to poor tumor prognosis and poor clinical features. NSUN2 is correlated with immune cell infiltration and drug resistance [45]. Zhu et al. reported that NSUN2 expression is increased in PCa and is associated with adverse outcomes. Both in vitro and in vivo studies have shown that it functions as an oncogene in PCa. NSUN2 depletion reduces AR expression and activity. NSUN2 enhances AR stability in a post-transcriptional manner through m5C cluster modification dependent on m5CYBX1. Notably, treatment with the AR inhibitor, enzalutamide, lowered NSUN2 levels and inhibited m5C modification in PCa cells. Hence, the AR transcriptionally influences the expression of NSUN2 [46]. Tan and coworkers identified an ALYREF-mediated 5 mC based signature to predict prognosis and therapeutic efficacy. ALYREF may be a prognostic biomarker and target for the treatment of PCa [47].

2.4. Hepatocellular carcinoma (HCC)

A high frequency of mutations in the m5C regulatory genes has been observed in patients with HCC. Dysregulation of m5C-related genes correlates with advanced stages and survival in patients with HCC. Notably, elevated NSUN4 and ALYREF levels were linked to survival outcomes. High NSUN4 expression is linked to methylation and demethylation activities, whereas increased ALYREF expression is involved in cell cycle and mitosis [48]. The expression of m5C regulatory genes varies among patients with HCC, depending on their clinical and pathological features, and mutations in these genes are common. A prognostic model with strong predictive power was developed using the following five m5C regulators: NOP2, NSUN2, TET1, YBX1, and DNMT3B. The risk score obtained using this model served as an independent prognostic predictor [49]. The association between the m6A/m5C/m1A-related genes and HCC has also been explored. Two m6A/m5C/m1A-associated molecular subtypes and prognostic signature have been identified in HCC patients [50]. Another study identified a liver cancer risk signature based on hypoxia and m6A/m5C/m1A modifications that are associated with various immune microenvironmental characteristics. Patients with HCC in the high-risk group showed better responses to both immunotherapy and several widely used chemotherapeutic drugs [51].

A risk signature based on four genes (YTHDF1, YBX1, TRMT10C, and TRMT61A) was developed. The high-risk group demonstrated a shorter OS than the low-risk group. Risk score was an independent prognostic factor. Additionally, the risk score was positively associated with the infiltration of many immune cells and most immune checkpoints [52]. The risk model included the overexpression of YBX1, ZC3H13, YTHDF1, TRMT10C, YTHDF2, RRP8, TRMT6, LRPPRC, and IGF2BP3, all of which were linked to worse outcomes in patients with HCC. The high-risk score correlated with various factors, including prognosis, grade, clinical stage, T stage, and M stage, in patients with HCC. The high-risk score involves processes such as the spliceosome, RNA degradation, and DNA replication. Additionally, a high-risk score was associated with the stromal score, various immune cells, such as CD4 memory-activated T cells, M0 and Mi1 macrophages, CD4 memory-resting T cells [53]. NSUN5 promotes HCC cell proliferation in a ZBED3-dependent manner. The overexpression of ZBED3 abrogated the tumor-suppressing impact of NSUN5 knockdown and restored the activity of the Wnt/β-catenin signaling pathway [54]. Similarly, Zhang et al. reported that NSUN5 is overexpressed in HCC and is associated with a poor prognosis. NSUN5 markedly enhances the proliferation and migration of HCC cells in vitro and promotes tumor growth in vivo. Positive correlation was found between NSUN5 and genes linked to translation in HCC. NSUN5 overexpression boosts ribosome functionality and overall protein synthesis, potentially facilitating the proliferation and migration of HCC cells [55]. Liu et al. reported the expression patterns of 5 mC regulators in HCC and their prognostic roles. Moreover, the m5C modification is involved in the TIME and HCC prognosis [56]. Xiang et al. found that m5C RNA methylation regulates the ErbB and PI3K-Akt pathways in gastrointestinal cancers, including liver cancer [57]. One group identified that ALYREF-induced m5C modification facilitates tumor progression by enhancing the stabilization of EGFR mRNA and pSTAT3 activation in HCC. ALYREF promoted cell proliferation, invasion, and EMT in HCC [58].

2.5. Lung cancer (LC)

RNA modifications including m5C have been known to modulate lung tumorigenesis [59]. Cao et al. developed a prognostic model for m5C-related immune genes in LUAD using machine learning based on the three prognostic genes: HLA-DMB, PPIA, and GPI [60]. One group has reported that NSUN2 governs NRF2-induced ferroptosis resistance in NSCLC. NSUN2 expression is increased in NSCLC tumor tissues and is associated with tumor grade and size. Depletion of NSUN2 inhibits the expression of NRF2 and increases the sensitivity of NSCLC cells to ferroptosis activators. NSUN2 maintained the expression of NRF2 via YBX1 in NSCLC cells [61]. Another group showed that the dysregulation of m5C hypermethylation leads to gefitinib resistance via the NSUN2/YBX1/QSOX1 (quiescin sulfhydryl oxidase 1) axis in NSCLC with EGFR mutations. Increased NSUN2 levels cause gefitinib resistance and cancer recurrence, whereas the depletion of NSUN2 causes tumor regression and reduces gefitinib resistance [62].

Pan et al. found that m5C RNA methylation regulators influence the TIME and predict tumor prognosis in lung squamous cell carcinoma. NSUN3 and NSUN4 are prognostic risk signatures. Increased NSUN3 and NSUN4 expression is associated with survival in patients with LC. NSUN3 is associated with $CD8^+$ T cells, whereas NSUN4 is associated with neutrophils, suggesting that m5C regulators are involved in the TIME regulation in LC [63]. Liu et al. have identified three clusters of m5C RNA modifications. These clusters exhibited different overall survival rates. The m5Csig, which includes TRDMT1, NSUN1, NSUN4, NSUN7, and ALYREF, categorizes patients with lung adenocarcinoma (LUAD) into high- and low-risk groups. Patients in the high-risk group, characterized by greater immune cell infiltration, had a significantly worse overall survival [64]. Zhang and colleagues identified a prognostic signature based on m6A/m5C/m1A-related genes in LC, including SNHG12, PABPC1, IGF2BP1, FOXM1, CBFA2T3, and CASC8 [65]. Ma et al. discovered a new m5C/m6A-related gene signature that can determine immunotherapy outcomes and predict the prognosis of LUAD. This study identified 29 m5C/m6A regulators that were differentially expressed in LUAD tissues and normal lung samples.

Moreover, four m5C/m6A-related gene signatures, including HNRNPA2B1, IGF2BP2, NSUN4, and ALYREF, could predict prognosis, immune checkpoint expression, and TMB [66].

Another group reported that in LC cells, NSUN6 expression is diminished, and its overexpression limits cell proliferation, migration, and EMT. NSUN6 controls NM23-H1 expression by modifying the 3′-UTR of NM23-H1 mRNA using m5C. Additionally, the overexpression of NSUN6 reduces the development of LC in mice [67]. Huang et al. uncovered that the levels of m5C modification in the leukocytes of patients with NSCLC were reduced, and these levels decreased progressively with advancing tumor stage. Notably, the m5C modification demonstrated greater diagnostic accuracy than traditional markers such as CEA, SCC, Cyfra21-1, and CA125 [68]. Yang et al. found that LINC02159 regulates the ALYREF/YAP1 pathway and enhances tumor progression in NSCLC. LINC02159 interacted with ALYREF to increase the stability of YAP1 mRNA via m5C modification, resulting in overexpression of YAP1 and activation of Hippo and β-catenin pathways in NSCLC [69]. THOC3 binds to YBX1 and increases PFKFB4 mRNA modification, promoting tumor progression in lung squamous cell carcinoma [70].

2.6. Head and neck squamous cell carcinoma (HNSCC)

Zhu et al. identified prognostic signatures based on m5C methylation patterns and EMT in HNSCC. An 8-gene signature was developed as a prognostic model, which included CAMK2N1, WNT7A, F2RL1, AREG, DEFB1, CNFN, TGFBI, and CAV1 [71]. Huang et al. established an m5C-related lncRNA model to assess the prognosis, TME, TMB, and clinical treatment options of patients with HNSCC. This system can accurately predict patient outcomes and distinctly categorize tumors into hot and cold subtypes in patients with HNSCC, thus offering new insights into clinical treatment strategies [72]. Similarly, one group developed an m6A/m5C/m1A-related lncRNAs signature to predict the prognostic value and immune infiltration in HNSCC. This prognostic signature consisted of six m6A/m5C/m1A-related lncRNAs: AL035587.1, AC009121.3, AF131215.5, FMR1-IT1, AC106820.5, and PTOV1-AS2 [73]. Han et al. identified the expression patterns and prognostic significance of m5C-related regulators in HNSCC. Specifically, the m5C modification plays a critical role in HNSCC progression. The expression patterns of NSUN5, DNMT1, and DNMT3A could predict the prognosis of patients with HNSCC [74]. Changes in m5C-regulatory genes have been linked to the clinicopathological features of patients with HNSCC. Ten m5C-regulatory genes showed correlations with copy number variation (CNV) patterns. Notably, the expression of m5C-regulatory genes, especially ALYREF and NSUN5, was elevated during the TNM stages. Expressions of DNMT1, TET2, and NSUN6 is associated with HNSCC prognoses. Additionally, DNMT1 and ALYREF expression levels were effective predictors of HNSCC risk. High ALYREF expression is linked to mitochondrial function, whereas increased DNMT1 expression is associated with humoral immunity [75]. NSUN3 expression is upregulated and associated with poor prognosis in HNSCC. Both in vitro and in vivo studies have shown that NSUN3 knockdown curtails tumor proliferation and growth. Furthermore, NSUN3 knockdown leads to an increase in M1 macrophage infiltration and a reduction in the proportion of M2 macrophages in HNSCC cells. Thus, NSUN3 may be a potential therapeutic target for HNSCC [76].

2.7. Cervical cancer (CC)

Wang et al. discovered numerous m6A/m5C/m1A RNA methylation-related genes, which are associated with prognosis and immunotherapy response in CC, including SLC2A1, CUX1 and CA2 [77]. Pan et al. reported an m6A/m5C/m1A-associted lncRNA signature in CC that was linked to prognosis and immunotherapy [78]. A signature for four genes–FNDC3A, VEGFA, OPN3, and CPE–was developed to predict the prognosis of CC. The expression levels of these genes were consistently elevated in the CC tissues. Lowering the expression of FNDC3A, VEGFA, or CPE reduces the growth, migration, and invasion of CC cells [79]. Chen et al. reported that LRRC8A overexpression due to m5C modification-induced mRNA stability by NSUN2 inhibited apoptosis and enhanced tumor progression in CC. Downregulation of NSUN2 inhibited cell proliferation and metastasis in CC [80]. Reducing levels of elevated NSUN2 significantly hindered the migration and invasion of CC cells. NSUN2 enhances cell migration and invasion by inducing the m5C methylation of keratin 13 (KRT13). Methylated KRT13 transcripts were identified and stabilized by YBX1 [81].

2.8. Glioma

One study showed that NSUN5 suppresses β-catenin by facilitating the breakdown of its mRNA, which in turn boosts the phagocytic activity of tumor-associated macrophages (TAMs) in glioma. The process by which NSUN5 attracts TET2 to the chromatin does not depend on its methyltransferase function. Additionally, NSUN5 increased the recruitment of RBFOX2 to chromatin. RBFOX2 serves as a specific reader of 5-hydroxymethylcytosine (5hmC), recognizing and aiding in the degradation of 5hmC-modified chromatin-associated RNA (caRNA) in gliomas [82]. NSUN5 acts as a tumor suppressor in gliomas. The absence of NSUN5 resulted in a lack of methylation at the C3782 position in 28S rRNA, leading to a reduction in protein synthesis. This reduction triggers the activation of an adaptive translational program that enables cellular survival under stressful conditions. Intriguingly, epigenetic silencing of NSUN5 made these gliomas more vulnerable to bioactivatable substrates of the stress-related enzyme NQO1. Notably, epigenetic inactivation of NSUN5 is a distinctive feature of patients with glioma who experience extended survival [83]. Wen et al. have described a prognostic risk-scoring signature for gliomas based on m5C methylation regulator-related genes [84]. Yang et al. performed an integrated analysis of bulk RNA-seq and scRNA-seq and reported m6A/m1A/m5C/m7G-related regulators, including EIF1, NSUN6, and TET1, to predict prognosis and TME in glioma [85]. Pan and coworkers found that the m5C modification of LINC00324 facilitated tumor angiogenesis by targeting the CBX3/VEGFR2 pathway in glioma. NSUN2 and LINC00324 are overexpressed in glioblastoma endothelial cells (GECs). Silencing NSUN2 or LINC00324 reduces angiogenesis in GECs. NSUN2 enhances LINC00324 stability through m5C

modification, leading to increased LINC00324 expression. LINC00324 binds to the AUH protein, which decreases CBX3 mRNA degradation. Additionally, CBX3 directly interacts with the promoter region of VEGFR2, increasing its transcription and promoting angiogenesis in GECs [86].

Xiao et al. uncovered m5C regulator-related patterns for the prediction of prognosis and TIME in glioma, including NSUN7 [87]. Huang et al. used an integrated analysis and reported ten lncRNAs related to RNA methylation to create a signature for survival and prognosis that demonstrated robust independent predictive power for patients. Silencing RP11-98I9.4 and RP11-752G15.8 led to a more invasive cellular phenotype, faster growth, and noticeable resistance to temozolomide (TMZ). Additionally, a significant increase in global m5C and m6A levels was observed in the glioma cells [88]. This prognostic signature was established based on eight m6A/m5C-related lncRNAs, including GDNF-AS1, HOXA-AS3, LINC00346, LINC00664, LINC00665, MIR155HG, NEAT1, and RHPN1-AS1, in the low-grade gliomas [89]. Similarly, Li et al. developed m1A/m5C/m6A methylation-related lncRNAs to predict clinical outcomes in low-grade gliomas [90]. Shao et al. identified an m6A/m5C/m1A/m7G-related lncRNA signature with 12 genes that can predict immune infiltration and prognosis in gliomas [91]. Zhou et al. reported eight m5C-related lncRNAs for predicting prognosis and TME in gliomas [92]. Zhang et al. dissected four lncRNAs, LINC00265, CIRBP-AS1, GDNF-AS1, and ZBTB20-AS4, and established an m5C-related lncRNAs signature to predict the prognosis of glioma [93]. In addition, five RNA:m5C methyltransferase genes were selected to develop a risk signature designed for overall survival and clinicopathological characteristics of gliomas [94]. Zhao and colleagues reported that m6A/m5C/m1A-related genes are involved in immune infiltration, and drug sensitivity in gliomas. The prognostic model included WTAP, TRMT6, DNMT1, and DNMT3B expression in gliomas [95]. Among the m5C regulators, the DNMT3A mutation is the most common among the m5C regulators in low-grade gliomas. In addition, NSUN3, TET2, TRDMT1, ALYREF, DNMT3B, DNMT1, NOP2, and NSUN2 were upregulated [96]. Taken together, m5C modification is involved in the tumorigenesis and progression of gliomas [97].

2.9. Bladder cancer (BLCA)

Pan et al. examined the clinicopathological features and prognostic significance of m5C regulators in BLCA. Of the 13 m5C RNA methylation regulators, nine showed differential expression between BLCA and normal samples, including NOP2, NSUN2, NSUN4, NSUN5, DNMT1, DNMT3A, DNMT3B, TRDMT1, and ALYREF. These nine regulators correlated with clinicopathological features such as high or low tumor risk, pT or pTNM stage, and migration [98]. Moreover, bioinformatics data showed 273 upregulated and 594 downregulated genes in BLCA. Importantly, only ALYREF expression was significantly associated with overall survival. Among macrophages, cells with ALYREF demonstrated significant levels of infiltration. Therefore, the ALYREF may serve as an independent prognostic indicator. Furthermore, ALYREF expression was elevated at both mRNA and protein levels. ALYREF is primarily localized in nuclear speckles. High ALYREF expression was associated with poorer OS [98]. Based on scRNA-seq and Bulk RNA seq data, Fan et al. identified six RNA methylation-related lncRNAs in BLCA that could predict prognosis and immunotherapeutic efficacy [99]. Li and coworkers discovered 17 5 mC-related lncRNAs that can be used as biomarkers for predicting survival and TIME in patients with BLCA [100].

One study showed that ALYREF and NSUN2 increased RABL6/TK1 mRNAs splicing and stabilization, leading to enhanced tumor malignant and tumor progression in BLCA [101]. Another study demonstrated that ALYREF stabilizes PKM2 mRNA and attaches to its m5C sites within the 3′-UTR. Increased ALYREF levels enhance proliferation via PKM2-driven glycolysis in BLCA. Additionally, high levels of both PKM2 and ALYREF are associated with poor survival outcomes in patients with BLCA. HIF-1α indirectly increased PKM2 expression by activating ALYREF, besides directly stimulating its transcription [102]. YBX1 maintains target mRNA stability through recruitment of ELAVL1. NSUN2 and YBX1 have been shown to contribute to the BLCA pathogenesis by targeting the m5C methylation site in the HDGF 3′-UTR. High expression of NSUN2, YBX1, and HDGF is associated with the poorest survival outcomes in patients with BLCA [103].

2.10. Gastric cancer (GC)

One group reported that the knockdown of ALYREF using siRNA hindered the proliferation of GC cells. Moreover, the reduced expression of ALYREF causes cell cycle arrest at the G1 phase and triggers apoptosis in GC cells [104]. Another group discovered that NSUN2 expression was elevated in GC samples, and its levels correlated with the degree of lymph node metastasis [105] and poor prognosis [106]. Transfection with NSUN2 shRNA curbed the increase in ERK1/2 phosphorylation and led to the downregulation of Bcl-2 and upregulation of Bax, and promotion of chemosensitivity in GC [105]. The NSUN2-methylated lncRNA NR_033928 stabilizes glutaminase mRNA and stimulates glutamine metabolism reprogramming, leading to increased cell proliferation in GC [106]. NSUN2-induced ORAI2 m5C methylation facilitates peritoneal metastasis in a peritoneal high-fat environment due to the upregulation of E2F1 and NSUN2 via the AMPK pathway in GC patients [107]. The lncRNA DIAPH2-AS1 stabilized NSUN2 and enhanced the m5C modification of NTN1, promoting neural invasion in GC [108].

Song et al. identified a m5C regulator-related signature, including APOD, ASCL2, MFAP2, and CREB3L3, which could predict prognosis and efficacy of immunotherapy in GC [109]. Zhang et al. uncovered eight m5C regulator-related genes that are involved in the TME and immune infiltration in GC [110]. SUMO-2/3 interacts with NSUN2, and enhances NSUN2 stabilization, and promotes its nuclear transport, leading to promotion of the carcinogenic activity of NSUN2, which accelerates GC progression [111]. Yan and coworkers reported that high expression of lncRNA FOXC2-AS1 was observed in GC tissues, and its overexpression was correlated with an advanced TNM stage and shorter overall survival. Functionally, reduced FOXC2-AS1 expression diminished cell proliferation, migration, and invasion, while its overexpression had the opposite effect. FOXC2-AS1 binds to FOXC2 mRNA and inhibits its

degradation. FOXC2-AS1 facilitates recruitment of NSUN2 to FOXC2 mRNA, enhancing its m5C modification and interaction with YBX1 [112].

2.11. Pancreatic cancer (PC)

Evidence has shown that NSUN2 is overexpressed in PC tissues and is associated with aggressive clinical features. Silencing NSUN2 reduces cell proliferation, migration, and invasion in vitro and decreases the tumor growth and metastasis in a xenograft mouse model. Conversely, NSUN2 overexpression displayed opposing effects. Mechanistic investigations revealed that the loss of NSUN2 resulted in a reduction in TIAM2 mRNA expression. Silencing NSUN2 enhances TIAM2 mRNA decay via YBX1. Most importantly, disruption of the NSUN2/TIAM2 axis suppresses the malignant characteristics of PC cells by inhibiting EMT [113]. Huang et al. identified 39 m6A/m5C/m1A-related lncRNAs that were linked to the prognosis and immunotherapy of PC [114]. Yun et al. also dissected an m5C regulator-related signature that could help predict prognosis and therapeutic outcomes in PC [115]. NSUN2 knockdown regulates the growth, morphology, and gemcitabine sensitivity of PC cells. NSUN2 suppresses the epithelial differentiation of PC cells [116]. In addition, several studies have reported signatures of m5C-related lncRNAs for predicting immune response and prognosis in PC [117,118]. Yu et al. uncovered the predictive value of m5C-related regulatory genes, including DNMT3A, for PC [119]. NSUN6 expression is associated with various clinicopathological parameters, including the T stage. Using in vitro cell lines and in vivo xenograft mouse models, NSUN6 inhibited cell proliferation and tumor growth in PC [120].

2.12. Esophageal squamous cell carcinoma (ESCC)

One study identified 10 m6A/m5C-related lncRNA signature that is useful for prognosis prediction and the judgement of immunotherapeutic efficacy in ESCC [121]. Ma and colleagues constructed a prognostic signature based on 9 m5C-related lncRNAs in ESCC [122]. YBX1 is highly expressed in ESCC tissues and enhances cell proliferation and metastasis. NSUN2 promotes YBX1-induced ESCC progression by stabilizing SMOX (spermine oxidase) mRNA. YBX1 increases activation of mTORC1 pathway by promoting SMOX mRNA stabilization in ESCC [123]. Depletion of NSUN6 accelerates tumor progression both in vitro and in vivo in ESCC, whereas overexpression of NSUN6 suppresses the malignant traits of ESCC cells. NSUN6 influences tRNA m5C modifications, which selectively boosts CDH1 mRNA translation efficiency. E-cadherin is a crucial downstream target through which NSUN6 regulates ESCC progression [124]. NSUN2 expression is increased in ESCC tumors and associated with poorer survival outcomes in patients. E2F1 positively regulates NSUN2 expression. Studies in Nsun2 knockout mouse models showed that depletion of NSUN2 retarded ESCC oncogenesis and progression. NSUN2 enhances m5C modification of GRB2 mRNA and its stability via the m5V mediator LIN28B in ESCC, leading to elevated activation of the ERK/MAPK and PI3K/AKT pathways [125].

2.13. Ovarian cancer (OC)

RNA methylation plays a role in ovarian tumorigenesis and progression [126,127]. NSUN2 establishes a positive feedback loop with the E2F1 in OC. NSUN2 elevates E2F1 mRNA stability via m5C modification of its mRNA, while E2F1 in turn interacts with the NSUN2 promoter and enhances NSUN2 transcription. Moreover, the m5C modification facilitated the phase separation of YBX1, leading to an increase in E2F1 expression. NSUN2 and YBX1 show amplified and elevated levels in OC, with higher expression correlating with poorer patient prognosis. E2F1 actively governs the expression of MYBL2 and RAD54L, which cause tumor progression in OC [128]. Liu et al. developed a signature based on six m5C RNA modification-related genes with a prognostic value in OC [129]. Gao et al. proposed a set of risk-predictive signatures consisting of ten lncRNAs for the development of prognostic signatures in OC [130]. Two studies also identified an m5C-related lncRNA risk model for prognosis prediction and biomarkers in OC [131,132]. Zheng et al. reported four RNA modification-related genes, ALYREF, ZC3H13, WTAP, and METTL1, which could be useful for the evaluation of prognosis, stratification of patients with OC, and judgment of the immunotherapy response [133]. Xu et al. proposed an m5C-related prediction model based on ALYREF, NOP2, and TET2 to predict the prognosis of OC [134]. Meng and coworkers reported an abnormal m5C lncRNA methylome in high-grade serous OC, and suggested the transcriptomic dysregulation of m5C in the ovarian tumorigenesis [135,136]. NOP2 expression increased in HGSOC tissues. Higher levels of NOP2 stimulated cell growth and enhanced cell migration and invasion capabilities of HGSOC. Additionally, RAPGEF4 may act as a downstream target of NOP2 in HGSOC. The control of NOP2 and RAPGEF4 may be linked to m5C methylation levels [137]. SIAH1 was reduced in chemo-resistant EOC samples and acted as an E3 ligase that facilitated the degradation of YBX-1 in the cytoplasm. Mechanistic investigations revealed that YBX-1 was ubiquitinylated at lys304 by SIAH1, leading to destabilization of its target m5C-modified mRNAs, thereby increasing the sensitivity of EOC cells to cisplatin. Furthermore, increased SIAH1 levels boost the anti-cancer effects of cisplatin [138].

2.14. Leukemia

Ding et al. reported that most m5C regulators are differentially expressed in AML and are associated with disease prognosis. Methylation levels of specific m5C regulators, such as DNMT3A and DNMT3B, influence the survival outcomes of patients with AML [139]. Two studies found that the m5C modification could play a crucial role in creating the diversity and complexity of the TME in AML [140,141]. Ma et al. identified SRSF2 as a reader of m5C and proposed that disruption of m5C binding by SRSF2 may contribute to the development of leukemia. Additionally, reduced NSUN2 expression lowered mRNA m5C levels, diminished SRSF2 binding, and affected RNA splicing. The SRSF2P95H mutation hindered the ability of the protein to recognize m5C-marked mRNA, decreasing its

association with crucial leukemia-related transcripts in leukemic cells. Furthermore, in patients with leukemia, decreased NSUN2 expression resulted in reduced mRNA m5C methylation and when combined with the SRSF2P95H mutation, correlated with worse clinical outcomes [142]. Tet2 deficiency accelerates leukemogenesis in various AML models by enhancing the homing of leukemia stem cells (LSCs) to the bone marrow (BM) niche, thereby boosting their self-renewal and proliferation. The absence of TET2 in AML blast cells leads to the upregulation of TSPAN13, which in turn activates the CXCR4/CXCL12 signaling pathway, resulting in enhanced homing and migration of LSCs to the BM niche. TET2 deficiency causes accumulation of m5C modifications in TSPAN13 mRNA. YBX1 selectively recognizes m5C modification, thereby enhancing the stability and expression of TSPAN13 transcripts. Overall, our findings underscore the critical role of TET2 as an m5C demethylase in leukemogenesis and LSC self-renewal [143].

2.15. Other cancer types

NSUN2 levers were elevated in ATC tissues and linked to dedifferentiation. Additionally, the downregulation of NSUN2 expression suppressed the proliferation, formation, migration, and invasion of ATC cells. Furthermore, inhibition of NSUN2 increased the sensitivity of ATC cells to genotoxic drugs. NSUN2 promotes m5C modifications related to the tRNA structure, stabilizes tRNA that sustains homeostasis and enhances the rapid transport of amino acids, particularly leucine. This stabilization allows for an efficient translation process involving proteins, such as c-Myc, BCL2, RAB31, JUNB, and TRAF2. Remarkably, targeting NSUN2 impaired the feedback loop between c-Myc and NSUN2 in ATC cells [144]. Li et al. reported a diagnostic model using the ten signature genes that was associated with the TME and immune infiltration in PTC [145]. Zhang et al. reported an m5C-related signature, including ALYREF, DNMT3B, and YBX1, which is associated with prognostic prediction in kidney renal papillary cell carcinoma. The expression levels of ALYREF, DNMT3B, and YBX1 were higher in Caki-2 kidney cancer cells than in normal HK-2 cells [146]. Another study dissected that the m5C methylation-related signature served as an independent prognostic indicator, with low-risk patients exhibiting a more robust immunoreactivity phenotype and a better response to immune checkpoint inhibitor (ICI) therapy. In contrast, high-risk patients showed enrichment of hallmark cancer pathways and demonstrated an immunosuppressive state, indicating a lower sensitivity to immunotherapy in rectal cancer [147].

3. Conclusion

In conclusion, the m5C RNA modification plays an essential role in tumorigenesis and tumor progression (Figs. 1 and 2). Targeting m5C regulator-related genes could be a novel strategy for improving therapeutic outcomes in cancer patients. Several issues regarding the role of the m5C modification in oncogenesis need to be clarified. In this study, we focus on m5C effector proteins rather than aberrant m5C modification, which are two distinct aspects. Hence, we mainly descript the role of NSUN1-7 in tumorigenesis via targeting their downstream molecules. Several known m5C reader proteins, including YBX1, ALYREF, FMRP and SRSF2, are not discussed. YBX1 as a reader protein for m5C RNA modifications, which has significant implications for cellular function and disease, particularly cancer [148]. FMRP has been identified as an m5C reader that coordinates the actions of the m5C writer and eraser to enhance mRNA-dependent repair and cell survival in cancer [149]. SRSF2 has been reported to play an unexpected role as reader of m5C on mRNA [142].

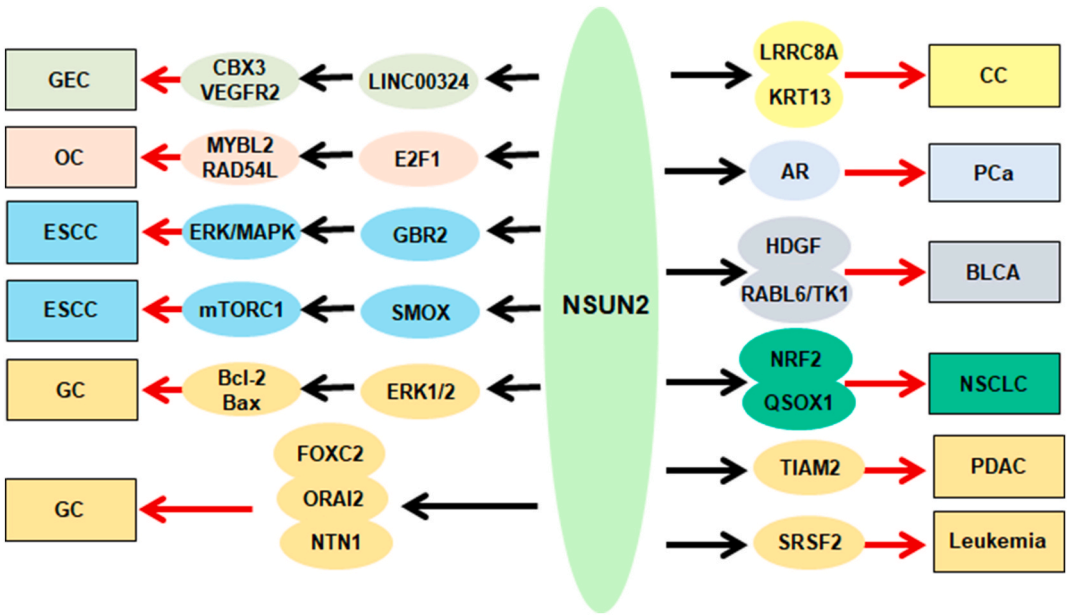

Fig. 1. The role of NSUN2 in tumorigenesis.

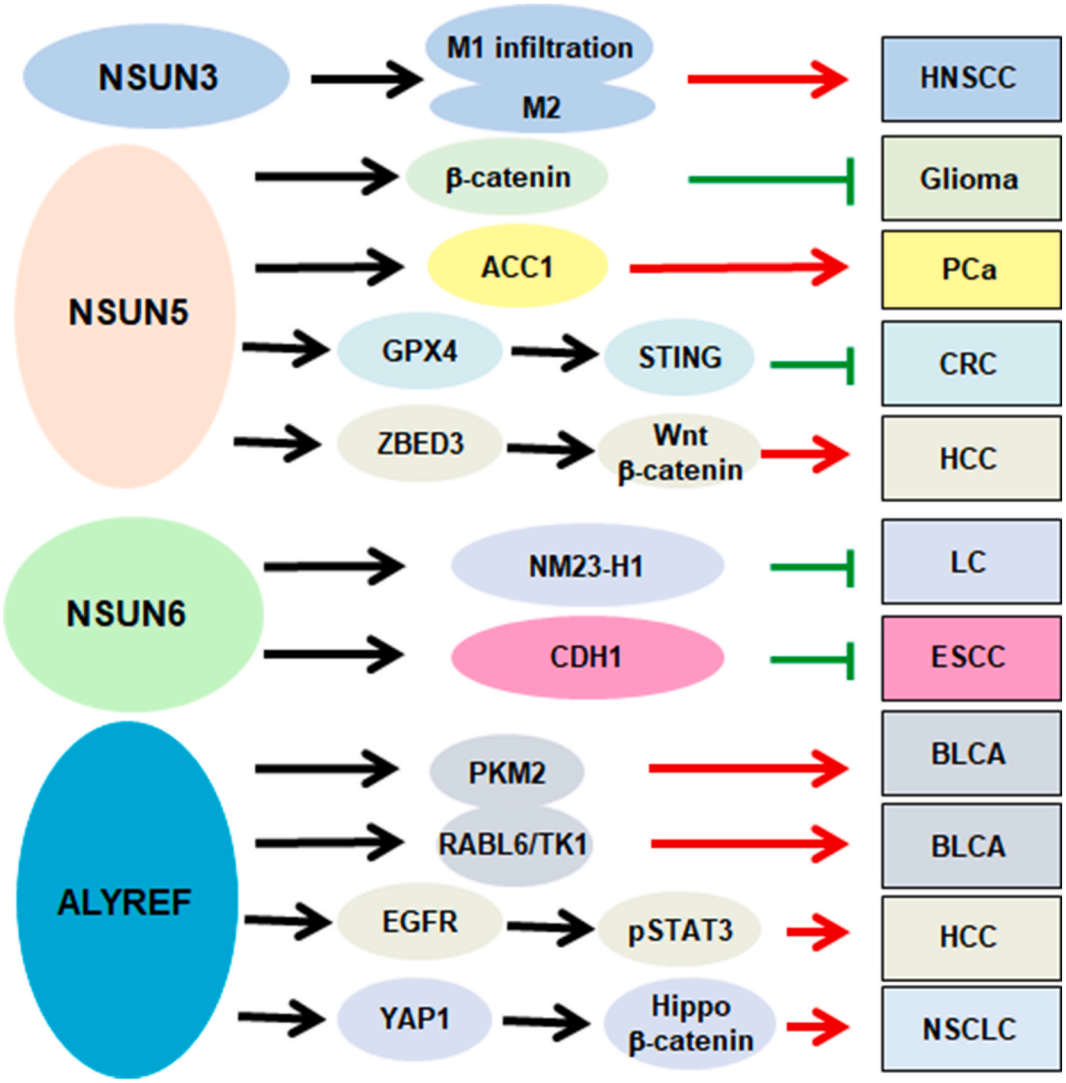

Fig. 2. The role of NSUN3, NSUN5, NSUN6 and ALYREF in tumorigenesis.

M6A RNA modification has been thoroughly explored in recent years and has been shown to play a critical role in tumorigenesis. In addition to m6A and m5C RNA modifications, m7G, m6Am, and m1A modifications are also involved in carcinogenesis and malignant progression. Furthermore, it is necessary to mention that m5C RNA modifications participate in tumorigenesis and development of other diseases. The specific patterns of m5C modifications could serve as biomarkers for cancer diagnosis, prognosis, and treatment response, allowing for more personalized therapeutic strategies. The m5C modifications could be targeted to sensitize them to chemotherapy and radiotherapy. Targeting the enzymes responsible for m5C modifications could lead to the development of novel anticancer drugs.

The regulation of m5C modifications is complex and not fully understood, which can complicate the development of targeted therapies. For example, drugs targeting m5C modifications might affect normal cells and tissues, leading to unintended side effects and toxicity. In addition, cancer cells might develop resistance to therapies targeting m5C modifications. Efficient and targeted delivery of m5C-modifying agents to cancer cells is a challenge, potentially limiting their therapeutic efficacy. While research is promising, there is still limited clinical data on the efficacy and safety of targeting m5C modifications in cancer therapy, requiring further investigation and clinical trials. In summary, an in-depth exploration of m5C modification in tumorigenesis could be important for discovering novel strategies for cancer treatment by targeting m5C RNA modification.

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Data availability statement

The data are available upon reasonable request.

CRediT authorship contribution statement

Li Yu: Writing – original draft, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hongen Xu:** Writing – original draft, Software, Resources, Methodology, Investigation, Formal analysis, Data curation. **Hanchu Xiong:** Resources, Methodology, Investigation, Formal analysis, Data curation. **Chunju Yang:** Resources, Investigation, Formal analysis, Data curation. **Ying Wu:** Resources, Methodology, Investigation, Formal analysis. **Qiong Zhang:** Writing – review & editing, Visualization, Validation, Supervision, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare no conflicts of interest.

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