Cancer Screening and Prevention **2026** vol. 5(1) | 42–54
DOI: 10.14218/CSP.2026.00002

Review Article

m6A RNA Modification in Colorectal Cancer: Regulatory Roles, Oncogenic Signaling, and Metabolic Pathways

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Received: January 16, 2026 | **Revised:** March 02, 2026 | **Accepted:** March 18, 2026 | **Published online:** March 29, 2026

Abstract

N6-methyladenosine (m6A), the most prevalent internal RNA modification in eukaryotic cells, is a dynamic regulator of RNA metabolism and cancer biology. In colorectal cancer (CRC), dysregulated m6A reshapes transcriptomic programs that control tumor growth, metastasis, immune evasion, and therapeutic resistance. However, the context-dependent functions of individual m6A regulators remain incompletely defined, the integration of m6A with canonical oncogenic signaling remains incomplete, and its role in metabolic reprogramming lacks a systematic overview. This review aims to integrate current evidence on m6A regulatory machinery in CRC, clarify its coordination with oncogenic signaling and metabolic pathways, and highlight emerging translational implications. The key players regulating m6A in CRC progression are m6A "writers", including methyltransferase-like 3 and methyltransferase-like 14; m6A "erasers", including fat mass and obesity-associated protein and AlkB homolog 5; and m6A "readers", including the YTH m6A RNA-binding protein family and the insulin-like growth factor 2 mRNA-binding protein family. m6A modification coordinates key oncogenic pathways, including Wnt/β-catenin, PI3K/Akt, MAPK, and p53 signaling. Moreover, m6A-dependent regulation of metabolic enzymes such as hexokinase 2, pyruvate kinase M2, and fatty acid synthase promotes the reprogramming of glucose, amino acid, and lipid metabolism, linking epitranscriptomic control to bioenergetic adaptation. We also discuss context-dependent and paradoxical functions of m6A regulators and advances in m6A-targeted therapies. In conclusion, m6A modification functions as a central regulatory hub in CRC by integrating signaling networks and metabolic pathways. Deeper mechanistic insights into spatiotemporal m6A regulation may accelerate the development of biomarkers and targeted therapies for precision CRC management.

Introduction

N6-methyladenosine (m6A), a prevalent epigenetic modification in RNA, is commonly found in eukaryotes.[1] The addition of a methyl group to the sixth nitrogen atom of adenine (A) enables reversible and dynamic regulation of RNA metabolism and function, influencing stability, splicing, translation, translocation, localization, and transport.[2] m6A modifications are found on a variety of coding and non-coding RNAs (messenger RNA (mRNA), microRNA, long non-coding RNA (lncRNA), circular RNA, and transfer RNA). Dysregulated m6A levels can affect tumorigenesis and cancer progression, highlighting the potential of m6A regulators as therapeutic targets in cancer.[3] With the advancement of high-throughput sequencing technologies such as methylated RNA immunoprecipitation sequencing and improved molecular biology tools, the role of m6A in development, disease, and cell regulation has become a frontier of research. This review aims to summarize the regulatory roles of m6A RNA modification in colorectal cancer (CRC), with a particular focus on its involvement in oncogenic signaling pathways and metabolic reprogramming, and to highlight its potential clinical implications for diagnosis and therapy.

Keywords: N6-methyladenosine; m6A; Colorectal cancer; Epitranscriptomics; Oncogenic signaling; Metabolic reprogramming; Tumor metabolism; RNA modification.
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How to cite this article: Sheng Q, Wang Y, Xu M, Cheng C, Xue Z, Chen L, *et al*. m6A RNA Modification in Colorectal Cancer: Regulatory Roles, Oncogenic Signaling, and Metabolic Pathways. *Cancer Screen Prev* 2026;5(1):42–54. doi: 10.14218/CSP.2026.00002.

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Table 1. The impact of m6A regulatory proteins on CRC

Category	Protein	Target	Functional role	Experimental evidence
Writer	METTL3	p38/ERK pathway	Inhibits proliferation and invasion	CRC cell lines + xenograft
Writer	METTL14	SCD1	Suppresses stemness and metastasis	*In vitro* + mouse model
Writer	WTAP	FLNA	Promotes proliferation and autophagy	CRC cell lines
Writer	WTAP	VEGFA	Activates MAPK signaling	*In vitro* + xenograft
Writer	ZC3H13	Ras-ERK pathway	Inhibits proliferation and invasion	CRC cell lines
Writer	ZCCHC4	DNA damage transcripts	Promotes chemoresistance	Clinical samples + cells
Eraser	FTO	PKM2	Promotes glycolysis and proliferation	CRC cell lines
Eraser	FTO↓	HK2	Enhances glycolysis via FOXO	*In vitro* metabolic assays
Eraser	ALKBH5	NEAT1	Promotes tumor progression	CRC cell lines
Eraser	ALKBH5	FABP5	Inhibits lipid metabolism	*In vitro* + xenograft
Eraser	ALKBH5↓	HK2	Enhances glycolysis	CRC cell lines
Reader	IGF2BP1	FZD6	Activates Wnt signaling	*In vitro* + xenograft
Reader	IGF2BP2	STAG3	Regulates proliferation	CRC cell lines
Reader	IGF2BP2	HK2	Stabilizes HK2, promotes glycolysis	*In vitro* metabolic assays
Reader	IGF2BP3	MYC (etc.)	Promotes tumorigenicity	Clinical cohorts + cells
Reader	YTHDF1	FZD9/WNT6	Activates Wnt signaling	Spheroid + xenograft
Reader	YTHDF1	GLS	Reduces cisplatin sensitivity	Resistant CRC cells
Reader	YTHDF2	GPX4	Regulates ferroptosis	*In vitro* + xenograft

ALKBH5, AlkB homolog 5; CRC, colorectal cancer; ERK, extracellular signal-regulated kinase; FABP5, fatty acid-binding protein 5; FLNA, filamin A; FOXO, forkhead box O; FTO, fat mass and obesity-associated protein; FZD6, frizzled class receptor 6; FZD9, frizzled class receptor 9; GLS, glutaminase; GPX4, glutathione peroxidase 4; HK2, hexokinase 2; IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; IGF2BP2, insulin-like growth factor 2 mRNA-binding protein 2; IGF2BP3, insulin-like growth factor 2 mRNA-binding protein 3; MAPK, mitogen-activated protein kinase; MYC, MYC proto-oncogene, bHLH transcription factor; PKM2, pyruvate kinase M2; Ras, rat sarcoma viral oncogene homolog; SCD1, stearoyl-CoA desaturase 1; STAG3, stromal antigen 3; VEGFA, vascular endothelial growth factor A; WNT6, Wnt family member 6; WTAP, Wilms tumor 1–associated protein; YTHDF1, YTH N6-methyladenosine RNA-binding protein 1; YTHDF2, YTH N6-methyladenosine RNA-binding protein 2; ZC3H13, zinc finger CCCH-type containing 13; ZCCHC4, zinc finger CCHC-type containing 4.

The regulatory proteins of m6A

The m6A modification is regulated by methyltransferases ("writers"), demethylases ("erasers"), and proteins that specifically recognize m6A-modified sites ("readers") (Table 1) (Figs. 1 and 2).

Writers

The methyltransferases that function as writers to facilitate methylation reactions include methyltransferase-like proteins such as methyltransferase-like 3 (METTL3), METTL14, METTL5, and METTL16, along with zinc finger CCHC-type containing 4 (ZCCHC4), Wilms tumor 1-associated protein (WTAP), vir-like m6A-associated methyltransferase (VIRMA), zinc finger CCCH domain-containing protein 13 (ZC3H13), and RNA binding motif protein 15/15B (RBM15/15B).[3]

The METTL3/METTL14 heterodimer is the core complex responsible for catalyzing methylation reactions, with METTL3 acting as the catalytic subunit and METTL14 providing structural support and aiding RNA substrate recognition.[4] Although METTL3 and METTL14 generally act as oncogenic drivers in multiple cancer types,[5] evidence suggests that in CRC, METTL3 instead exerts tumor-suppressive effects by inhibiting cell proliferation, migration, and invasion via the p38 mitogen-activated protein kinase/extracellular signal-regulated kinase (p38/ERK) pathway.[6] Conversely, METTL14 reduces the stemness and metastasis of colorectal tumors by regulating the m6A modification of stearoyl-CoA desaturase 1.[7]

METTL5 independently catalyzes m6A modification on structured RNAs (U6 snRNA, 28S rRNA, and 18S rRNA).[8] METTL16 primarily targets U6 snRNA and the S-adenosylmethionine (SAM) synthase methionine adenosyltransferase 2A as its substrates.[9] The RNA-binding protein ZCCHC4 contributes to chemotherapy resistance in patients with CRC, hepatocellular carcinoma, and pancreatic cancer by interfering with DNA damage-induced apoptosis.[10]

WTAP interacts with the METTL3-METTL14 complex to direct it to specific regions of nuclear RNA, such as near stop codons or 3′ UTRs.[4] In CRC, WTAP is upregulated, promoting tumor proliferation and inhibiting apoptosis. It also modulates autophagy by m6A-mediated suppression of filamin A in CRC cells.[11]

VIRMA functions as a scaffold protein in methylation reactions by recruiting WTAP and ZC3H13 to form binding sites for METTL3 and METTL14, thereby enhancing their catalytic activity.[12] In CRC tissues, elevated mRNA and protein levels of VIRMA may contribute to tumorigenesis and immune cell infiltration.[13]

ZC3H13 interacts with the m6A methyltransferase complex and regulates m6A deposition through its interaction with nuclear RNA-binding proteins.[3] It inhibits the proliferation and invasion of CRC by suppressing the Ras-ERK signaling pathway.[14]

Additionally, RBM15/RBM15B work with WTAP to localize the m6A methyltransferase complex to a specific RNA region, playing

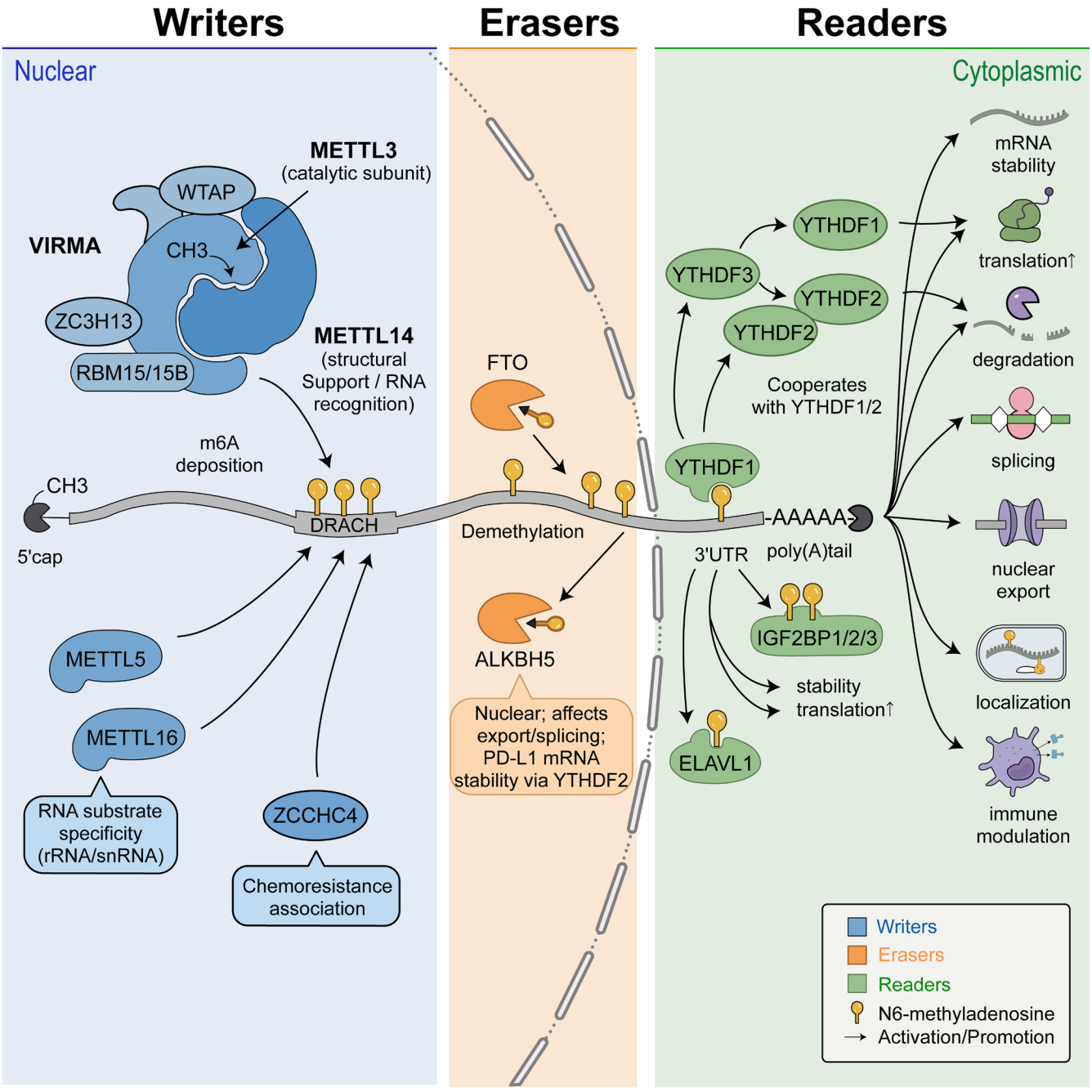


Fig. 1. Core regulatory machinery of m6A RNA modification. This schematic illustrates the core regulatory system of m6A RNA modification. m6A deposition is catalyzed by the methyltransferase complex ("writers"), primarily composed of METTL3, METTL14, and associated cofactors such as WTAP, VIRMA, ZC3H13, and RBM15/15B. The modification is dynamically removed by demethylases ("erasers"), including FTO and ALKBH5, ensuring reversibility and context-dependent regulation. m6A-modified transcripts are recognized by specific binding proteins ("readers"), such as the YTH domain family proteins (YTHDF1/2/3, YTHDC1/2) and IGF2BP family members, which determine RNA fate by modulating mRNA stability, translation efficiency, splicing, nuclear export, and degradation. Together, this coordinated writer–eraser–reader network establishes a dynamic epitranscriptomic layer of gene regulation that fine-tunes RNA metabolism and cellular function. 3′ UTR, 3′ untranslated region; 5′ cap, 7-methylguanosine cap; ALKBH5, AlkB homolog 5; CH3, methyl group; DRACH, D (A/G/U), R (A/G), A (adenosine), C (cytosine), H (A/C/U) consensus motif; ELAVL1, ELAV-like RNA binding protein 1; FTO, fat mass and obesity-associated protein; IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; IGF2BP2, insulin-like growth factor 2 mRNA-binding protein 2; IGF2BP3, insulin-like growth factor 2 mRNA-binding protein 3; m6A, N6-methyladenosine; METTL14, methyltransferase-like 14; METTL16, methyltransferase-like 16; METTL3, methyltransferase-like 3; METTL5, methyltransferase-like 5; mRNA, messenger RNA; PD-L1, programmed death-ligand 1; poly(A) tail, polyadenylate tail; RBM15/15B, RNA binding motif protein 15/15B; rRNA, ribosomal RNA; snRNA, small nuclear RNA; VIRMA (KIAA1429), vir-like m6A methyltransferase associated protein; WTAP, Wilms tumor 1-associated protein; YTHDF1, YT521-B homology domain family protein 1; YTHDF2, YT521-B homology domain family protein 2; YTHDF3, YT521-B homology domain family protein 3; ZC3H13, zinc finger CCCH-type containing 13; ZCCHC4, zinc finger CCHC-type containing 4.

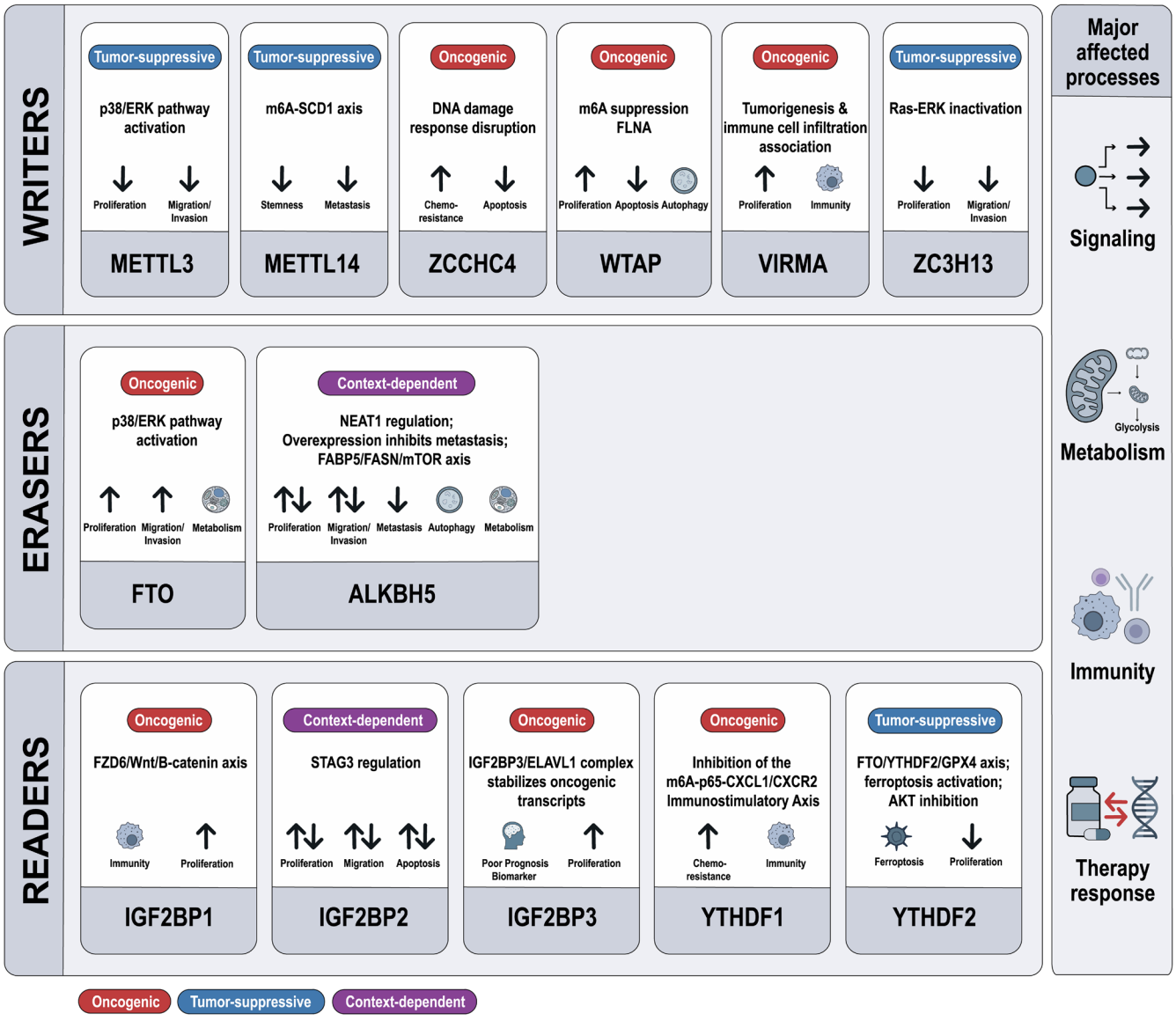


Fig. 2. Functional classification and key targets of core m6A regulatory proteins in CRC. This schematic complements Table 1 by summarizing the functional classification and representative targets of core m6A regulatory proteins in CRC. The m6A machinery consists of writers (METTL3, METTL14, WTAP, VIRMA, ZC3H13), erasers (FTO, ALKBH5), and readers (YTHDF1/2/3, IGF2BP1/2/3), which dynamically regulate RNA methylation and transcript fate. Through modulation of key targets within the Wnt/β-catenin, PI3K/Akt, MAPK, and p53 pathways, these regulators influence β-catenin activation, Akt signaling, ERK/p38 phosphorylation, and p53-mediated responses, thereby contributing to CRC progression, metastasis, stemness, immune evasion, and therapy resistance. Akt, protein kinase B; ALKBH5, AlkB homolog 5; CXCL1, C-X-C motif chemokine ligand 1; CXCR2, C-X-C motif chemokine receptor 2; ELAVL1, ELAV-like RNA binding protein 1; ERK, extracellular signal-regulated kinase; FABP5, fatty acid-binding protein 5; FASN, fatty acid synthase; FLNA, filamin A; FTO, fat mass and obesity-associated protein; FZD6, frizzled class receptor 6; GPX4, glutathione peroxidase 4; IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; IGF2BP2, insulin-like growth factor 2 mRNA-binding protein 2; IGF2BP3, insulin-like growth factor 2 mRNA-binding protein 3; m6A, N6-methyladenosine; METTL3, methyltransferase-like 3; METTL14, methyltransferase-like 14; mTOR, mechanistic target of rapamycin; NEAT1, nuclear paraspeckle assembly transcript 1; p38, p38 mitogen-activated protein kinase; p65, nuclear factor kappa-B p65 subunit; Ras, rat sarcoma viral oncogene homolog; SCD1, stearoyl-CoA desaturase 1; STAG3, stromal antigen 3; VIRMA, vir-like m6A methyltransferase associated protein; Wnt, Wingless/Integrated; WTAP, Wilms tumor 1-associated protein; YTHDF1, YT521-B homology domain family protein 1; YTHDF2, YT521-B homology domain family protein 2; ZC3H13, zinc finger CCCH-type containing 13; ZCCHC4, zinc finger CCHC-type containing 4.

a role in various stages of RNA metabolism by binding to RNA.[3]

Erasers

Erasers, acting as demethylases, counteract the effects of writer proteins by removing m6A modifications, thereby regulating RNA molecules. Notable examples include FTO and ALKBH5.[3]

FTO, the first identified m6A demethylase, primarily targets m6A modifications in mRNA and snRNA. Dysregulated expression of FTO can impact fat metabolism, energy balance, and contribute to various cancers.[15] In CRC, FTO overexpression promotes

cell proliferation, invasion, and migration, while also influencing glycolytic metabolism by regulating PKM2.[16]

ALKBH5, primarily localized in the nucleus, plays a role in nuclear export and mRNA splicing.[17] Its depletion increases m6A levels in the 3′ UTR of programmed death-ligand 1 mRNA, relying on YTHDF2 to promote its degradation,[18] which underscores its role in modulating the tumor immune microenvironment and influencing immunotherapy outcomes. In CRC, ALKBH5 exhibits a dual function: it decreases lncRNA nuclear paraspeckle assembly transcript 1 methylation to enhance tumor progression,[19] while its overexpression inhibits cancer cell metastasis *in vivo* and invasion *in vitro*.[20] FTO and ALKBH5 knockdown can accelerate CRC cells' malignant biological behaviors.[21] Additionally, ALKBH5 acts as a positive regulator of fatty acid-binding protein 5 (FABP5), reducing fatty acid synthase (FASN) expression and suppressing CRC progression through mTOR-mediated autophagy.[22] This apparent discrepancy may be attributed to substrate specificity and pathway context. ALKBH5-mediated demethylation of distinct RNA targets may differentially influence tumor proliferation versus metastatic behavior. ALKBH5 may function as either an oncogene or tumor suppressor depending on cellular state, metastatic stage, metabolic context, and tumor microenvironment.

Readers

Readers mediate the downstream effects of m6A modifications by recognizing and binding to m6A sites, thus determining their functional outcomes. Key readers include IGF2BP1/2/3, YTHDF1/2/3, and embryonic lethal abnormal vision-like protein 1 (ELAVL1).[3]

The IGF2BP family stabilizes mRNAs, such as MYC, and enhances their translation without promoting mRNA degradation.[23] Overexpressed in various cancers, its aberrant expression is linked to tumor aggressiveness and drug resistance, driving tumor progression by regulating key genes like PEG10, SOX2, FSCN1, MYC, HMGA1, YAP, LEF1, FOXM1, ABCB1, CCND1, VEGF, HIF1A, TMBIM6, and lncRNA HAGLR, relying on m6A.[4] IGF2BP1 inhibits $CD8^+$ T cell-mediated cytotoxicity and apoptosis in CRC cells,[24] and promotes tumor progression through modulation of frizzled class receptor 6 (FZD6)/Wnt/β-catenin pathway.[25] Downregulation of IGF2BP2 enhances CRC cell proliferation and migration by regulating stromal antigen 3 but also increases apoptosis.[26] IGF2BP3 serves as a poor prognosis biomarker in CRC,[27] and the IGF2BP3/ELAVL1 complex further promotes tumorigenicity.[28]

The YTHDF family is localized in the cytoplasm, where YTHDF1 promotes mRNA translation, YTHDF2 enhances mRNA degradation, and YTHDF3 works alongside YTHDF1 and YTHDF2 to regulate both translation and degradation.[29] Overexpression of YTHDF1 reduces cisplatin sensitivity in CRC cells and facilitates tumor progression by impairing anti-tumor immunity through the m6A-p65-CXCL1/CXCR2 axis.[30,31] Inhibition of Akt suppresses CRC progression by activating ferroptosis via the FTO/YTHDF2/glutathione peroxidase 4 axis.[32]

The m6A-regulated oncogenic signaling pathways

Wnt/β-catenin

The Wnt/β-catenin pathway plays a key role in regulating cell pluripotency and determining cell differentiation during development. It is considered a major driver of CRC and is linked to various biological processes,[33] including mechanisms of malignancy, drivers of metastasis, and regulation of tumor behavior.[34]

Alterations in m6A modification and its regulatory proteins have been observed in the Wnt/β-catenin pathway across various cancers, particularly gastrointestinal tumors. In hepatoblastoma, elevated METTL3 expression correlates with distant metastasis, tumor recurrence, and vascular invasion.[35] In contrast, miR-186 targets the 3′-UTR of METTL3 mRNA, downregulating METTL3 expression. Low miR-186 levels and high METTL3 expression in hepatoblastoma lead to the overexpression of Wnt/β-catenin pathway components (β-catenin, APC, cyclin D1, and c-Myc), promoting cell progression.[36] In pancreatic cancer, reduced ALKBH5 expression overcomes the inhibition of the Wnt/β-catenin pathway by Wnt inhibitory factor-1, driving tumor progression and chemoresistance. In gastric cancer, overexpression of YTHDF1 hyperactivates the Wnt/β-catenin pathway, contributing to tumor progression.[37] Similarly, in CRC, YTHDF1 overexpression enhances the translation of m6A-modified Wnt signaling components FZD9 and WNT6, activating the Wnt/β-catenin pathway and accelerating tumor growth. These findings have been confirmed through *in vitro* tumor spheroid models, cellular assays, and *in vivo* mouse xenograft studies.[38]

PI3K/Akt

PI3K is an intracellular lipid kinase that plays a crucial role in cell proliferation, differentiation, and survival.[39] Overactivation of the PI3K/Akt pathway contributes to the progression from colorectal adenoma to adenocarcinoma and drives both tumor growth and metastasis in CRC.[40,41]

In gastrointestinal tumors, reduced m6A methylation, resulting from decreased METTL3 and increased FTO, activates the PI3K/Akt pathway, thereby enhancing the proliferation and invasiveness of gastric cancer cells.[42] A CEACAM5-associated ceRNA network analysis identified the LCMT1-AS2/RPS6KA5 axis as a potential regulator of the PI3K/Akt pathway, which can alter the tumor immune microenvironment and promote CRC progression. This axis is also associated with ferroptosis, m6A modification, and tumor stemness, while affecting tumor cell sensitivity to 5-fluorouracil and immunotherapy.[43]

MAPK

The MAPK pathway is a crucial signaling cascade involved in cellular processes—proliferation, differentiation, survival, and apoptosis. Its four subfamilies—ERK, p38, JNK, and ERK5—are implicated in the development of CRC.[44] This pathway can be activated by hormones, cytokines, growth factors, endoplasmic reticulum stress, and oxidative stress.[45] In CRC, the ERK pathway promotes cancer progression.[45] Epidermal growth factor receptor (EGFR), a well-established therapeutic target in CRC, regulates tumor cell proliferation through ERK1/ERK2 activation. Oncogenes downstream of this pathway, such as rat sarcoma viral oncogene homolog (RAS), B-Raf proto-oncogene serine/threonine kinase (BRAF), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), and phosphatase and tensin homolog (PTEN), are closely linked to CRC.[46] Around 10% of CRCs harbor the BRAF V600E mutation,[47] while 10–20% exhibit PIK3CA mutations.[48] RAS, frequently mutated in CRC, further activates the ERK pathway,[49] while PTEN, a tumor suppressor gene with dual phosphatase activity, inhibits the ERK pathway. Loss of PTEN function contributes to CRC progression and recurrence.[50]

Basic leucine zipper ATF-like transcription factor 2 (BATF2) inhibits gastric cancer progression by suppressing ERK, but METTL3 overexpression diminishes this tumor-suppressive effect through m6A-mediated downregulation of BATF2.[51] In CRC, reduced METTL3 expression activates MAPK, leading to significant activation of ERK and p38. This enhances cellular proliferation,

migration, and invasion, thereby accelerating disease progression.[6] WTAP promotes CRC progression, particularly angiogenesis, by activating MAPK signaling through YTHDC1-mediated m6A methylation of VEGFA mRNA.[52]

p53

The p53 tumor suppressor pathway is activated in response to hypoxia, DNA damage, excessive proliferation, oxidative stress, or nutrient deprivation. It participates in inducing cell cycle arrest, senescence, or apoptosis. TP53, a critical driver gene in cancer development across various organs, is mutated in approximately 55%–60% of CRC cases.[53]

In hepatocellular carcinoma, METTL3 overexpression significantly induces m6A modification of RAD52 motif containing 1 (RDM1) mRNA, leading to its downregulation. RDM1, a tumor suppressor gene, binds to p53 and stabilizes its protein expression.[54] In pancreatic cancer, ALKBH5 overexpression reduces tumor cell progression *in vitro*, while also inhibiting tumor growth *in vivo*. ALKBH5 activates PER1 in an m6A-YTHDF2-dependent manner, reactivating the p53 pathway to suppress tumor cell progression.[55] In CRC, m6A-mediated modification of p53 precursor mRNA by METTL3 not only enhances the stability of p53 mRNA but also affects its downstream target genes, such as p21, Bax, and PUMA, which are key regulators of the apoptotic response and cell cycle arrest. Silencing METTL3 activates the p53 pathway, increasing the expression of p-p53, p21, Bax, and PUMA, thereby resensitizing CRC cells to chemotherapy (Fig. 3).[56]

The m6A-regulated metabolic pathways

Metabolic reprogramming plays a critical role in tumor growth and resistance to chemotherapy. Disruptions in glucose, amino acid, and fatty acid metabolism are closely linked to the regulation of transcription factors, signaling pathways, and metabolic enzymes. These changes ultimately influence tumor cell proliferation, drug resistance, invasion, and metastasis (Figs. 4 and 5).[57]

Glucose metabolism

In CRC, cells predominantly rely on the "Warburg effect," engaging in aerobic glycolysis even in the presence of sufficient oxygen. This metabolic shift leads to extensive glucose consumption and lactate production, providing rapid energy (ATP) and biosynthetic precursors (e.g., nucleotides, lipids), while also fostering an acidic tumor microenvironment that suppresses immune cell function.[58] Key glycolytic enzymes—HK2, LDHA, and PKM2—are overexpressed in CRC tissues, driving tumor proliferation and metastasis.[59] In individuals with hyperglycemia, high-sugar diets may increase CRC risk through glycemic fluctuations and obesity, with epidemiological studies indicating a 30%–40% higher risk in those with type 2 diabetes mellitus.[60] Hyperinsulinemia associated with hyperglycemia activates the PI3K/Akt pathway, promoting cell proliferation and inhibiting apoptosis.[61] Excess glucose also leads to mitochondrial reactive oxygen species accumulation, causing DNA damage and genomic instability.[62] Interestingly, even a short-term high-sugar diet can alter gut microbiota composition—reducing Bacteroidetes and increasing Firmicutes—while decreasing short-chain fatty acids (SCFAs, such as butyrate). This shift in microbiota enhances intestinal permeability, weakens the colonic epithelial barrier, and exacerbates inflammation.[63] Furthermore, microbiota-derived glucose metabolites, such as secondary bile acids (BAs) (e.g., deoxycholic acid), can damage the intestinal mucosa and promote carcinogenesis.[64] Key glycolytic intermediates, such as acetyl-CoA, influence tumor behavior by regulating histone acetylation, chromatin structure, and gene expression, including the activation of oncogenes.[65] α-Ketoglutarate (α-KG), a critical metabolite, participates in DNA demethylation through TET enzymes, affecting epigenetic modifications.[66]

Overexpression of the m6A reader protein IGF2BP2 stabilizes the ZFAS1/OLA1 axis, increasing OLA1 expression, ATP hydrolysis, and glycolytic flux. The Warburg effect enhances CRC cell proliferation.[67] Downregulation of FTO and ALKBH5 has been reported to cooperatively activate FOXO signaling by enhancing IGF2BP2-mediated m6A methylation of HK2 mRNA, thereby promoting glycolysis in CRC.[21] METTL3, through direct interaction with the 5′ and 3′ UTR regions of HK2 and the 3′ UTR of SLC2A1 (GLUT1), stabilizes their mRNAs, thereby activating the glycolytic pathway. This m6A-mediated regulation of glycolysis promotes CRC progression.[68]

Amino acid metabolism

Amino acid metabolism impacts CRC progression through various mechanisms, including regulating tumor energy supply, biosynthesis of precursors, modulating signaling pathways, mediating immune evasion, and interacting with the gut microbiota. CRC cells utilize glutaminase (GLS1) to convert glutamine into glutamate, which enters the tricarboxylic acid cycle to generate ATP and provide nitrogen.[69] α-KG, a byproduct of glutamine metabolism, also aids in the synthesis of antioxidant molecules (glutathione), supporting tumor cell survival.[70] Serine metabolism via serine hydroxymethyltransferase produces glycine and one-carbon units, which contribute to purine and thymidine synthesis, fueling tumor proliferation.[71] One-carbon metabolism further influences DNA methylation and histone modifications by affecting the production of SAM.[72] Leucine and arginine, transported through SLC7A5/SLC3A2 transporters, activate mTORC1 signaling, promoting protein synthesis and tumor growth.[73] Tryptophan is catabolized by indoleamine 2,3-dioxygenase 1 (IDO1) into kynurenine, which suppresses T-cell function and promotes the differentiation of regulatory T cells, thereby shaping the tumor microenvironment.[74] In response to amino acid deprivation, GCN2 activation reduces protein translation and induces autophagy, helping cancer cells adapt to metabolic stress.[75] Gut microbiota interactions also influence tumorigenesis; for example, sulfate-reducing bacteria metabolize sulfur-containing amino acids, like cysteine, to produce hydrogen sulfide, which damages intestinal DNA, triggers inflammation, and aids immune evasion.[76] Microbial metabolism of arginine generates polyamines (e.g., putrescine, cadaverine), disrupting the intestinal barrier and promoting epithelial proliferation.[77] Argininosuccinate synthase 1 enhances p53-mediated DNA damage responses by utilizing exogenous arginine, inducing apoptosis in CRC cells.[78] Inhibition of the IDO-tryptophan-AhR axis alleviates immune tolerance and suppresses colitis-associated CRC.[79] Additionally, Sestrin2, a leucine sensor, transmits signals regarding leucine availability to mTORC1, and its polyubiquitination is regulated by E3 ubiquitin ligase RNF167 and deubiquitinase STAMBPL1. Knockout of STAMBPL1 inhibits xenograft tumor growth in CRC models.[80] Dietary factors also influence amino acid metabolism, as seen with high-temperature cooking of red meat, which generates PhIP, a heterocyclic amine that forms DNA adducts in intestinal cells, increasing CRC risk.[81]

The lncRNA Linc00266-1 encodes a 71-amino acid peptide—RBRP—that interacts with IGF2BP1 to facilitate the recognition of m6A-modified sites on c-Myc mRNA. This interaction enhances mRNA stability and elevates c-Myc expression, driving colorectal tumorigenesis. Clinically, higher RBRP levels in CRC patients

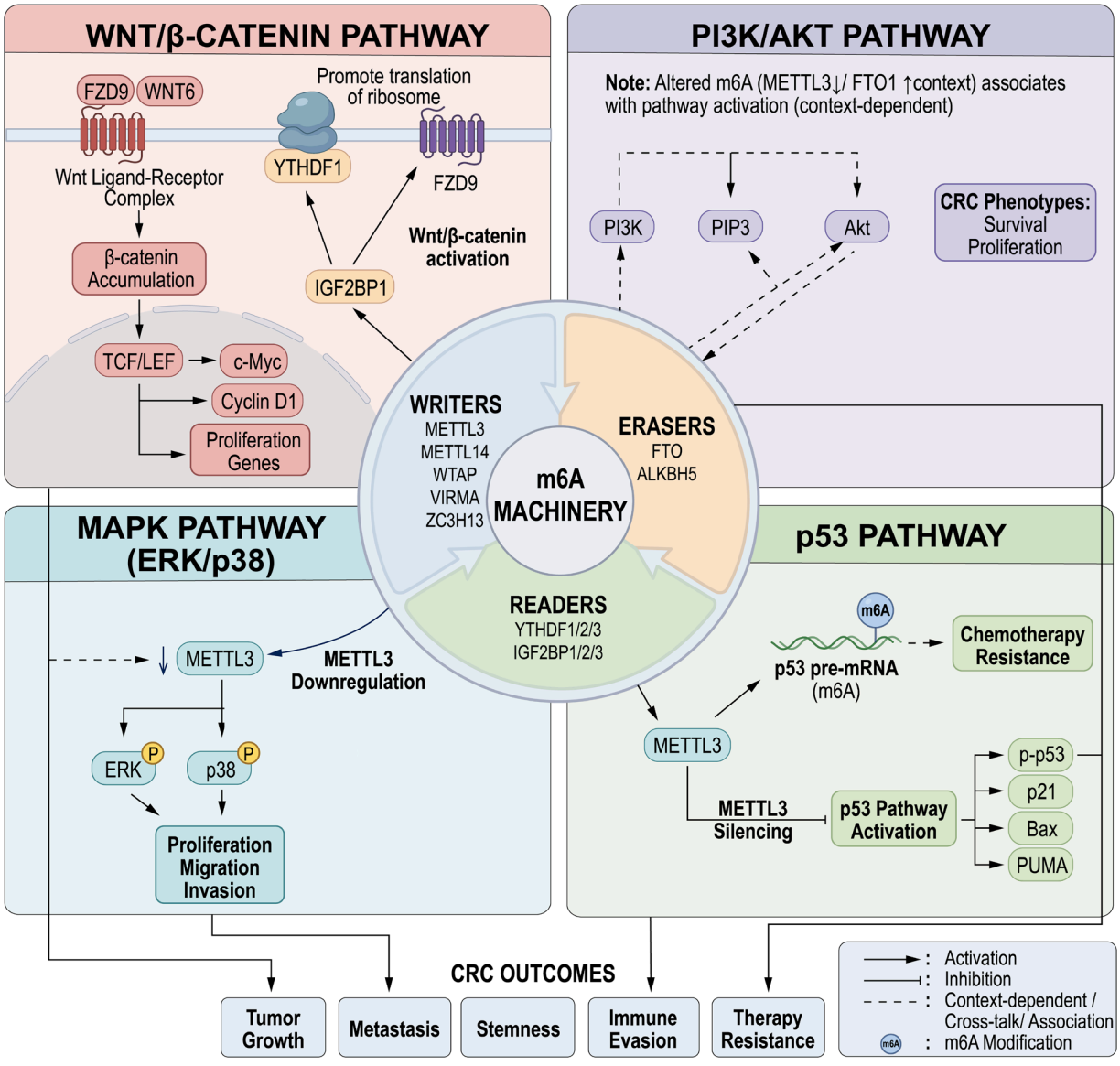


Fig. 3. Integrated regulatory mechanisms of m6A modification in core oncogenic signaling pathways of CRC. This schematic illustrates the integrated role of m6A RNA modification in regulating core oncogenic signaling pathways in CRC. The dynamic m6A machinery modulates the stability, translation, and processing of pathway-related transcripts. Through context-dependent regulation of key components within the Wnt/β-catenin, PI3K/Akt, MAPK (ERK/p38), and p53 pathways, m6A modification influences β-catenin activation, Akt signaling, MAPK phosphorylation cascades, and p53-mediated tumor suppressive responses. These coordinated epitranscriptomic mechanisms collectively drive malignant phenotypes, including enhanced proliferation, survival, invasion, metastasis, immune evasion, and therapeutic resistance in CRC. Akt, protein kinase B; ALKBH5, AlkB homolog 5; Bax, Bcl-2-associated X protein; CRC, colorectal cancer; ERK, extracellular signal-regulated kinase; FTO, fat mass and obesity-associated protein; FZD9, frizzled class receptor 9; IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; IGF2BP2, insulin-like growth factor 2 mRNA-binding protein 2; IGF2BP3, insulin-like growth factor 2 mRNA-binding protein 3; LEF, lymphoid enhancer-binding factor; m6A, N6-methyladenosine; MAPK, mitogen-activated protein kinase; METTL3, methyltransferase-like 3; METTL14, methyltransferase-like 14; mRNA, messenger RNA; p21, cyclin-dependent kinase inhibitor 1A; p38, p38 mitogen-activated protein kinase; p53, tumor protein p53; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PI3K, phosphoinositide 3-kinase; PUMA, p53 upregulated modulator of apoptosis; TCF, T-cell factor; VIRMA, vir-like m6A methyltransferase associated protein; WNT6, Wnt family member 6; WTAP, Wilms tumor 1-associated protein; YTHDF1, YT521-B homology domain family protein 1; YTHDF2, YT521-B homology domain family protein 2; YTHDF3, YT521-B homology domain family protein 3; ZC3H13, zinc finger CCCH-type containing 13.

are associated with more aggressive clinicopathological features and shorter survival.[82]

Fatty acid metabolism

Fatty acid metabolism influences CRC progression through various mechanisms, including lipogenesis, oxidative energy production, immune microenvironment modulation, and microbiota interactions. FASN, which is upregulated in CRC cells and tissues, catalyzes the conversion of acetyl-CoA to palmitate, facilitating lipid droplet formation that provides membrane components and

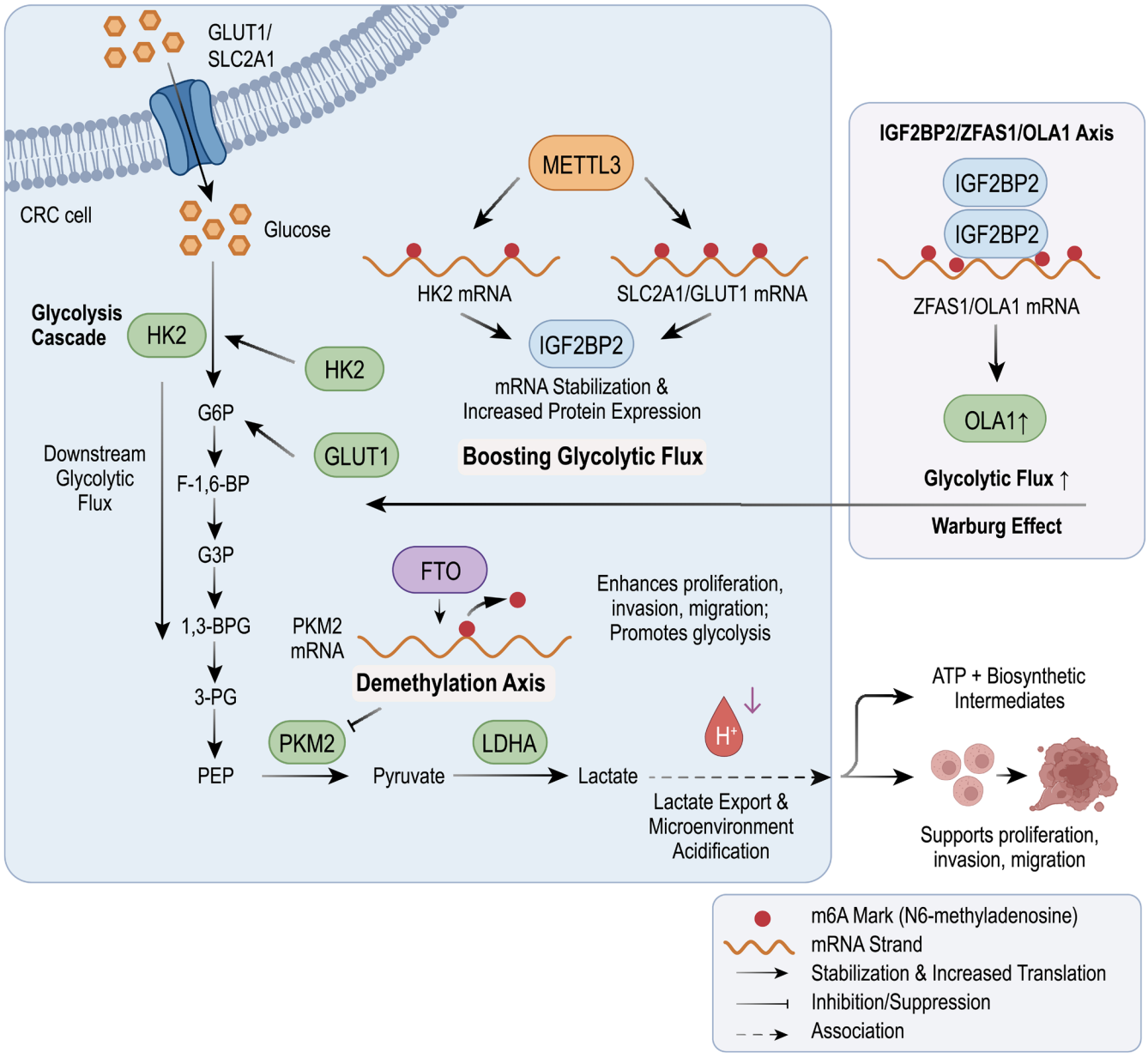


Fig. 4. Molecular mechanisms of m6A-mediated regulation of glycolysis in CRC. This schematic illustrates the molecular mechanisms by which m6A RNA modification regulates glycolysis in CRC. m6A modulates the stability and translation of key glycolytic transcripts, including HK2, PKM2, and SLC2A1 (GLUT1). METTL3-mediated m6A deposition enhances the stability and expression of glycolytic enzymes, whereas FTO and ALKBH5 dynamically reshape methylation levels in a context-dependent manner. Reader proteins such as IGF2BP2 recognize m6A-modified mRNAs and promote their stabilization, sustaining aerobic glycolysis (the Warburg effect). Through coordinated regulation of glucose uptake, glycolytic flux, and ATP production, m6A modification supports metabolic reprogramming, tumor cell proliferation, and survival in CRC. 1,3-BPG, 1,3-bisphosphoglycerate; 3-PG, 3-phosphoglycerate; CRC, colorectal cancer; F-1,6-BP, fructose-1,6-bisphosphate; FTO, fat mass and obesity-associated protein; G3P, glyceraldehyde-3-phosphate; G6P, glucose-6-phosphate; GLUT1, glucose transporter 1; H+, hydrogen ion; HK2, hexokinase 2; IGF2BP2, insulin-like growth factor 2 mRNA-binding protein 2; LDHA, lactate dehydrogenase A; m6A, N6-methyladenosine; mRNA, messenger RNA; METTL3, methyltransferase-like 3; OLA1, Obg-like ATPase 1; PEP, phosphoenolpyruvate; PKM2, pyruvate kinase M2; SLC2A1, solute carrier family 2 member 1; ZFAS1, zinc finger antisense 1.

signaling molecules, such as phospholipids, essential for cancer cell proliferation. FASN promotes CRC cell progression and phosphatidylcholine metabolism via the SP1/PLA2G4B axis, while also suppressing NK cell-mediated antitumor immunity.[83] Acetyl-CoA carboxylase influences fatty acid chain elongation and desaturation, affecting membrane fluidity and pro-tumorigenic signaling pathways, including EGFR and Wnt/β-catenin.[84] Lipid accumulation further activates the PI3K/Akt pathway, inhibiting apoptosis and enhancing cell proliferation.[85] Drp1 supports Wnt/β-catenin signaling by inducing fatty acid oxidation-dependent acetylation of β-catenin, promoting CRC progression.[86] Secondary BAs and SCFAs, key bacterial metabolites in the colon, are diet-dependent.

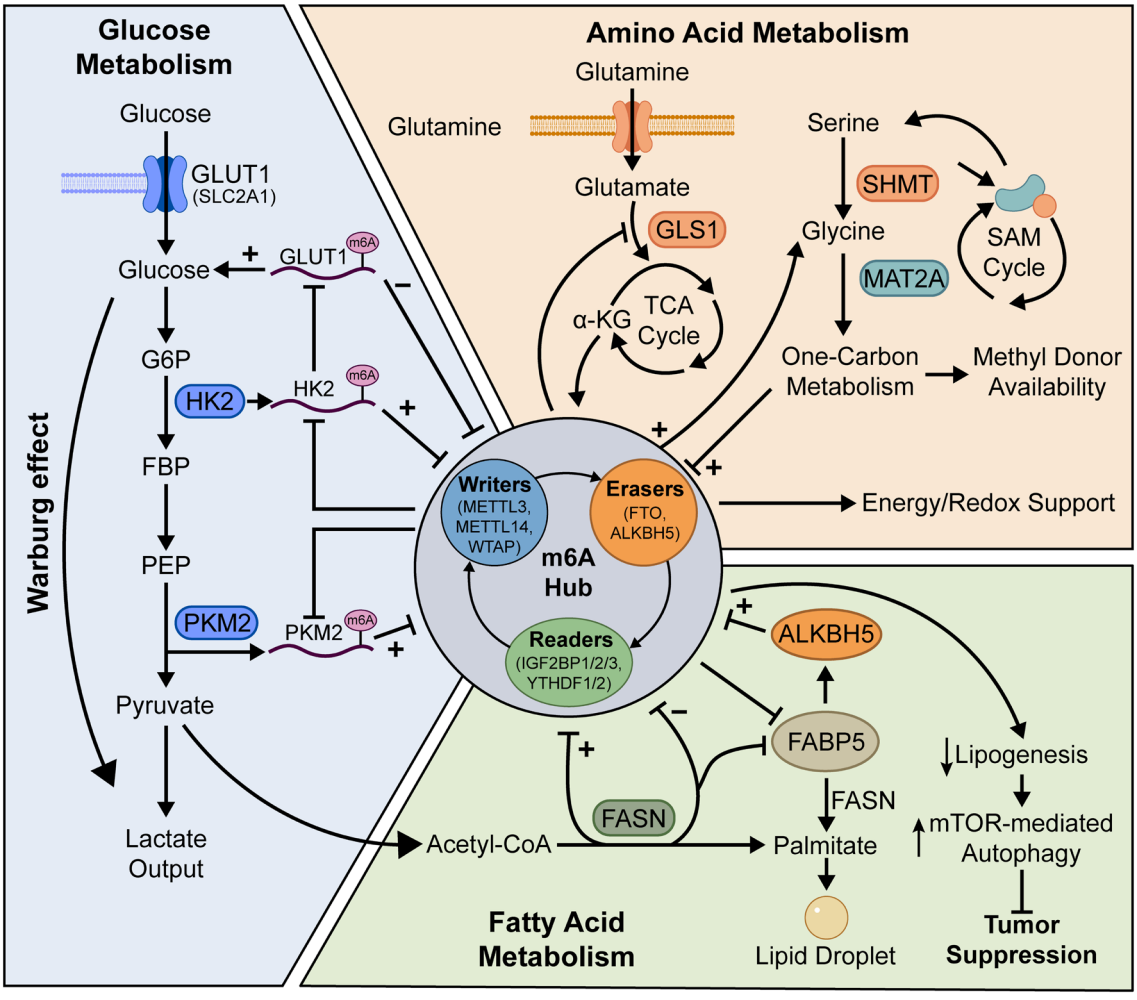


Fig. 5. Comprehensive m6A-mediated regulatory network of metabolic reprogramming in CRC. This schematic illustrates the integrated regulatory network by which m6A RNA modification modulates three major metabolic pathways in CRC: glucose metabolism, amino acid metabolism, and fatty acid metabolism. The dynamic m6A machinery regulates the stability and translation of key metabolic enzymes and transporters, including HK2, PKM2, SLC2A1 (GLUT1), GLS, c-Myc, FASN, and FABP5. Through these targets, m6A modification enhances aerobic glycolysis (Warburg effect), supports glutamine and one-carbon metabolism, and reshapes lipid synthesis and fatty acid oxidation. These coordinated epitranscriptomic events promote bioenergetic adaptation, macromolecular biosynthesis, redox balance, and interaction with the tumor microenvironment, collectively facilitating CRC growth, progression, and therapeutic resistance. α-KG, alpha-ketoglutarate; ALKBH5, AlkB homolog 5; FABP5, fatty acid-binding protein 5; FASN, fatty acid synthase; FBP, fructose-1,6-bisphosphate; FTO, fat mass and obesity-associated protein; G6P, glucose-6-phosphate; GLS1, glutaminase 1; GLUT1, glucose transporter 1; HK2, hexokinase 2; IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; IGF2BP2, insulin-like growth factor 2 mRNA-binding protein 2; IGF2BP3, insulin-like growth factor 2 mRNA-binding protein 3; m6A, N6-methyladenosine; MAT2A, methionine adenosyltransferase 2A; METTL3, methyltransferase-like 3; METTL14, methyltransferase-like 14; mTOR, mechanistic target of rapamycin; PEP, phosphoenolpyruvate; PKM2, pyruvate kinase M2; SAM, S-adenosylmethionine; SHMT, serine hydroxymethyltransferase; SLC2A1, solute carrier family 2 member 1; TCA, tricarboxylic acid cycle; WTAP, Wilms tumor 1-associated protein; YTHDF1, YT521-B homology domain family protein 1; YTHDF2, YT521-B homology domain family protein 2.

High-fat diets increase secondary BAs (deoxycholic and lithocholic acids), which are associated with colonic inflammation and carcinogenesis.[87] BAs also drive tumorigenesis by activating the TGR5/STAT3/KLF5 pathway.[88] Additionally, long-chain fatty acid metabolism, particularly unsaturated fatty acids, regulates the immunosuppressive phenotype of tumor-associated macrophages. Experimental data show that myeloid cells infiltrating CRC tissues accumulate lipid droplets.[89]

FABP5 is notably downregulated in CRC. The demethylase ALKBH5 enhances FABP5 expression through m6A modification. FABP5 interacts with FASN and decreases FASN expression and lipid accumulation. This process has been shown to inhibit mTOR signaling, promote cellular autophagy, and suppress CRC progression.[22]

Crosstalk between m6A-mediated metabolic reprogramming and oncogenic signaling

Emerging evidence suggests that m6A-dependent regulation of metabolic enzymes indirectly reshapes canonical oncogenic signaling pathways. For example, METTL3-mediated stabilization of HK2 and SLC2A1 enhances glycolytic flux in CRC.[68] Elevated glycolysis increases lactate production and activates PI3K/Akt signaling,[44,90] thereby promoting proliferation and survival.

FTO regulates PKM2 expression to enhance glycolytic metabo-

lism,[16] while IGF2BP2 stabilizes HK2 mRNA to sustain aerobic glycolysis.[91] Given that PI3K/Akt signaling promotes glucose uptake and HK2 activity,[44] m6A-driven metabolic rewiring may establish a positive feedback loop between glycolysis and PI3K/Akt activation.

In lipid metabolism, ALKBH5/FABP5-mediated suppression of FASN reduces lipid accumulation and attenuates mTOR signaling.[22] Since lipid metabolism can activate PI3K/Akt and Wnt/β-catenin pathways,[84,85] m6A-dependent control of fatty acid synthesis may indirectly regulate oncogenic signaling intensity.

Fatty acid oxidation has been shown to promote Wnt/β-catenin signaling through metabolic acetylation mechanisms.[86] Therefore, m6A-regulated lipid enzymes may influence Wnt activity by altering intracellular acetyl-CoA pools.

These findings indicate that m6A modification acts as a molecular bridge connecting metabolic reprogramming with oncogenic signaling networks, integrating nutrient availability with tumor growth and therapeutic resistance.

Current limitations and future perspectives

Despite rapid progress in understanding m6A RNA modification in CRC, several important limitations hinder clinical translation. Most mechanistic studies rely on *in vitro* cell models or xenograft systems, which cannot fully reflect the genetic heterogeneity, metabolic plasticity, and immune microenvironment of human CRC. Recent studies emphasize the importance of integrating transcriptomics, epitranscriptomics, and spatial profiling to validate m6A regulators in large clinical cohorts.[1,12,29] Therefore, validation using patient-derived organoids, spatial transcriptomics, and prospective datasets is urgently required.

The spatiotemporal dynamics of m6A regulation also remain insufficiently defined. m6A deposition is highly context-dependent and may change during tumor progression, metastasis, and therapy resistance. Emerging single-cell and epitranscriptomic technologies have begun to reveal dynamic m6A landscapes in cancer,[2,92,93] but their application in CRC remains limited. A better understanding of how m6A remodeling contributes to intratumoral heterogeneity and metastatic evolution is needed.

Functional redundancy and cross-regulation among m6A regulators further complicate mechanistic interpretation. Writers, erasers, and readers frequently function within coordinated regulatory networks. For example, METTL3 and METTL14 may exert oncogenic or tumor-suppressive roles depending on cellular context,[5] while ALKBH5 demonstrates dual functions across tumor types.[4] Systems-level approaches integrating transcriptome-wide m6A mapping with proteomic and metabolic analyses are required to clarify these context-dependent effects.

Moreover, the integration between m6A modification, oncogenic signaling, and metabolic reprogramming remains incompletely understood. m6A has been shown to regulate key metabolic enzymes such as HK2, PKM2, and FASN,[68,83] yet the reciprocal influence of metabolic states on m6A machinery remains largely unexplored. Given the close interplay between metabolic rewiring and signaling pathways such as Wnt/β-catenin and PI3K/Akt in CRC,[44,86] defining this bidirectional regulatory loop may uncover new therapeutic vulnerabilities.

Although m6A-targeted therapies are emerging, clinical translation remains at an early stage. The METTL3 inhibitor STM2457 has demonstrated promising preclinical activity in leukemia models,[5] supporting the feasibility of targeting the m6A machinery. However, the efficacy and safety of such strategies in solid tumors, including CRC, require further investigation, particularly considering the essential physiological roles of m6A in normal tissue homeostasis.[1,93]

Future research should focus on mapping the spatiotemporal m6A epitranscriptome in CRC, elucidating its role in immune metabolism within the tumor microenvironment, and developing selective m6A-targeted therapeutics with predictive biomarkers. Such advances will be crucial for translating m6A biology into precision strategies for CRC management.

Conclusions

As a key element of the "RNA epigenetic code," m6A plays a pivotal role in the regulation of RNA metabolism and the progression of CRC. Through the dynamic interactions of its regulatory proteins—writers, erasers, and readers—m6A modification fine-tunes various cellular processes such as gene expression, cell proliferation, migration, and metastasis. These m6A-regulated processes are intricately linked to oncogenic signaling pathways, including the Wnt/β-catenin, PI3K/Akt, MAPK, and p53 pathways, which are critical drivers of CRC pathogenesis. Additionally, m6A-modifying enzymes present opportunities to develop targeted therapies, with studies predicting potential binding sites, offering new avenues for precision medicine and RNA-based treatments in CRC. Future clinical translation will require the development of selective and safe m6A-targeting agents. Preclinical evidence supporting METTL3 inhibition and the prognostic significance of m6A readers such as IGF2BP3 and YTHDF1 underscore the feasibility of targeting the m6A machinery. Integrating m6A-based biomarkers with metabolic and signaling signatures may improve patient stratification and therapeutic response prediction. Ultimately, precision epitranscriptomic intervention may represent a novel avenue for CRC management.

Acknowledgments

None.

Funding

This work was supported by the Project of Administration of Traditional Chinese Medicine of Jiangsu Province, China (MS2024139); Project of Changshu Science and Technology Development (CS202218); Zhongda Hospital Affiliated to Southeast University, Jiangsu Province High-Level Hospital Construction Funds (Nos. YKK24268).

Conflict of interest

The authors declare no potential conflicts of interest.

Author contributions

Conceptualization (QL), writing – original draft (QS), writing – review & editing (YW, MX, LC, YD, MN, QZ, JJ, QL), funding acquisition (CC, ZX), and supervision (QL). All authors have read and approved this manuscript.

Figure preparation and AI-use statement

The graphical abstract and all figures (Figures 1–5) were independently created and redrawn by the authors using Adobe Illustra-

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