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The SAM-m^{6}A axis as an unexplored therapeutic hub for plant-derived regulation of disease metabolism

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ABSTRACT

S-adenosylmethionine (SAM) is the main cellular methyl donor and a core product of one-carbon metabolism. Its balance with S-adenosylhomocysteine (SAH) defines methylation potential and shapes epigenetic and epitranscriptomic outputs. RNA N^6-methyladenosine (m^{6}A) directly depends on SAM and is controlled by a writer-reader-eraser system. This review summarizes how altered SAM supply, SAH accumulation, and shifts in the SAM/SAH ratio can reprogram m^{6}A landscapes. These changes can occur in cancer, metabolic disease,

Abbreviations: 5-methyl-THF, 5-Methyltetrahydrofolate; ACC, Acetyl-CoA carboxylase; AD, Alzheimer's disease; ADPKD, Autosomal dominant polycystic kidney disease; ALKBH5, AlkB homolog 5; AMD1, Adenosylmethionine decarboxylase 1; ATP, Adenosine triphosphate; BHMT, Betaine-homocysteine methyltransferase; ChREBP, Carbohydrate response element-binding protein; CKD, Chronic kidney disease; CTLA-4, Cytotoxic T-lymphocyte-associated protein 4; Cyp2e1, Cytochrome P450 2E1; DcSAM, Decarboxylated S-adenosylmethionine; EMT, Epithelial-mesenchymal transition; FASN, Fatty acid synthase; FGF23, Fibroblast growth factor 23; FTO, Fat mass and obesity-associated protein; G6pc, Glucose-6-phosphatase; GSDMD, Gasdermin D; Gzmb, Granzyme B; HAKAI, E3 ubiquitin-protein ligase HAKAI; HBV, Hepatitis B virus; HCoV-OC43, Human coronavirus OC43; Hcy, Homocysteine; HFD, High-fat diet; ICAM2, Intercellular adhesion molecule 2; IGF2BP, Insulin-like growth factor 2 mRNA-binding protein; IRF4, Interferon regulatory factor 4; Km, Michaelis-Menten constant; KSHV, Kaposi's sarcoma-associated herpesvirus; LgBiT, Large BiT; LncRNA, Long noncoding RNA; LOX, Lysyl oxidase; M1A, 1-Methyladenosine; M5C, 5-Methylcytosine; M^{6}A, N^6-Methyladenosine; M^{6}Am, N6,2'-O-Dimethyladenosine; MAT, Methionine adenosyltransferase; MAT1A, Methionine adenosyltransferase isoenzyme 1 A; MAT2A, Methionine adenosyltransferase isoenzyme 2 A; MAT2B, Methionine adenosyltransferase regulatory subunit 2B; MCMV, Maize chlorotic mottle virus; Met, Methionine; METTL3, Methyltransferase-like protein 3; METTL14, Methyltransferase-like protein 14; METTL16, Methyltransferase-like protein 16; METTL5, Methyltransferase-like protein 5; MiCLIP, m^{6}A individual-nucleotide-resolution crosslinking and immunoprecipitation; MMP2, Matrix metalloproteinase 2; MRNA, Messenger RNA; MTA, Methylthioadenosine; MTC, Methyltransferase complex; MTHFD, Methylenetetrahydrofolate dehydrogenase/cyclase; MTHFD2, Methylenetetrahydrofolate dehydrogenase 2; MTORC1, Mechanistic target of rapamycin complex 1; MTR, Methionine synthase; NAD, Nicotinamide adenine dinucleotide; NADP, Nicotinamide adenine dinucleotide phosphate; NAFLD, Non-alcoholic fatty liver disease; NanoLuc, NanoLuc luciferase; NcRNA, Noncoding RNA; NGAL, Neutrophil gelatinase-associated lipocalin; NLRP3, NOD-like receptor family pyrin domain-containing 3; NTD, Neural tube defect; PCK1, Phosphoenolpyruvate carboxykinase 1; PD, Parkinson's disease; PD-1, Programmed cell death protein 1; PPARα, Peroxisome proliferator-activated receptor alpha; Prf1, Perforin 1; PRPP, Phosphoribosyl pyrophosphate; PRPS, Phosphoribosyl pyrophosphate synthetase; PRPS2, Phosphoribosyl pyrophosphate synthetase 2; PTEN, Phosphatase and tensin homolog; RA, Rheumatoid arthritis; RBM15, RNA-binding motif protein 15; RBM15B, RNA-binding motif protein 15B; RNA-seq, RNA sequencing; ROS, Reactive oxygen species; RRNA, Ribosomal RNA; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SCD1, Stearoyl-CoA desaturase 1; SFTSV, Severe fever with thrombocytopenia syndrome virus; SHMT, Serine hydroxymethyltransferase; SHMT2, Serine hydroxymethyltransferase 2; SLE, Systemic lupus erythematosus; SmBiT, Small BiT; SnoRNA, Small nucleolar RNA; SnRNA, Small nuclear RNA; SREBP1, Sterol regulatory element-binding protein 1; THF, Tetrahydrofolate; TMPRSS2, Transmembrane protease serine 2; TRAIL-DR4, TNF-related apoptosis-inducing ligand receptor DR4; VIRMA, Vir-like m^{6}A methyltransferase associated protein; VPS11, Vacuolar protein sorting-associated protein 11; WTAP, Wilms' tumor 1-associating protein; WYMV, Wheat yellow mosaic virus; YTHDC, YT521-B homology domain-containing proteins; YTHDF, YT521-B homology domain family proteins; ZC3H13, Zinc finger CCCH-type containing 13; ZCCHC4, Zinc finger CCHC-type containing 4.

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inflammation, and neurodegeneration. We integrate metabolic control of SAM generation and consumption with regulation of METTL3/METTL14, WTAP and related cofactors, and the erasers FTO and ALKBH5. We also assess plant-derived bioactive compounds proposed to act on this coupling. Most phytochemicals do not behave as potent, selective m^{6}A enzyme inhibitors. They more often act upstream by reshaping one-carbon metabolism, redox state, and protein expression. This profile contrasts with canonical synthetic inhibitors that block a single node with higher affinity and more predictable pharmacodynamics. Together, the evidence supports the SAM-m^{6}A axis as a practical framework to connect nutrient state with RNA fate decisions. It also highlights key gaps for translation, including target engagement, dose-exposure alignment, and causal validation of m^{6}A-dependent phenotypes.

1. Introduction

S-adenosylmethionine (SAM) is the principal biological methyl donor in eukaryotic cells and occupies a central position in one-carbon metabolism [1]. It is synthesized from methionine and ATP through the methionine cycle and serves as an essential substrate for a wide range of methyltransferase reactions, including DNA, RNA, protein, and lipid methylation [2]. The intracellular availability of SAM, together with the SAM/S-adenosylhomocysteine (SAH) ratio, reflects cellular methylation capacity and dynamically integrates nutritional status, metabolic flux, and redox balance [3]. Consequently, fluctuations in SAM homeostasis provide a direct metabolic input that can modulate epigenetic and epitranscriptomic processes, including N^6-methyladenosine (m^{6}A) RNA modification.

m^{6}A is the most abundant internal modification in eukaryotic mRNA and functions as a dynamic regulator of gene expression [4]. The efficiency of m^{6}A deposition largely depends on the availability of the universal methyl donor SAM, which is synthesized from the methionine cycle [5,6]. Therefore, the SAM-m^{6}A axis integrates cellular nutritional status and epitranscriptome regulation. When SAM production is impaired, m^{6}A levels decrease, leading to widespread alterations in RNA stability, translation, and metabolic signaling. Conversely, excessive SAM or aberrant m^{6}A dynamics may promote oncogenic or inflammatory pathways [7].

In parallel, nutritional epigenetics has highlighted that dietary components and plant-derived bioactive compounds can modulate epigenetic and epitranscriptomic regulation. Beyond classical vitamins and methyl donors, many phytochemicals influence one-carbon metabolism, SAM-consuming enzymes, or components of the m^{6}A machinery. Tea polyphenols, curcumin, tanshinone IIA, and related compounds have been reported to alter SAM homeostasis, writer or eraser abundance, and reader-dependent RNA decay or translation [8,9]. However, existing studies are often fragmented, focusing on isolated molecules or disease models, and a unifying mechanistic framework is still lacking.

Here, we propose the SAM-m^{6}A axis as an integrative framework to organize these findings. Rather than treating m^{6}A regulation or plant interventions as isolated phenomena, this review emphasizes how metabolic control of SAM supply, writer activity, and downstream reader selection collectively shape disease-relevant RNA programs. We systematically summarize the molecular basis of SAM metabolism and m^{6}A machinery, analyze how plant-derived compounds engage this axis, and compare their systems-level modulation with canonical small-molecule inhibitors. We further integrate disease-specific evidence to identify common patterns, dominant regulatory nodes, and translational implications.

2. SAM biosynthesis and regulatory mechanisms

2.1. SAM metabolism and homeostasis

SAM is the most universal methyl donor in cells, participating in a variety of methylation reactions, including DNA, RNA, proteins, lipids, and small molecules. Its intracellular level is primarily maintained by the methionine cycle and one-carbon metabolism [10,11]. The synthesis reaction is catalyzed by methionine adenosyltransferase (MAT): L-methionine + ATP → SAM + PPi + Pi [12]. In mammals, MAT1A is primarily expressed in the liver, while MAT2A is widely distributed in non-hepatic tissues. MAT2B is a regulatory subunit that regulates MAT2A activity and SAM production (Fig. 1) [13,14].

Methionine (Met) in the body can be derived from dietary intake or generated through remethylation of homocysteine (Hcy). There are two primary pathways for its production. The first is the MTR pathway, where folate and vitamin B12 react with methionine synthase to produce Met using 5-methyltetrahydrofolate (5-methyl-THF) as a methyl donor. Furthermore, the betaine homocysteine methyltransferase (BHMT) pathway produces Met using betaine as a methyl donor. These two pathways work together to generate Met, which in turn regulates SAM synthesis [15–18].In addition, methionine salvage can reuse methylthioadenosine (MTA) produced by polyamine synthesis, further stabilizing methionine synthesis [19,20].

SAM synthesis is also related to one-carbon metabolism. Serine/glycine donate a single carbon unit to THF in the one-carbon pathway. The resulting 5-methyl-THF participates in the MTR reaction. This process is regulated by key enzymes such as serine hydroxymethyltransferase (SHMT) and methylenetetrahydrofolate dehydrogenase/cyclase (MTHFD). It is closely linked to NAD(P)H and carbon-nitrogen skeleton metabolism. Consequently, nutritional and stress conditions dynamically influence the production of Met and SAM [21].

Elevated SAH represents a common epigenetic stress signal in vascular disease because it reflects impaired SAH clearance and inhibition of methylation reactions. Studies using SAHH inhibition consistently show that increased SAH promotes endothelial dysfunction and accelerates atherosclerosis. A shared upstream mechanism is the downregulation of DNMT1 and promoter hypomethylation of pathogenic genes. However, the dominant downstream effect differs across disease contexts. In vascular aging models, SAH induces endothelial senescence mainly by upregulating DRP1, disrupting mitochondrial dynamics, and promoting cellular aging phenotypes [22]. In atherosclerosis-prone settings, SAH primarily enhances oxidative stress and impairs nitric oxide bioavailability through epigenetic activation of the p66shc pathway [23]. Both mechanisms are reversible by targeting the respective downstream nodes, such as DRP1 inhibition or antioxidant and p66shc suppression. Human data further support these findings by linking plasma SAH levels to endothelial dysfunction and methylation changes. Together, these studies indicate that SAH-driven methylation imbalance follows a shared epigenetic logic but manifests through distinct effector pathways depending on vascular state and disease stage.

SAM is also regulated by upstream signals. For example, mechanism of rapamycin complex 1 (mTORC1) can promote the one-carbon cycle and methionine remethylation by upregulating the expression of MAT2A and one-carbon metabolism enzymes. This rapidly and significantly increases intracellular SAM levels, providing substrates for downstream RNA and histone methylation [24,25]. Concurrently, in liver tissue, phosphoenolpyruvate carboxykinase 1 (PCK1) regulates carbon cycling and chromatin methylation. PCK1 influences SAM synthesis and histone modifications such as H3K9me3 [26].

In summary, Met synthesis, MAT2A/2B catalytic regulation, the one-

carbon cycle, and the SAM/SAH ratio form the core mechanisms influencing SAM levels. This pathway is regulated by both dietary factors (Met, folate, vitamin B12, and betaine) and signaling pathways such as mTORC1 and PCK1. SAM is the sole methyl donor for m^{6}A modification insertion, and this pathway provides the foundation for subsequent post-transcriptional regulation mediated by the SAM-m^{6}A axis [27].

2.2. SAM/SAH ratio and methylation potential

SAM-dependent methylation should be interpreted as a coupled system rather than an isolated increase or decrease in SAM. The intracellular SAM/SAH ratio integrates methyl-donor supply with product inhibition and is therefore a practical proxy for methylation capacity [28]. SAH is generated after methyl transfer and can inhibit multiple methyltransferases. SAH accumulation can lower the SAM/SAH ratio even when SAM is not limiting, and this shift is accompanied by reduced methylation activity [29]. This balance is thus better viewed as a dynamic homeostatic variable than a static marker.

Nutritional state is a major driver of SAM/SAH dynamics. Dietary methyl donors and co-factors modulate flux through one-carbon metabolism and change both SAM synthesis and SAH clearance. Vitamin B12 deficiency reduces methionine synthase activity and decreases the SAM/SAH ratio, which is linked to neurological dysfunction [30]. In contrast, betaine supplementation can raise the SAM/SAH ratio and improve metabolic outcomes, including liver-related phenotypes [31]. These findings support a model in which SAM/SAH responds to nutrient availability and can mediate downstream epigenetic outputs.

Tissue context further shapes how SAM/SAH varies and what it predicts. The liver has high one-carbon turnover and can rapidly adjust SAM/SAH across fasting-feeding transitions to match metabolic demand [32]. In the nervous system, SAM/SAH balance is tightly linked to neurodevelopmental and cognitive processes, and exogenous SAM has been explored for depression and cognitive impairment, suggesting functional sensitivity to methylation capacity in this tissue [33,34]. In chronic kidney disease, urinary SAM/SAH has been proposed as a non-invasive marker reflecting systemic methylation imbalance and disease progression [35]. In cardiovascular disease, decreased SAM/-SAH has been associated with higher atherosclerosis risk, and SAM supplementation has been reported to improve vascular function [36]. Together, these examples emphasize that SAM/SAH is not uniform across the body and may change with stage, compartment, and disease burden.

Overall, the SAM/SAH ratio is best positioned as a context-dependent indicator that links nutrition, tissue metabolism, and methyltransferase activity. Its interpretation should therefore consider tissue type, nutritional status, and disease stage, rather than assuming a fixed relationship with methylation output.

3. Mechanistic basis of the SAM-m^{6}A axis

The SAM-m^{6}A axis is a complete system from metabolism to epigenetics. The intracellular supply level of SAM and its balance with SAH serve as upstream metabolic inputs. Based on this metabolic input, m^{6}A writers (such as the METTL3/METTL14/WTAP complex and METTL16), demethylases (such as FTO and ALKBH5), and readers (such as the YTH family and IGF2BP family) reshape the m^{6}A modification map at specific transcripts and sites [31]. Changes in this modification map further influence key RNA fate decisions, including splicing and processing, and nuclear export, ultimately being translated into differences in cellular functional reprogramming and disease-related phenotypes.

3.1. SAM as the core regulator of m^{6}A modification

SAM is the sole methyl donor for m^{6}A modification. SAM directly determines the efficiency and extent of m^{6}A insertion. m^{6}A modification is catalyzed by the multicomponent methyltransferase complex (MTC). METTL3 is responsible for binding to SAM and catalyzing methyl transfer. METTL14 is responsible for substrate recognition, while WTAP and VIRMA assist in localization. Furthermore, METTL16, ZCCHC4, and METTL5 can independently catalyze m^{6}A modification of specific RNAs [37,38]. SAM binding is an essential step in the active reactions of these enzymes, and SAM levels and availability play a central role in regulating m^{6}A modification (Fig. 2).

Low SAM levels lead to a global decrease in m^{6}A modification. It has been reported that when cells are in a low methyl donor state, the m^{6}A content of RNA decreases significantly. This decrease in m^{6}A content inhibits post-transcriptional effects of transcripts and promotes abnormal cell proliferation [39,40]. This result suggests that SAM

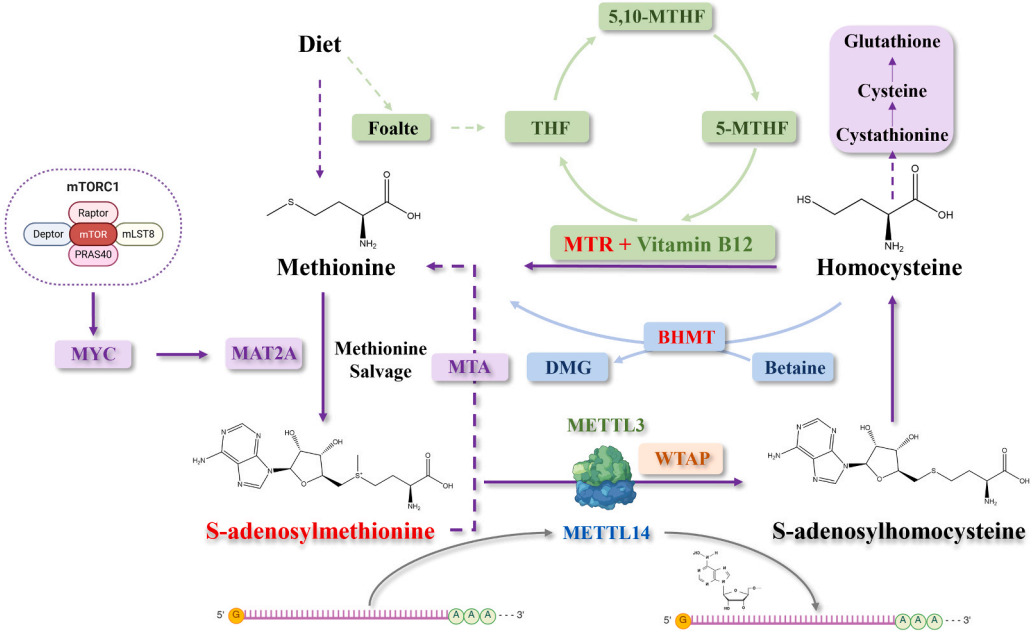

Fig. 1. Overview of SAM metabolism and homeostasis linking dietary methyl donors, one-carbon cycling, and MAT2A-mediated SAM synthesis to m^{6}A RNA methylation.

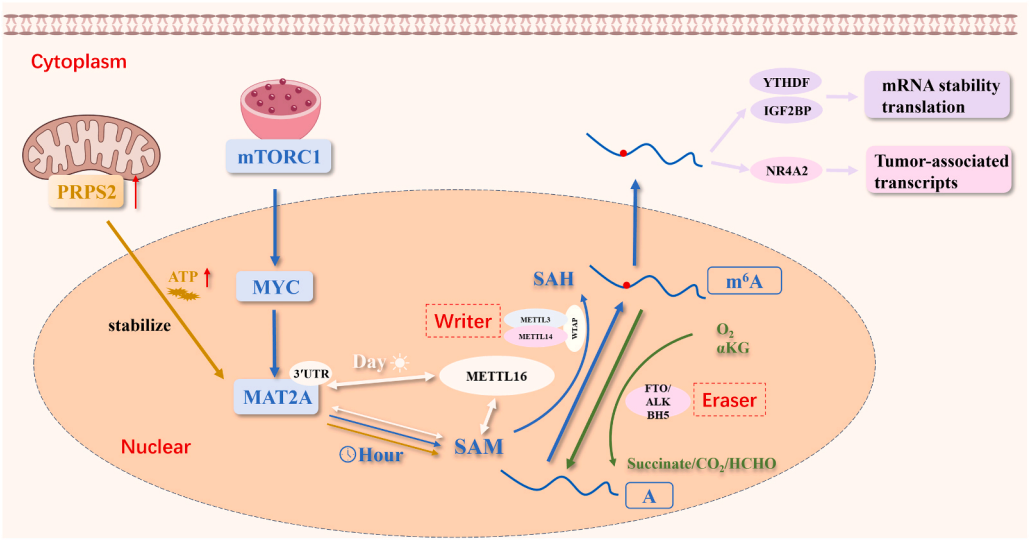

Fig. 2. SAM regulates m^{6}A modification through MAT2A synthesis and mTORC1-MYC-METTL signaling.

deficiency impairs methylation modification capacity. SAM deficiency can also affect the fate of key gene transcripts and promote disease development.

High levels of SAM can amplify m^{6}A signals. In response to nutrient abundance or activated signaling pathways, MAT2A expression is upregulated. This leads to increased intracellular SAM levels, which in turn enhances global mA modification [41]. For example, mTORC1 promotes SAM elevation, triggering mA reprogramming in NK cells. This improves the mRNA stability and translation efficiency of target factors, which in turn enhances immune function [42]. This suggests that changes in SAM are closely linked to metabolic status and immune responses.

The SAM/SAH ratio is closely related to the efficiency of m^{6}A modification. The SAM/SAH ratio reflects the methylation capacity of cells. SAH accumulation competitively inhibits the activity of writer enzymes such as METTL3/14, which reduces the efficiency of m^{6}A modification [9]. Clinical and animal studies have shown that increasing the SAM/SAH ratio can enhance m^{6}A modification. Supplementing with betaine or alleviating the inhibitory effects of S-adenosylhomocysteine hydrolase (SAHH) can improve neurological function [9].

An imbalance in the SAM-m^{6}A axis can also play a significant role in disease development. Arsenic exposure depletes SAM through As3MT, leading to decreased m^{6}A levels. This blocks miRNA maturation and induces NAFLD [43]. Similarly, vitamin B12 deficiency reduces SAM levels. This reduced SAM level leads to abnormal m^{6}A modification of neural genes, resulting in neurodevelopmental and cognitive deficits [44]. These findings suggest that an imbalance in the SAM-m^{6}A axis can contribute to disease.

SAM influences m^{6}A modification by influencing writer enzymes. Furthermore, the SAM/SAH ratio can regulate methylation potential. In disease, the SAM-m^{6}A axis is imbalanced. Results indicate that SAM is not only a metabolic intermediate but also a rate-limiting factor in m^{6}A modification. Its content changes connect metabolism and epigenetic interactions.

3.2. *Upstream signaling and the MAT2A-SAM-m^{6}A pathway*

This section summarizes how different upstream signals influence the MAT2A-SAM-m^{6}A axis.

Phosphoribosyl pyrophosphate synthetase (PRPS) is the rate-limiting enzyme in the purine biosynthesis pathway, catalyzing the production of PRPP. PRPP is a key substrate for the synthesis of purines and pyrimidines. It is also a key substrate for the synthesis of coenzymes such as NAD and NADP [45]. PRPS regulates the MAT2A-SAM-m^{6}A axis. PRPS promotes ATP production, regulates MAT2A, and leads to an increase in SAM [41]. MAT2A connects the signal input to the m^{6}A modification.

The mTORC1 signaling pathway is an important regulator of metabolic adaptations in response to nutritional changes [46]. The mTORC1-MYC pathway rapidly upregulates MAT2A. This pathway also increases the levels of one-carbon enzymes such as SHMT and MTHFD. This enhances remethylation, promotes SAM production, and increases the SAM/SAH ratio.

In NK cells, mTORC1 activation elevates MAT2A and SAM levels. Subsequently, m^{6}A rapidly reprograms. The stability and translation efficiency of target factor mRNAs increase. Inhibiting mTORC1 activity or downregulating MAT2A levels reverses these changes [42].

Similar findings have been observed in tumors. mTORC1 activation promotes one-carbon cycling and SAM production. METTL3 stabilizes the oncogenic transcript NR4A2. Similarly, upregulation of SHMT2 and MTHFD2 maintains one-carbon metabolism, promoting rapid proliferation and immune evasion. Furthermore, PRPS2 promotes SAM production by upregulating ATP and stabilizing MAT2A. It also amplifies m^{6}A through WTAP/METTL3/METTL14 [47,48].

This pathway has a clear temporal sequence. First, SAM and SAM/SAH levels rise, followed by m^{6}A enhancement and site redistribution, and finally, conversion into functional output by readers such as YTH/IGF2BP. This pathway also has a limiting mechanism, the METTL16-MAT2A pathway [49]. Excessive SAM levels restrict MAT2A; low SAM levels promote its splicing and stabilization. Thus, the pathway strikes a balance between amplification and restriction, maintaining rapidity and reversibility.

3.3. *METTL16-mediated SAM feedback regulation*

Unlike the rapid mTORC1-MAT2A-SAM-m^{6}A reaction, a feedback loop centered on METTL16 maintains SAM stability. METTL16 recognizes an adenine-containing hairpin structure in the 3'UTR of pre-mRNA and can also target other structured RNA sites, such as U6 snRNA. Furthermore, its methyltransferase activity uses SAM as a substrate and is modulated by SAM levels. METTL16 functions as both a transmembrane enzyme and a metabolic sensor [38,50]. When SAM is low, METTL16 binds to the MAT2A 3'UTR hairpin, promoting terminal intron splicing and stabilizing the MAT2A transcript. This leads to a rebound in MAT2A protein and SAM production. When SAM is high, METTL16's methyltransferase activity is enhanced. It inhibits MAT2A expression through both methylation at specific sites and direct binding.

This prevents excessive accumulation of methyl donors, forming a negative feedback loop that maintains SAM homeostasis [50,51].

This has physiological and pathological implications. Under low SAM levels, knockdown or inactivation of METTL16 leads to a block in MAT2A splicing and a further decrease in SAM. This can trigger an imbalance in posttranscriptional processes, such as m^6A readout and writeout. This phenomenon can be alleviated by exogenous methionine supplementation or by enhancing remethylation capacity [52]. In diffuse midline glioma (DMG, H3K27M), upregulation of AMD1 leads to abnormal accumulation of dcSAM, interfering with METTL16's regulation of SAM splicing. Inhibition of METTL16 significantly suppresses tumor cell growth and survival [53]. In conditions of vitamin B12 deficiency or inadequate one-carbon metabolism, the METTL16-MAT2A circuit can mitigate the epigenetic and posttranscriptional abnormalities caused by SAM fluctuations.

4. m^6A writer enzymes and the write-read-erase system

In RNA epitranscriptomic regulation, writers are methyltransferases that install m^6A and thereby generate the modification signal. METTL16 shows preference for structured RNA substrates. CAPAM deposits m^6A at the mRNA cap. ZCCHC4 and METTL5 modify 28S rRNA and 18S rRNA, respectively. Readers, including YTH-domain proteins and IGF2BPs, bind m^6A -marked RNAs and modulate RNA stability, splicing, and translation. Erasers, such as FTO and ALKBH5, remove m^6A and enable reversibility [54,55]. Together, writers, readers, and erasers form a coordinated regulatory system. In metabolic-epitranscriptomic coupling, writers often act as the main entry point because their catalytic activity depends on methyl-donor availability and sets the substrate for downstream decoding by readers.

4.1. Structure and function of the METTL3/METTL14 complex

It uses SAM as the methyl donor and catalyzes methyl transfer at specific RNA sites. METTL3 and METTL14 form a stable heterodimer that creates the catalytic pocket. In this pocket, the target adenine is positioned for methyl transfer from SAM, with SAH generated as the product [56].

Structural studies show that the methyltransferase domain of METTL3 adopts a Rossmann-like fold. METTL3 contains a conserved SAM-binding pocket and catalytic motifs that support SAM binding and methyl transfer chemistry [57]. METTL14 is a structural homolog of METTL3. It lacks key catalytic residues and has little or no intrinsic methyl transfer activity. Its main role is to support RNA binding and substrate positioning. METTL14 provides a positively charged nucleic-acid-binding surface that stabilizes RNA substrates and promotes productive loading. Through this scaffold function, METTL14 improves both efficiency and site selectivity of m^6A deposition [58–60].

At the sequence level, m^6A sites show preference for the DRACH consensus motif, and they are enriched near stop codons and within 3' untranslated regions [61,62]. Site selection is further refined by auxiliary proteins. WTAP promotes complex assembly and localizes the writer machinery to nuclear speckles. VIRMA biases m^6A deposition toward the 3' end of transcripts and contributes to the typical 3'-enriched distribution. RBM15 and RBM15B, together with ZC3H13, help recruit the writer complex to specific RNA regions, including lncRNA-associated sites and intron-proximal regions. HAKAI contributes to complex stability and appropriate subcellular localization [63,64]. These cofactors help convert basic sequence preference into context-dependent site selection, which can differ across cell types and stimulation conditions.

Writer activity is also constrained by cellular methylation potential. METTL3-METTL14 requires SAM during catalysis, and its effective activity depends on local SAM availability. SAH, the reaction product, can inhibit SAM-dependent methyltransferases. The SAM to SAH ratio is therefore a more informative indicator of methylation potential than SAM abundance alone [65–67]. When methylation potential is high, writer reactions can proceed more efficiently. When SAH accumulates, product inhibition can limit reaction throughput. This metabolic control provides a direct route by which changes in one-carbon metabolism can reshape m^6A writing capacity. In this context, MAT2A is an important node because it controls SAM synthesis and can therefore influence m^6A output through substrate supply.

Structural knowledge has also enabled rational inhibition of the writer complex. A targeted peptide inhibitor, RSM3, was designed to bind METTL3 and block its transmethylase activity. RSM3 showed anticancer efficacy in a PC3 prostate cancer xenograft model, supporting METTL3 as a druggable target [68]. In addition, small molecules can occupy the SAM-binding pocket of METTL3. Competitive SAM-site inhibitors have shown in vivo activity in hematopoietic tumor models, which demonstrates a feasible strategy to modulate m^6A by targeting the substrate-binding site [69].

Overall, METTL3 provides the catalytic core that binds SAM and transfers the methyl group. METTL14 primarily supports RNA recognition and substrate positioning. Auxiliary factors regulate assembly, recruitment, and nuclear localization, and they shape context-specific site selection. Metabolic state, reflected by SAM availability and SAH-mediated product inhibition, further sets the efficiency range of m^6A writing by this complex [56,57].

4.2. Structure and function of the METTL16

METTL16 is an m^6A writer with dual properties as an RNA methyltransferase and a metabolic sensor. Its N-terminus features a typical Rossmann-like methyltransferase fold, catalyzing the transfer of methyl groups from SAM to SAH. A conserved RNA-binding region (VCR) at the C-terminus mediates recognition of a specific hairpin structure. This allows METTL16 to specifically target structured RNAs, such as the A site of U6 snRNA. It also recognizes mRNA elements with similar secondary structures, such as the MAT2A 3'UTR hairpin [70,71]. METTL16 methylates U6 snRNA stably and participates in spliceosome maintenance. Its regulation of MAT2A exhibits both sensing and execution characteristics. Specifically, METTL16's RNA binding ability, catalytic activity, and nuclear localization dynamically change with SAM levels [51].

When SAM levels decrease, METTL16 preferentially binds to the MAT2A 3'UTR hairpin. This promotes terminal intron splicing and enhances transcript stability, thereby upregulating MAT2A protein levels and restoring SAM synthesis. When SAM levels increase, METTL16 displays higher catalytic activity and inhibits MAT2A splicing and expression at specific sites. This regulation prevents excessive SAM accumulation, forming a negative feedback loop of SAM/METTL16/MAT2A [72,73].

Overall, METTL16 translates changes in SAM levels into bidirectional regulation of MAT2A splicing and expression. Concurrently, it catalyzes the relatively stable m^6A modification on U6 snRNA to support the structural and functional maintenance of the spliceosome.

4.3. m^6A erasers: dynamic counterbalance within the SAM-m^6A axis

m^6A methylation is a reversible RNA modification. Its dynamic nature depends not only on methyltransferase writers, but also on dedicated demethylases, referred to as erasers. Among them, fat mass and obesity-associated protein (FTO) and ALKBH5 are the two best-characterized m^6A erasers [55]. Together, they provide a counterbalance to writer-mediated methylation and enable rapid remodeling of RNA fate in response to metabolic and environmental cues.

FTO was the first identified m^6A demethylase and primarily targets m^6A and m^6A m residues in mRNA. Structural studies indicate that FTO belongs to the Fe(II)/α-ketoglutarate-dependent dioxygenase family, linking its catalytic activity to cellular metabolic state. Functionally, FTO-mediated demethylation often increases mRNA stability or

translation by removing m^{6}A marks recognized by decay-promoting readers such as YTHDF2 [74]. As a result, FTO activity can shift transcript output toward persistence and protein accumulation.

ALKBH5 shares structural similarity with FTO but exhibits distinct substrate preference and biological roles. ALKBH5-mediated demethylation mainly affects mRNA export, splicing, and RNA stability, and its activity is frequently linked to nuclear RNA processing [75]. Compared with FTO, ALKBH5 is more tightly associated with transcriptional and post-transcriptional coordination rather than metabolic sensing per se.

Within the SAM-m^{6}A axis, erasers do not operate independently of methyl donor metabolism. Writer activity requires SAM and is inhibited by SAH, whereas eraser activity determines how long a deposited m^{6}A mark persists on a given transcript [76]. When SAM availability is high, increased writer activity can elevate global or transcript-specific m^{6}A levels, thereby increasing the substrate load for erasers. Conversely, when SAM is limited, reduced writer output amplifies the relative impact of eraser-mediated demethylation [77,78]. In this context, erasers function as amplifiers or dampeners of methylation potential rather than primary drivers.

Disease studies illustrate this complementary relationship. In metabolic disorders, elevated FTO expression promotes lipogenesis by demethylating transcripts such as SREBP-1c and ChREBP, thereby enhancing their stability and translation [79]. In contrast, ALKBH5-mediated demethylation can restore autophagic flux and reduce lipid accumulation by targeting transcripts involved in vesicle trafficking. These outcomes depend on the balance between writer-driven deposition and eraser-driven removal of m^{6}A marks, rather than on either component alone.

Importantly, many plant-derived compounds discussed later in this review influence erasers indirectly. Polyphenols such as EGCG and curcumin have been reported to reduce FTO protein abundance or activity, thereby shifting the effective balance toward higher m^{6}A levels without directly inhibiting writer enzymes [80,81]. This mode of action differs fundamentally from canonical small-molecule writer inhibitors and highlights the systems-level modulation characteristic of phytochemicals.

Taken together, m^{6}A erasers provide a critical dynamic layer within the SAM-m^{6}A axis. Writers determine where and when methylation is installed under metabolic constraints, whereas erasers control the persistence and functional impact of these marks. Integrating erasers into the conceptual framework is therefore essential for understanding how metabolic state, dietary inputs, and disease signals collectively shape RNA fate.

5. Plant compounds targeting the SAM-m^{6}A regulatory axis

Nutritional epigenetics offers a mechanistic framework for gene-diet interactions. It highlights that diet can shape gene regulation through chemical modifications at multiple layers. Canonical epigenetic regulation includes DNA methylation and histone post-translational modifications [82]. One-carbon metabolism is a central determinant of cellular methylation capacity. Nutrients such as folate, vitamins B12 and B6, riboflavin, methionine, choline, and betaine regulate the abundance of S-adenosylmethionine and S-adenosylhomocysteine. The SAM/SAH ratio is widely used as a proxy for methylation potential. In addition to essential nutrients, many phytochemicals have been proposed to reshape methylation landscapes. They may alter SAM/SAH balance or modulate methylation-related enzymes. These concepts provide a

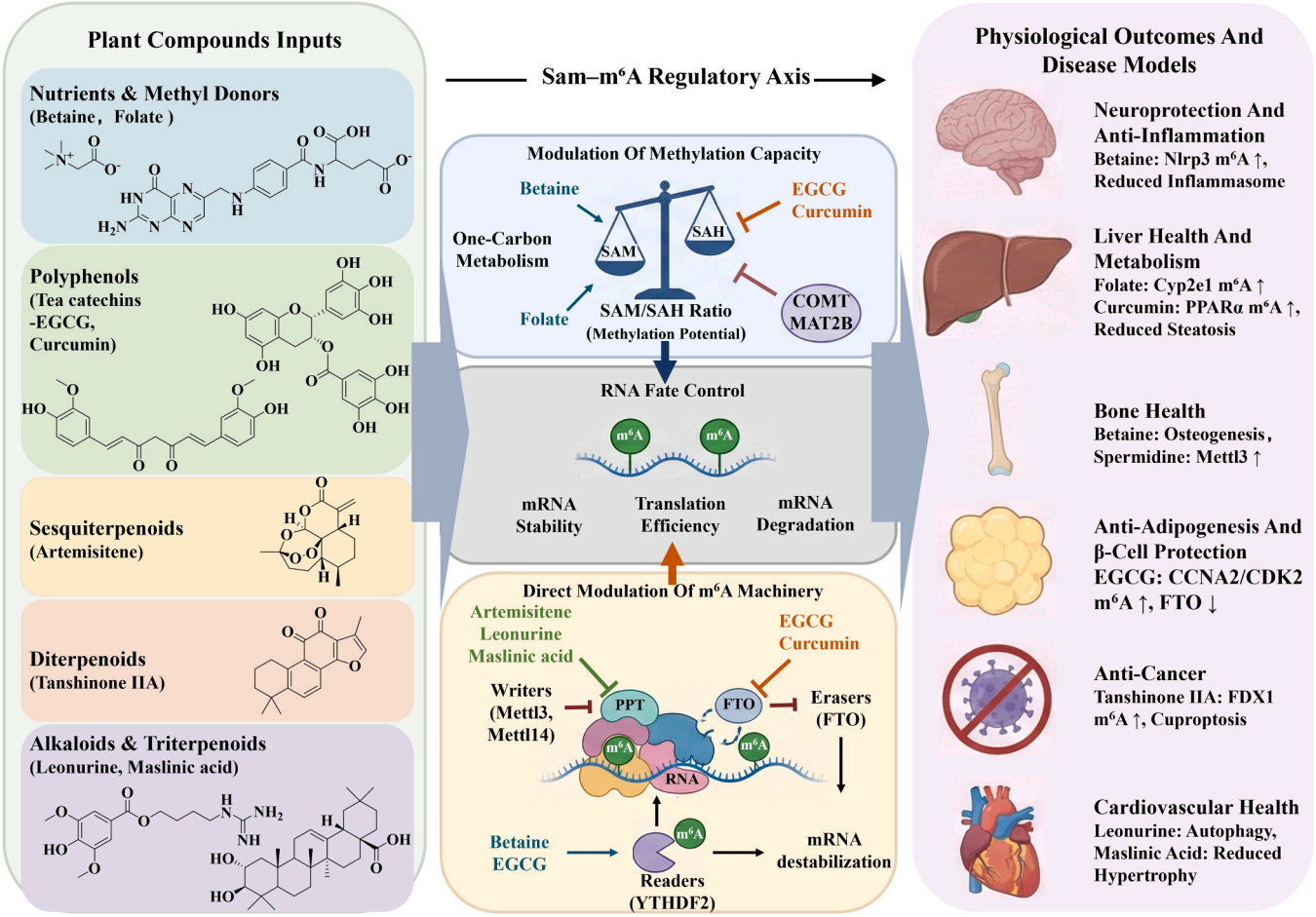

Fig. 3. Plant compounds targeting the SAM-m^{6}A regulatory axis and associated disease outcomes.

rationale to discuss phytochemicals within the SAM-m^{6}A axis. This axis links methyl-donor metabolism to RNA fate control. It therefore connects metabolic state to post-transcriptional regulation (Fig. 3 and Table 1).

5.1. Betaine

Betaine is a compound that is naturally found in plants such as sugar beets. In Hcy-induced cognitive impairment models, betaine improved behavior and reduced microglial activation [83]. Yang et al. supplemented betaine at 2.5 % (w/v) in drinking water for 14 days in rats challenged with homocysteine (400 μg/kg/day). This regimen was estimated to provide 2000–2500 mg/kg body weight. In vitro, HMC3 microglial cells were pretreated with 10 mM betaine for 4 h before homocysteine exposure. It inhibited inflammasome activation and pyroptosis-related signaling. Importantly, betaine increased the SAM/-SAH ratio and enhanced m^{6}A enrichment on NLRP3 mRNA. YTHDF2 was implicated in the destabilization of NLRP3 transcripts, and YTHDF2 knockdown weakened the protective effect [84]. This work provides a relatively complete multi-layer chain linking methyl-donor status, m^{6}A remodeling, and inflammatory outcomes.

Folate supplementation also supports axis coupling in drug-induced liver injury. In isoniazid-induced hepatotoxicity, folate reduced liver injury and downregulated CYP2E1 expression. In the study by Jiang et al., folic acid was administered through the diet. Mice received an AIN-93M diet supplemented with 0.66 g/kg isoniazid, while the intervention group received an additional 0.01 g/kg folic acid for 72 days. It increased m^{6}A modification on Cyp2e1 transcripts and raised the SAM/SAH ratio, supporting coordination between methylation potential and transcript-level m^{6}A changes [85]. In contrast, several NAFLD studies on betaine report improvements in hepatic lipid metabolism with changes in m^{6}A regulators or m^{6}A landscapes. In addition, in a high-fat diet (HFD) mouse model of hepatic steatosis, betaine was provided in drinking water at 2 % (w/v) for 17 weeks. In AML12 hepatocytes, lipid loading was induced by oleic acid (200 μM) and palmitic acid (100 μM), and betaine was applied at 2 mM. These defined regimens were used to link betaine to altered hepatic m^{6}A methylation profiles and reduced lipid accumulation, with Trub2 identified as an m^{6}A-associated target [94].

Bone-related studies provide additional support for the functional relevance of the SAM-m^{6}A axis. In BMSC osteogenesis, inhibition of one-carbon metabolism reduced SAM production, lowered global m^{6}A levels, and impaired osteogenic differentiation. Methotrexate (2 μM) was used to inhibit one-carbon metabolism, and betaine (2 mM) was used as a methyl donor. m^{6}A methylation was inhibited by S-adenosylhomocysteine (2 μM), and HIF-1α was modulated by dimethyloxalyl glycine (0.1 mM). In rats, methotrexate was administered at 0.75 mg/kg/day for 5 days, and betaine was injected intraperitoneally at 1 mg/kg/day for 9 days. Betaine restored SAM and m^{6}A and rescued osteogenesis. SAH reduced m^{6}A and impaired osteogenesis, supporting the requirement of methylation reactions for differentiation. In vivo data further indicated that betaine mitigated MTX-induced bone loss [86]. In inflammatory bone disease models, inflammatory stress was induced with lipopolysaccharide at 1 μg/mL. Spermidine was applied at 1 μM, while m^{6}A methylation was inhibited using S-adenosylhomocysteine at 5 μM. Betaine was used as a methyl donor at 2 mM, and autophagy was modulated with rapamycin at 100 nM. Spermidine increased SAM abundance, elevated METTL3 and METTL14 expression, increased m^{6}A levels, and promoted osteogenesis. SAH impaired these effects. Autophagy modulation contributed to phenotype execution, and in vivo regeneration data supported translational potential [87]. Similar logic was reported in BRONJ models, where betaine restored SAM, m^{6}A, and osteogenic capacity and improved lesions in vivo [88].

5.2. Tea polyphenols

Green tea, a member of the Theaceae family, is widely recognized for its diverse pharmacological properties. It is particularly rich in polyphenols, especially catechins such as epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), and epigallocatechin gallate (EGCG). Among these, EGCG is the predominant catechin and has been extensively reported to exert multiple bioactivities, including antioxidant, anti-inflammatory, antidiabetic, anti-obesity, and antitumor effects [95]. Tea catechins may also influence methylation capacity through

Table 1
Phytochemicals regulating the SAM-m^{6}A methylation axis.

Pathology Model	Key Component	Target	Signaling Cascade	Main Outcome	Reference
Cognitive Impairment	Betaine	NLRP3, YTHDF2	↑ SAM/SAH ratio → ↑ m^{6}A on *NLRP3* mRNA → YTHDF2-mediated transcript destabilization.	Inhibited inflammasome activation and pyroptosis; improved behavior.	[83,84]
Drug-induced Liver Injury	Folate	CYP2E1	↑ SAM/SAH ratio → ↑ m^{6}A on *Cyp2e1* transcripts.	Reduced liver injury; downregulated CYP2E1 expression.	[85]
Bone Loss / Osteogenesis	Betaine	SAM Biosynthesis	Restores SAM production → Restores global m^{6}A levels (reverses inhibition of 1-carbon metabolism).	Rescued osteogenic differentiation; mitigated bone loss.	[86]
Inflammatory Bone Disease	Spermidine	METTL3, METTL14	↑ SAM abundance → ↑ METTL3/14 expression → ↑ m^{6}A levels → Autophagy modulation.	Promoted osteogenesis and regeneration.	[87]
BRONJ	Betaine	SAM / m^{6}A	Restores SAM levels and downstream m^{6}A modification.	Improved jaw lesions; restored osteogenic capacity.	[88]
Adipogenesis	EGCG	FTO, YTHDF2	↓ FTO, ↑ YTHDF2 → ↑ m^{6}A on *CCNA2 & CDK2* → Decreased protein abundance.	Inhibited mitotic clonal expansion; anti-adipogenic effects.	[80]
β-cell Injury	EGCG	FTO	Promotes FTO degradation (ubiquitin-proteasome) → Restores m^{6}A on *Tlr4*, *Rela*, *Src* → ↓ Oxidative stress.	Reduced β-cell injury; suppressed excessive autophagy.	[89]
Hepatic Fibrosis	Curcumin	MAT2B	↓ p38 MAPK → ↓ MAT2B expression → Reduced SAM biosynthetic capacity.	Suppressed fibrotic activation of hepatic stellate cells.	[90]
NAFLD	Curcumin	FTO, PPARα	↓ FTO → ↑ m^{6}A on *PPARα* mRNA → Activates PPARα/CPT1α pathway.	Reduced hepatic steatosis; promoted fatty acid oxidation.	[81]
Rheumatoid Arthritis	Artemisitene	METTL3, ICAM2	↓ p300/PI3K/AKT axis → ↓ METTL3 → ↓ m^{6}A on *ICAM2* mRNA.	Suppressed synovial proliferation and invasion; improved arthritis.	[91]
Bladder Cancer	Tanshinone IIA	FDX1	↑ m^{6}A enrichment on *FDX1* → ↑ FDX1 expression → Copper-dependent cell death.	Induced cuproptosis; inhibited tumor growth.	[9]
Atherosclerosis	Leonurine	METTL3, AKT1S1	Regulates METTL3 → Modulates m^{6}A on autophagy-related transcripts (*AKT1S1*).	Reduced plaque burden; enhanced macrophage autophagy; ↓ lipid accumulation.	[92]
Cardiac Hypertrophy	Maslinic Acid	METTL3	Suppresses METTL3 expression → ↓ Global m^{6}A levels.	Attenuated cardiac remodeling and hypertrophic growth.	[93]

SAM-consuming methyltransferases. Human hepatic COMT represents a relevant SAM-dependent methylation sink. Structure-activity studies showed that galloylated catechins are potent COMT inhibitors. EGCG was the most potent inhibitor, with IC_{50} values of 0.07–0.08 μM, followed by ECG (0.20–0.30 μM). In contrast, non-gallated catechins such as EGC and EC were markedly less active, with IC_{50} values in the tens of micromolar range. EGCG and methylated EGCG metabolites inhibited COMT at submicromolar concentrations, whereas catechins lacking the galloyl D-ring were markedly weaker. Kinetic analyses suggested that certain methylated EGCG forms display competitive features toward the SAM-binding site. Molecular modeling supported the contribution of the galloyl moiety to binding within the catalytic pocket [96]. These data provide a quantitative basis for the hypothesis that catechins can modulate methylation flux by inhibiting SAM-dependent methyltransferases.

Green tea catechins provide some of the most direct evidence that a dietary polyphenol can modulate m^6A machinery and alter metabolic phenotypes. In 3T3-L1 preadipocytes, EGCG increased global RNA m^6A levels, as quantified by HPLC-QqQ-MS/MS. EGCG also decreased FTO protein abundance and increased YTHDF2 expression. During early differentiation, EGCG increased m^6A enrichment on CCNA2 and CDK2 transcripts, as assessed by meRIP-qPCR. This was accompanied by reduced CCNA2 and CDK2 protein levels and impaired mitotic clonal expansion. Functional rescue experiments supported the involvement of the FTO and YTHDF2 nodes. FTO overexpression or YTHDF2 knockdown partially reversed the anti-adipogenic effects of EGCG and restored CCNA2/CDK2 protein abundance [80]. These results support an m^6A-dependent mechanism for EGCG in adipogenesis.

EGCG has also been linked to β-cell protection through regulation of FTO in models of glucocorticoid receptor-driven stress. Shao et al. administered EGCG at 50 mg/kg by daily oral gavage for 10 weeks in mice, with PBS as the vehicle control. In vitro, EGCG was mainly used at 50 μM for 2–48 h in cell and human islet assays. In β-cell specific NR3C1 overexpression mice and in vitro β-cell systems with enhanced NR3C1 signaling, EGCG reduced β-cell injury and suppressed excessive autophagy. Mechanistic experiments indicated that FTO promoted oxidative stress and autophagy by lowering m^6A on transcripts including Tlr4, Rela, and Src. EGCG promoted FTO degradation through the ubiquitin-proteasome pathway. This was associated with restoration of m^6A on these transcripts and attenuation of oxidative stress. FTO overexpression abolished the protective effect of EGCG, supporting a causal role for FTO in this setting [89].

5.3. Curcumin

Curcumin, a natural polyphenol from Curcuma longa, exhibits broad pharmacological activities including antioxidant, anti-inflammatory, metabolic, and anticancer effects [97]. Curcumin also targets SAM supply machinery in fibrotic settings. Curcumin was administered at 400 mg/kg/day by oral gavage for 4 weeks in a thioacetamide-induced liver fibrosis mouse model. In hepatic stellate cells, curcumin was mainly used at 20 μM for 24 h to suppress MAT2B expression and p38 MAPK signaling. MATII activity depends on MAT2A and its regulatory subunit MAT2B. MAT2B supports stellate cell activation. Curcumin suppressed MAT2B expression through inhibition of p38 MAPK signaling and reduced fibrotic activation in vitro and in vivo [90]. This evidence supports regulation of SAM biosynthetic capacity by a phytochemical.

Curcumin has been proposed to regulate lipid metabolism through m^6A demethylation pathways in NAFLD models. In a high-fat diet-induced NAFLD mouse model, curcumin was administered by oral gavage at 200 mg/kg/day for 4 weeks. In vitro, hepatocytes exposed to free fatty acids were treated with curcumin at 20–40 μM for 24 h. Curcumin reduced hepatic steatosis and decreased FTO protein abundance. Similar effects were observed in FFA-induced steatotic HepG2 and THLE-2 cells. Target engagement was supported by docking analyses and cellular thermal shift assays. Curcumin increased m^6A modification on PPARα mRNA and activated the PPARα/CPT1α pathway, which promotes fatty acid oxidation [81]. This study provides a relatively coherent chain from phenotype to m^6A regulator and a defined metabolic effector pathway.

5.4. Artemisia sesquiterpenoids

Artemisitene is a natural sesquiterpene-derived compound from Artemisia annua that exhibits notable anti-inflammatory, immunomodulatory, and disease-modifying activities [98]. Artemisitene has been reported to suppress rheumatoid arthritis phenotypes by targeting m^6A writing pathways. Artemisitene was administered intraperitoneally at 10 mg/kg/day in a collagen-induced arthritis mouse model, while fibroblast-like synoviocytes were treated in vitro with 1–5 μM artemisitene for 24 h to modulate METTL3-dependent m^6A methylation. Artemisitene improved clinical and pathological outcomes. In RA fibroblast-like synoviocytes, it inhibited proliferation and invasive behavior and induced apoptosis. Transcriptomic analyses identified ICAM2 as a critical pathogenic factor. Artemisitene reduced METTL3-dependent m^6A modification of ICAM2 mRNA and attenuated ICAM2-driven signaling through the PI3K/AKT/p300 axis. The study also indicated that p300 promotes METTL3 transcription and that artemisitene interferes with this regulatory loop. Patient synovial tissue data supported associations between METTL3, ICAM2, and p300 and clinical features [91]. These findings provide a disease-relevant example of writer-centered regulation by a plant-derived compound.

5.5. Salvia diterpenoids

Tanshinone IIA is a lipophilic diterpene quinone isolated from Salvia miltiorrhiza and is known for its cardiovascular, anti-inflammatory, antioxidant, and anticancer activities [99]. Tanshinone IIA provides evidence that a plant-derived compound can promote an m^6A-dependent cell death program in cancer. In bladder cancer models, Tanshinone IIA was applied to bladder cancer cells at 0.25–4 μg/mL for 12–48 h. Mechanistic assays mainly used 1 μg/mL Tanshinone IIA for 48 h. S-adenosylhomocysteine was used at 1 μM to inhibit METTL3/METTL14 activity. In vivo, Tanshinone IIA was administered intraperitoneally at 1 mg/kg for 3 weeks in a xenograft model. Tanshinone IIA induced copper-dependent cell death and increased expression of cuproptosis-associated regulators, including FDX1. It increased m^6A enrichment on FDX1 transcripts and promoted FDX1 expression. SAH attenuated these effects, consistent with suppression of methyltransferase-dependent reactions. Functional experiments showed that FDX1 knockdown reduced cuproptosis induction. Reader involvement and 3'UTR reporter assays supported m^6A-dependent post-transcriptional regulation. In xenograft models, SAH affected the antitumor efficacy of tanshinone IIA, indicating functional dependence on methylation processes [9]. This study is notable because it pharmacologically links m^6A writing to methylation inhibitory conditions.

5.6. Alkaloids and Triterpenoids

Leonurine is a bioactive alkaloid isolated from Leonurus japonicus with reported cardioprotective, anti-inflammatory, antioxidant, and metabolic regulatory effects [100]. Leonurine has been proposed to ameliorate atherosclerosis by regulating METTL3 and autophagy in macrophages. In an $ApoE^{-/-}$ mouse model of atherosclerosis, leonurine was administered at 30 or 60 mg/kg/day during high-fat diet feeding, while in vitro experiments used 25–100 μM leonurine to treat ox-LDL-induced macrophage-derived foam cells, with the most robust effects observed at 100 μM. Leonurine reduced plaque burden and inflammation. In ox-LDL-stimulated macrophage models, it reduced lipid accumulation and enhanced autophagy. m^6A-seq suggested changes in m^6A patterns on autophagy-related transcripts, and AKT1S1

was highlighted as a candidate mediator. Genetic perturbation supported a role for AKT1S1 in autophagy induction and lipid handling [92]. These data support a link between a natural product and writer-centered m^{6}A regulation in cardiovascular pathology.

Maslinic acid is a natural pentacyclic triterpenoid widely found in olives and other edible plants, and it exhibits antioxidant, anti-inflammatory, cardioprotective, and metabolic regulatory activities [101]. Maslinic acid has been reported to attenuate cardiac hypertrophy through METTL3-associated m^{6}A regulation. In Ang-II-stimulated neonatal cardiomyocytes, maslinic acid suppressed hypertrophic growth. Maslinic acid inhibited Ang II-induced cardiomyocyte hypertrophy at 10–10 ^{3} μg/mL in vitro. In vivo, it was injected intraperitoneally at 30 mg/kg/day in TAC mice. In TAC-induced hypertrophy models, it reduced cardiac remodeling. The study reported reduced global m^{6}A levels and decreased METTL3 expression. METTL3 overexpression weakened the protective effect, supporting a functional role for METTL3 in this context [93].

Overall, current evidence suggests that plant-derived compounds can influence the SAM-m^{6}A axis through two principal routes. One route involves direct modulation of m^{6}A machinery, including writers, erasers, and readers. The other route involves modulation of methylation capacity through SAM synthesis pathways or SAM-consuming methyltransferases. The strongest mechanistic support emerges when SAM/SAH and m^{6}A outcomes are measured together and combined with functional perturbation of key m^{6}A regulators. Such integrated designs remain limited for most phytochemicals. Future studies should prioritize simultaneous quantification of methyl-donor status, transcript-resolved m^{6}A profiling, and causal validation in disease-relevant tissues.

Plant-derived compounds should be interpreted in parallel with canonical small-molecule inhibitors of the SAM-m^{6}A machinery. Synthetic agents such as the METTL3 inhibitor STM2457 are designed to act as high-affinity, single-node blockers that directly suppress writer catalytic output, enabling relatively predictable pharmacodynamic control of m^{6}A deposition. By contrast, most phytochemicals do not function as selective enzyme inhibitors with comparable potency [102]. Instead, they more often modulate the axis at a systems level by reshaping SAM/SAH balance through one-carbon metabolism, altering the abundance or stability of writers and erasers, or biasing reader-dependent RNA fate decisions. This distinction implies different translational positioning [51]. Small-molecule inhibitors may be preferable when a disease is dominated by writer hyperactivity and requires rapid pathway shutdown. Phytochemicals may be more suitable for chronic settings where gradual rebalancing of methylation capacity and transcript selectivity is desired, and where multi-target modulation could be advantageous.

6. Roles of the SAM-m^{6}A axis in diseases

The SAM-m^{6}A axis is crucial in connecting methyl donor metabolism with RNA epitranscriptome regulation [43]. Potential intervention points are not concentrated in a single isolated protein, but rather distributed across SAM supply and SAM/SAH balance, the dynamic regulation of m^{6}A writer/eraser/reader, and its downstream RNA stability and translational networks [24,50]. Therefore, the SAM- m^{6}A axis is discussed as a conceptual and mechanistic framework for therapeutic intervention, rather than as a single, discrete drug target (Fig. 4).

6.1. *Tumor: metabolic-epitranscriptomic coupling*

In tumors, SAM- m^{6}A coupling links one-carbon metabolism to RNA regulation. Changes in SAM synthesis and turnover can reshape cellular m^{6}A patterns. These changes then alter RNA stability, splicing, translation, and decay. The net effect is a shift in gene expression programs that support proliferation, invasion, immune evasion, and therapy failure [48,103,104]. This shared framework is consistent across cancers. However, mechanistic heterogeneity arises because different tumors place the dominant control point at different levels of the axis.

A first layer of divergence sits upstream at SAM supply. Many tumors show elevated methyl donor availability, but they reach this state through distinct entry nodes. In lung cancer, PRPS2 promotes SAM synthesis and increases RNA m^{6}A. This route is closely linked to tumorigenesis and metastasis [51]. In hepatocellular carcinoma, IGF2BP3 upregulates MAT2B, increases SAM generation, and strengthens m^{6}A-associated programs that correlate with drug resistance [27]. These examples illustrate a key similarity and a key difference. The similarity is convergence on higher SAM and higher m^{6}A output. The difference is that the upstream driver and the dominant phenotype are not the same [27,51]. This difference implies that supply-side interventions may need to be tailored to the specific metabolic node that anchors the coupling.

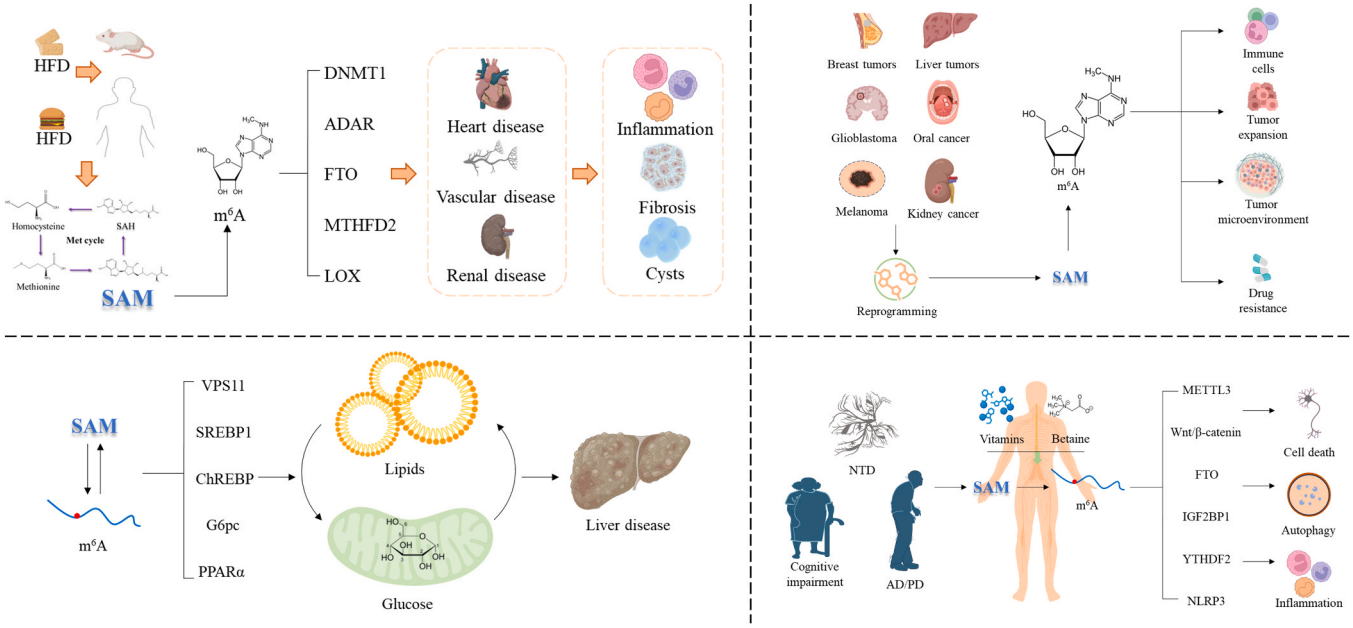

Fig. 4. The SAM-m^{6}A axis links metabolism to disease progression across multiple systems.

A second layer of divergence emerges at the m^{6}A machinery level. Writers can expand or reinforce methylation programs, whereas readers impose transcript selectivity and determine which RNAs become functional effectors [48,104]. YTHDF1 provides a reader-centered example. It recognizes m^{6}A -modified FOXM1 mRNA and enhances FOXM1 translation in breast cancer, thereby linking m^{6}A marking to oncogenic protein production [105]. In contrast, IGF2BP proteins can stabilize oncogenic transcripts and thus bias m^{6}A effects toward persistence of pro-tumor RNA states. In hepatocellular carcinoma, IGF2BP3 further connects this reader activity to SAM supply through MAT2B regulation [27,106]. Together, these mechanisms show why similar global m^{6}A shifts can yield distinct outputs. The decisive factor can be whether tumors rely more on broad writer-driven programming or on reader-driven selection of key targets [91,107]

A third layer of divergence becomes evident when considering the tumor microenvironment. In some settings, the major consequence of m^{6}A regulation is not confined to cancer cells. METTL3 can regulate tumor-infiltrating immune cells and influence immune evasion and therapy response [108]. In renal cancer, METTL5 expression associates with immune cell infiltration and immune-related pathways, which supports tumor-type specificity in the m^{6}A nodes that shape immune context [109]. This aligns with broader evidence that m^{6}A can regulate metabolic gene expression and activate metabolic signaling, thereby promoting metabolic reprogramming while altering immune properties of the microenvironment [110]. Consistent with this concept, single-atom catalysts have been reported to modulate m^{6}A, reprogram tumor-associated macrophages, and enhance anti-tumor immune responses [27,106]. These observations strengthen a key comparison. In cancer-cell dominant models, m^{6}A primarily drives intrinsic growth and invasion programs. In microenvironment dominant models, m^{6}A shapes immune states that determine immune escape and treatment response [110].

This layered comparison naturally leads to translational implications. When writer or reader nodes dominate, direct targeting of the m^{6}A machinery becomes rational. Inhibiting METTL3 or YTHDF1 can suppress tumor proliferation and metastasis [105]. STM2457 is a METTL3 inhibitor that inhibits proliferation and metastasis in oral squamous cell carcinoma, and combination with anlotinib further improves therapeutic efficacy [102]. When microenvironmental remodeling dominates, stratification based on integrated m^{6}A states becomes equally important. In melanoma, low m^{6}A scores have been associated with greater sensitivity to PD-1 and CTLA-4 inhibitors, whereas high m^{6}A scores correlate with resistance [110]. In glioblastoma, high glioma m^{6}A scores align with an immune-tolerant phenotype and poor response to CTLA-4 blockade, while low scores indicate a better response [111]. Overall, tumors share a common SAM-m6A coupling logic, but the dominant control node varies. It may reside in SAM supply, in writer and reader decoding, or in microenvironmental regulation. This variability explains differences in metastasis, drug resistance, and immunotherapy response across cancers [7,51,68].

6.2. *Neurological disorders: linking metabolism to neuroplasticity*

Neurological disorders provide a clear setting to connect methyl donor metabolism with neuroplasticity through m^{6}A regulation. One-carbon metabolism supports SAM synthesis, and vitamins B9 and B12 are important contributors to this process [7]. When this metabolic input is insufficient, the epitranscriptomic output changes. Vitamin B12 deficient neurons show global mRNA m^{6}A hypomethylation, which supports a direct link between methyl donor status and m^{6}A capacity [112]. This supply-related change provides a metabolic starting point for understanding how RNA methylation can shift in the nervous system.

Metabolic reinforcement can also reshape m^{6}A programs, but the biological outcome depends on the responding cell type and the downstream reader pathway. In cognitive impairment and inflammation-related injury, betaine supplementation increases the SAM to SAH ratio and improves cellular methylation capacity. In microglia, this shift increases m^{6}A modification of NLRP3 mRNA and upregulates the m^{6}A reader YTHDF2. Higher YTHDF2 accelerates NLRP3 mRNA degradation and reduces its stability. This suppresses NLRP3 caspase 1 GSDMD pyroptosis and alleviates neuroinflammation and behavioral impairment [84]. These findings show how a metabolic intervention can be translated into an anti-inflammatory effect through an m^{6}A reader-controlled decay pathway in microglia.

After methyl donor status sets the baseline, the m^{6}A machinery shapes how metabolic signals influence neural development, repair, and plasticity. METTL3 is the most frequently implicated writer in neurological and psychiatric diseases, with METTL16 and METTL14 also reported. Many studies focus on neuroinflammation, synaptic plasticity, and injury repair [113]. METTL3 dysfunction is repeatedly linked to neurological disease susceptibility [114]. Developmental models illustrate this logic with clear pathway outputs. In neural tube defect models, changes in intracellular SAM levels reshape the m^{6}A landscape, and METTL3 is enriched in neurons. METTL3 knockdown inhibits Wnt and beta catenin signaling, reduces proliferation, and increases apoptosis. ALKBH5 overexpression also inhibits proliferation, but its effect on apoptosis is weaker [115]. This comparison suggests that neural tube formation depends strongly on writer-driven m^{6}A programs, while demethylation can modify the program but does not fully mimic loss of METTL3. It also indicates that methyl donor status can influence neural stem cell fate and tissue morphology through a SAM dependent m^{6}A pathway that converges on Wnt beta catenin signaling [115].

m^{6}A regulation remains important beyond early morphogenesis and contributes to neurogenesis and cognitive function. m^{6}A controls proliferation and differentiation of neural stem cells and supports neuronal generation, which underlies brain development and function. It is also associated with learning and memory, and abnormal m^{6}A patterns are linked to cognitive impairment [116,117]. Consistent with this role, m^{6}A patterns show temporal changes in the cerebral cortex during embryonic and postnatal stages, suggesting that dynamic m^{6}A remodeling is part of normal developmental timing [118,119]. Mechanistically, m^{6}A can regulate transcription factors and neurodevelopmental genes, thereby shaping neuronal generation and function [119]. These studies connect m^{6}A dynamics to neuroplasticity-related outputs, because they affect how neurons are generated and how neural circuits mature.

In neurodegenerative diseases, the main downstream consequences shift toward RNA metabolism instability and stress response pathways. In Alzheimer's disease and Parkinson's disease, abnormal m^{6}A modification is linked to disrupted RNA metabolism of key genes and accelerated neuronal degeneration [120]. m^{6}A also regulates autophagy-related genes and influences neuronal autophagy, which provides a mechanistic route to altered proteostasis in neurodegeneration [121]. In addition, abnormal expression of METTL3 and FTO can affect neuroinflammation, autophagy, and mitochondrial function, thereby influencing neuronal survival. This has motivated efforts to develop small molecule inhibitors targeting METTL3 and FTO to modulate m^{6}A levels in neurodegenerative disease settings [121,122]. Compared with developmental models that converge on Wnt beta catenin signaling, neurodegenerative models more often converge on RNA metabolism and stress handling, including autophagy and mitochondrial dysfunction [115,121,122].

Reader proteins provide an additional layer that explains why similar m^{6}A shifts can produce different inflammatory outcomes in the brain. Microglia are the main immune cells of the central nervous system, and their inflammatory responses are shaped by m^{6}A-dependent RNA control. YTHDF2 promotes decay of m^{6}A-marked RNAs and can limit inflammation when it targets inflammatory transcripts such as NLRP3 in microglia [84]. In contrast, IGF2BP1 can stabilize inflammation-related mRNAs such as Gbp11 and Cp, which supports sustained inflammatory signaling and progression of neuroinflammation [123]. This contrast between decay-promoting and stabilization-promoting readers

highlights a key principle for neurological disorders. Metabolism can change m^{6}A capacity, but reader-mediated selection determines whether the net output dampens or sustains neuroinflammation [84,123].

Overall, neurological disorders share a common SAM-m^{6}A framework, but they differ in dominant control nodes and therefore in phenotypic outputs. Methyl donor limitation, such as vitamin B12 deficiency, is associated with global m^{6}A reduction in neurons [112]. Methyl donor reinforcement, such as betaine supplementation, can engage microglial YTHDF2 and suppress pyroptosis-driven inflammation through accelerated decay of NLRP3 mRNA [84]. Writer-centered regulation is prominent during development and links SAM availability to m^{6}A programs that shape neural stem cell fate and Wnt beta catenin signaling [115]. In later-stage disorders, altered m^{6}A is more often connected to RNA metabolism disruption, autophagy, and mitochondrial stress, which aligns with neurodegenerative progression and therapeutic interest in METTL3 and FTO modulation [120,121].

6.3. Metabolic diseases: hepatic glucose-lipid balance

In metabolic diseases, the liver is a central organ for glucose and lipid metabolism. Hepatic dysfunction is therefore closely linked to the onset and progression of multiple disorders [124,125]. A common mechanism involves SAM-dependent control of m^{6}A. When methylation potential changes, m^{6}A patterns shift and metabolic gene expression is remodeled.

Supply-sensitive models show how restoring methylation potential can reshape m^{6}A on specific transcripts and improve hepatic outcomes. In isoniazid-induced liver injury, folic acid supplementation increases the hepatic SAM to SAH ratio and increases m^{6}A modification of Cyp2e1 mRNA. Cyp2e1 mRNA and protein levels then decrease. Transaminase elevation is reduced, and liver necrosis is alleviated [85]. This example links methyl donor status to a defined transcript and a measurable liver phenotype. It also shows that metabolic input can be translated into gene-specific regulation rather than only global methylation changes.

Beyond methyl donor supply, many studies in metabolic and endocrine diseases focus on the writer layer, especially METTL3, with reported roles in lipid accumulation, islet function, and inflammatory responses. In some contexts, METTL3 or METTL14 deficiency reduces m^{6}A levels and increases expression of lipogenic genes, which is associated with greater hepatic lipid accumulation [126]. However, writer-dependent effects can differ across pathways and target sets. METTL14 has been reported to increase m^{6}A modification of G6pc mRNA. This enhances G6pc mRNA stability and translation and increases hepatic glucose production. The effect is elevated in obese mouse livers and supports a role for m^{6}A in impaired glucose metabolism [127].

Eraser pathways add another layer of transcript selectivity and often converge on lipid handling. m^{6}A methylation is dynamic and reversible and has been recognized as an important regulator of hepatic glucose and lipid metabolism [79,126]. ALKBH5 can remove m^{6}A from VPS11 mRNA and promote VPS11 translation. This restores autophagic flux and reduces hepatic lipid deposition [128]. FTO provides a complementary demethylation mechanism that promotes lipogenesis. It reduces m^{6}A levels in SREBP-1c and ChREBP mRNAs, increases their stability, and enhances expression of lipid synthesis genes including FAS, SCD1, and ACC. This promotes hepatic lipid accumulation and contributes to NAFLD development [79,81]. These eraser-centered mechanisms differ from the folic acid model in entry point, but they converge on pathway-level outcomes through changes in mRNA stability and translation.

m^{6}A regulation can also affect hepatic oxidative capacity and thereby influence both lipid and glucose balance. m^{6}A has been linked to regulation of genes such as PPARα, which impacts mitochondrial function and lipid oxidation. This provides an additional route by which m^{6}A can shape glucose metabolism through changes in substrate utilization and energy handling [129].

Overall, hepatic phenotypes depend on the dominant control node within the SAM-m^{6}A axis. Some models are driven by methyl donor availability and respond to restoration of methylation potential, as shown by folic acid effects on the SAM to SAH ratio and Cyp2e1 regulation [85]. Other models are driven by writers or erasers and show transcript-specific biases between glucose output and lipid storage, as illustrated by METTL14 control of G6pc and FTO control of SREBP-1c and ChREBP [79,81,127]. Methodologically, studies should quantify methylation potential together with transcript-specific m^{6}A changes, because global m^{6}A is not sufficient to infer pathway direction [79,126]. Causal work should prioritize defined transcripts and sites in representative pathways, including CYP2E1, G6PC, SREBP-1c, and ChREBP [81,85,127]. Cell-type-resolved mapping is also needed, because hepatocytes and non-parenchymal cells such as Kupffer cells and stellate cells may deploy different m^{6}A effectors under the same stress [129]. Finally, combined strategies should be explored. Methyl donor supplementation may be paired with selective writer or eraser modulation to rebalance hepatic glucose and lipid flux in a context-dependent manner.

6.4. Cardiovascular and renal disorders: inflammation and fibrosis

Cardiovascular and renal disorders share core pathological features. Inflammation, oxidative stress, and endothelial dysfunction are common drivers. These processes also connect to fibrosis and organ remodeling [130–133]. Within this shared background, the SAM-m^{6}A axis provides a mechanism that links metabolic stress to RNA-level regulation. A consistent theme is that altered methylation capacity can shift m^{6}A programs and reshape inflammatory and fibrotic outputs. The dominant control node, however, differs between cardiovascular and renal settings.

In cardiovascular disease models, systemic metabolic stress often appears upstream of the epitranscriptomic changes. High-fat diet exposure alters the expression and activity of methylation-related enzymes. It increases DNMT1 and the RNA-editing enzyme ADAR. It reduces the activity of demethylases such as TET and FTO. These shifts are associated with elevated m^{6}A levels. They also correlate with hyperuricemia and cardiac and renal dysfunction [134]. Functional evidence supports a causal contribution of this methylation program to remodeling. DNMT1 knockout mitigates high-fat-diet-induced cardiac and renal remodeling and reduces markers including NGAL, FGF23, TMPRSS2, and MMP2 [134]. This suggests that metabolic stress can engage methylation and RNA modification pathways that amplify inflammation and tissue remodeling, and that targeting this axis may have therapeutic value in cardiovascular disease [134].

Renal disease studies provide more direct links between methyl donor metabolism, m^{6}A machinery, and fibrosis-related gene control. In autosomal dominant polycystic kidney disease, METTL3 and m^{6}A levels are elevated in patients and mouse models. Kidney-specific METTL3 overexpression induces renal tubular cysts. METTL3 deletion reduces cyst growth in multiple disease models [135]. These effects align with a supply-linked driver. Methionine and SAM levels are increased in disease models. Exogenous methionine or SAM induces METTL3 expression and worsens cyst phenotypes. Dietary methionine restriction slows disease progression [135]. This creates a coherent chain in which methyl donor availability strengthens writer activity, raises m^{6}A output, and promotes cyst growth.

Renal fibrosis models also highlight a one-carbon enzyme node that channels metabolic input into a defined pro-fibrotic transcript. In sepsis-associated acute kidney injury, the one-carbon enzyme MTHFD2 is upregulated in myofibroblasts. This increase raises SAM content and m^{6}A modification. m^{6}A then stabilizes LOX mRNA, which promotes collagen deposition and renal fibrosis. MTHFD2 knockdown alleviates the pathological phenotype. When MTHFD2 is inhibited, LOX overexpression partially restores fibrosis and tissue damage [136]. This study supports a node-level mechanism in which a one-carbon enzyme controls SAM, SAM supports m^{6}A, and m^{6}A stabilizes a fibrotic effector

transcript [136].

Across cardiovascular and renal disorders, several m^{6}A enzymes are repeatedly studied. METTL14, METTL16, and METTL3 are prominent, and research focuses on endothelial function, vascular smooth muscle phenotypic transitions, and inflammation and fibrosis. Taken together, cardiorenal disorders follow a shared SAM-m^{6}A logic. The cardiovascular literature more often emphasizes systemic metabolic stress with broad methylation shifts. The renal literature provides clearer node-level causality through methyl donor availability, METTL3, and one-carbon enzymes such as MTHFD2 [134–136].

6.5. Immune diseases: metabolic-epitranscriptomic integration

Immune cells respond rapidly to metabolic cues, and this response is closely coupled to changes in the SAM-m^{6}A axis. Upon immune activation, upstream signaling pathways regulate SAM availability through MAT2A and one-carbon metabolism. Increased SAM supply then supports m^{6}A writing by enzymes such as METTL3, METTL14, and METTL16. Through this mechanism, metabolic state is directly translated into transcript-selective regulation of RNA stability and translation. This coupling provides a fast and flexible way to control immune effector output.

At a general level, the SAM-m^{6}A axis regulates RNA stability, translation, and degradation in immune cells. These processes shape immune cell development, differentiation, and function, and they contribute to the initiation and progression of immune diseases [137–139]. A defining feature of immune systems is the need for rapid functional switching. m^{6}A modification is well suited for this role because it allows post-transcriptional control without requiring new transcriptional programs.

Natural killer cells provide a clear example of metabolic-epitranscriptomic integration during immune activation. Short-term activation of NK cells leads to a rapid increase in m^{6}A levels. Deletion of METTL3 or METTL14 disrupts NK cell homeostasis, maturation, and anti-tumor activity, and dual knockout produces a stronger defect. In this setting, mTORC1 activity is required for the activation-induced increase in m^{6}A. Inhibition of mTORC1 blocks m^{6}A elevation, whereas exogenous SAM supplementation restores it. Transcriptome analysis shows that effector genes such as Prf1 and Gzmb carry enriched m^{6}A modifications, which increase their translation efficiency. These findings define an mTORC1-MAT2A-SAM-m^{6}A pathway that converts metabolic signals directly into cytotoxic effector programs [42].

In chronic immune diseases, the same framework operates, but the dominant responding cell type and pathological outcome differ. METTL3 is the most frequently studied m^{6}A writer in immune diseases, although its functional direction depends on cellular context and inflammatory stage. In rheumatoid arthritis, METTL3-mediated m^{6}A modification regulates genes such as ICAM2 and TRAIL-DR4. This promotes synovial fibroblast proliferation and amplifies inflammatory responses [91,107]. In this disease context, m^{6}A primarily supports pathogenic activation of non-immune stromal cells within inflamed joints.

In systemic lupus erythematosus, m^{6}A regulation highlights a different cellular axis. m^{6}A modification promotes plasma cell infiltration and aggravates renal damage by regulating IRF4 expression [140]. This indicates that m^{6}A-dependent control of B cell differentiation and antibody-producing cells plays a central role in disease progression. In parallel, m^{6}A modification also regulates NLRP3 inflammasome activation, which influences inflammatory responses in rheumatoid arthritis and contributes to disease severity [141]. Clinical studies further show that abnormal m^{6}A patterns in rheumatoid arthritis patients are associated with disease subtype, immune cell infiltration, and therapeutic response [142,143]. These observations suggest that m^{6}A states reflect both immune composition and inflammatory activity.

Taken together, immune diseases share a common SAM-m^{6}A framework that links metabolic state to immune effector function. Upstream signaling increases SAM supply through MAT2A and one-carbon metabolism, which supports m^{6}A writing on key transcripts by METTL3, METTL14, or METTL16. This enables rapid and transcript-specific control of RNA fate during immune activation, as clearly illustrated in NK cells. Disease specificity arises from which cell type responds most strongly and which transcripts are targeted. Rheumatoid arthritis emphasizes METTL3 driven programs in synovial fibroblasts, whereas systemic lupus erythematosus highlights m^{6}A-regulated plasma cell pathways and renal injury. Inflammasome control, including NLRP3 regulation, represents a shared module that produces distinct outcomes across diseases. Future studies should integrate measurements of SAM availability with transcript-level m^{6}A mapping in defined immune cell subsets and relate these patterns to disease stage and treatment response.

6.6. Infectious diseases: viral-host epigenetic interactions

Viral infection is tightly coupled to host immunity, and m^{6}A modification is an important layer of antiviral regulation [144,145]. m^{6}A can reshape host RNA fate and thereby tune innate immune signaling. m^{6}A modification can regulate PTEN mRNA stability and influence interferon production and PI3K AKT signaling. In hepatitis B virus infection, this mechanism modulates the immune response and is linked to liver cancer development [146]. Compared with other disease areas, fewer studies address infectious diseases. Among the reported regulators, METTL16 appears repeatedly, which suggests that recognition of structured RNA sites may be important for host-pathogen interactions and antiviral responses.

A key feature of viral infection is that the functional direction of m^{6}A is virus dependent. In several models, m^{6}A favors infection by supporting viral RNA stability or translation. Severe fever with thrombocytopenia syndrome virus recruits host m^{6}A regulators and increases m^{6}A on viral RNA, which enhances replication efficiency and infectivity [147]. Wheat yellow mosaic virus shows a similar pattern, in which m^{6}A increases stability of RNA1 and promotes infection and replication [148]. Viruses can also shift host methyl donor metabolism to raise host m^{6}A output. In an HCoV-OC43 model, the viral protein nsp14 activates mTORC1 signaling, increases MAT2A expression, and promotes SAM synthesis. Higher SAM is associated with a global increase in m^{6}A on host RNA, which ultimately favors viral replication [149]. These studies support a proviral mode in which viruses either decorate their own RNAs with m^{6}A or remodel host SAM supply to create an m^{6}A -permissive environment.

In other models, m^{6}A supports host defense by enhancing innate recognition or maintaining SAM homeostasis. Reduced m^{6}A on SARS-CoV-2 RNA enhances RIG-I binding, strengthens innate signaling, and inhibits viral replication [150]. METTL16 provides a second antiviral route that acts through the SAM supply axis. In Kaposi's sarcoma-associated herpesvirus infection, METTL16 recognizes a hairpin structure in the 3'UTR of MAT2A mRNA and installs m^{6}A, which supports normal splicing and expression of MAT2A and stabilizes intracellular SAM. Knockdown of METTL16 or MAT2A reduces SAM and enhances lytic replication. Exogenous SAM supplementation suppresses lytic replication and reverses the knockdown phenotype [73]. Host-directed m^{6}A changes can also shape resistance by reprogramming host gene expression. After maize chlorotic mottle virus infection, host m^{6}A levels are upregulated, which alters host expression patterns and affects viral replication [151].

Overall, infectious disease models show a shared SAM-m^{6}A framework, but the outcome depends on which RNA pool is most affected and how the virus engages innate sensing. In proviral settings, m^{6}A enhances viral RNA stability or translation, or viruses increase SAM supply through mTORC1 and MAT2A to raise host m^{6}A output [147–149]. In antiviral settings, reduced m^{6}A on viral RNA can increase RIG-I recognition, and METTL16 can maintain MAT2A splicing and SAM homeostasis to restrain herpesvirus lytic replication [73,150]. This

bidirectional behavior supports a central conclusion. The same SAM-m^{6}A pathway can favor infection or strengthen host defense. The balance is determined by virus type, RNA structure, and the relative impact on viral versus host m^{6}A targets.

6.7. *Developmental and environmental disorders: SAM deficiency and m6A imbalance*

SAM availability sets the ceiling for m^{6}A modification. During embryogenesis, SAM synthesis and utilization are tightly controlled. This control helps maintain appropriate m^{6}A levels on regulatory RNAs. When SAM is insufficient, m^{6}A decreases and key developmental transcripts become dysregulated. This can disrupt normal developmental progression. In early embryos, METTL16 deficiency or limited SAM supply causes arrest at the blastocyst stage. This phenotype is accompanied by reduced m^{6}A and broad transcriptome disruption, which supports a critical role for the SAM-m^{6}A axis in developmental failure [152].

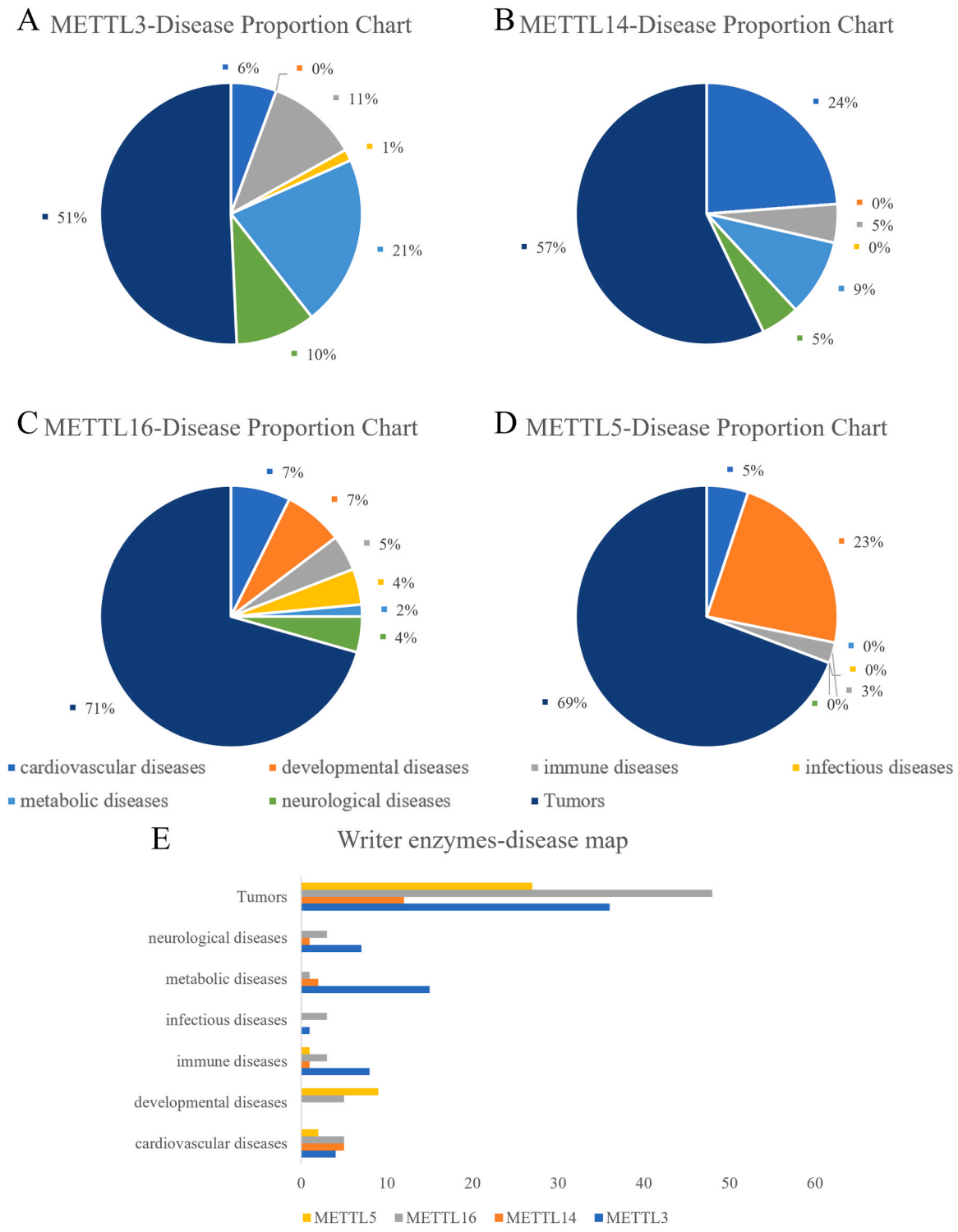

Fig. 5. Distribution of major m^{6}A writer enzymes across different human disease types.

Environmental exposure can push the same axis toward deficiency. Maternal arsenic exposure consumes SAM during methylation reactions catalyzed by As3MT. This reduces intracellular methylation capacity and decreases m^6A levels. In the placenta, arsenic exposure lowers m^6A and reduces CYR61 protein expression. Trophoblast invasion is impaired, which contributes to fetal growth restriction. These effects can be partially reversed by As3MT knockdown, exogenous SAM, or folic acid supplementation during pregnancy [153]. This model also points to a mechanistic intersection between SAM supply control and RNA structure sensing. METTL16 preferentially recognizes structured RNA and regulates MAT2A splicing and expression. Loss of Mettl16 reduces MAT2A mRNA and causes early embryonic arrest, which emphasizes that maintaining SAM supply is required for transcriptome stability and normal development [153].

Arsenic-driven SAM depletion can also impair metabolic homeostasis in adult tissues through transcript-selective m^6A disruption. In the liver, arsenic depletes SAM and blocks m^6A modification of pri-miR-142. This reduces miR-142–5p maturation and increases SREBP1 and lipogenic gene expression, which promotes NAFLD. Supplementation with SAM, folic acid, vitamin B12, or As3MT knockdown reverses lipid deposition [154]. This liver model mirrors the developmental and placental findings. In each case, arsenic shifts methylation potential downward, m^6A regulation is disrupted on defined RNA targets, and the resulting gene expression changes drive a tissue-specific phenotype [153,154].

Together, these studies support a unified mechanism in which development and tissue homeostasis require stable SAM supply to maintain m^6A on key regulatory RNAs. METTL16 is a central node because it links structured RNA recognition to MAT2A expression and SAM maintenance. Environmental toxicants can drain SAM and destabilize this control, which produces m^6A imbalance and impairs embryonic development, placental function, and hepatic metabolism [43,152,153].

7. Comparative distribution of m^6A writer enzymes across diseases

We mapped the distribution of m^6A writer enzymes across seven disease categories to identify disease-associated "writer hotspots" and to extract actionable patterns for hypothesis generation. After normalization and grouping, METTL3, METTL14, METTL16, METTL5, and ZCCHC4 emerged as the main writers represented in the current literature, and their relative proportions are summarized in Fig. 5.

A consistent trend is that the literature is strongly tumor-weighted, but different writers occupy different niches. METTL3 studies are concentrated in tumors (approximately 50 %), with substantial representation in metabolic disease (approximately 21 %), followed by immune (approximately 11 %) and neurological disorders (approximately 10 %), while cardiovascular and renal disease accounts for a smaller fraction (approximately 6 %). METTL14 shows an even stronger tumor emphasis (approximately 57 %), but it is comparatively more represented in cardiovascular and renal disease (about 24 %). METTL16 is most frequently studied in tumors (approximately 71 %) and is also present across developmental and reproductive, cardiovascular and renal, immune and inflammatory, infectious, and neuropsychiatric categories. METTL5 is largely captured by tumor research (approximately 69 %) and developmental studies (approximately 23 %), while current ZCCHC4 reports are confined to tumor contexts. These distributions indicate that "writer relevance" is not uniform across diseases and that the dominant writer in a field often reflects the RNA substrate and phenotype that the field prioritizes.

This pattern becomes clearer when writers are viewed through RNA substrate preference rather than only disease labels. METTL3 and METTL14 are most often discussed in the context of mRNA m^6A deposition, which aligns with phenotypes that depend on transcript abundance and translation efficiency. By contrast, METTL16 and METTL5 are frequently linked to structured RNA and rRNA-related regulation, which may better explain their enrichment in tumor and developmental studies. This distinction supports a broader inference: methylation of different RNA classes may drive different biological "outputs," and the literature's disease focus may partially reflect which RNA layer is most informative or experimentally accessible in that system.

Oncology illustrates how these writers biases translate into mechanistic themes. In cancer-focused studies, METTL16 and METTL3 appear most prominent, followed by METTL5 and METTL14. The commonly reported phenotypes include proliferation, invasion and metastasis, apoptosis resistance, stemness maintenance, therapy resistance, and immune microenvironment remodeling. Importantly, these outputs often depend on reader-mediated target selection, frequently involving YTHDF and IGF2BP families, and they interface with signaling programs such as MYC, AKT/MAPK, JAK-STAT, and EMT (Fig. 5E). This implies that writer prevalence alone is not sufficient to predict functional dependence, because the same writer can support different outputs depending on the reader axis and the dominant transcript set in a given tumor type.

These observations motivate a future-facing shift in how the field selects targets and designs studies. Writer research should move beyond METTL3-centric screening toward a node- and RNA-substrate-guided strategy. In tumors and metabolic diseases, where METTL3 and METTL14 dominate mRNA-centered work, the key question is not only whether m^6A increases or decreases, but which reader programs decode these marks to drive phenotype. A practical direction is to test dual-layer intervention strategies that align the dominant writer with the key reader axis, especially in settings where IGF2BP- or YTHDF-driven transcript selection sustains oncogenic states. In developmental and stress-sensitive contexts, where METTL16 and METTL5 are enriched, future studies should prioritize structure-dependent mechanisms and RNA-class specificity, rather than relying on global m^6A measurements that may miss the relevant layer of regulation. Across all categories, improved comparability will require standardized reporting that includes RNA-type specificity, cell-type resolution, and quantitative exposure or dosing information. This framework would convert a descriptive distribution map into a mechanism-guided roadmap for target prioritization, patient stratification, and therapeutic design (Fig. 5 and Table 2).

8. Conclusion

The SAM-m^6A axis provides a coherent framework to link metabolic state with RNA fate regulation. SAM availability, SAH accumulation, and the SAM/SAH ratio act as central constraints on m^6A deposition and turnover. Disruption of one-carbon metabolism can therefore translate into transcriptome-wide effects through the writer-reader-eraser machinery. Current evidence indicates that many plant-derived bioactive compounds engage this axis indirectly. They tend to remodel methyl-donor metabolism, redox balance, and protein abundance rather than acting as high-affinity m^6A enzyme inhibitors. This mode of action distinguishes phytochemicals from synthetic single-target inhibitors and suggests different translational roles. Phytochemicals may be better suited for long-term modulation of methylation capacity in chronic diseases, whereas direct inhibitors may be preferable for conditions requiring rapid pathway suppression. Future studies should prioritize quantitative SAM/SAH profiling, causal mapping of m^6A-dependent effects, and standardized exposure-response designs. Such efforts will be essential to define efficacy, specificity, and safety. Together, these advances will clarify when and how nutritional or phytochemical strategies can be harnessed to modulate the SAM-m^6A axis for disease prevention and therapy.

CRediT authorship contribution statement

Yuxuan Zhao: Writing – original draft. **Jingyimei Liang:** Writing – review & editing. **Jianbo Xiao:** Writing – review & editing,

Table 2
Summary of studies on m^6A writer enzymes and their disease-related mechanisms.

Writer enzyme	Classification	Intervention	Model	Target	Function	Keywords	DOI
METTL3	cardiovascular diseases	-	RPE cells	Metabolic Reprogramming	Promote	Retinal angiogenesis	10.1186/s12974–024–03279–1
	cardiovascular diseases	Leonurine	Foam cells	AKT1S1 mRNA	Improve	Atherosclerosis	10.1016/j.phymed.2024.155939
	cardiovascular diseases	-	-	CCN2	Prevent	Bladder remodeling	10.1002/nau.25233
	cardiovascular diseases	Maslinic acid	-	-	Prevent	Pressure-overload-induced cardiac hypertrophy	10.18632/aging.203860
	immune diseases	-	-	-	-	Associated with autoimmune thyroid disease susceptibility	10.1007/s12020–020–02503–1
	immune diseases	EZH2	B cells	-	Promote	Autoimmunity	10.1016/j.jaut.2024.103341
	immune diseases	Hypoxia	Pancreatic cancer cells	lncRNA NNT-AS1/METTL3-HuR	Promote	Immune escape	10.1016/j.yexcr.2023.113764
	immune diseases	-	Systemic lupus erythematosus	IRF4	Promote	Renal injury	10.1186/s12916–024–03735-y
	immune diseases	-	-	-	Promote	Synovitis	10.1016/j.yexcr.2024.114237
	immune diseases	-	Systemic lupus erythematosus	CD4 + T Cell and Effector T Cell	-	Lupus erythematosus	10.1186/s10020–023–00643–4
	immune diseases	-	-	NF-κB	Promote	Rheumatoid arthritis	10.3389/fmed.2021.607585
	immune diseases	-	-	Traf6	Inhibit	Inflammatory response	10.4049/jimmunol.1801151
	infectious diseases	-	Pancreatic cancer cells	-	Block	Vesicular stomatitis virus	10.1128/jvi.02284–24
	metabolic diseases	-	-	Mettl3-m6A-YTHDF1	Promote	Mitochondrial dysfunction in fatty liver	10.1016/j.cellsig.2024.111303
	metabolic diseases	-	-	METTL3-IGF2BP2, HDAC1, FGF21	Promote; Inhibit	Overexpression; Liver injury	10.1139/bcb-2022–0314
	metabolic diseases	-	-	Glucose Metabolism Hub Gene	Promote	Steatotic liver disease	10.1186/s12864–025–11377–4
	metabolic diseases	-	-	m6A-IGF2BP2	Aggravate	Ferroptosis in sepsis-induced acute lung injury	10.1002/ctm2.1389
	metabolic diseases	-	Kupffer cells	STING	Lead	Radiation-induced liver disease	10.1016/j.ijrobp.2023.10.041
	metabolic diseases	-	-	CD36	-	Dysregulated follicular glucose metabolism and inflammation in polycystic ovary syndrome	10.1016/j.intimp.2024.113327
	metabolic diseases	Saccharomyces boulardii	-	-	Relieve	Allergic asthma	10.1016/j.imlet.2024.106853
	metabolic diseases	-	-	Cadmium	Participate	Liver injury	10.1016/j.envpol.2023.121887
	metabolic diseases	Butyric acid	Granular cells	FOSL2	Improve	Cellular inflammation	10.1186/s13148–023–01487–9
	metabolic diseases	-	-	-	-	Associated with the development of dry eye in primary Sjögren's syndrome	10.1186/s12886–023–02988–0
	metabolic diseases	Intermittent hypoxia	Adipocytes	MGLL	Promote	Lipolysis	10.1038/s41420–022–01149–4
	metabolic diseases	-	Dental pulp stem cells	-	-	Dental pulp stem cell differentiation	10.1177/00220345211051594
	metabolic diseases	-	Mouse	-	-	Liver homeostasis, hepatocyte ploidy, and circadian rhythms	10.1016/j.ajpath.2021.09.005
	metabolic diseases	Artemisinin	Fibroblast-like synoviocytes	ICAM2 mRNA	Inhibit	Rheumatoid arthritis	10.1002/ctm2.1148
	metabolic diseases	STM2457	Mouse	Mitochondria	Improve	Fatty liver disease	10.12122/j.issn.1673–4254.2023.10.06
	neurological diseases	-	-	Lingo2	-	Alzheimer's disease	10.1038/s41380–025–02984–4
	neurological diseases	-	NDUFA10	-	-	Alzheimer's disease	10.3390/ijms241210111
	neurological diseases	-	-	-	-	Alzheimer's disease	10.1523/ENEURO.0125–20.2020
	neurological diseases	-	Microglia	α-Synuclein	-	Neuroinflammation	10.1016/j.celrep.2025.115618
	neurological diseases	-	-	-	-	Aluminum-induced neurotoxicity	10.1016/j.ecoenv.2023.115878

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Table 2 (*continued*)

Writer enzyme	Classification	Intervention	Model	Target	Function	Keywords	DOI
	neurological diseases	KDM1A	-	STUB1	Improve	Alzheimer's disease	10.1016/j.freeradbiomed.2022.12.099
	neurological diseases	-	-	-	-	Nervous system	10.3390/biom13040664
	Tumors	Exosomal circLPAR1	-	BRD4	Inhibit	Colorectal cancer diagnosis and oncology	10.1186/s12943–021–01471-y
	Tumors	-	Mesenchymal stem cells	-	Promote	Chemotherapy resistance in acute myeloid leukemia	10.1038/s41419–023–06325–7
	Tumors	-	-	PSMA3-AS1	-	FLT3-ITD+ Acute myeloid leukemia	10.1080/15384101.2023.2204770
	Tumors	-	-	-		Prognostic potential of METTL3 expression in gastric cancer patients	10.3892/ol.2022.13651
	Tumors	METTL3 small molecule inhibitor	Non-small cell lung cancer	-	-	Cell carcinoma	10.1016/j.jpha.2023.04.009
	Tumors	-	-	-	Inhibit	Melanoma and colon cancer cells	10.1007/s00418–024–02346–1
	Tumors	-	-	-	-	Thyroid cancer	10.62347/THJB4749
	Tumors	-	Platinum-induced mouse	-	Relieve	Renal fibrosis; chemotherapy efficacy	10.7150/ijbs.117443
	Tumors	-	-	-	-	Pan-cancer tumor immune microenvironment	10.3390/jcm12010155
	Tumors	-	Human	-	-	Cervical cancer clinical features	10.1186/s12967–020–02553-z
	Tumors	ACAT1	Breast cancer cells	-	Inhibit	Cancer cell migration and invasion	10.1038/s41435–023–00202–1
	Tumors	-	-	RNA LINC00969	Relieve	Papillary thyroid carcinoma	10.17219/acem/188367
	Tumors	-	-	-	-	Colorectal cancer	10.3892/ol.2021.12936
	Tumors	RNA LINC00240	miR-338–5p/METTL3	-	Promote	Gastric cancer progression	10.1080/21655979.2021.1983276
	Tumors	Eltrombopag	Cells	-	-	Acute myeloid leukemia cells	10.3390/ph15040440
	Tumors	-	Gastric cancer cells	-	Inhibit	Cell proliferation	10.3892/ol.2020.11794
	Tumors	-	-	-		Gynecologic cancers	10.3389/fphar.2023.1156629
	Tumors	-	-	Myc	Promote	Cervical cancer	10.24976/Discov.Med.202436188.176
	Tumors	NSUN6	-	5-methylcytosine	Promote	Colon adenocarcinoma	10.1002/jbt.23749
	Tumors	-	-	p38/ERK	Inhibit	Proliferation and migration of colorectal cancer	10.2147/OTT.S201052
	Tumors	-	-		-	Prostate cancer	10.1158/1541–7786.MCR-21–0014
	Tumors	-	Hepatocytes	ZNF384; ACSM1	Promote	Hepatocellular carcinoma progression	10.1007/s12094–024–03701–3
	Tumors	-	-	HDAC5/YY1; IFFO1	Promote	Tumor development and chemoresistance	10.1016/j.canlet.2022.215971
	Tumors	M2-TAM	-	-	Promote	Immune resistance in lung adenocarcinoma	10.21037/atm-22–6104
	Tumors	-	Esophageal squamous cell	Nectin-4; VNN1	Promote	Progression of esophageal squamous cell carcinoma	10.3724/abbs.2025108
	Tumors	-	Hepatocytes	-	-	Prognosis of hepatocellular carcinoma patients	10.21037/atm-22–5964
	Tumors	-	-	YY1; pri-microRNA-27	Promote	Development of multiple myeloma	10.1007/s10565–021–09690–1
	Tumors	-	-	-	-	Esophageal cancer; Squamous cell carcinoma	10.3389/fonc.2022.824190
	Tumors	-	Human	-	Premonition	Poor prognosis in patients with esophageal squamous cell carcinoma	10.2147/CMAR.S245019
	Tumors	-	-	MYC	Promote	Prostate cancer	10.7150/jca.42338
	Tumors	-	-	FGD5-AS1; PD-1/PD-L1	-	Enhanced resistance to paclitaxel in endometrial cancer	10.1111/jcmm.17971
	Tumors	-	Nasopharyngeal carcinoma cells	pri-miRNA-19a	Promote	Proliferation and invasion of nasopharyngeal carcinoma cells	10.1152/physiolgenomics.00007.2022
	Tumors	lncRNA NUTM2A-AS1	Lung adenocarcinoma cells	miR-590–5p/METTL3	Inhibit	Lung adenocarcinoma cells	10.3892/ol.2021.13059
	Tumors	-	Human β cells	-	-	Innate immune response in type 1 diabetes	10.1101/2023.02.16.528701
	Tumors	-	-	SRSF1	Promote	MDS/AML progression	10.1016/j.ymthe.2025.08.042
METTL14	cardiovascular diseases	-	Mice	GLUT9	Reduce	Renal tubular epithelial cell fibrosis	10.1038/s41418–025–01561–0
	cardiovascular diseases	-	-	-	Promote	Intimal hyperplasia	10.1080/16078454.2025.2535819
	cardiovascular diseases	Smoking and Tetrameric Tryptase	-	DIXDC1	Accelerate	Intervertebral disc degeneration	10.1016/j.cellsig.2024.111304

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Table 2 (*continued*)

Writer enzyme	Classification	Intervention	Model	Target	Function	Keywords	DOI
	cardiovascular diseases		-	TEAD1 mRNA	Promote	Vascular smooth muscle cell proliferation and neointimal formation	10.1016/j.intimp.2024.113308
	cardiovascular diseases	-	-	-	Weaken	Cardiotoxicity	10.1172/jci.insight.184444
	immune diseases	-	-	MyD88/NF-κB	Promote	MAFLD progression	10.1007/s12033–023–00843–7
	metabolic diseases	-	-	TUG1	Promote	Diabetic nephropathy	10.1016/j.ymthe.2023.06.010
	metabolic diseases	-	-	-	-	Dysregulated RNA	10.31083/j.fbl2908298
	neurological diseases	-	-	TUG1;GDF15	Inhibit	Ferothrombosis in Alzheimer's disease	10.1186/s12964–025–02130–1
	Tumors	-	-	-	Promote	Juvenile myelomonocytic leukemia	10.1002/tox.24187
	Tumors	-	-	-	-	Chronic myeloid leukemia	10.1007/s00592–023–02145–5
	Tumors	-	-	TCP1 mRNA	Promote	Acute myeloid leukemia	10.1002/jbt.70284
	Tumors	-	-	SCD1	Inhibit	Tumor stemness and metastasis in colon cancer cells	10.1101/2024.06.17.599413
	Tumors	-	-	-	-	Acute myeloid leukemia	10.1161/JAHA.124.040700
	Tumors	-	-	pri-microRNA-129	Promote	Docetaxel resistance in prostate cancer	10.2147/DDDT.S506702
	Tumors	Sijunzi Decoction	-	-	Inhibit	Gastric cancer metastasis	10.3892/ol.2021.13108
	Tumors	-	-	Twist	Inhibit	Non-small cell lung cancer	10.3389/fonc.2021.696371
	Tumors	-	-	Cytidine deaminase	Promote	Gemcitabine resistance in pancreatic cancer	10.1038/s41392–024–01797–1
	Tumors	LncRNA UCA1	-	-	Promote	Breast cancer	10.1038/s41417–021–00390-w
	Tumors	-	Human	-	-	Acute lymphoblastic leukemia	10.2147/CMAR.S335925
	Tumors	-	-	PI3K/AKT/mTOR	Inhibit	Proliferation, migration, and invasion in gastric cancer	10.1002/jcla.23655
METTL16	cardiovascular diseases	-	-	TET2	Lead to	Coronary artery disease	10.1111/cpr.13782
	cardiovascular diseases	-	-	METTL16/Akt	Improve	Thrombocytopenia	10.1186/s13045–024–01599–6
	cardiovascular diseases	-	-	-	-	Hematologic disorders	10.7150/ijbs.105391
	cardiovascular diseases	-	Human	-	-	Myocardial cells	10.1038/s41556–021–00835–2
	cardiovascular diseases	-	PM2.5	-	-	Susceptibility to sudden cardiac death	10.1016/j.stem.2022.12.006
	developmental diseases	-	Spermatogonia	YTHDC1	-	Pulmonary microvasculature	10.1016/j.canlet.2025.217698
	developmental diseases	-	-	-	-	Spermatogonia differentiation	10.1186/s13045–024–01526–9
	developmental diseases	-	Mice	Alternative splicing and translation control	-	Chromosomes	10.1016/j.exer.2025.110514
	developmental diseases	-	-	-		Spermatozoa	10.7150/ijbs.97886
	developmental diseases	-	Mice	-	-	Nonsyndromic maxillofacial cleft palate	10.1016/j.celrep.2023.112150
	immune diseases	-	-	-	Weaken	Embryonic development	10.1002/advs.202406332
	immune diseases	Oxidative stress	-	MAT2A	Aggravate	Apoptosis	10.1186/s13059–024–03332–5
	immune diseases	-	Human	Glutamine		Nucleus pulposus cell apoptosis	10.2147/JIR.S487828
	infectious diseases	-	-	S-adenosylmethionine cycle	Control	Airway inflammation	10.1038/s41419–023–06121–3
	infectious diseases	Miichthys miiuy	-	-	Inhibit	Kaposi's sarcoma-associated herpesvirus	10.1038/s41467–023–42025–8
	infectious diseases	-	-	HLA-DPB1	-	Antiviral; immune response	10.1007/s10238–025–01669–0
	metabolic diseases	-	-	CIDEA	Promote	Chronic hepatitis B	10.1186/s12885–025–14729–1
	neurological diseases	-	-	-	Promote	Nonal fatty liver disease	10.1186/s13046–023–02732-y
	neurological diseases	-	-	MAT2A	Destroy	Corneal nerve regeneration	10.18632/aging.206210

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Table 2 (*continued*)

Writer enzyme	Classification	Intervention	Model	Target	Function	Keywords	DOI
	Tumors	-	Mice	METTL16; SENP3; IAP	Promote	Learning and memory	10.1016/j.bbr.2025.116116
	Tumors	-	-	Metabolic reprogramming	Promote	Tumorigenesis in hepatocellular carcinoma	10.1186/s12885–025–14291-w
	Tumors	-	-	-	Promote	Colorectal cancer	10.1002/bdr2.2403
	Tumors	-	-	BCAA	Promote	Translation and tumorigenesis	10.1007/s00018–024–05146-x
	Tumors	-	-	-	-	Leukemogenesis and leukemic stem cells	10.1002/jcp.31068
	Tumors	-	Liver Cancer Stem Cells	Ribosomes; mRNA	Promote	Cancer	10.1016/j.celrep.2025.115926
	Tumors	-	-	ATF4	Inhibit	Hepatocellular carcinoma	10.1016/j.jhazmat.2024.136093
	Tumors	-	-	Cytoplasmic eIF4E	Promote	Ferroptosis in cholangiocarcinoma	10.1038/s41420–022–01220–0
	Tumors	-	-	FDX1 mRNA	Promote	Translation and lung cancer	10.3389/fcell.2022.759020
	Tumors	-	-	TCF-1	Promote	Goblet cell apoptosis in gastric cancer	10.1016/j.abb.2025.110510
	Tumors	-	-	GPX4 m6A	-	Acute myeloid leukemia	10.1016/j.isci.2023.108495
	Tumors	-	-	Metabolic reprogramming	-	Ferroptosis and TKI resistance in non-small cell lung cancer	10.1186/s13046–023–02844–5
	Tumors	Cinnamic acid derivatives	-	-	Treat	Colorectal cancer	10.1111/cpr.13590
	Tumors	-	-	-	Promote	Hepatocellular carcinoma	10.1016/j.bbrc.2024.149802
	Tumors	-	-	MROH8;CAPN2	Inhibit	Pancreatic cancer proliferation and metastasis	10.1016/j.aohep.2025.101776
	Tumors	Planthophylloside D	-	-	Promote	Docetaxel therapy for prostate cancer	10.1186/s12885–025–14041-y
	Tumors	-	-	m6A/YTHDC2/SCD1	Inhibit	Papillary thyroid carcinoma Adenocarcinoma	10.1186/s11658–022–00342–8
	Tumors	-	-	VPS33B	Promote	Osteosarcoma	10.1016/j.ijbiomac.2024.136176
	Tumors	SSB	-	-	Promote	Chemoresistance in colorectal cancer cells	10.1007/s11010–025–05346–4
	Tumors	-	-	Glutamine; glutamine transpeptidase (GLUL)	-	Chromium and lung cancer	10.7150/ijbs.86719
	Tumors	-	-	-	Predict	Pancreatic ductal adenocarcinoma	10.3389/fonc.2023.1138238
	Tumors	Norcantharidine	-	METTL16/MAT2A	Inhibit	Ovarian cancer cell apoptosis	10.1186/s40170–024–00351–5
	Tumors	Hypoxia	Liver Cells	HIF-1α/METTL16/lnc-CSMD1–7/RBFOX2	Induce	Hepatocellular carcinoma metastasis	10.1111/bjh.19722
	Tumors	-	-	PRDM15;FGFR4	Promote	Cholesterol duct carcinoma	10.2147/IJN.S520329
	Tumors	-	-	Soga1	Maintain	Colorectal cancer; Chromosomes	10.1002/cam4.70772
	Tumors	-	-	POU3F2/METTL16/PFKM	Promote	Glycolysis; Tumors	10.18632/aging.204980
	Tumors	-	-	miR-146b-5p; PI3K/AKT	Sensitize	Non-small cell lung cancer; Osimertinib	10.7150/jca.85860
	Tumors	-	-	RAB11B-AS1	Promote	Hepatocellular carcinoma	10.1155/2023/9952234
	Tumors	-	-	SAMD11	Inhibit	Thyroid cancer	10.3390/ijms21218139
	Tumors	-	-	KLK4	Promote	Renal cell carcinoma	10.7150/ijbs.95375
	Tumors	-	-	PMEPA1	Inhibit	Bladder cancer	10.1016/j.dci.2023.104713
	Tumors	-	-	p21	Inhibit	Pancreatic adenocarcinoma	10.1016/j.bbrc.2022.10.065
	Tumors	-	-	FBXO5	Promote	Breast cancer	10.1615/CritRevEukaryotGeneExpr.2025058118
	Tumors	-	-	-	Inhibit	Triple-negative breast cancer	10.1186/s13008–025–00156-y
	Tumors	-	-	UBXN1	Induce	Gastric cancer	10.1111/jcmm.16664
	Tumors	Rectal cancer cells	-	PD-L1	Mediate	Colorectal cancer	10.3389/fgene.2022.996245
	Tumors	-	-	DVL2; Wnt/β-catenin	Inhibit	Pancreatic cancer	10.1155/2022/4036274
	Tumors	-	-	lncRNA MALAT1/β-catenin	Inhibit	Epithelial ovarian cancer	10.7150/jca.90379
	Tumors	-	-	COL10A1; SYNPO2L	Lead to	Lung metastasis	10.3389/fnagi.2025.1572976
	Tumors	-	-	GPX4	Promote	Breast cancer	10.1016/j.molcel.2018.08.004
	Tumors	-	-	FGD5-AS1;miR-195–5p/SLC7A2	Promote	Osteosarcoma	10.1371/journal.pone.0306043
	Tumors	-	-	GTSE1;p53	Accelerate	Lung adenocarcinoma	10.1016/j.amjcard.2023.06.062
	Tumors	-	-	D1	Promote	Gastric cancer	10.7717/peerj.14379
	Tumors	-	-	-	-	Epithelial ovarian cancer	10.1038/s43018–022–00429–3
	Tumors	-	-	-	-	Hemoglobin H disease	10.1016/j.ecoenv.2024.117518
	Tumors	-	-	MRE11; PARP	-	Pancreatic ductal adenocarcinoma	10.1016/j.envpol.2022.119115
	Tumors	-	-	AMD1;MAT2A	-	H3K27M histone mutant glioma	10.1093/neuonc/noad073.083

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Table 2 (*continued*)

Writer enzyme	Classification	Intervention	Model	Target	Function	Keywords	DOI
	Tumors	-	-	MRE11; PARP	-	Pancreatic ductal adenocarcinoma	10.21203/rs.3.rs-598847/v1
METTL5	cardiovascular diseases	-	Cells	-	-	Atherosclerosis	10.1038/s41598–025–03411-y
	cardiovascular diseases	-	-	SUZ12	Promote	Cardiac hypertrophy	10.1016/j.freeradbiomed.2025.05.392
	developmental diseases	-	Human; Mice	18S rRNA m6A	Induce	Oligostematospermia	10.4251/wjgo.v16.i5.1925
	developmental diseases	-	-	-	Lead	Recessive intellectual disability	10.1038/s41419–025–07904–6
	developmental diseases	-	-	-	Promote	Corticospinal tract	10.1016/j.ymthe.2025.08.009
	developmental diseases	-	Mice	-	Promote	Embryonic stem cells	10.1016/j.ymthe.2023.09.014
	developmental diseases	-	Human	-	Lead	Microcephaly	10.1080/14796694.2024.2442296
	developmental diseases	-	-	CHCHD2	-	Neurodevelopment	10.1016/j.cellsig.2025.111740
	developmental diseases	-	Mice	-	Improve	Embryology	10.1016/j.biocel.2025.106822
	developmental diseases	-	-	-	-	Developmental program	10.1002/cac2.12403
	developmental diseases	-	Human	-	-	Syndrome of intellectual disability	10.1111/jop.13601
	immune diseases	-	-	M2 macrophages	Relieve	Respiratory allergy	10.1007/s11033–024–10207–2
	Tumors	Breviscapine	-	-	Inhibit	Ovarian cancer	10.3389/fonc.2025.1522157
	Tumors	-	-	Ferroptosis	Trigger	Myocardial injury	10.1002/cam4.7165
	Tumors	-	-	Sphingomyelin metabolism	Promote	Gastric cancer progression	10.18632/aging.205755
	Tumors	-	-	SEPHS2; selenoprotein	Promote	Multiple myeloma	10.1038/s41420–024–02166–1
	Tumors	-	-	-	Promote	Intrahepatic bile duct carcinoma	10.1016/j.ajhg.2019.09.007
	Tumors	-	-	-	-	Hepatocellular carcinoma	10.1007/s10735–025–10495–3
	Tumors	-	-	SLC7A11; ferroptosis	Promote	Cervical cancer	10.1016/j.expneurol.2024.115000
	Tumors	-	-	USP5; c-Myc; glucose metabolism	Promote	Hepatocellular carcinoma	10.15252/embr.201949863
	Tumors	-	-	Myc	Promote	Oral squamous cell carcinoma	10.1038/s10038–025–01354-w
	Tumors	-	-	-	Predict	Gastrointestinal cancer	10.1101/2025.07.13.664555
	Tumors	-	-	DEPDC1	Promote	Lung squamous cell carcinoma	10.1530/REP-22–0169
	Tumors	-	Cells	-	-	Hepatocellular carcinoma	10.1038/s41598–023–37807–5
	Tumors	-	-	-	Inhibit	Gastric cancer	10.3389/fcvm.2022.852775
	Tumors	-	-	UBE3C; AHNAK	Promote	Osteosarcoma	10.1016/j.celrep.2020.108544
	Tumors	-	-	-	Biomarker	Hepatocellular carcinoma	10.3892/ijo.2021.5299
	Tumors	-	-	-	Promote	Breast cancer cells	10.1016/j.yexcr.2024.114219
	Tumors	-	-	c-Myc	Promote	Pancreatic cancer	10.1089/gtmb.2023.0531
	Tumors	-	-	TPRKB	Promote	Hepatocellular carcinoma cells	10.1101/gad.333369.119
	Tumors	-	-	IGF2BP3	Promote	Cancer cell proliferation	10.4251/wjgo.v16.i5.2006
	Tumors	-	Cells	Toll-like receptor 8	Promote	Cell proliferation, invasion, and migration	10.1186/s12935–021–02274–3
	Tumors	-	-	-	Predict	Gastric cancer	10.3389/fgene.2020.617174
	Tumors	-	-	-	Predict	Lung adenocarcinoma immunity	10.7150/jca.90379
	Tumors	-	Human	-	-	Epithelial ovarian cancer	10.1080/1120009X.2022.2143614
	Tumors	-	Liver cells	Myc; PD-L1	Inhibit	Hepatocellular carcinoma cells	10.1016/j.heliyon.2022.e12078
	Tumors	-	-	-	Biomarker can	Renal cancer	10.24953/turkjped.2020.3992
	Tumors	-	-	-	-	Lung adenocarcinoma	10.3934/mbe.2021327
	Tumors	-	Human	-	Lead	Microcephaly-associated intellectual disability	10.1007/s12041–023–01441-x
ZCCHC4	Tumors	-	Human	DNA damage	Promote	Cancer	10.1038/s41392–022–01033–8

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Table 2 (*continued*)

Writer enzyme	Classification	Intervention	Model	Target	Function	Keywords	DOI
	Tumors	-	-	ITGB1	Promote	Osteosarcoma	10.1615/CritRevEukaryotGeneExpr.2023047798
	Tumors	-	-	ROS/c-myc	Regulate	Esophageal cancer	10.1038/s41598–025–89628–3
	Tumors	-	-	LncGHRLOS	Promote	Colorectal cancer	10.1186/s13046–024–02965–5

Conceptualization, Funding acquisition, Project administration, Resources, Visualization. **Hui Cao:** Writing – review & editing, Conceptualization, Funding acquisition, Project administration, Resources, Visualization. **Wanning Ma:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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