REVIEW ARTICLE OPEN

RNA m5C methylation in cancer: mechanisms and biological impact

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RNA modification, a prominent epigenetic mechanism, has been implicated in regulating RNA function, stability, processing, and interactions, including pseudouridylation, acetylation, and methylation. Recent evidence highlights that 5-methylcytosine (m5C) influences key cellular processes such as proliferation, differentiation, apoptosis, and stress responses by modulating RNA stability, translation, transcription, nuclear export, and cleavage. This review consolidates current insights into the role and mechanisms of m5C methylation across various tumor types, underscoring its pivotal involvement in post-transcriptional regulation and its profound effects on gene expression, cellular dynamics, and tumor biology. The mechanisms through which m5C methylation impacts tumor progression, including modulation of glucose and iron metabolism, as well as resistance to therapeutic agents, are also discussed. Finally, the review identifies critical future research avenues, focusing on elucidating the underlying mechanisms, developing targeted therapies, and advancing personalized medicine approaches to leverage m5C methylation in cancer treatment.

Oncogenesis (2025)14:44 ; https://doi.org/10.1038/s41389-025-00587-w

INTRODUCTION

Epigenetics has transformed our understanding of gene regulation and cellular identity by focusing on modifications beyond the DNA sequence itself [1, 2]. These modifications regulate gene transcription, splicing, stability, and chromatin structure, influencing both physiological and pathological cellular processes. Common epigenetic modifications include DNA methylation, histone modifications, non-coding RNA modifications, and RNA modifications [3–5]. Among these, DNA methylation has been extensively studied due to its critical role in gene expression and chromatin dynamics. However, recent attention has increasingly turned to RNA methylation, which plays a pivotal role in post-transcriptional regulation and gene expression [6–8].

RNA methylation refers to a chemical modification process involving the addition of methyl groups to RNA molecules [6–12]. This modification regulates gene expression, maintains RNA stability, and plays critical roles in biological development, disease pathogenesis, and progression [13, 14]. Among these modifications, N6-methyladenosine (m6A) is the most prevalent and extensively studied RNA methylation in eukaryotes. It is distributed across diverse RNA types, including mRNA, long non-coding RNA (lncRNA), and circular RNA (circRNA). 5-methylcytosine (m5C) modifications are commonly found in tRNA, ribosomal RNA (rRNA), and specific regions of mRNA, where they influence RNA folding, stability, and protein interactions. In contrast, N1-methyladenosine (m1A) is a structurally distinct modification predominantly localized to tRNA and rRNA, where it alters RNA secondary structure and functional properties [14–17].

Among these modifications, m5C has emerged as a critical regulator of gene expression. Accumulating evidence indicates that m5C modulates RNA stability, translation, transcription, nuclear export, and cleavage, thereby influencing cellular proliferation, differentiation, apoptosis, stress responses, and other biological functions [18–22]. For example, one study demonstrated that Aly/REF (ALYREF) supports colorectal cancer (CRC) growth and migration by promoting RNA m5C recognition and nuclear export through recruitment of ELAVL1 [23]. Another study showed that enhancing RNA m5C modification via the NSUN2/ALYREF pathway promotes hexavalent chromium [Cr(VI)]-induced malignant transformation and lung cancer by accelerating metabolic reprogramming [24]. Furthermore, Xing et al. reported that NSUN2 regulates the Wnt signaling pathway through m5C modification, thereby promoting hepatocellular carcinoma (HCC) progression [25]. Building on these foundational findings, this review aims to consolidate current insights into the roles and mechanisms of m5C methylation across various tumor types. By synthesizing the latest research, the review seeks to provide a comprehensive understanding of how m5C methylation contributes to tumor development and progression, as well as its potential as a therapeutic target.

THREE REGULATORS OF RNA M5C; "READERS", "WRITERS" AND "ERASERS"

RNA methylation is mediated by three classes of proteins: "writers," which catalyze the addition of methyl groups; "readers," which

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Received: 26 May 2025 Revised: 10 October 2025 Accepted: 14 October 2025
Published online: 21 November 2025

recognize these modifications; and "erasers," which remove them (Table 1) [11, 26–29]. Each class of proteins operates through distinct mechanisms (Fig. 1). These proteins regulate various RNA types and associated signaling pathways, including mRNA, tRNA, lncRNA, and small RNAs (sRNAs) [15, 16, 29]. The expression levels of these regulators across different tumor types, along with their roles in tumor progression and impact on prognosis, are summarized in Table 2.

Writers

RNA cytosine methyltransferases (RCMTs) utilize S-adenosylmethionine (SAM) as a methyl donor to catalyze the methylation of the fifth carbon atom of cytosine, forming m5C. The "writers" of m5C methylation primarily consist of the NSUN family (NOP2/Sun RNA methyltransferase family members 1–7) and DNA methyltransferase 2 (DNMT2), which recognize specific RNA sequences or structures to catalyze m5C modifications.

NSUN1 (also known as NOP2, NOL1, or p120) primarily catalyzes m5C modification at position 4447 of 28S rRNA and participates in ribosome biogenesis. By forming non-catalytic complexes with box C/D small nucleolar RNAs (snoRNAs), NSUN1 regulates pre-rRNA processing, promotes the recruitment of U3 and U8 snoRNAs to pre-90S ribosomal particles, and maintains the stable assembly of snoRNP complexes [30].

NSUN2, one of the most extensively studied m5C methyltransferases, catalyzes m5C modifications on mRNA and non-coding RNAs such as tRNA and ribosomal RNA (rRNA) [31–33]. NSUN2 enhances mRNA stability and promotes nuclear export through m5C modifications. For example, NSUN2 stabilizes circular RNA 505 (circRNA505) via m5C modification and facilitates its nuclear transport through interaction with the binding protein ALY export/import factor (ALYREF) [33]. NSUN2-mediated tRNA modifications regulate tRNA conformation and function, improving mitochondrial tRNA translation efficiency [32].

NSUN3 specifically targets mitochondrial tRNA (mt-tRNA) for cytosine methylation, maintaining mitochondrial translation and oxidative phosphorylation (OXPHOS) [34].

NSUN4 modifies mitochondrial RNA (mtRNA), particularly the terminal m5C of light-strand lncRNA, recruiting polynucleotide phosphorylase (PNPase) via the C1QBP protein to regulate mitochondrial double-stranded RNA (mt-dsRNA) expression [35].

NSUN5 is a conserved rRNA methyltransferase that catalyzes m5C modification at position C3782 of human 28S rRNA and C3438 of mouse 28S rRNA [36]. In glioblastoma (GBM), NSUN5 knockdown significantly reduces protein synthesis, whereas overexpression enhances synthesis, suggesting that it directly regulates translational efficiency through rRNA methylation [37].

Previous studies have demonstrated that NSUN6 influences tRNA stability and function by methylating specific regions of tRNA, such as the variable loop or anticodon loop. This modification regulates tRNA folding and its interaction with ribosomes, thereby impacting translation efficiency [38]. Recent studies have revealed that NSUN6 not only targets tRNA but also specifically binds to the 3′ untranslated region (3′UTR) of mRNA, where it regulates mRNA stability and translation efficiency through m5C modification [39]. For example, in lung cancer, NSUN6 upregulates NM23-H1 expression by methylating m5C sites in the 3′UTR of NM23-H1 mRNA, thereby suppressing tumor cell proliferation, migration, and epithelial-mesenchymal transition (EMT) [40]. In cervical cancer, NSUN6 mediates m5C modification of the 3′UTR of NDRG1 mRNA, enhancing its binding to the m5C reader protein ALYREF. This interaction stabilizes NDRG1 mRNA, promoting homologous recombination repair and conferring resistance to radiotherapy [41]. In osteosarcoma (OS), NSUN6 maintains the stability of EEF1A2 mRNA in an m5C-dependent manner, driving tumor progression by activating the Akt/mTOR signaling pathway [42].

NSUN7 was initially identified as an enhancer RNA (eRNA) m5C methyltransferase [43]. In hepatocyte models, Aza-IP-seq combined with RNA immunoprecipitation quantitative PCR (RIP-qPCR) confirmed that NSUN7 specifically catalyzes m5C modifications on eRNAs associated with key genes such as PFK1, SIRT5, IDH3B, and HMOX2. Methylamp RNA bisulfite sequencing further demonstrated that NSUN7-mediated methylation significantly enhances the stability of these eRNAs.

DNMT2/TRDMT1, a member of the DNMT family, exhibits dual substrate specificity, methylating both DNA and RNA [44]. This suggests that other DNMT family members (e.g., DNMT1, DNMT3A, DNMT3B) may also possess RNA methylation activity, though their specific substrates and mechanisms require validation [45]. The NSUN family and DNMT2 regulate RNA metabolism and function by modifying distinct RNA molecules (mRNA, tRNA, rRNA), thereby influencing critical biological processes such as cell proliferation, mitochondrial energy metabolism, and DNA repair. Dysregulation of these enzymes is closely linked to cancer, neurodegenerative diseases, and metabolic disorders, highlighting their potential as therapeutic targets.

Readers

Readers recognize m5C-modified sites via specific domains to regulate RNA stability, localization, or translation. Core readers include ALYREF and Y-box binding protein 1 (YBX1).

ALYREF facilitates mRNA nucleocytoplasmic transport by recognizing m5C-modified mRNA. In nasopharyngeal carcinoma (NPC), ALYREF binds m5C sites on NOTCH1 mRNA, enhancing its stability and nuclear export [46]. Similar mechanisms are observed in esophageal cancer (EC), where ALYREF stabilizes TBL1XR1 and KMT2E mRNA by binding their m5C sites [47].

YBX1, a multifunctional m5C reader, plays key roles in cancer progression, viral replication, autophagy regulation, and bone metabolism. YBX1 stabilizes target mRNA by directly binding m5C sites. For example, in esophageal squamous cell carcinoma (ESCC), YBX1 stabilizes SMOX mRNA in an m5C-dependent manner, promoting tumor progression [48].

Serine/arginine-rich splicing factor 2 (SRSF2) is a validated m5C reader involved in RNA splicing and leukemogenesis. Leukemia-associated SRSF2 mutations (e.g., P95H) impair its binding to m5C-modified mRNA, reducing interactions with leukemia-related transcripts and potentially driving disease progression [49].

C1QBP (complement component 1Q binding protein) is identified as a reader of m5C-modified mitochondrial double-stranded RNA (mt-dsRNA). It recognizes NSUN4-catalyzed m5C sites (e.g., light-strand lncRNA termini) and recruits polynucleotide phosphorylase (PNPT1) to maintain mtRNA stability and mitochondrial gene expression [50].

In zebrafish, methyl-CpG binding domain protein 5 (MBD5) directly binds m5C-modified RNA, interacting with the Polycomb repressive deubiquitination (PR-DUB) complex to link RNA methylation with histone modifications (e.g., H2A-K119 ubiquitination) and transcriptional silencing [51].

Fragile X mental retardation protein (FMRP), a cytoplasmic RNA-binding protein, coordinates with the m5C writer TRDMT1 and eraser ten-eleven translocation 1 (TET1) to regulate mRNA-dependent DNA repair and cancer cell survival, revealing its role as a novel m5C reader [52, 53].

ALYREF and YBX1 are central readers in cancer, modulating epitranscriptomic regulation, chromatin interactions, and signaling pathways [54]. Their expression levels and functional states correlate with disease progression and treatment response, making them potential diagnostic markers and therapeutic targets [55].

Erasers

Erasers dynamically and reversibly regulate RNA methylation by removing m5C modifications. Key erasers include AlkB homolog 1 (ALKBH1) and the ten-eleven translocation (TET) family (TET1, TET2, TET3) [56, 57].

Table 1. Regulator proteins of RNA m5C methylation.

Category	Regulator	Target RNA	Function	Ref
Writers	NSUN1/NOP2	28S rRNA	Ribosomal biosynthesis	[30]
	NSUN2	mRNA/circRNA/tRNA	Enhance mRNA stability and promote the nuclear output of mRNA	[31–33]
	NSUN3	mt-tRNA	Affect mitochondrial translation and oxidative phosphorylation	[34]
	NSUN4	mt-mRNA/lncRNA	Stabilization of mtRNA by C1QBP/PNPase complex regulates mitochondrial metabolic reprogramming and antiviral immune response	[35]
	NSUN5	28S rRNA	Regulate ribosomal biosynthesis and translation fidelity	[36, 37]
	NSUN6	tRNA/mRNA	Regulation of tRNA folding and its interaction with ribosomes, which affects translation efficiency, and regulation of mRNA stability and translation efficiency	[38–42]
	NSUN7	eRNA	Enhance the stability of eRNA and promote its transcriptional activation	[43]
	DNMT2	tRNA-Asp (C38)/Viral RNA	Maintenance of translational fidelity and replication inhibition by methylated viral RNA	[44, 45]
Readers	ALYREF	mRNA	Promote the nucleoplasmic transport of mRNA	[46, 47]
	YBX1	mRNA	Bind and stabilize the target mRNA, promote its translation or inhibit degradation	[48]
	SRSF2	mRNA	Regulate processes such as RNA splicing and the occurrence of leukemia	[49]
	C1QBP	mt-RNA	Bind NSUN4-modified mtRNA to regulate mitochondrial RNA degradation and immune response balance.	[50]
	MBD5	mRNA	Mediates transcriptional silencing by linking RNA methylation to histone modifications via the PR-DUB complex.	[51]
	FMRP	mRNA	Regulating mRNA translation and stability	[52, 53]
Erasers	ALKBH1	tRNA/mRNA	Catalyze the oxidation of m5C to hm5C, regulate RNA stability, and participate in stress response and DNA damage repair.	[58, 59]
	TET1	caRNA	Oxidized m5C is hm5C/f5C, which synergizes with ALKBH1 to regulate RNA epigenetic modifications and affect gene silencing.	[52, 60]
	TET2	caRNA	Synergizes with NSUN5 in glioma to oxidize m5C-modified RNA and activate anti-tumor immunity	[60]
	TET3	mRNA	Functions similar to TET1/2, may be involved in developmental regulation and RNA metabolism, the specific mechanism needs to be further investigated	[60]

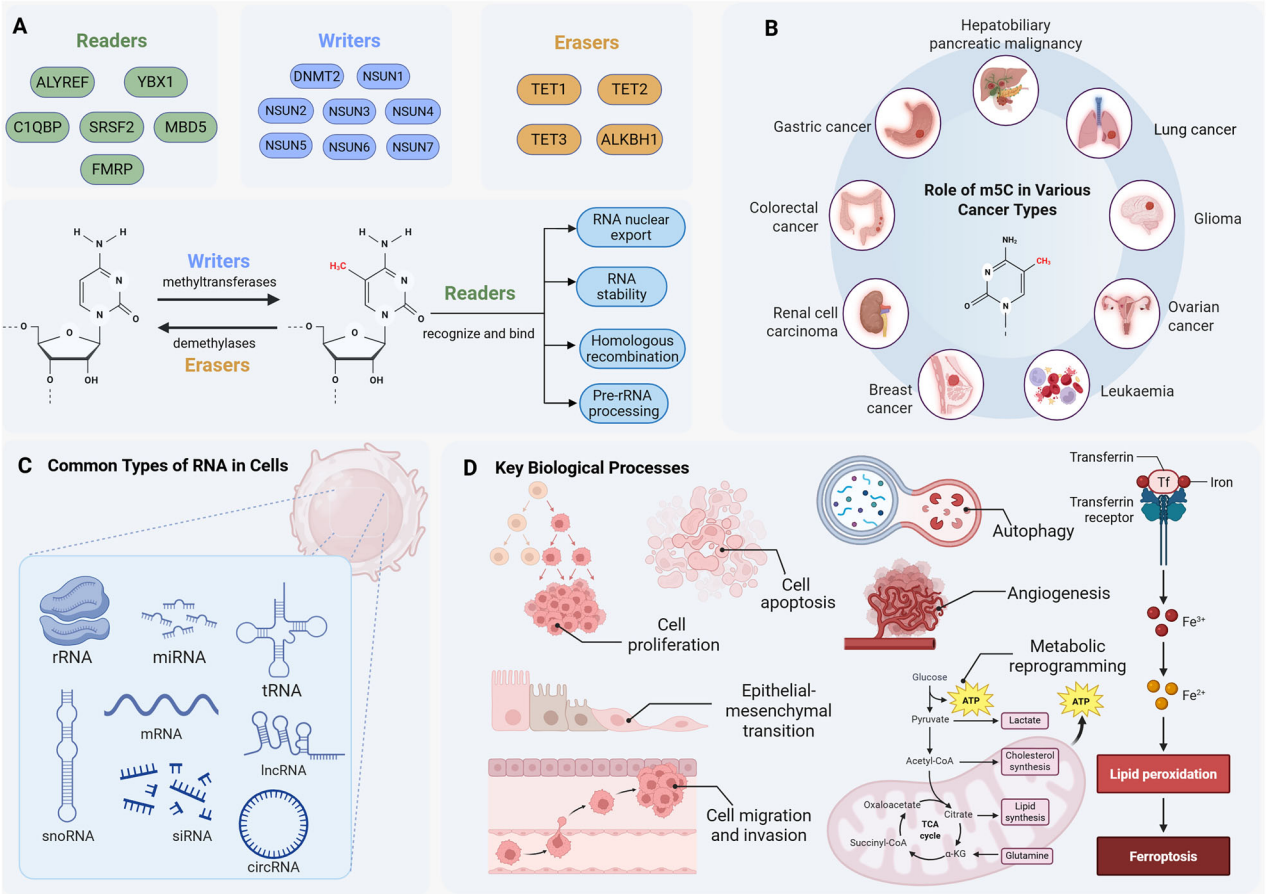

Fig. 1 Three regulators associated with RNA m5C methylation: the writer, reader, and eraser. A "Writers" are methyltransferase enzymes that catalyze the addition of m5C methylation modifications. "Erasers" are demethylases responsible for removing these modifications. "Readers" recognize and bind specific m5C methylations, influencing RNA export, stabilization, homologous recombination, and pre-rRNA processing. **B** The role of m5C in various cancer types. **C** Common types of RNA involved in m5C methylation modification in cells. **D** Key Biological Processes involved in m5C methylation modification in tumors. Created with BioRender.com.

ALKBH1, a key RNA m5C demethylase, oxidizes m5C to 5-hydroxymethylcytosine (hm5C) and 5-formylcytosine (f5C) via its α-ketoglutarate- and Fe(II)-dependent dioxygenase activity [58]. 5-ethynylcytidine (5-EC) labeling revealed ALKBH1's broad activity on tRNA and mRNA, particularly in ribosomal RNA processing and translational regulation [59].

TET proteins, initially known for oxidizing DNA 5-methylcytosine (5mC), also catalyze RNA m5C oxidation [60]. For example, TET2 binds chromatin-associated RNA (caRNA) to oxidize m5C to 5hmC, independent of its DNA methyltransferase activity [61]. TET2 dysfunction in gliomas reduces RNA m5C oxidation, potentially promoting tumor progression by altering oncogenic RNA stability [62].

Expression, regulation, and physiological functions of m5C machinery

The expression patterns of m5C regulators are not uniform and exhibit distinct tissue specificity, which underlies their context-dependent roles in oncogenesis. For instance, NSUN2 is highly expressed in tissues with inherently high regenerative and proliferative capacity, such as the testes, intestinal crypts, and skin [63]. This baseline expression profile predisposes these tissues to oncogenic transformation when NSUN2's pro-growth functions are further amplified. Conversely, the aberrant de novo activation or overexpression of such regulators in tissues where they are normally silent, such as NSUN2 in the lung or liver, can unleash potent oncogenic activity, driving aggressive tumor phenotypes. This paradigm of tissue-specific vulnerability, governed by the physiological expression landscape of the m5C regulatory machinery, provides a critical framework for understanding why certain cancers differentially depend on specific epitranscriptomic pathways.

The expression and activity of m5C regulatory factors are governed by a multi-layered regulatory system operating at transcriptional, post-transcriptional, and post-translational levels [64, 65]. At the transcriptional level, their genes are regulated by oncogenic and tumor-suppressive signaling pathways; for example, TET2 transcription is modulated by diverse cellular signals, and its promoter methylation status is frequently altered in cancer. At the post-transcriptional level, miRNAs and lncRNAs fine-tune mRNA stability and translation efficiency. Post-translational modifications (PTMs), meanwhile, provide a rapid and reversible mechanism to precisely regulate protein activity, stability, and subcellular localization. NSUN2 can be post-translationally modified through both lysyl oxidation by lactate and SUMOylation [37, 66, 67]. The reader protein ALYREF is subject to ubiquitination. Recent studies by Huang et al. have demonstrated that RNF31-mediated ubiquitination of ALYREF represents a promising therapeutic target for reversing paclitaxel resistance in triple-negative breast cancer [68]. Collectively, these examples highlight that PTMs represent a widespread and essential regulatory mechanism across all functional classes of the m5C machinery.

Loss-of-function studies underscore the critical physiological importance of m5C regulators. Genetic deletion of key writers such as NSUN2 or NSUN3, or readers like YBX1, in murine models

Table 2. The role of regulators in various cancer types.

Systerm	Cancer type	Regulators	Targets	Regulation axis	Functions	Expression alteration	Role	Clinical characters	Clinical sample size	Ref
Respiratory system	LUAD	NOP2	EZH2	NOP2/E2H2	Promote lung cancer progression	Up-regulation	Oncogene	Poor prognosis	43	[78]
		NSUN2	PIK3R2	MAZ/NSUN2/PI3K-AKT	Promote LUAD progression	Up-regulation	Oncogene	Poor prognosis	8	[74]
		NSUN2	YAP	NSUN2/ALYREF/YAP	Promote the transcription of exosome secretion-related genes in LUAD	Up-regulation	/	/	/	[75]
	LUSC	YBX1	PFKFB4	THOC3/YBX1/PFKFB4	Promote LUSC cell carcinoma progression	Up-regulation	Oncogene	Poor prognosis	90	[79]
	LC	NSUN2	ME1,GLUT3,CDK2	NSUN2/ALYREF/ME1,GLUT3,CDK2	Promote Cr(VI)-induced malignant transformation and LC	Up-regulation	Oncogene	Poor prognosis	120	[24]
		NSUN4	circERI3	NSUN4/circERI3/DDB1/PGC-1α	Promote the development of LC	Up-regulation	Oncogene	Poor prognosis	63	[76]
		NSUN6	NM23-H1	NSUN6/NM23-H1	Inhibite lung cancer cell proliferation, migration and EMT	Down-regulation	Antioncogene	/	/	[40]
	NSCLC	ALYREF	YAP1	LINC02159/ALYREF/YAP1/β-catenin	Promote NSCLC progression	Up-regulation	Oncogene	Poor prognosis	50	[77]
		NSUN2	NRF2	NSUN2/NRF2/YBX1	Govern proliferation, migration, and ferroptosis tolerance mediated by NSUN2 overexpression	Up-regulation	Oncogene	Poor prognosis	10	[82]
		NSUN2	QSOX1	NSUN2/YBX1/QSOX1	Mediate intrinsic resistance to gefitinib	Up-regulation	Oncogene	Poor prognosis	215	[80]
Digestive system	ESCC	YBX1	SMOX	YBX1/SMOX/mTORC1	Promote the proliferation and metastasis of ESCC cells	Up-regulation	Oncogene	Poor prognosis	16	[48]
		NSUN2	GRB2	NSUN2/GRB2/PI3K-AKT,ERK-MAPK	Enhances oncogenesis and progression in ESCC	/	/	/	/	[83]
		NSUN2	/	/	Promote ESCC progression and radiochemotherapy resistance	Up-regulation	Oncogene	Poor prognosis	94	[85]
		NSUN6	CDH1	NSUN6/tRNA/CDH1	Reduces tumor progression in ESCC	Down-regulation	Antioncogene	/	79	[84]
	GC	YBX1	SLC7A11 and G6PD	HCP5-132aa/YBX1/ELAVL1/SLC7A11,G6PD	Drive the progression of GC	Up-regulation	Oncogene	Poor prognosis	70	[86]
		NSUN2	p57Kip2	NSUN2/p57Kip2	Promote GC cell proliferation	Up-regulation	Oncogene	Poor prognosis	20	[87]
		NSUN2	ERK1/2	NSUN2/ERK1/2	Promote chemosensitivity in GC	Up-regulation	Oncogene	Poor prognosis	30	[88]

Table 2. continued

Systerm	Cancer type	Regulators	Targets	Regulation axis	Functions	Expression alteration	Role	Clinical characters	Clinical sample size	Ref
		NSUN2	NR_033928	NSUN2/NR 033928	Promote GC proliferation	Up-regulation	Oncogene	Poor prognosis	24	[89]
		NSUN2	ORAI2	NSUN2/YBX1/ORAI2	Promote peritoneal metastasis and colonization of GC	Up-regulation	Oncogene	Poor prognosis	/	[90]
		NSUN2	NTN1	DIAPH2-AS1/ NSUN2/NTN1	Promote neural invasion of GC	Up-regulation	Oncogene	Poor prognosis	84	[91]
		NSUN5		NSUN5/WNT	Promote tumorigenic phenotypes	Up-regulation	/	Poor prognosis	80	[158]
	COAD	NSUN6	METTL3	NSUN6/METTL3	Promote the cell cycle progression and cell proliferation of COAD	Up-regulation	Oncogene	/	/	[92]
	CRC	ALYREF	RPS6KB2,RPTOR	ALYREF/ELAVL1/ m5C	Promote colorectal tumorigenesis	Up-regulation	Oncogene	Poor prognosis	88	[23]
		NSUN2	ENO1	NSUN2/YBX1/m5C-ENO1	Promote the Progression of CRC	Up-regulation	Oncogene	Poor prognosis	126	[93]
		NSUN2	SKIL	NSUN2/SKIL/TAZ	Promote CRC progression	Up-regulation	Oncogene	Poor prognosis	267	[94]
		NSUN5	/	NSUN5/cell cycle-related pathway	Promote cell proliferation in CRC	Up-regulation	/	Poor prognosis	30	[159]
	HCC	ALYREF	/	/	Promote HCC progression	Up-regulation	/	Poor prognosis	34	[64]
		ALYREF	EGFR	ALYREF/EGFR/STAT3	Promote the progression of human LIHC	Up-regulation	Oncogene	Poor prognosis and malignant characteristics	27	[96]
		NOP2	XPD	NOP2/XPD	Inhibit proliferation, migration, and invasion of HCC cells	Down-regulation	/	Poor prognosis	36	[97]
		NSUN2	SREBP2	LINC00618/NSUN2/ SREBP2	Promote HCC growth and metastasis	Up-regulation	Oncogene	Poor prognosis	30	[98]
		NSUN2	/	/	Affect the sensitivity of HCC cells to sorafenib	Up-regulation	Oncogene	/	20	[99]
		NSUN2	H19 lncRNA	NSUN2/H19 RNA	Promote the occurrence and development of tumors	Up-regulation	Oncogene	Poor differentiation	55	[100]
	CCA	NSUN2	NKILA	NSUN2/NKILA/miR-582-3p/YAP1	Accelerate CCA progression	Up-regulation	Oncogene	Poor prognosis	84	[101]
	PC	YBX1	/	PIAT/YBX1/ EGR1,NTRK1,SMAD7	Drive neural remodeling	Up-regulation	Oncogene	Poor prognosis	90	[103]
		NSUN2	TIAM2	NSUN2/TIAM2	Stimulate PC progression	Up-regulation	Oncogene	Poor prognosis	90	[102]
	PDAC	ALYREF	JunD	ALYREF/JunD/ SLC7A5/mTORC1	Promote PDAC progression	Up-regulation	Oncogene	Poor prognosis and immunosuppression	20	[104]

Table 2. continued

Systerm	Cancer type	Regulators	Targets	Regulation axis	Functions	Expression alteration	Role	Clinical characters	Clinical sample size	Ref
Urinary system	ccRCC	YBX1	PEBP1	STAT4/PEBP1P2/YBX1/ELAVL1/PEBP1	Inhibit migration, invasion, and metastasis formation of ccRCC	Down-regulation	Antioncogene	/	21	[85]
		NOP2	APOL1	NOP2/APOL1/PI3K-Akt	Promote tumor progression	Up-regulation	Oncogene	Poor prognosis	90	[105]
	PCa	NSUN2	AR	NSUN2/AR	Promote PCa progression	Up-regulation	Oncogene	Poor prognosis	88	[109]
		NSUN5	ACC1	CDK13/NSUN5/ACC1	Increase in ACC1 expression and lipid deposition in PCa cells	Up-regulation	Oncogene	Poor prognosis	/	[110]
	BCa	ALYREF	PKM2	HIF-1α/ALYREF/PKM2	Promote glycolysis and tumorigenesis	Up-regulation	Oncogene	Poor prognosis	162	[107]
	BCa	NSUN2	HDGF	NSUN2/YBX1/HDGF	Promote pathogenesis of BCa	Up-regulation	Oncogene		36	[108]
Female reproductive system	BC	NSUN2	HGH1	NSUN2/HGH1	Promote the malignant phenotype of BC	Up-regulation	Oncogene	Poor prognosis	5	[111]
	TNBC	YBX1	mTOR	SAT1/YBX1/mTOR	Promote TNBC progression	Up-regulation	Oncogene	Poor prognosis	100	[112]
	ATC	NSUN2	c-Myc	NSUN2/tRNA	Enhance ATC growth and formation	Up-regulation	Oncogene	Poor prognosis	9	[123]
	BLCA	NSUN6	HDAC10	NSUN6/HDAC10	Orchestrate BLCA progression	/	/	/	/	[160]
	CC	NSUN2	LRRC8A	NSUN2/LRRC8A/PI3K/AKT	Suppress apoptosis and facilitates tumorigenesis in CC	Up-regulation	Oncogene	Poor prognosis	/	[113]
	CC	NSUN6	NDRG1	NSUN6/ALYREF/NDRG1	Promote radioresistance in CC	Up-regulation	Oncogene	Radioresistance	42	[41]
	EC	NSUN2	SLC7A11	NSUN2/YBX1/SLC7A11	Inhibit tumor growth	Up-regulation	Oncogene	Poor prognosis	/	[114]
	OC	YBX1	CHD3	YBX1/CHD3	Facilitate tumor cells to withstand platinum-induced apoptotic stress	Up-regulation	Oncogene	Poor prognosis	315	[115]
	OC	NSUN2	E2F1	NSUN2/E2F1/NSUN2	Promote tumor progression in OC	Up-regulation	Oncogene	Poor prognosis	161	[96]
Nervous system	Glioblastoma	NSUN2	LINC00324	NSUN2/LINC00324/CBX3	Promote angiogenesis in glioma	/	/	/	/	[117]
	Glioma	NSUN4	CDC42	NSUN4/ALYREF/CDC42/PI3K-AKT	Promote the malignant progression of glioma	Up-regulation	Oncogene	Poor prognosis	30	[62]
	Glioma	NSUN5	β-catenin,RBFOX2	NSUN5/TET2/RBFOX2	Boost the phagocytic activity of TAMs in glioma	Down-regulation	Antioncogene	/	/	[60]

Table 2. continued

Systerm	Cancer type	Regulators	Targets	Regulation axis	Functions	Expression alteration	Role	Clinical characters	Clinical sample size	Ref
Blood system	MM	NSUN2	MALT1	NSUN2/YBX1/MALAT1	Bone destruction in MM	Up-regulation	Oncogene	Poor prognosis	36	[118]
	Leukaemia	TET2	MBD6	NSUN2/TET2/MBD6/BAP1	Regulate chromatin state and leukaemogenesis	Down-regulation	Antioncogene	Poor prognosis	/	[119]
	Leukaemia	TET2	TSPAN13	TET2/TSPAN13	Regulate leukemia stem cell homing and self-renewal	Down-regulation	Antioncogene	Poor prognosis	4	[161]
Other cancer types	OS	NSUN2	FABP5	NSUN2/FABP5	Promote fatty acid metabolism in OS cells, and promote the progression of OS.	Up-regulation	Oncogene	Poor prognosis	48	[120]
	HNSCC	NSUN3	M1,M2 macrophages	NSUN3/M1,M2	Promote proliferation and growth of HNSCC cells	Up-regulation	Oncogene	Poor prognosis	93	[162]
	HPSCC	NSUN2	TEAD1	NSUN2/TEAD1	Promote the proliferation and invasion of HPSCC	Up-regulation	Oncogene	Poor prognosis	65	[124]
	NPC	ALYREF	NOTCH1	ALYREF/NOTCH1	Promote metastasis	Up-regulation	Oncogene	Poor prognosis	32	[105]
	UM	NSUN2	CTNNB1	NSUN2/CTNNB1	Regulate UM cell proliferation and migration	Up-regulation	Oncogene	Poor prognosis	7	[122]
	RB	NSUN2	PFAS	NSUN2/PFAS	Dictate retinoblastoma progression	Up-regulation	Oncogene	Poor prognosis	3	[121]

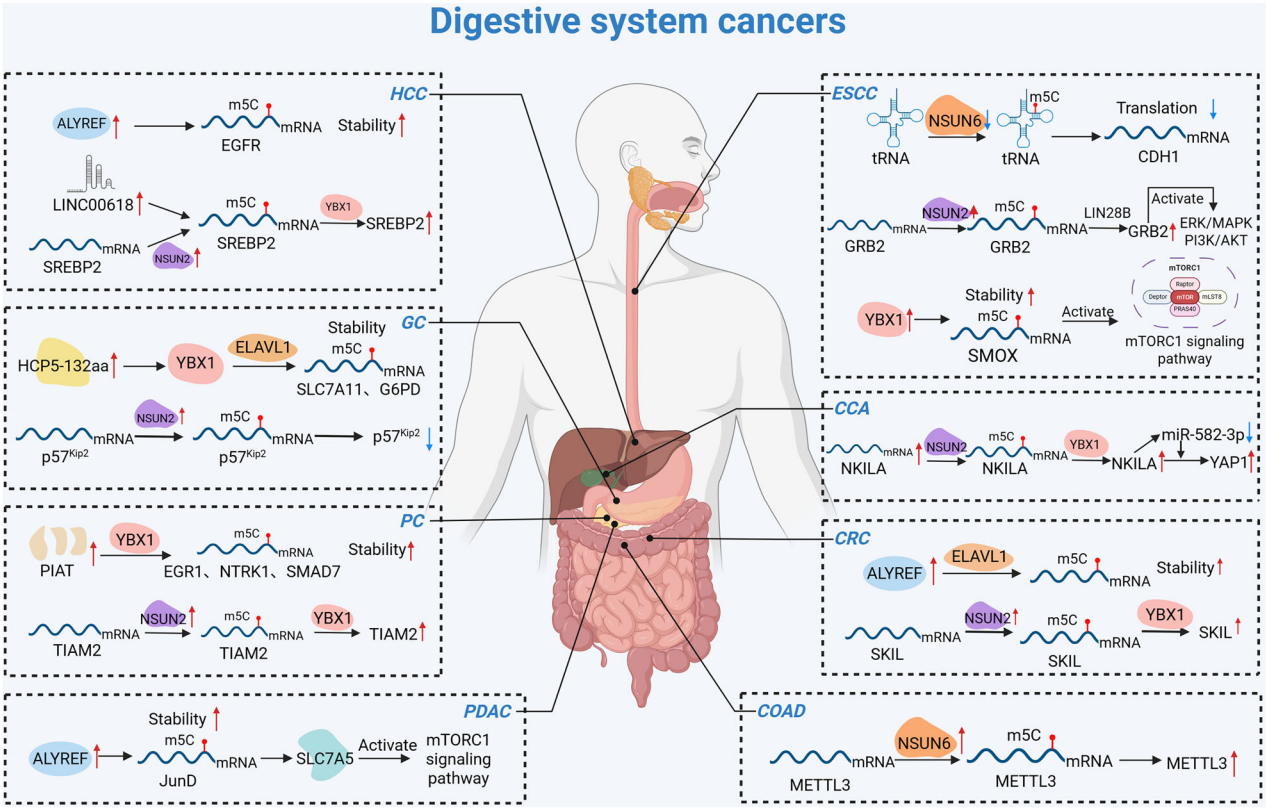

Fig. 2 Mechanism of abnormal RNA m5C methylation modification involved in digestive system cancer. In Esophageal squamous cell carcinoma, YBX1 promotes ESCC progression via m5C-dependent SMOX mRNA stabilization. NSUN2-mediated RNA m5C promotes cancer progression via LIN28B-dependent GRB2 mRNA stabilization.NSUN6 mediated tRNA m5C modifications selectively enhance the translation efficiency of CDH1 mRNA in a codon dependent manner. In hepatocellular carcinoma, ALYREF-mediated RNA m5C modification promotes cancer progression via stabilizing EGFR mRNA and pSTAT3 activation. In addition, LINC00618 promotes the growth and metastasis of hepatocellular carcinoma by promoting NSUN2-mediated SREBP2 m5C modification and by enhancing cholesterol synthesis. These examples highlight the complex role of RNA m5C methylation in regulating the development of various gastrointestinal cancers. Created with BioRender.com.

leads to embryonic lethality or severe postnatal phenotypes, including growth retardation and neurological deficits [69–71]. These outcomes demonstrate that m5C regulators perform non-redundant functions in fundamental biological processes, including protein synthesis, mitochondrial metabolism, and embryonic development. Therefore, their dysregulation in cancer typically does not confer novel oncogenic activities but rather reflects the aberrant activation or amplification of pre-existing physiological programs.

Moreover, the genes encoding m5C regulators are themselves frequent targets of genetic alterations in cancer. Somatic mutations lead to inactivation of erasers such as TET2 in myeloid leukemias, while copy number alterations result in amplification and overexpression of writers like NSUN2 and readers such as YBX1 across various solid tumors. These recurrent genomic changes provide strong evidence that m5C regulators act as bona fide drivers of tumorigenesis and are central to understanding the pathophysiological consequences of m5C epitranscriptomic dysregulation.

Role of m5C in various cancer types

The dysregulation of m5C methylation is a hallmark of numerous cancers, driven by aberrant expression, mutations, or altered activity of its regulatory machinery [72]. Although the specific target RNAs and downstream pathways differ across cancer types, recurring mechanistic themes have emerged. m5C modifications primarily promote tumorigenesis by enhancing the stability and translational efficiency of oncogenic transcripts, facilitating their nuclear export, and optimizing the translation of proteins critical for cell proliferation, survival, and metabolic reprogramming [6, 18, 73]. The following sections will examine these roles in a tissue-specific manner, highlighting both context-specific adaptations and conserved molecular principles that define the contribution of m5C to cancer biology (Table 2) (Figs. 2 and 3).

Respiratory system

m5C methylation exerts multidimensional roles in the initiation and progression of lung cancer by regulating RNA stability, metabolic reprogramming, and activation of key signaling pathways. Its dynamic regulatory network involves the coordinated actions of methyltransferases, recognition proteins, and downstream effector molecules, exhibiting high heterogeneity across different lung cancer subtypes.

As a core Writer protein, NSUN2 drives lung cancer progression by targeting m5C modifications of key oncogenes. For instance, NSUN2 activates the PI3K-AKT signaling pathway by stabilizing PIK3R2 mRNA, promoting malignant transformation in LUAD [74]. Simultaneously, its synergistic interaction with ALYREF regulates YAP mRNA methylation, enhancing Hippo pathway activation mediated by YAP expression and inducing AZD9291 resistance via exosome secretion [75]. Notably, other NSUN family members exhibit differential regulation in lung cancer: NSUN4 remodels mitochondrial energy metabolism through the circERI3-DDB1-PGC-1α axis to promote tumorigenesis [76], while NSUN6 suppresses lung cancer cell proliferation and EMT by modifying the 3′ UTR of NM23-H1 mRNA, suggesting dual tumor-suppressive

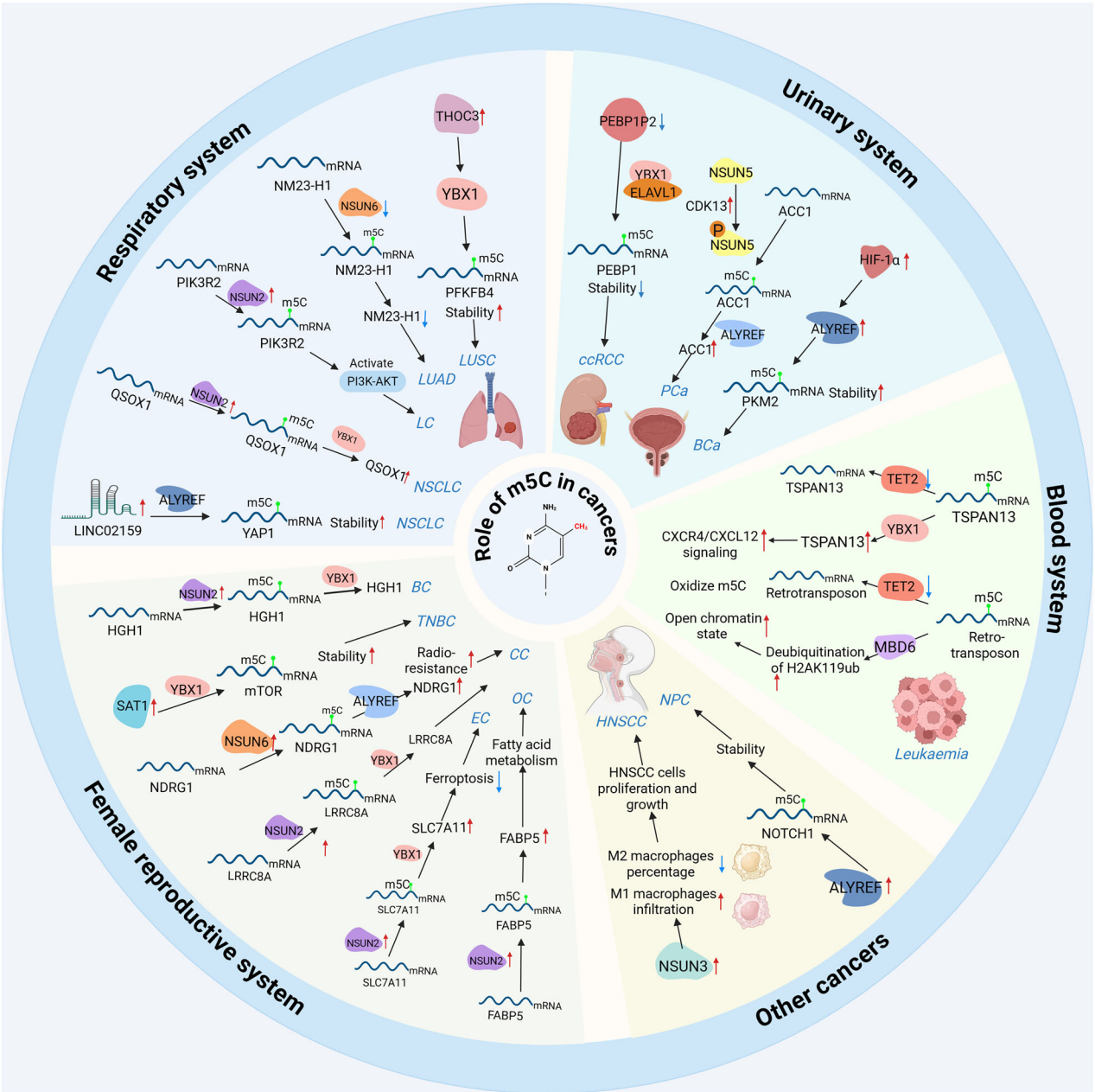

Fig. 3 Abnormal RNA m5C methylation modification is involved in respiratory, urinary, nervous, female reproductive system, and other cancer mechanisms. THOC3 promotes the progression of lung squamous cell carcinoma by modifying PFKFB4 mRNA and interacting with YBX1. The m5C modification in PKM2 mRNA in the HIF-1α/ALYREF/PKM2 axis promotes the glucose metabolism of bladder cancer. In breast cancer, NSUN2/YBX1 enhances the stability of HGH1 mRNA through m5C methylation, thus promoting cancer progression. In head and neck squamous cell carcinoma, NSUN3 promotes tumor progression by regulating the immune invasion of the cancer. These examples highlight the complex role of RNA m5C methylation in regulating the development of other types of cancer. Created with BioRender.com.

and oncogenic functions within this family [40]. The oncogenic effects of m5C modifications depend on Reader proteins for target RNA recognition and stabilization. For example, ALYREF enhances YAP1 mRNA stability by binding LINC02159, activating the Hippo/β-catenin signaling axis to drive NSCLC progression [77], while its collaboration with NOP2 stabilizes EZH2 mRNA to promote EMT [78]. Another critical Reader protein, YBX1, promotes glycolysis and tumor growth in LUSC by recognizing the 3′ UTR m5C site of PFKFB4 mRNA [79]. Additionally, the m5C-YBX1 regulatory axis formed by YBX1 and NSUN2 sustains NRF2 and QSOX1 expression, conferring resistance to ferroptosis and gefitinib in NSCLC cells [80–82], highlighting the close link between m5C modifications and oxidative stress or targeted therapy resistance. m5C methylation profoundly influences metabolic adaptability in lung cancer cells by regulating the stability of metabolic enzyme-encoding RNAs. For instance, THOC3 synergizes with YBX1 to facilitate PFKFB4 mRNA nucleocytoplasmic transport and stabilization, enhancing glycolytic capacity in LUSC [79], while NSUN4-mediated transcriptional activation of mitochondrial PGC-1α drives oxidative phosphorylation reprogramming [76]. Notably, m5C modifications also enable intercellular regulation via exosomes. NSUN2/ALYREF-regulated YAP mRNA transmitted via exosomes to neighboring cells may remodel the tumor immune microenvironment and promote drug-resistant clone expansion [75], underscoring the transcellular regulatory functions of m5C modifications in the lung cancer ecosystem.

Digestive system

In ESCC, m5C modifications drive tumor progression through a multidimensional regulatory network. Studies reveal that YBX1 stabilizes SMOX mRNA in an m5C-dependent manner, activating polyamine metabolism to promote ESCC development [48]. Notably, this process is not isolated; NSUN2, as a key methyltransferase, enhances GRB2 mRNA stability via a LIN28B-mediated mechanism, forming a positive feedback loop in growth signaling pathways [83]. Further research demonstrates that m5C regulation extends beyond mRNA stability: NSUN6-mediated tRNA m5C modifications significantly enhance CDH1 mRNA translation efficiency through codon preference selection, uncovering a novel dimension of epigenetic regulation at the protein translation level [84]. Importantly, NSUN2 genetic variants (cis-eQTL) not only promote ESCC progression via mRNA methylation but also correlate with radiotherapy resistance, providing an epigenetic explanation for clinical treatment resistance mechanisms [85].

In gastric cancer (GC), the m5C regulatory network exhibits complex hierarchical interactions. The HCP5-132aa protein bridges YBX1 and ELAVL1 to form a ternary complex that specifically recognizes m5C sites on SLC7A11 and G6PD mRNA. This synergy stabilizes ferroptosis-related transcripts and drives tumor progression via metabolic reprogramming [86]. Meanwhile, NSUN2 participates in gastric carcinogenesis through dual mechanisms: suppressing CDKN1C expression to relieve cell cycle arrest [81, 87] and modulating the Bcl-2/Bax balance to influence chemotherapy sensitivity [88]. Notably, m5C regulation extends to non-coding RNAs-methylated lncRNA NR_033928 remodels glutamine metabolism by stabilizing GLS mRNA, revealing crosstalk between metabolic reprogramming and epigenetic regulation [89]. In the tumor microenvironment, peritoneal adipocytes promote GC peritoneal metastasis via the AMPK/NSUN2/ORAI2 axis, connecting energy-sensing mechanisms with m5C networks [90]. Remarkably, the interaction between DIAPH2-AS1 and NSUN2 stabilizes NTN1 mRNA via ubiquitination regulation, offering new molecular insights into neural invasion mechanisms [91].

In CRC, the m5C regulatory network exhibits unique positive feedback features. NSUN6 not only catalyzes METTL3 m5C modifications to form an oncogenic loop [92], but its synergy with ALYREF enhances RPS6KB2/RPTOR mRNA export via nucleocytoplasmic transport mechanisms, highlighting the role of nuclear transport systems in epigenetic regulation [23]. More intricately, the NSUN2/YBX1/m5C-ENO1 signaling loop establishes a self-sustaining mechanism through histone H3K18 lactylation, dynamically coupling metabolic products with epigenetic modifications [93]. This multi-tiered regulation is further evidenced in SKIL mRNA stability control, confirming the central role of m5C networks in maintaining oncogenic transcripts [94]. Notably, m5C modifications on NXPH4 mRNA influence SQSTM1-mediated RNA autophagy, opening new research directions at the intersection of epigenetic regulation and autophagy [95].

In HCC, m5C modifications exhibit multi-target regulatory properties. ALYREF stabilizes EGFR mRNA to activate the STAT3 pathway, establishing an epigenetic-signal transduction axis [96], while NOP2-mediated XPD mRNA methylation reveals potential links between DNA repair mechanisms and epigenetic regulation [97]. At the metabolic level, the LINC00618/NSUN2 axis drives cholesterol synthesis by stabilizing SREBP2 mRNA, integrating non-coding RNA regulation with lipid metabolism reprogramming [98]. Importantly, NSUN2 modulates key Ras pathway nodes to influence sorafenib sensitivity, offering new strategies for targeted therapy [99]. Additionally, m5C modifications on H19 lncRNA drive tumor progression via the G3BP1/MYC axis, underscoring the pivotal role of non-coding RNA epigenetic modifications in oncogenic networks [100].

In other digestive tumors, m5C networks also play critical roles. In cholangiocarcinoma (CCA), NSUN2 promotes YBX1 binding by modifying NKILA, with its expression significantly correlating with clinical stage and metastasis [101]. In pancreatic cancer (PC), the NSUN2-TIAM2 axis and PIAT/YBX1-mediated neural invasion mechanisms form a complex progression network [102, 103]. Notably, ALYREF alters tumor microenvironment amino acid metabolism via the m5C-dependent JunD/SLC7A5 axis, revealing a novel mechanism by which epigenetic regulation influences immune microenvironments [104].

Urinary system

The study by Tian et al. first elucidated that NOP2 drives clear cell renal cell carcinoma (ccRCC) progression by stabilizing APOL1 mRNA via m5C modifications, activating the PI3K-Akt signaling axis and revealing interactions between epigenetic regulation and classical oncogenic pathways [105]. Notably, this regulatory mechanism exhibits multi-target specificity in ccRCC. The Yang team further discovered that PEBP1P2 downregulation promotes tumor metastasis by stabilizing PEBP1/KLF13 mRNA, suggesting that m5C modifications in ccRCC may form a hierarchical regulatory network through spatiotemporal-specific control of different targets [106]. Together, these studies outline dual dimensions of m5C regulation in ccRCC: directly activating signaling pathways to drive progression while modulating metastasis-related genes to influence disease evolution.

In bladder cancer research, the m5C network displays unique metabolic intervention properties. Wang et al. demonstrated that ALYREF-mediated PKM2 mRNA methylation enhances glycolysis to promote tumor proliferation, a process closely linked to the synergistic action of the YBX1/ELAVL1 complex [107]. Correspondingly, the Chen team revealed that the NSUN2/YBX1 axis targets the 3′ UTR m5C site of HDGF mRNA, constructing an epigenetic-clinical prognostic association network in urothelial carcinoma of the bladder (UCB). High expression of the triple marker (NSUN2/YBX1/HDGF) correlates significantly with poor patient survival [108]. These studies collectively delineate dual regulatory dimensions of m5C in bladder cancer: driving malignant phenotypes via metabolic reprogramming and influencing clinical outcomes through oncogenic transcript stabilization.

Prostate cancer research reveals self-reinforcing features of m5C modifications. Zhu et al. found that NSUN2 establishes a positive feedback loop by clustering m5C modifications on AR mRNA, dynamically coupling androgen signaling with epigenetic regulation [109]. Building on this, the Zhang team further dissected metabolic regulation: CDK13-mediated NSUN5 phosphorylation enhances lipid synthesis via ACC1 mRNA methylation, with ALYREF-dependent nuclear export playing a critical role [110]. This "kinase-methyltransferase-transporter" triad not only clarifies the epigenetic basis of lipid metabolic dysregulation in prostate cancer but also provides a theoretical foundation for combination therapies targeting the m5C network.

Female reproductive system

The role of m5C modifications in female reproductive cancers extends across multiple molecular pathways and cancer subtypes. For instance, NSUN2-YBX1 protein interactions have been identified as critical drivers of breast cancer progression, where they modulate HGH1 expression through site-specific m5C modifications [111]. Expanding on the oncogenic role of YBX1 in hormone-related cancers, subsequent studies revealed that SAT1 (spermidine/arginine N1-acetyltransferase 1) acts as a pivotal regulator in triple-negative breast cancer (TNBC) invasion by engaging the SAT1/YBX1/mTOR axis, highlighting its potential as a therapeutic target [112]. Beyond breast cancer, m5C-mediated RNA stabilization mechanisms also dominate in cervical cancer pathogenesis. Yu et al. demonstrated that NSUN6 induces m5C modifications in NDRG1 mRNA, enabling ALYREF binding to enhance mRNA stability, which promotes homologous recombination-mediated DNA repair and radioresistance [41]. This

aligns with findings by Chen et al., who reported that NSUN2 upregulates LRRC8A protein levels via m5C modifications, with YBX1 further stabilizing LRRC8A RNA. Depleting NSUN2 suppressed cervical cancer proliferation and metastasis, underscoring the clinical relevance of the NSUN2-LRRC8A axis [113]. In endometrial cancer, m5C modifications take on a distinct role in apoptosis resistance. Chen et al. linked NSUN2-mediated m5C modifications of SLC7A11 mRNA to iron-induced apoptosis evasion, revealing an epigenetic mechanism underlying therapeutic resistance [114]. Similarly, in ovarian cancer, Meng et al. demonstrated that YBX1 recognizes m5C-modified CHD3 mRNA, stabilizing it via PABPC1 recruitment to enhance chromatin accessibility and homologous recombination repair. This process enables ovarian cancer cells to resist platinum-induced apoptosis, offering a mechanistic basis for overcoming chemoresistance [115]. Further emphasizing the interplay between m5C writers and transcription factors, Liu et al. uncovered a self-reinforcing loop in ovarian cancer: NSUN2 stabilizes E2F1 mRNA via m5C modifications, while E2F1 reciprocally activates NSUN2 transcription, accelerating tumor progression [116].

Nervous system

m5C modifications also play context-dependent roles in gliomas by regulating angiogenesis and immune evasion. A notable example involves glioblastoma endothelial cells (GECs), where Pan et al. observed elevated NSUN2 and LINC00324 levels. NSUN2 stabilizes LINC00324 through m5C modifications, which in turn protects CBX3 mRNA from degradation by competing with AUH binding. CBX3 then activates VEGFR2 transcription to drive angiogenesis, positioning this axis as a therapeutic target [117]. Conversely, in glioma immune regulation, Wu's group revealed that NSUN5 suppresses tumor growth by promoting CTNNB1 (β-catenin) mRNA degradation. NSUN5-mediated m5C modifications enable TET2 to oxidize m5C to 5hmC on caRNA, which recruits RBFOX2 to degrade these transcripts. This NSUN5/TET2/RBFOX2 network enhances phagocytosis by tumor-associated macrophages (TAMs), suggesting a dual role for m5C in both tumor promotion and immune activation [60].

Blood system

In hematological malignancies, m5C modifications influence both tumor cell behavior and microenvironmental interactions. For instance, Yu et al. demonstrated that NSUN2 and YBX1 upregulate LncRNA MALAT1 via m5C in multiple myeloma (MM) cells. MALAT1 is shuttled to osteoclasts via exosomes, exacerbating bone destruction—a key clinical complication in MM [118]. Beyond RNA stability, m5C also regulates chromatin dynamics in leukemia. Zou et al. discovered that m5C-modified anti-transposon RNA recruits MBD6 to deubiquitinate H2AK119ub, enhancing chromatin accessibility. TET2 counteracts this by oxidizing m5C, and its loss in leukemias creates dependency on MBD6-mediated gene activation. Targeting MBD6 selectively inhibits TET2-mutated leukemia growth, offering a precision therapy strategy [119].

The critical role of TET2 mutations in leukemia highlights the broader pathophysiological consequences of genetic alterations in m5C regulators. Somatic mutations in the m5C eraser TET2 are among the most frequent epigenetic alterations in hematological malignancies, particularly in myeloproliferative neoplasms (MPNs) and acute myeloid leukemia (AML). These loss-of-function mutations disrupt normal hematopoietic differentiation and are recognized as early drivers of leukemogenesis. While the role of TET2 in DNA demethylation is well established, its function as an RNA m5C eraser adds a crucial layer to its tumor-suppressive activity. The consequent loss of TET2-mediated RNA demethylation contributes to the stabilization of oncogenic transcripts and creates a therapeutic vulnerability—such as dependency on the MBD6 pathway—as described above [119]. This paradigm underscores that beyond the expression levels of the m5C machinery, the genetic alteration status of these regulators (e.g., mutations in TET2 or SRSF2 49) is central to understanding disease etiology and to developing targeted therapies for specific molecular subtypes of leukemia.

Other cancer types

The oncogenic impact of m5C extends to diverse solid tumors through metabolic and translational reprogramming. In osteosarcoma, Yang et al. found that NSUN2 stabilizes FABP5 mRNA via m5C, enhancing fatty acid metabolism to fuel tumor progression [81, 120]. Similarly, in retinoblastoma, Zuo et al. linked NSUN2-mediated PFAS mRNA methylation to increased stability and tumor aggressiveness [121]. Uveal melanoma provides another example, where NSUN2 knockdown reduces m5C levels, impairing migration and proliferation by destabilizing β-catenin (CTNNB1) mRNA [122]. In thyroid cancer, NSUN2 supports anaplastic thyroid cancer (ATC) progression by stabilizing tRNAs, which sustain pro-oncogenic translation programs (e.g., c-Myc, BCL2). NSUN2 depletion sensitizes ATC to genotoxic drugs, highlighting its role in therapeutic resistance [21, 123]. Finally, in nasopharyngeal and hypopharyngeal cancers, ALYREF and NSUN2 drive metastasis by stabilizing NOTCH1 RNA and upregulating TEAD1, respectively, through m5C-dependent mechanisms [105, 124].

In summary, despite the vast heterogeneity of cancer types and tissue origins, the oncogenic roles of m5C methylation converge on several fundamental mechanisms that transcend cellular context. A central theme is the pervasive function of m5C in enhancing the stability and translational efficiency of a diverse repertoire of oncogenic transcripts, including messenger RNAs, long non-coding RNAs, and circular RNAs. This epitranscriptomic enhancement fuels core hallmarks of cancer, most notably sustained proliferative signaling, metabolic reprogramming such as enhanced glycolysis, glutaminolysis, and lipid synthesis, and activation of key oncogenic pathways such as the PI3K-Akt, Hippo-YAP, and Wnt-β-catenin pathways. Furthermore, m5C modifications are intricately linked to therapy resistance, mediating evasion from ferroptosis and apoptosis, as well as resistance to targeted therapies including EGFR tyrosine kinase inhibitors and platinum-based chemotherapy. The functional output is orchestrated by a limited set of highly conserved regulator axes, particularly the NSUN2-ALYREF and NSUN2-YBX1 complexes, which emerge as central nodes coordinating RNA nuclear export, stability, and translation. Importantly, the context-dependent consequences of m5C dysregulation are dictated by the specific target RNAs methylated in different tissues, explaining how a common mechanism can drive a wide spectrum of cancer phenotypes. This synthesis underscores that m5C methylation is not merely a passive marker but a dynamic and powerful effector of tumorigenesis, positioning the m5C machinery as a compelling target for the development of novel epigenetic therapies across cancer types.

DIFFERENT MECHANISMS OF ACTION OF M5C AFFECTING TUMOR PROGRESSION

Emerging research suggests that RNA m5C modifications can influence tumor formation and progression through various complex mechanisms [20, 125]. This compendium highlights recent studies categorized by their mechanisms of action (Fig. 4), which include influencing tumor cell proliferation, migration, invasion, metabolic reprogramming, EMT, ferroptosis, resistance to therapy, and other regulatory pathways (Table 3).

Cell proliferation, migration, and invasion

Cell proliferation refers to the process by which cells divide to produce new cells [126]. Cell migration is the movement of cells triggered by migration signals or the sensing of a substance gradient [126–130]. Cell invasion involves the ability of a cell to

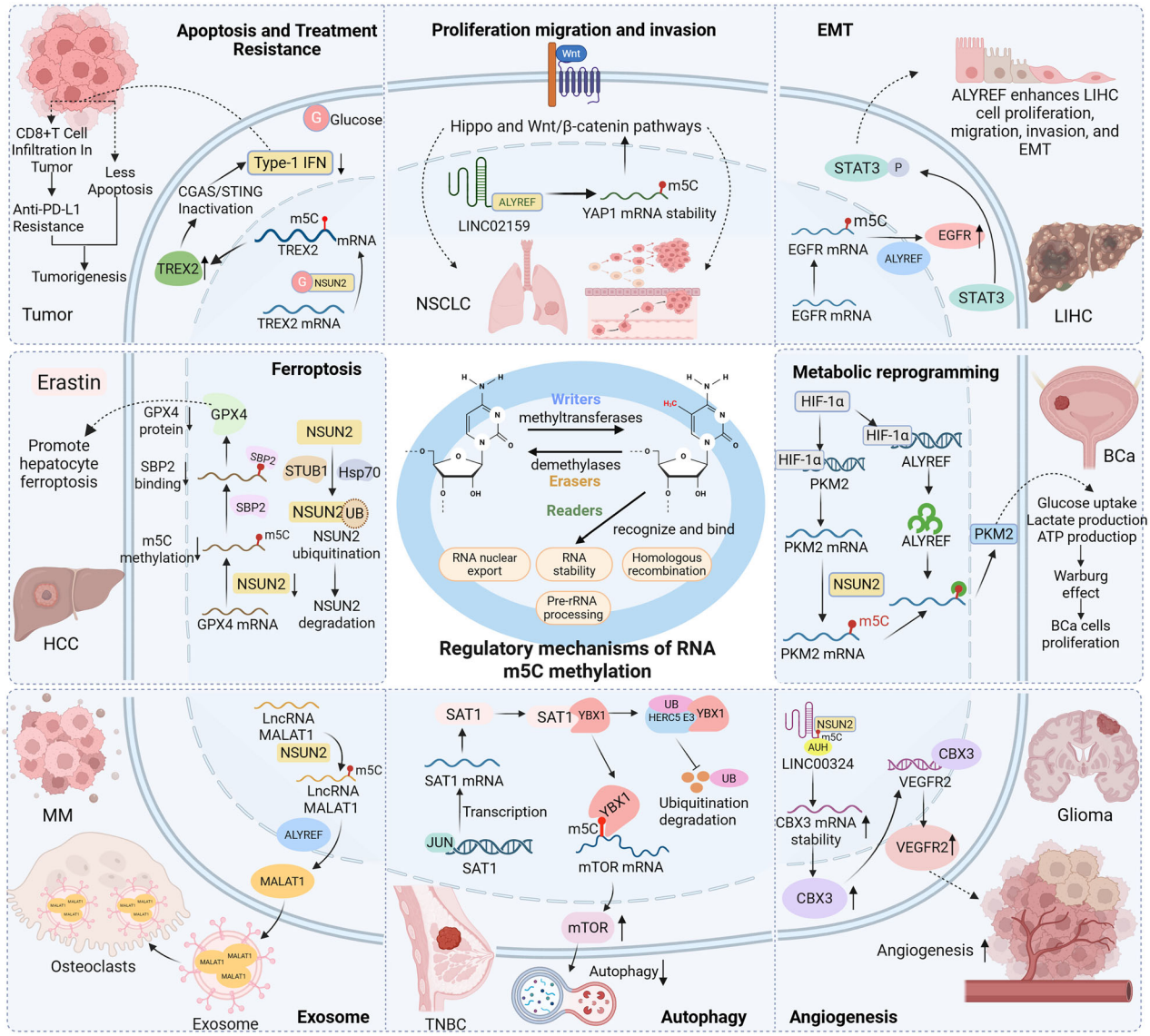

Fig. 4 Regulatory mechanisms of RNA m5 C methylation in cancer progressions. "Writers", "Readers" and "Erasers" are widely involved in cancer initiation and development by mediating m5C methylation of target RNA and its regulatory mechanisms include cell proliferation, cell migration and invasion, epithelial-mesenchymal transformation (EMT), iron death, apoptosis, autophagy, angiogenesis, and metabolic reprogramming. Created with BioRender.com.

migrate through the extracellular matrix from one area to another [131]. For example, LINC02159 knockdown in NSCLC suppresses tumor growth by inhibiting proliferation, migration, and invasion while inducing apoptosis and cell cycle arrest, whereas its overexpression exacerbates these malignant behaviors [77]. Beyond NSCLC, m5C-mediated mechanisms also drive aggressiveness in colorectal cancer, where ALYREF recruits ELAVL1 to stabilize RPS6KB2 and RPTOR transcripts via m5C recognition, fueling tumor growth and migration [23]. Similarly, in esophageal squamous cell carcinoma (ESCC), YBX1 promotes proliferation and metastasis by stabilizing oncogenic transcripts, underscoring its role as a universal m5C reader across cancer types [48]. This theme extends to renal cell carcinoma, where NOP2 stabilizes APOL1 mRNA in an m5C-dependent manner, activating PI3K-Akt signaling to enhance proliferation, migration, and invasion in ccRCC [111]. Intriguingly, NSUN2 exhibits dual roles in renal and gastric cancers: it suppresses p57Kip2 via m5C to drive ccRCC progression [87] and stabilizes DIAPH2-AS1 in gastric cancer by masking NSUN2 degradation sites, thereby promoting migration and invasion [113]. Finally, in hypopharyngeal squamous cell carcinoma (HPSCC), NSUN2 upregulates TEAD1 via m5C modifications, with knockdown experiments confirming its critical role in sustaining proliferation and invasion both in vitro and in vivo [124].

Metabolic reprogramming

Metabolic reprogramming refers to the adaptive changes in cellular metabolism in response to various stimuli and stresses [132–137]. It is a common phenomenon in many diseases, involving alterations in metabolic pathways such as glucose, lipid, and amino acid metabolism. These changes are closely linked to disease progression and development [138]. There is a complex bidirectional regulatory relationship between m5C methylation and metabolic reprogramming, which mainly affects tumorigenesis and development by regulating RNA stability, gene expression and metabolic enzyme activities. For instance, ALYREF stabilizes JunD mRNA via m5C recognition in pancreatic ductal adenocarcinoma (PDAC), enabling JunD to activate SLC7A5 and

Table 3. Different mechanisms of action of m5C methylation affecting tumor progression.

Mechanisms	Cancer type	Items	Regulation axis	Target	Functions	Ref
Cell proliferation, migration and invasion	NSCLC	ALYREF	LINC02159/ALYREF/YAP1/β-catenin	YAP1	Promote NSCLC cell proliferation, migration, and invasion	[77]
	CRC	ALYREF	ALYREF/ELAVL1/m5C	RPS6KB2,RPTOR	ALYREF supports CRC growth and migration	[23]
	ESCC	YBX1	YBX1/SMOX/mTORC1	SMOX	Promote the proliferation and metastasis of ESCC cells	[48]
	ccRCC	NSUN2	NSUN2/APOL1/PI3K-Akt	APOL1	NSUN2 alters ccRCC cell proliferation, migration, and invasion	[111]
	GC	NSUN2	NSUN2/p57Kip2	p57Kip2	Promote GC cell proliferation	[87]
	GC	NSUN2	DIAPH2-AS1/NSUN2/NTN1	NTN1	Promote neural invasion of GC	[113]
	HPSCC	NSUN2	NSUN2/TEAD1	TEAD1	Promote the proliferation and invasion of HPSCC	[124]
Metabolic reprogramming	PDAC	ALYREF	ALYREF/JunD/SLC7A5/mTORC1	JunD	Promote PDAC progression through epitranscriptome-metabolism reprogramming and immune evasion	[104]
	LC	NSUN2	NSUN2/ALYREF/ME1,GLUT3,CDK2	ME1,GLUT3,CDK2	NSUN2-mediated m5C modification induces metabolic reprogramming and cell cycle by promoting the mRNA stabilities of ME1, GLUT3 and CDK2	[24]
	CRC	NSUN2	NSUN2/YBX1/m5C-ENO1	ENO1	Promote the progression of CRC	[93]
	/	NSUN2	NSUN2/TREX2	TREX2	Drive tumorigenesis and immunotherapy resistance	[139]
	BCa	ALYREF	HIF-1α/ALYREF/PKM2	PKM2	Promote glycolysis and tumorigenesis of BCa	[107]
	LUSC	YBX1	THOC3/YBX1/PFKFB4	PFKFB4	Promote LSC cell carcinoma progression	[79]
EMT	HCC	ALYREF	ALYREF/EGFR/STAT3	EGFR	ALYREF enhances LIHC cell proliferation, migration, invasion, and EMT in vitro and tumor formation in vivo	[96]
	LUAD	NOP2	NOP2/E2H2	EZH2	Facilitate the malignant phenotype of LUAD cells by inducing EMT both in vitro and in vivo.	[78]
Ferroptosis	EC	NSUN2	NSUN2/YBX1/SLC7A11	SLC7A11	Confer ferroptosis resistance in EC	[114]
	NSCLC	NSUN2	NSUN2/NRF2/YBX1	NRF2	Drive ferroptosis resistance in NSCLC	[82]
	HCC	NSUN2	STUB1-NSUN2-GPX4	GPX4	Degradation of NSUN2 promotes hepatocyte ferroptosis	[144]
	GC	YBX1	HCP5-132aa/YBX1/ELAVL1/SLC7A11,G6PD	SLC7A11 and G6PD	HCP5 derives novel microprotein triggers progression of GC through regulating ferroptosis	[86]
Resistance	CC	NSUN6	NSUN6/ALYREF/NDRG1	NDRG1	Promote radioresistance in CC	[41]
	NSCLC	NSUN2	NSUN2/YBX1/QSOX1	QSOX1	Intrinsic resistance to gefitinib in NSCLC	[80]
	ESCC	NSUN2	/	/	Promote ESCC progression and radiochemo-resistant phenotype	[85]
	OC	YBX1	YBX1/CHD3	CHD3	Facilitate tumor cells to withstand platinum-induced apoptotic stress	[115]
	ESCC	NSUN2	/	/	Promote ESCC progression and radiochemotherapy resistance	[85]
Exosome	MM	NSUN2	NSUN2/YBX1/MALAT1	MALAT1	Transport MALAT1 to OCs via exosomes and promote bone lesions	[118]
	LUAD	NSUN2	NSUN2/ALYREF/YAP	YAP5	Enhance the exosome secretion effect	[75]
Angiogenesis	Glioma	NSUN2	NSUN2/LINC00324/CBX3	LINC00324	Promote angiogenesis in glioma	[117]
Mitochondrial energy metabolism	LC	NSUN4	NSUN4/circERI3/DDB1/PGC-1α	circERI3	Affect mitochondrial function and energy metabolism, Promotes the development of LC	[76]
Autophagy	TNBC	YBX1	SAT1/YBX1/mTOR	mTOR	Induce autophagy defects and promotes tumor progression in TNBC	[112]

mTORC1 signaling. This enhances amino acid uptake in tumor cells while impairing CD8+ T cell function, linking m5C to immune-metabolic crosstalk [104]. In addition to amino acid metabolism, m5C modifications regulate glucose utilization. Zhang et al. demonstrated that NSUN2 stabilizes ME1, GLUT3, and CDK2 mRNAs to induce metabolic reprogramming and cell cycle progression [24], while Chen et al. revealed that NSUN2 enhances glucose metabolism in CRC by stabilizing ENO1 mRNA. Lactate produced via this pathway further activates NSUN2 transcription through histone acetylation, creating a feedforward loop that sustains tumor growth [93]. Glycolytic reprogramming also underpins bladder cancer aggressiveness, where ALYREF stabilizes PKM2 mRNA via m5C, accelerating glycolysis and proliferation [107]. Notably, NSUN2 itself acts as a glucose sensor, promoting TREX2 expression and suppressing the cGAS/STING pathway to drive tumorigenesis and immunotherapy resistance. Disrupting glucose-NSUN2 interactions reverses these effects, highlighting its therapeutic potential [139].

EMT

EMT is a key process for tumor cells to acquire migration and invasion abilities, and m5C methylation plays an important role in EMT by regulating the RNA stability and translation efficiency of key genes. For example, ALYREF stabilizes EGFR mRNA via m5C in liver hepatocellular carcinoma (LIHC), activating STAT3 signaling to promote EMT, migration, and tumor formation [96]. This mechanism is not limited to LIHC: the NOP2/ALYREF/EZH2 axis induces EMT in lung cancer by stabilizing transcripts that drive mesenchymal transformation, further linking m5C readers to metastatic progression [78].

Ferroptosis

Ferroptosis is an iron-dependent, non-apoptotic form of regulated cell death. Its core mechanism involves the excessive accumulation of lipid peroxides within cells, leading to oxidative damage to cellular membrane systems [140–143]. m5C methylation directly or indirectly modulates ferroptosis-related pathways by regulating the RNA stability and translation efficiency of key genes. In endometrial cancer, NSUN2-mediated m5C modifications stabilize SLC7A11 mRNA, elevating its protein levels to inhibit ferroptosis and promote tumor growth. Targeting this axis restores ferroptosis sensitivity, offering a therapeutic strategy [114]. Similarly, NSUN2 enhances antioxidant capacity in other cancers by stabilizing NRF2 mRNA via YBX1 interaction. Reduced NRF2 expression reverses NSUN2-driven proliferation and ferroptosis resistance, underscoring the centrality of this axis [82]. Expanding beyond transcriptional regulation, Zhang et al. showed that NSUN2 stabilizes GPX4 mRNA via 3′UTR m5C modifications. NSUN2 knockdown impairs GPX4 synthesis, triggering ferroptosis in hepatocytes—a mechanism reversible by NSUN2 reexpression [144].

Therapeutic resistance

Drug resistance in cancer cells significantly diminishes treatment efficacy, contributing to recurrence and metastasis. A major factor in this resistance is the epigenetic modification of gene expression through RNA modifications [11, 145, 146]. These modifications play a pivotal role in regulating RNA splicing, translation, transport, degradation, and stability [11, 145, 147]. In cervical cancer, NSUN6-mediated m5C modifications stabilize NDRG1 mRNA, enhancing homologous recombination repair and conferring radioresistance [41]. Beyond radioresistance, m5C modifications drive resistance to targeted therapies: NSUN2 hypermethylates QSOX1 mRNA in EGFR-TKI-resistant NSCLC, stabilizing it via YBX1 to sustain gefitinib resistance. NSUN2 depletion restores drug sensitivity, linking m5C to adaptive therapeutic evasion [80]. Genomic studies further support this role, as NSUN2-driven m5C hypermethylation upregulates oncogenes in ESCC, promoting tumor progression and radioresistance [85].

Other mechanisms

Exosomes are small, single-membrane organelles ranging from 30 to 200 nm in diameter, exhibiting the same topology as their parent cells. These vesicles contain a variety of biomolecules, including nucleic acids, lipids, and proteins, which can be transferred between cells, influencing the behavior of recipient cells [148–151]. Exosomes play critical roles in numerous biological processes, such as development, immunity, tissue homeostasis, cancer, and neurodegenerative diseases [152–154]. Research has shown that NSUN2 and YBX1-induced m5C methylation enhances the expression of the long non-coding RNA MALAT1 in MM cells. This upregulation results in the transfer of MALAT1 to osteoclasts via exosomes, exacerbating bone destruction [118]. Additionally, m5C modification of YAP has been shown to promote the secretion of exosomes, contributing to the aggressive behavior and resistance to AZD9291, a third-generation EGFR tyrosine kinase inhibitor, in LUAD cells [75].

Autophagy is a lysosome-dependent degradation process that recycles damaged cellular components, organelles, and aggregation-prone proteins [155–157]. Tian et al. demonstrated that SAT1 accumulation effectively suppresses autophagy by stabilizing mTOR mRNA through YBX1-mediated m5C modification [112].

Wu et al. found that the circular RNA circERI3 interacts with the DNA-binding protein DDB1, modulating its ubiquitination and stabilizing it. This stabilization enhances the transcription of PGC-1α, a key coactivator of peroxisome proliferator-activated receptor gamma (PPARγ), affecting mitochondrial function and energy metabolism, and contributing to lung cancer progression [76]. Furthermore, Meng et al. revealed that the ALYREF-JunD-SLC7A5 axis drives epitranscriptomic metabolic reprogramming and immune evasion strategies, promoting pancreatic ductal adenocarcinoma progression [104].

CONCLUSION

This review explores the multifaceted roles of m5C methylation in gene regulation and its profound impact on tumor biology. The evidence presented emphasizes the critical role of m5C modification in regulating key biological processes, including RNA stability, translation, and nuclear export, which, in turn, influence cellular proliferation, differentiation, apoptosis, and stress responses.

The mechanisms underlying m5C methylation, involving its “readers,” “writers,” and “erasers,” have been carefully examined, along with the specific RNA types they regulate. Notably, the NSUN2/ALYREF pathway and YBX1-mediated recognition of m5C modifications have emerged as critical regulators in the context of cancer progression.

In tumor biology, m5C methylation has been implicated in the development and progression of various cancer types, including those of the respiratory, digestive, urinary, female reproductive, nervous, and blood systems. The mechanistic roles of m5C in tumor progression—such as in glucose metabolism, ferroptosis, and resistance to therapeutic agents—have been elucidated, offering valuable insights for potential therapeutic targets.

Furthermore, the expression of m5C machinery is not uniform across normal tissues but is instead developmentally regulated and tissue-restricted. This baseline expression pattern likely contributes to tissue-specific vulnerabilities. Cancers may arise in organs where these regulators are normally highly expressed (e.g., NSUN2 in regenerative tissues) by further amplifying their pro-growth functions. Conversely, the cancer-associated reprogramming of these factors in tissues where they are normally quiescent could unleash new oncogenic potential. The embryonic lethality observed upon knockout of key m5C regulators underscores their fundamental role in development and suggests that therapeutic targeting will need to carefully balance efficacy against essential physiological functions.

Further investigation is needed to unravel the precise mechanisms by which m5C modifications influence gene expression and tumor biology. This includes identifying novel m5C modification sites and understanding their interactions with other epigenetic modifications. Moreover, developing therapies that modulate m5C methylation presents a promising strategy for cancer treatment. Targeting m5C "writers" or "erasers," or enhancing the function of m5C "readers," could offer alternative approaches to combat cancer drug resistance and promote tumor regression. Given the varying role of m5C methylation across different cancer types, personalized medicine strategies based on m5C profiles could enhance patient prognosis by tailoring treatments to the unique characteristics of individual tumors. A comprehensive understanding of how m5C methylation interacts with other epigenetic modifications, such as DNA methylation and histone modifications, is essential to fully grasp the epigenetic regulation of cancer. In conclusion, the study of m5C methylation in cancer biology holds significant potential for advancing our understanding of tumorigenesis and progression, while also offering new avenues for therapeutic intervention. As research in this field continues to progress, the insights gained will pave the way for more effective and personalized cancer therapies.

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ACKNOWLEDGEMENTS

The authors would like to express their gratitude to all participants and relevant personnel for their contribution to this study.

AUTHOR CONTRIBUTIONS

Wenzhi Guo and Yuting He designed the manuscript. Zhenyu Guan and Wendong Li wrote the manuscript. Zhenyu Guan helped with reference collection and draw the figures. Wenzhi Guo and Yuting He revised the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was funded by Leading Talents of Zhongyuan Science and Technology Innovation (214200510027), Science and technology department of Henan Province (222102310365), Henan Medical Science and Technology Joint Building Program (LHGJ20210324), Gandan Xiangzhao Research Fund (GDXZ2023001), Henan Provincial Medical Science and Technology Research Plan (SBGJ2018002 and SBGJ202102117), and Outstanding Foreign Scientist Studio in Henan Province (GZS2020004).

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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