

## REVIEW ARTICLE

# N6-methyladenosine: A pivotal regulator in glioma oncogenesis and progression

Jingjing Li<sup>1†</sup>, Xiaoguang Zhang<sup>2†</sup>, Yaoyao Wang<sup>1</sup>, Chen Dong<sup>1</sup>,  
Haotian Li<sup>1</sup>, Ying Wang<sup>3\*</sup>, and Shuangyu Lv<sup>1,2,4\*\*</sup>

<sup>1</sup>Henan International Joint Laboratory for Nuclear Protein Regulation, School of Basic Medical Sciences, Henan University, Kaifeng, Henan, China

<sup>2</sup>Department of Neurosurgery, The First Affiliated Hospital of Henan University, Henan University, Kaifeng, Henan, China

<sup>3</sup>Department of Anesthesiology, The First Affiliated Hospital of Henan University, Henan University, Kaifeng, Henan, China

<sup>4</sup>The Zhongzhou Laboratory for Integrative Biology, Henan University, Zhengzhou, Henan, China

## Abstract

Gliomas are the most prevalent primary neoplasms of the central nervous system and arise from glial cells present in the brain or spinal cord. N6-methyladenosine (m6A) is one of the most frequently occurring modifications in RNA, and its potential implications in glioma have received widespread attention in recent years. In glioma, m6A-related enzymes are capable of modifying target RNAs, influencing their translation, degradation, and splicing, which can promote or inhibit biological processes such as ferroptosis and glycolysis, ultimately impacting the progression of glioma. Furthermore, upstream modulators are capable of regulating the expression of m6A-associated enzymes, ultimately affecting glioma development by modulating m6A modification on target RNAs. In addition, the m6A modification influences glioma resistance to temozolomide, resulting in an impact on glioma patient survival. This review comprehensively delineates the molecular mechanisms by which m6A and its upstream signaling molecules regulate glioma development, emphasizing their potential value in exploring new therapeutic approaches and improving patient prognosis.

**Keywords:** Glioma; N6-methyladenosine; Epigenetic and transcriptomic modifications; Molecular mechanism

<sup>†</sup>These authors contributed equally to this work.

### \*Corresponding authors:

Ying Wang  
(Wangy1528@126.com)  
Shuangyu Lv  
(shuangyulv@henu.edu.cn)

**Citation:** Li J, Zhang X, Wang Y, et al. N6-methyladenosine: A pivotal regulator in glioma oncogenesis and progression. *Gene Protein Dis.* 2026;5(2):025400073.  
doi: 10.36922/GPD025400073

**Received:** October 1, 2025

**Revised:** December 16, 2025

**Accepted:** December 26, 2025

**Published online:** January 19, 2026

**Copyright:** © 2026 Author(s).

This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

**Publisher's Note:** AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

## 1. Introduction

Glioma, a predominant intracranial malignancy,<sup>1</sup> originates from glial cells and is marked by its pronounced invasive nature and associated high mortality rates, resulting in an extremely poor prognosis.<sup>2</sup> In accordance with the 2021 World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS) (5<sup>th</sup> edition), the classification of gliomas is anchored in the core principle of “molecular phenotype integrated with histological characteristics” and falls into three primary categories.<sup>3</sup> First, adult-type diffuse gliomas comprise three subtypes: astrocytoma (*IDH*-mutant, often co-occurring with genetic aberrations including *ATRX* and *TP53* mutations, spanning CNS WHO grades 2–4); oligodendroglioma (*IDH*-mutant with

1p/19q codeletion, which serves as the pivotal diagnostic basis); and glioblastoma (GBM; *IDH*-wildtype, CNS WHO Grade 4, often associated with *TERT* mutation, *EGFR* amplification, and other molecular alterations).<sup>3,4</sup> Second, pediatric-type diffuse gliomas, a newly added independent category,<sup>5</sup> are subdivided into low-grade (4 subtypes, e.g., diffuse astrocytoma with *MYB/MYBL1* alterations, all involving specific molecular changes) and high-grade (4 subtypes, e.g., diffuse midline glioma with H3-K27 alterations, CNS WHO grade 4, characterized by high malignancy).<sup>6</sup> Thirdly, circumscribed astrocytic gliomas, defined by clear boundaries and non-diffuse growth, include subtypes such as pilocytic astrocytoma (predominantly CNS WHO grade 1) and pleomorphic xanthoastrocytoma, with each subtype exhibiting distinct characteristic molecular abnormalities.<sup>3,4,6</sup>

GBM, recognized as the most lethal subtype, arises from primitive glial precursors that exhibit aberrant differentiation.<sup>7</sup> Histopathological hallmarks of GBM include prominent nuclear atypia, marked cellular pleomorphism, and exuberant mitotic activity, often accompanied by microvascular proliferation and pseudopalisading necrosis.<sup>8</sup> The clinical presentation of glioma patients varies significantly depending on tumor location and size.<sup>9</sup> Common symptoms include visual disturbances,<sup>10</sup> seizures,<sup>11</sup> and manifestations of elevated intracranial pressure such as headache, nausea, and projectile vomiting.<sup>12</sup> Tumor location can also cause focal neurological deficits, including motor and sensory dysfunction.<sup>13</sup> These symptoms profoundly impair quality of life and can be life-threatening. Therefore, the treatment of glioma is crucial and cannot be delayed.

Epitranscriptomics refers to the transcriptome-wide analysis of post-transcriptionally added chemical moieties (e.g., methyl/adenosyl groups) on RNA, serving as critical regulators of RNA stability, localization, and translational efficiency. These epitranscriptomic modifications dynamically regulate RNA function, influencing not only the aforementioned processes but also messenger RNA (mRNA) splicing, interactions with RNA-binding proteins (RBPs), and other forms of molecular crosstalk.<sup>14</sup>

Within the diverse landscape of epitranscriptomic modifications, N6-methyladenosine (m6A) is recognized as the predominant and extensively characterized internal chemical alteration occurring on mammalian mRNA. Notably, its deposition exhibits a distinct spatial bias, displaying pronounced enrichment in specific genomic contexts, particularly within the vicinity of translational termination signals (stop codons) and across extended internal exonic regions.<sup>15</sup> As an evolutionarily conserved epitranscriptomic modification, m6A exhibits a broad

phylogenetic distribution, detectable in species as evolutionarily distant as viruses and *Saccharomyces cerevisiae* (yeast), extending through plants and *Mus musculus* (mice) to *Homo sapiens* (humans).<sup>2,16</sup>

Beyond mRNA, m6A also occurs in various other RNA species, including ribosomal RNA, transfer RNA (tRNA), small nuclear RNA, microRNA (miRNA), long non-coding RNA (lncRNA), and circular RNA (circRNA).<sup>2,17,18</sup> The m6A modification acts as a key regulator, significantly modulating core functions in RNA metabolism: the control of transcript stability, the accuracy of splicing events, the efficiency of RNA transport and localization, and the rate of protein synthesis (translation).<sup>19</sup> Precise control over m6A RNA modification is achieved through a coordinated interplay of three functionally specialized protein families: writers (methyltransferases that install the m6A mark), erasers (demethylases that reverse this modification by erasing the methyl group), and readers (effector proteins that decode the m6A signal through specific binding and ultimately govern its impact on RNA metabolism and gene expression).<sup>20</sup> Collectively, these writer proteins, eraser proteins, and reader proteins dynamically and reversibly modulate m6A deposition and interpretation, thereby influencing nearly all aspects of RNA metabolism. This intricate regulatory system serves key functions in governing basic cellular processes, including cell growth, differentiation, tissue homeostasis, and contributes significantly to disease pathogenesis, including cancer.<sup>21</sup>

While present ubiquitously, m6A modification is exceptionally abundant and functionally critical in the brain,<sup>22</sup> where it regulates key processes such as embryonic stem cell differentiation, brain development, and neurodevelopmental disorders.<sup>23</sup> Accumulating evidence demonstrates dysregulation of m6A regulators (writers, erasers, and readers) in glioma, with distinct expression patterns observed between normal brain tissue and glioma tissues.<sup>24</sup> These dysregulated m6A regulators contribute to gliomagenesis and progression by modulating diverse oncogenic pathways, including cell proliferation, apoptosis, cancer stem cell maintenance, and tumor immunity.<sup>25,26</sup> Consequently, targeting the m6A modification machinery represents a promising avenue for novel glioma therapies. Therefore, a comprehensive understanding of m6A dysregulation and its functional mechanisms in glioma is essential for elucidating disease pathogenesis and formulating effective therapeutic strategies.

## 2. Enzymes related to m6A modification

### 2.1. Writers—methyltransferase

Writers orchestrate site-directed methylation at the N6 position of adenosine nucleotides in specific RNA

molecules. Specifically, this reaction involves the enzymatic transfer of a methyl group ( $-\text{CH}_3$ ) provided by the cofactor S-adenosylmethionine, followed by its covalent attachment to the target adenine base.<sup>27</sup> Subsequently, the installed m6A modification serves as a dynamic post-transcriptional regulator influencing structural features and biological activities of RNA. Notably, the catalytic core is embodied by the methyltransferase-like protein (METTL3)–METTL14 heterodimer.<sup>26</sup> METTL3 provides substrate recognition and methyltransferase activity while METTL14 stabilizes RNA binding and optimizes METTL3's catalytic conformation.<sup>28</sup> Collectively, this complex controls key cellular activities, such as proliferation, differentiation, and stress responses.<sup>29</sup> Furthermore, the core further associates with regulatory subunits (e.g., Wilms tumor 1-associated protein, RNA binding motif protein 15/15B, Vir-like m6A methyltransferase associated, Cbl proto-oncogene-like 1, and zinc finger CCHH-type containing 13 [ZC3H13]) that mediate target RNA recruitment and subcellular localization.<sup>30</sup> In essence, these components ensure spatiotemporally precise m6A deposition, which is essential for regulating RNA metabolism in physiological and pathological contexts.<sup>31</sup>

## 2.2. Erasers—demethylase

Counteracting writer activity, m6A erasers dynamically remove methyl groups to maintain RNA modification homeostasis. The two principal erasers are fat mass and obesity-associated protein (FTO) and AlkB homolog 5, RNA demethylase (ALKBH5).<sup>20</sup> Functioning as  $\alpha$ -ketoglutarate-dependent dioxygenases, they catalyze m6A demethylation in an Fe(II)- and  $\alpha$ -ketoglutarate-dependent oxidation reaction.<sup>32,33</sup> Mechanistically, the enzymatic process proceeds through three steps: (i) Oxidation of m6A to N6-hydroxymethyladenosine (hm6A); (ii) Further oxidation of hm6A to N6-formyladenosine (f6A); (iii) Hydrolysis of f6A to yield unmodified adenosine (A).<sup>33</sup> Notably, dysregulation of these erasers disrupts m6A-dependent RNA regulation, contributing to diseases such as glioma.

## 2.3. Readers—m6A-binding protein

Completing the m6A regulatory triad, readers specifically recognize m6A marks and decode their functional implications. Following methylation by writers, readers bind these sites and recruit effector complexes to govern RNA processing outcomes—from nucleocytoplasmic transport and stability maintenance to translational regulation and catabolism.<sup>31</sup> Readers constitute a class of RBPs that harbor m6A-specific recognition domains.<sup>14</sup> Major reader families include:

- (i) YTH domain-containing proteins (YTHDC): Cytoplasmic effectors (YTH domain-containing

family protein [YTHDF]1, YTHDF2, and YTHDF3) and nuclear regulators (YTHDC1 and YTHDC2)<sup>14,28</sup>

- (ii) Non-YTH-domain readers: Heterogeneous nuclear ribonucleoprotein (HNRNP)C, HNRNPG, HNRNPA2B1, insulin-like growth factor 2 mRNA-binding protein (IGF2BP)1, IGF2BP2, IGF2BP3, and fragile X mental retardation 1 protein.<sup>34</sup>

By adjusting the activity or expression level of readers, the recognition and functional regulation of m6A modifications can be altered, thus influencing the onset and progression of diseases (Figure 1).

The close cooperation and precise regulation among these three types of proteins enable m6A modifications to perform their vital physiological functions in cells. These three factors serve as the fundamental pillars of the m6A modification mechanism, each indispensable in building the intricate network of m6A modifications. However, dysfunction in any part of this process—such as functional abnormalities or expression dysregulation of the involved proteins—can lead to abnormal accumulation or loss of m6A modifications. This disrupts cellular homeostasis and can trigger a series of diseases. Therefore, precise regulation of m6A modification is vital for maintaining cellular homeostasis and preventing disease.

## 3. The effect of downstream signals modified by m6A on glioma

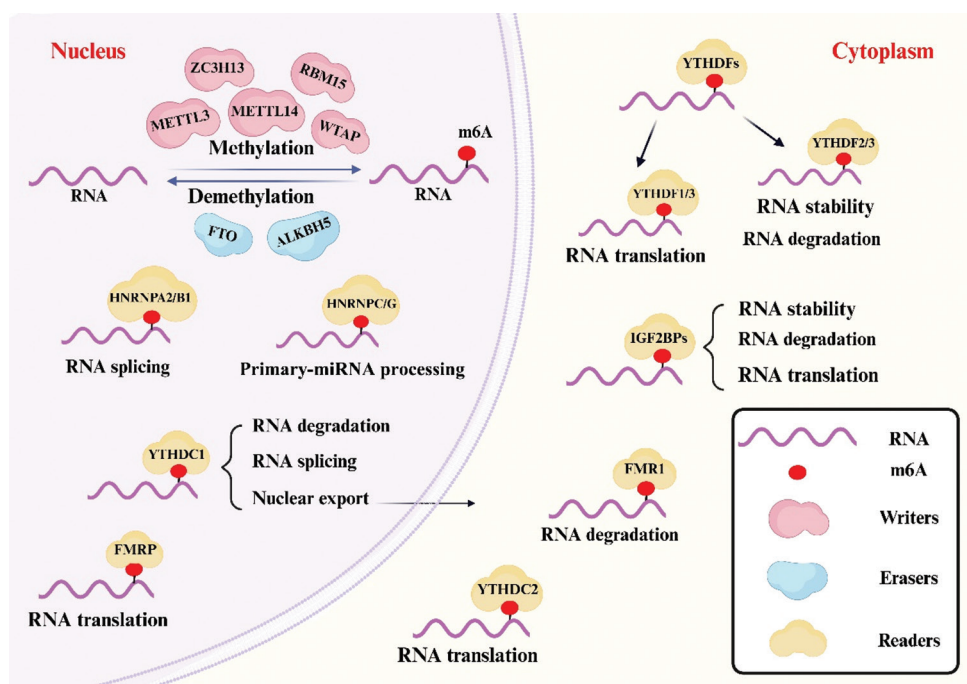
The modification of RNA represents a critical regulatory mechanism contributing to the onset and development of glioma, including m6A, m1A, m5C, m7G, hm5C, and pseudouridine modifications.<sup>35,36</sup> Functioning as the cardinal epitranscriptomic mark, m6A modification manifests unparalleled prevalence in eukaryotic RNAs, where it is enzymatically installed co-transcriptionally as an internal adenine alteration—a process demonstrating remarkable conservation spanning over 500 million years of evolutionary history.<sup>37</sup> Here, we summarize the effects of various RNAs modified by m6A-related enzymes on glioma (Figure 2).

### 3.1. mRNAs

The generation of m6A within mRNA constitutes the most prevalent form of intrinsic alteration that occurs within this class of RNA,<sup>38</sup> and different m6A mRNAs have varying effects on various aspects of glioma.

#### 3.1.1. Ferroptosis suppressor protein 1 (FSP1) mRNA

FSP1 functions as a primary regulator of ferroptosis, a distinctive mode of regulated cellular demise driven by iron-dependent oxidative damage culminating in membrane rupture.<sup>39</sup> Researchers have found that stress-related signals



**Figure 1.** The dynamic and reversible process of N6-methyladenosine (m6A) modification. The m6A modification is dynamically and reversibly regulated by three types of enzymes: methyltransferases, demethylases, and m6A-binding proteins.<sup>20,21</sup> Methyltransferases include methyltransferase-like protein (METTL3), METTL14, Wilms tumor 1-associated protein (WTAP), RNA binding motif protein 15 (RBM15), and zinc finger CCCH-type containing 13 (ZC3H13).<sup>28-30</sup> Demethylases include fat mass and obesity-associated protein (FTO) and AlkB homolog 5, RNA demethylase (ALKBH5).<sup>32,33</sup> After RNA is modified by methylation, YTH family proteins, insulin-like growth factor 2 mRNA-binding protein (IGF2BP) family proteins, and heterogeneous nuclear ribonucleoproteins (HNRNPs) can specifically bind to m6A-modified RNA, thereby further participating in the regulation of various RNA functions, including nuclear export, degradation, stability, and translation.<sup>14,28,34</sup> Image created using BioRender.com. Tyt (2025) <https://BioRender.com/v54b788>. Abbreviations: FMR1: Fragile X mental retardation 1; FMRP: Fragile X mental retardation protein; YTHDC: YTH domain-containing protein; YTHDF: YTH domain-containing family protein.

can promote glioma progression via METTL3-mediated m6A modification of *FSP1* mRNA.<sup>40</sup> METTL3 promotes methylation modification of *FSP1* mRNA in the U251 human GBM cell line, which can be recognized by YTHDF1. The elevation of *FSP1* inhibits the occurrence of ferroptosis and promotes further deterioration of U251 (Table 1).<sup>40</sup>

### 3.1.2. Glutathione peroxidase 4 (GPX4) mRNA

Ferroptosis, a type of regulated cellular demise, is fueled by the peroxidation process of phospholipids.<sup>41</sup> GPX4 serves as a key inhibitory factor in ferroptosis, making a substantial contribution to preventing this process by eliminating phospholipid hydroperoxides.<sup>42</sup> According to Deng *et al.*,<sup>43</sup> IGF2BP3 selectively engages m6A deposition sites on *GPX4* mRNA in U87, U251, and HS683 cells, positively regulating the expression of GPX4 protein to inhibit ferroptosis in glioma.

### 3.1.3. mind bomb homolog 1 (MIB1) mRNA

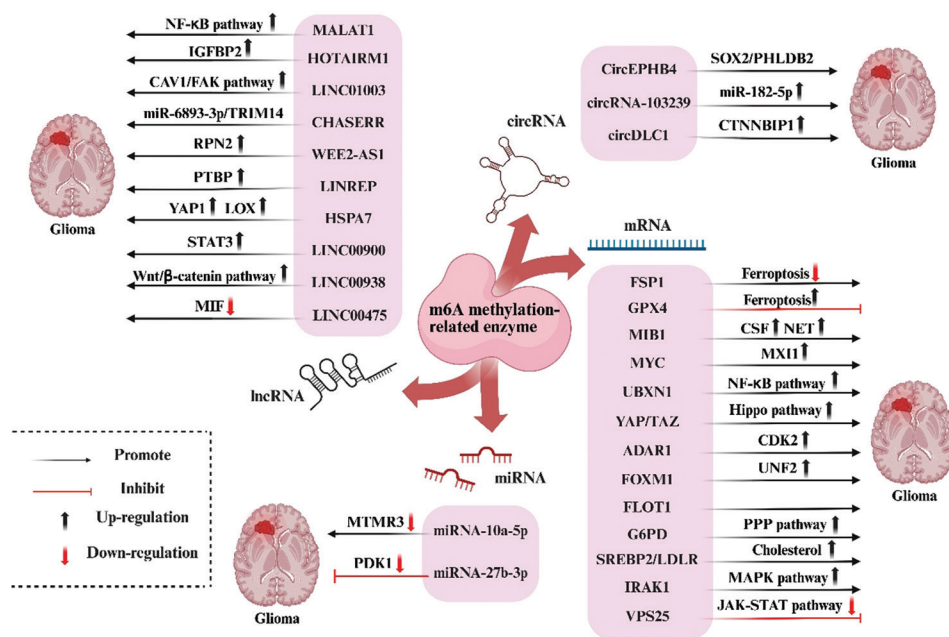
Functioning as an E3 ubiquitin ligase, MIB1 modulates neurodevelopmental processes through targeted protein ubiquitination.<sup>44</sup> In U87, GL261, U251, and T98G, IGF2BP3

can enhance the expression of MIB1 and promote FTO protein degradation through the ubiquitin proteasome pathway, leading to m6A-mediated upregulation of granulocyte colony-stimulating factor (CSF3) expression and increased neutrophil extracellular trap (NET) formation.<sup>45</sup> CSF3 contributes to the maturation and mobilization of neutrophils and can promote the formation of NETs.<sup>45,46</sup> Research indicates that the formation of NETs can stimulate the growth, movement, and infiltration of LN229 and HG7 cell lines.<sup>47</sup> On the other hand, NETs can also induce thrombosis in glioma patients, who may experience thrombotic complications.<sup>48</sup>

### 3.1.4. MYC mRNA

*MYC* is among the most frequently misregulated genes found in cancerous conditions, consisting of three similar genes: *MYCC*, *MYCN*, and *MYCL*.<sup>49</sup> As a validated tumor suppressor, max-interacting protein 1 (MXI1) operates through competitive blockade of C-MYC-mediated transcriptional activation.<sup>50</sup> Xiao *et al.*<sup>7</sup> discovered that FTO enhances the translational efficiency of *MYC* through an m6A-mediated mechanism and inhibits the expression





**Figure 2.** The mechanism of m6A modification-related enzymes affecting glioma. In glioma, m6A modification-related enzymes<sup>35</sup> can affect signaling pathways or metabolic processes by influencing the methylation modification process of messenger RNA, long non-coding RNA, circular RNA, and microRNA,<sup>36,37</sup> ultimately promoting or inhibiting the development of glioma.<sup>25,26,38</sup> Image created by the authors using BioRender.com. Tyt (2025) <https://biorender.com/m85k820>.

of MXI1 through the MYC-miR-155/23a cluster-MXI1 loop, thereby promoting the proliferation of U87, U251, and A172. Another study found that YTHDF2 directly binds to MYC mRNA and m6A-dependent stabilizes this mRNA, thereby promoting MYC protein production. Subsequently, MYC exerts its influence on the survival and growth of GBM stem cells (GSCs) by modulating the abundance of IGFBP3 (Table 2).<sup>51</sup>

### 3.1.5. *UBX domain-containing protein 1 (UBXN1) mRNA*

UBXN1 functions as a suppressive factor by disrupting nuclear factor-kappa B (NF-κB) inhibitor alpha degradation-dependent NF-κB activation.<sup>52</sup> In U87, LN229, and N33, YTHDF2 accelerates the degradation of *UBXN1* mRNA by specifically identifying the m6A site, thereby activating the NF-κB signaling pathway.<sup>53</sup> Soon after, NF-κB activation transcriptionally elevates epithelial-mesenchymal transition (EMT) markers (cluster of differentiation [CD]44, vimentin, and N-cadherin), which subsequently drive signal transducer and activator of transcription 3 (STAT3) phosphorylation, CCAAT/enhancer-binding protein beta (CEBPB) nuclear translocation, and transcriptional coactivator with PDZ-binding motif (TAZ) co-activation. This ultimately contributes to the enhancement of glioma invasion, angiogenesis, and resistance to therapeutic interventions.<sup>53</sup>

### 3.1.6. *YAP/TAZ mRNA*

YAP and TAZ are homologous genes to the fruit fly Yorkie and are two co-transcriptional regulatory factors in the Hippo signaling pathway, commonly activated in human malignant tumors.<sup>54,55</sup> In GSCs, IGFBP1 induces yes-associated protein (YAP) translation by identifying and associating with m6A-modified YAP mRNA, thereby activating the Hippo signaling pathway. During this process, TAZ can also enhance the transcription level of *IGFBP1*.<sup>56</sup> Overexpression of YAP/TAZ in U87, U251, and GSCs promotes cell proliferation, tumor formation, chemotherapy resistance, and radiation resistance, thereby encouraging the emergence and spread of glioma (Table 3).<sup>57,58</sup>

### 3.1.7. *Adenosine deaminase acting on RNA-1 (ADAR1) mRNA*

ADAR1 is a ubiquitously expressed RNA deaminase that mediates the conversion of adenosine to inosine at designated locations within target RNAs through a deamination process.<sup>59,60</sup> Cyclin-dependent kinase (CDK) 2 is a governing factor of the cell cycle involved in regulating a series of oncogenic signaling pathways that control cancer cell proliferation.<sup>61</sup> In U87 and U118, after METTL3 methylates *ADAR1* mRNA, YTHDF1 stimulates the translation of *ADAR1* mRNA. Subsequently, ADAR1 binds to and stabilizes *CDK2* mRNA through its

Table 1. The mechanisms of writers in glioma

Writers	Molecules	Related mechanism	Experimental samples	Biological outcomes	References
METTL3	<i>FSP1</i> mRNA	METTL3/YTHDF1+ <i>FSP1</i> mRNA → <i>FSP1</i> protein ↑ → Ferroptosis ↓	U251	Ferroptosis ↓	40
	<i>MYC</i> mRNA	METTL3/YTHDF2+ <i>MYC</i> mRNA → <i>MYC</i> protein ↑ → IGFBP3 ↑	GSCs	GSC vitality ↑ Colony-forming ability ↑ Proliferation ↑	51
	<i>UBXN1</i> mRNA	METTL3/YTHDF2+ <i>UBXN1</i> mRNA → <i>UBXN1</i> mRNA ↓ → NF-κB signaling pathway ↑ → CD44, vimentin, N-cadherin ↑ → STAT3/CEBPB/TAZ activation ↑	U87, LN229, N33	Invasion ↑ Angiogenesis ↑ Treatment resistance ↑	53
	<i>ADAR1</i> mRNA	METTL3/YTHDF1+ <i>ADAR1</i> mRNA → <i>ADAR1</i> protein ↑ → CDK2 ↑	U87, U118	Proliferation ↑	62
	<i>LDLR</i> mRNA <i>SREBP2</i> mRNA	METTL3/HNRNPA2B1+ <i>LDLR</i> mRNA, <i>SREBP2</i> mRNA → <i>LDLR</i> protein, <i>SREBP2</i> protein ↑; <i>SREBP2</i> protein → <i>LDLR</i> protein, <i>HMGCR</i> ↑ → Cholesterol homeostasis ↑	U251, U118, NCH421K, NCH644	Cholesterol homeostasis ↑ Glioma cell stemness ↑	72
	<i>VPS25</i> mRNA	METTL3/YTHDC1+ <i>VPS25</i> mRNA → <i>VPS25</i> protein ↓ → p-JAK1, p-STAT1 ↓ → JAK-STAT signaling pathway ↓	U87, U251	Proliferation ↓	74
	LncRNA <i>MALAT1</i>	METTL3/HuR+LncRNA <i>MALAT1</i> → LncRNA <i>MALAT1</i> expression ↑ → NF-κB signaling pathway ↑	U87, LN229, N33	Proliferation ↑ Invasion ↑ Migration ↑ Apoptosis ↓	76,77
	LncRNA <i>HOTAIRM1</i>	METTL3+LncRNA <i>HOTAIRM1</i> → LncRNA <i>HOTAIRM1</i> stability ↑ → IGFBP2 ↑	U87, U251	Vascular mimicry ↑	79
	LINC01003	METTL3+LINC01003 → LINC01003 expression ↑ → CAV1, p-FAK ↑	U87, U251	Proliferation ↑ Migration ↑	84
	LncRNA <i>CHASERR</i>	METTL3/YTHDC1+LncRNA <i>CHASERR</i> → LncRNA <i>CHASERR</i> expression ↑; LncRNA <i>CHASERR</i> +miR-6893-3p → TRIM14 ↑ → AKT/mTOR/P70S6K signaling pathway, Wnt/β-catenin signaling pathway ↑	T98G, A172	Proliferation ↑ Invasion ↑ Migration ↑	88
	LncRNA <i>WEE2-AS1</i>	METTL3/IGF2BP3+LncRNA <i>WEE2-AS1</i> → LncRNA <i>WEE2-AS1</i> expression ↑ x LncRNA <i>WEE2-AS1</i> +RPN2 → RPN2 expression ↑ → xpressKT signaling pathway ↑	U251, U118, A172, LN229, GSC20, GSC267	Proliferation ↑ Invasion ↑ Migration ↑	89
	LncRNA <i>LINREP</i>	METTL3+LncRNA <i>LINREP</i> → PTBP1 degradation ↓ → egradati of exon 3 in <i>RTN4</i> transcript ↑ → <i>RTN4B</i> ↑	U87, U251, T98G	Proliferation ↑ Invasion ↑ Migration ↑	90
	LINC00839	METTL3/YTHDF2+LINC00839 → LINC00839 expression ↑ → c-Src-mediated β-catenin phosphorylation ↑ → Wnt/β-catenin signaling pathway ↑	GSCs	Stem cell characteristics ↑ Radiation resistance ↑	94
	LINC00475	METTL3/HNRNPH 1+LINC00475 → LINC00475-S ↑ → MIF ↓ → Mitochondrial fission ↑	U251, U87, U138	Mitochondrial fission ↑ isroliferation ↑ Migration ↑	95
	CircEPHB4	METTL3/YTHDC1+CircEPHB4 → Cytoplasmic localization of CircEPHB4 ↑ → Binding of CircEPHB4 to <i>IGF2BP2</i> and <i>SOX2</i> mRNA in cytoplasm ↑ → <i>SOX2</i> protein ↑ → PHLDB2 ↑	SHG44, A172	Proliferation ↑ Stem cell characteristics ↑ haigration ↑	101
	circDLC1	METTL3+circDLC1 → circDLC1 expression ↑ → Binding of circDLC1 to miR-671-5p ↑ → CTNNBIP1 ↑	LN229, A172	Proliferation ↓	104
	miR-27b-3p	METTL3/DGCR8+pri-miR-27b → miR-27b-3p ↑ → iR-2 ↓	T98G, U251	Proliferation ↓ Aerobic glycolysis ↓	110
METTL4	circRNA_103239	METTL4 ↓ → circRNA_103239 ↓ → miR-182-5p ↑ → MTSS1 ↓ → EMT ↑	A172, U251	Proliferation ↑ Invasion↑Migration ↑ EMT ↑	103

(Cont'd...)

**Table 1. The mechanisms of writers in glioma**

Writers	Molecules	Related mechanism	Experimental samples	Biological outcomes	References
WTAP	<i>FLOT1</i> mRNA	WTAP/IGF2BP2+ <i>FLOT1</i> mRNA → <i>FLOT1</i> protein ↑	U251, T98G, U87, U118	Proliferation ↑ Invasion ↑	68
	LncRNA HSPA7	WTAP+lncRNA HSPA7A EN.C LOX ↑ → Macrophage infiltration, SPP1 ↑ → Immunosuppressive microenvironment ↑	GSCs	Immunosuppressive microenvironment ↑	92

Abbreviations: ADAR1: Adenosine deaminase acting on RNA 1; CAV1: Caveolin 1; CD: Cluster of differentiation; CDK2: Cyclin-dependent kinase 2; CEBPB: CCAAT/enhancer-binding protein beta; CTNNB1: Beta-catenin-interacting protein 1; DGCR8: DiGeorge syndrome critical region 8; EMT: Epithelial-mesenchymal transition; FAK: Focal adhesion kinase; FLOT1: Flotillin 1; FSP1: Ferroptosis suppressor protein 1; GSC: Glioblastoma stem cell; HMGCR: 3-Hydroxy-3-methylglutaryl-CoA reductase; HNRNP: Heterogeneous nuclear ribonucleoprotein; HuR: Human antigen R; IGF2BP3: Insulin-like growth factor 2 mRNA-binding protein 3; IGFBP: Insulin-like growth factor-binding protein; JAK: Janus kinase; LDLR: Low-density lipoprotein receptor; LOX: Lysyl oxidase; METTL: Methyltransferase-like protein; MIF: Macrophage migration inhibitory factor; mTOR: Mammalian target of rapamycin; MTSS1: Metastasis suppressor 1; NF-κB: Nuclear factor kappa B; PDK1: Pyruvate dehydrogenase kinase 1; PHLDB2: Pleckstrin homology-like domain family B member 2; PI3K: Phosphoinositide 3-kinase; PTBP1: Polypyrimidine tract-binding protein 1; RPN2: Ribophorin 2; SPP1: Secreted phosphoprotein 1; SREBP2: Sterol regulatory element-binding protein 2; SOX2: SRY-box transcription factor 2; STAT: Signal transducer and activator of transcription; TAZ: Transcriptional coactivator with PDZ-binding motif; TRIM14: Tripartite motif-containing protein 14; VPS25: Vacuolar protein sorting-associated protein 25; WTAP: Wilms tumor 1-associated protein; YAP1: Yes-associated protein 1; YTHDC: YTH domain-containing protein; YTHDF: YTH domain-containing family protein.

**Table 2. The mechanism of erasers in glioma**

Erases	Molecules	Related mechanism	Experimental samples	Biological outcomes	References
FTO	<i>MYC</i> mRNA	FTO+m6A-modified <i>MYC</i> mRNA → <i>MYC</i> mRNA stability and translation ↑ → <i>MYC</i> protein ↑ → miR-155/23a cluster ↑ → MXI1 ↓	U87, U251, A172	Proliferation ↑ TMZ resistance ↑	7
	miRNA-10a-5p	FTO ↓ → m6A-modified miRNA-10a ↑; HNRNPA2B1/DGCR8+m6A-modified miRNA-10a → miRNA-10a-5p → MTMR3 ↓	U87, LN229, U251, A172, U118	Proliferation ↑ Invasion ↑ Migration ↑	107
ALKBH5	<i>FOXM1</i> mRNA	ALKBH5+m6A-modified <i>FOXM1</i> mRNA → <i>FOXM1</i> mRNA ↑ → <i>FOXM1</i> ↑ → NUF2 ↑ → PI3K/AKT/mTOR signaling pathway ↑	GSCs	Proliferation ↑ Autophagy ↓ TMZ resistance ↑	64,65
	<i>G6PD</i> mRNA	ALKBH5+m6A-modified <i>G6PD</i> mRNA → <i>G6PD</i> mRNA stability and translation ↑ → <i>G6PD</i> protein ↑ → PPP ↑	U87, U251	PPP ↑ Proliferation ↑	71

Abbreviations: ALKBH5: AlkB homolog 5, RNA demethylase; FOXM1: Forkhead box protein M1; FTO: Fat mass and obesity-associated protein; G6PD: Glucose-6-phosphate dehydrogenase; GSC: Glioblastoma stem cell; MTMR3: Myotubularin-related protein 3; mTOR: Mammalian target of rapamycin; MXI1: Max-interacting protein 1; PI3K: Phosphoinositide 3-kinase; PPP: Pentose phosphate pathway; TMZ: Temozolomide.

RNA-binding domains (RBDs), thereby promoting the proliferation of GBM cells.<sup>62</sup>

### 3.1.8. Forkhead box protein M1 (FOXM1) mRNA

As a transcription factor that fosters proliferation, FOXM1 stimulates the progression of the cell cycle during the crucial G1-S and G2-M transitions.<sup>63</sup> In GSCs, ALKBH5 enhances the expression of FOXM1 by removing methyl groups from its newly synthesized transcripts. Meanwhile, the antisense lncRNA of FOXM1 (FOXM1-AS) can promote the interaction between ALKBH5 and the nascent transcripts of *FOXM1*.<sup>64</sup> *FOXM1* is overexpressed and positively correlated with *ALKBH5* expression, which can promote the proliferation and self-renewal ability of GSCs.<sup>64</sup> Furthermore, FOXM1 will specifically attach to the *NUF2* promoter, transcriptionally activating the expression of *NUF2*.

Subsequently, *NUF2* may enhance the tolerance of GBM toward temozolomide (TMZ) treatment through the activation of the phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathway.<sup>65</sup>

### 3.1.9. Flotilin-1 (FLOT1) mRNA

FLOT1 is a scaffold protein for lipid rafts, involved in various signaling pathways, membrane transport, and EMT.<sup>66</sup> In various types of cancers, *FLOT1* has long been considered an oncogene.<sup>67</sup> As the reader of m6A, IGF2BP2 is capable of recognizing and associating with the m6A site of *FLOT1* mRNA, upregulating its expression by maintaining the stability of *FLOT1* mRNA.<sup>68</sup> High expression of *FLOT1* exhibits oncogenic effects by inducing cell growth and invasion, ultimately promoting the progression of GBM.<sup>67,68</sup>

Table 3. The mechanism of readers in glioma

Readers	Molecules	Related mechanism	Experimental samples	Biological outcomes	References
YTHDF1	LINC00900	YTHDF1+m6A-modified LINC00900 → LINC00900 expression ↑ → Binding of LINC00900 to miR-1205 ↑ → STAT3 ↑	GSC-U87, GSC-U250	Vitality ↑ Self-renewal ability ↑ Proliferation ↑	93
IGF2BP1	YAP/TAZ mRNA	TAZ→IGF2BP1 ↑ + m6A-modified YAP mRNA→YAP protein ↑ → Hippo signaling pathway ↑ → TAZ ↑	GSCs	Stem cell characteristics ↑ Colony formation ↑ Proliferation ↑	56
IGF2BP3	GPX4 mRNA	IGF2BP3+m6A-modified GPX4 mRNA → GPX4 protein ↑ → Ferroptosis ↓	U87, U251, HS683	Ferroptosis ↓	42,43
	MIB1 mRNA	IGF2BP3 → MIB1 ↑ → Ubiquitination degradation of FTO → CSF3 ↑ → Formation of NETs ↑	U87, U251, T98G	Formation of NETs ↑ Proliferation ↑ Invasion ↑ Migration ↑	45,47
HNRNPC	IRAK1 mRNA	HNRNPC+m6A-modified IRAK1 mRNA→IRAK1 protein ↑ → MAPK signaling pathway ↑	U87, U251	Proliferation ↑ Invasion ↑ Migration ↑ Stem cell characteristics ↑	73

Abbreviations: FTO: Fat mass and obesity-associated protein; GPX4: Glutathione peroxidase 4; GSC: Glioblastoma stem cell; HNRNP: Heterogeneous nuclear ribonucleoprotein; IGF2BP: Insulin-like growth factor 2 mRNA-binding protein; IRAK1: Interleukin-1 receptor-associated kinase 1; MAPK: Mitogen-activated protein kinase; MIB1: Mind bomb homolog 1; NETs: Neutrophil extracellular traps; STAT3: Signal transducer and activator of transcription 3; TAZ: Transcriptional coactivator with PDZ-binding motif; YAP: Yes-associated protein; YTHDF: YTH domain-containing family protein.

### 3.1.10. G6PD mRNA

The pentose phosphate pathway (PPP), a metabolic pathway distinct from but related to glycolysis, is instrumental in helping cancer cells meet their synthetic metabolic needs and combat oxidative stress.<sup>69</sup> Glucose-6-phosphate dehydrogenase (G6PD) participates in facilitating the PPP and is intimately linked to the regulation of energy metabolism.<sup>70</sup> Liu *et al.*<sup>71</sup> discovered that ALKBH5 may improve the mRNA stability of *G6PD* by eliminating m6A modifications, which subsequently promotes the translation of *G6PD* and activates the PPP, ultimately stimulating the proliferation of U87 and U251.

### 3.1.11. Sterol regulatory element-binding protein 2 (SREBP2)/low-density lipoprotein receptor (LDLR) mRNA

Serving as an m6A-recognizing protein, HNRNPA2B1 facilitates the stability of *SREBP2* and *LDLR* through attachment to *SREBP2* and *LDLR* mRNAs that have undergone m6A modification. Then *SREBP2* induces the production of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) while also promoting the transcription of *LDLR*. Finally, high levels of *LDLR* and *HMGCR* facilitate cholesterol uptake and biosynthesis, which in turn drives the progression of glioma (U251, U118, NCH421K, and NCH644) stemness and malignancy.<sup>72</sup> Therefore, a combined therapy targeting HNRNPA2B1 and cholesterol metabolism may represent a viable method for glioma treatment.

### 3.1.12. interleukin-1 receptor-associated kinase 1 (IRAK1) mRNA

In U251 and U87, researchers observed a decrease in the m6A modification level of *IRAK1* mRNA after knocking

down *HNRNPC*. They further demonstrated that HNRNPC recognizes m6A-modified *IRAK1* transcripts and increases *IRAK1* mRNA stability.<sup>73</sup> Afterwards, high levels of *IRAK1* activate the mitogen-activated protein kinase signaling pathway, promoting the malignant development of glioma.<sup>73</sup>

### 3.1.13. Vacuolar protein-sorting-associated protein 25 (VPS25) mRNA

Research has uncovered the presence of numerous m6A modification sites within the *VPS25* mRNA. However, METTL3 and METTL14 affect the *VPS25* mRNA level but not its protein level. Interestingly, YTHDC1 can regulate the *VPS25* protein level without affecting its mRNA level.<sup>74</sup> By downregulating *VPS25*, YTHDC1 impairs Janus kinase (JAK)-STAT signaling via diminished JAK1/STAT1 phosphorylation. Consequently, this reduces downstream gene expression in the pathway and ultimately inhibits U87 and U251 cells' proliferation.<sup>74</sup>

Within the intricate network of gene expression, m6A assumes a distinct role, profoundly influencing the post-transcriptional regulation of mRNA. This modification mechanism, by delicately regulating the stability and translation efficiency of mRNA, forms a complex network that controls the biological characteristics of tumor cells. Specifically, m6A modification can enhance or weaken the stability of mRNA, determining its half-life within the cell, which in turn affects the expression level of specific genes. Furthermore, it regulates the translation process of mRNA, influencing the rate and spectrum of protein synthesis, which in turn alters critical biological characteristics of glioma cells, including proliferation, migration, invasion, and metabolism.



### 3.2. lncRNAs

Rigorous investigations have elucidated the molecular pathogenesis of glioma, revealing that lncRNAs occupy an essential position in the angiogenesis, invasion, and metastasis of glioma,<sup>75</sup> and their functions are often regulated by epitranscriptomic modifications. Focusing on the glioma context, this work compiles evidence for m6A-modified lncRNAs as potential master regulators of malignancy hallmarks.

#### 3.2.1. lncRNA MALAT1

In U87, LN229, and N33, METTL3 promotes the “longevity” of the lncRNA *MALAT1* by bolstering its stability, which requires the involvement of human antigen R (HuR).<sup>76</sup> Then, upregulated *MALAT1* can activate NF- $\kappa$ B, a critical regulator of cellular stress and DNA damage responses.<sup>77</sup> Its functions include inhibiting apoptosis and promoting migration and invasive cell behaviors related to tumor progression, thereby playing a role in promoting *IDH*-wildtype glioma.<sup>78</sup>

#### 3.2.2. lncRNA HOTAIRM1

Elevated expression of METTL3 in U87 and U251 enhances the m6A modification and maintains the stability of *HOTAIRM1*. As an oncogene, *HOTAIRM1* induces upregulation of insulin-like growth factor-binding protein 2 (*IGFBP2*) by binding to *IGFBP2* mRNA, promoting vascular mimicry (VM) formation and tumor progression.<sup>79,80</sup> VM refers to the “phenotypic transformation into endothelial cells” channels formed by tumor cells through a sequence of alterations, such as their intrinsic deformation and matrix remodeling.<sup>81</sup> Although VM is different from angiogenesis, it can serve as a supplement to ensure tumor blood supply and promote the growth of GSCs and GBM.<sup>82</sup>

#### 3.2.3. LINC01003

Among the members of the caveolin family, caveolin-1 (CAV1) protein stands out as the most abundantly expressed in numerous cancer cells and tumor samples.<sup>83</sup> It stimulates the proliferation of glioma cells and facilitates the VM by modulating the phosphorylation of focal adhesion kinase (FAK).<sup>84</sup> In U87 and U251, METTL3-catalyzed m6A modification contributes to the elevated level of *LINC01003*. The significant upregulation of *LINC01003* enhances the proliferation and migration capabilities by regulating the CAV1/FAK signaling pathway.<sup>84</sup>

#### 3.2.4. lncRNA CHASERR

The AKT/mTOR/p70S6K signaling pathway is implicated in various biological functions.<sup>85,86</sup> Meanwhile, the Wnt/ $\beta$ -catenin signaling is linked to proliferation, apoptosis,

and invasion in GBM.<sup>87</sup> These two signaling pathways are indirectly regulated by the lncRNA *CHASERR*.<sup>88</sup> METTL3-YTHDF1-mediated m6A modification promotes the upregulation of lncRNA *CHASERR*, which activates the AKT/mTOR/p70S6K and Wnt/ $\beta$ -catenin signaling pathways by regulating the miR-6893-3p/tripartite motif-containing protein (TRIM) 14 axis, thereby promoting the growth and migration of T98G and A172.<sup>88</sup>

#### 3.2.5. lncRNA WEE2-AS1

In U251, U118, LN229, A172, GSC20, and GSC267, m6A modification facilitated by METTL3 upregulates the level of *WEE2-AS1*, a process that is dependent on IGF2BP3. Subsequently, high levels of *WEE2-AS1* stabilize the ribophorin 2 (RPN2) protein through the suppression of cullin-2-mediated RPN2 K322 ubiquitination. The stabilization of RPN2 activates the PI3K-AKT signaling pathway, leading to the malignant progression of glioma.<sup>89</sup>

#### 3.2.6. lncRNA LINREP

*LINREP* represents a recently identified lncRNA characterized by m6A modification that engages in interaction with a complex comprising the polypyrimidine tract-binding protein 1 (PTBP1) and HuR proteins, protecting PTBP1 against ubiquitin-proteasome degradation.<sup>90</sup> As the main inhibitory splicing factor of alternative splicing, the protected PTBP1 enhances its mediated alternative splicing events. Reticulon-4 (*RTN4*) is a key splicing target of PTBP1, and its splicing changes affect the proliferation characteristics of U251 and LN229 cells.<sup>91</sup> Furthermore, PTBP1-mediated skipping of exon 3 in the *RTN4* transcript can generate more *RTN4B* (skipped form), and increased levels of *RTN4B* exhibit a link with a more aggressive phenotype in U87, U251, and T98G.<sup>90</sup>

#### 3.2.7. lncRNA HSPA7

As an m6A-regulated lncRNA, *HSPA7* promotes macrophage infiltration and upregulates secreted phosphoprotein 1 (SPP1) expression in GSCs by increasing the level of YAP1 and lysyl oxidase, thereby modulating the immune microenvironment of GSCs.<sup>92</sup> On the other hand, researchers found that knocking down *HSPA7* may improve the efficacy of anti-programmed cell death protein 1 (PD-1) treatment, suggesting *HSPA7* may represent a potential new candidate target for immunotherapy in GSCs.<sup>92</sup>

#### 3.2.8. LINC00900

Zhang *et al.*<sup>93</sup> found that YTHDF1 recognizes and interacts with the m6A modification site present on *LINC00900*, leading to an increase in the stability of *LINC00900*.

Following this, LINC00900 upregulates the level of STAT3 by sponging miR-1205, which enhances the survival and regenerative capacity of GSCs.

### 3.2.9. LINC00839

In GSCs, METTL3-YTHDF2-mediated m6A modification promotes the upregulation of LINC00839, and highly expressed LINC00839 induces Wnt/ $\beta$ -catenin activation through the promotion of c-Src-mediated  $\beta$ -catenin phosphorylation, enhancing the radiation resistance of GSCs.<sup>94</sup>

### 3.2.10. LINC00475

The METTL3 protein is robustly expressed in U251, U87, and U138. It enhances the m6A-dependent association between HNRNPH1 and LINC00475, ultimately leading to the generation of the splicing variant LINC00475-S.<sup>95</sup> Subsequently, LINC00475-S induces mitochondrial fission by downregulating the level of macrophage migration inhibitory factor (MIF), ultimately promoting the development of glioma.<sup>95</sup>

These m6A-modified lncRNAs, as crucial regulatory molecules, modulate the activity of multiple signaling pathways, including those regulating cell proliferation, differentiation, and apoptosis, thereby influencing the malignant phenotypes of glioma cells. Moreover, by targeting specific lncRNAs involved in their regulation, m6A modification indirectly regulates metabolic processes, such as glycolysis. This can either promote energy production or limit the availability of metabolic substrates for glioma cells, thereby promoting or suppressing their malignant phenotypes. Therefore, m6A-orchestrated lncRNA dynamics in glioma constitute a highly intricate regulatory mechanism, offering potential new targets for glioma treatment.

## 3.3. CircRNAs

Circular RNAs—covalently closed non-coding RNAs formed through back-splicing—exhibit topological configurations distinct from linear transcripts, conferring enhanced stability and resistance to degradation that facilitate post-transcriptional regulation and potentially play important roles in gene regulation and cellular processes.<sup>96,97</sup> Specifically, a number of circRNAs control the transcription and translation of peptides and proteins by functioning as miRNA sponges or by interacting with RBPs.<sup>98</sup> They have a strong association with the origin and evolution of glioma.<sup>99</sup> Mechanistically, circRNAs are crucial regulators of glioma cell phenotypes, including migration and cell cycle progression.<sup>100</sup> Given these roles, circRNAs are indispensable for accurate diagnosis, prediction of disease outcomes, and development of effective treatments for glioma.<sup>100</sup>

### 3.3.1. CircEPHB4

Liao *et al.*<sup>101</sup> found that METTL3 upregulates the m6A level of CircEPHB4, then YTHDC1 attaches to the m6A-modified CircEPHB4, promoting its cytoplasmic localization. In the cytoplasm, CircEPHB4 interacts with IGF2BP2, stimulating the growth, metastasis, and stemness of SHG44 and A172 by regulating the SRY (sex determining region Y)-box (SOX)2/pleckstrin homology-like domain family B member 2 (PHLDB2) axis.

### 3.3.2. circRNA\_103239

As an evolutionarily conserved developmental program, EMT is intricately linked to carcinogenesis, equipping cancer cells with metastatic abilities by bolstering their migratory and invasive capabilities, as well as their resistance to apoptotic signals.<sup>102</sup> In A172 and U251, the downregulation of METTL14 leads to reduced levels of methylated circRNA\_103239, inducing the expression of miR-182-5p.<sup>103</sup> Soon afterwards, miR-182-5p inhibits *MTSS1* mRNA expression, resulting in a downregulated level of metastasis suppressor 1 (MTSS1), and ultimately promotes EMT and tumor progression.<sup>103</sup>

### 3.3.3. circDLC1

Notably, Wu *et al.*<sup>104</sup> considered that METTL3 is reduced rather than increased in LN229 and A172—a finding distinct from its common upregulation in other tumor types. In addition, they observed a significant co-expression pattern between METTL3, circDLC1, and beta-catenin-interacting protein 1 (CTNNBIP1). METTL3 facilitates the stabilization of circDLC1 and enhances its expression by catalyzing m6A modification. Then, circDLC1 promotes the expression of the tumor suppressor CTNNBIP1 by binding to miR-671-5p, and high levels of CTNNBIP1 inhibit LN229 and A172 proliferation.

## 3.4. miRNAs

miRNA, minute yet potent endogenous RNA molecules, intricately orchestrate the delicate balance of gene expression following the transcription process.<sup>105</sup> In glioma, miRNAs can influence the formation, proliferation, and apoptosis of tumors, as well as the function of genes regulated post-transcriptionally by anti-cancer genes.<sup>106</sup>

### 3.4.1. miRNA-10a-5p

An analysis conducted by Zhang *et al.*<sup>107</sup> indicated that FTO expression is decreased in GBM (U87, LN229, U251, A172, and U118), and this reduction enhances the m6A methylation of pri-miR-10a. Then, HNRNPA2B1 identifies the modified pri-miR-10a, and subsequently recruits DiGeorge syndrome critical region 8 (DGCR8) to process it, ultimately resulting in the production of mature

miRNA-10a-5p. Eventually, miRNA-10a-5p promotes the progression of GBM malignancy by suppressing the expression of the tumor suppressor protein myotubularin-related protein 3 (MTMR3).

### 3.4.2. miR-27b-3p

Cancer cells, in comparison to their normal counterparts, exhibit not only an elevated rate of glucose uptake but also undergo a metabolic transition, shifting from oxidative phosphorylation toward aerobic glycolysis.<sup>108</sup> Aerobic glycolysis is a crucial component of metabolic reprogramming in glioma, promoting cell proliferation and the development of malignant phenotypes. By inactivating mitochondrial pyruvate dehydrogenase, pyruvate dehydrogenase kinase 1 (PDK1), a pivotal Ser/Thr kinase, effectively redirects glucose metabolism away from mitochondrial oxidation toward aerobic glycolysis.<sup>109</sup> Inhibition of PDK1 expression has been shown to significantly reduce aerobic glycolysis in glioma.<sup>110</sup> Researchers have discovered that METTL3 induces the methylation of pri-miR-27b, which facilitates the recognition and processing of methylated pri-miR-27b by DGCR8, leading to the production of mature miR-27b-3p.<sup>110</sup> The resulting miR-27b-3p can directly inhibit the expression of PDK1, thereby limiting T98G and U251 proliferation and their aerobic glycolysis.

In summary, within the pathogenesis of glioma, RNA methylation modifications—particularly m6A—profoundly influence disease progression. A deeper investigation into m6A's multifaceted mechanisms will not only enhance our thorough comprehension of the nature of this disease but also potentially pave new avenues for glioma treatment. Notably, while the regulatory function of m6A in RNA has garnered considerable attention, relatively limited research has explored the particular impacts of m6A on certain RNA types (such as miRNAs and tRNAs). These RNA molecules play equally crucial roles within cells, and their interactions with m6A may harbor even more intricate regulatory mechanisms. Consequently, future research endeavors should intensify the investigation of these RNA categories to unravel the full extent of m6A's functions and significance in biological systems.

## 4. The effect of upstream signals of m6A on the development of glioma

The m6A modification exerts a substantial influence on the initiation and development of glioma, and key regulators of this process concurrently modulate glioma progression. The abnormal expression and dysregulation of these molecular structures may lead to abnormal proliferation,

invasion, and drug resistance in glioma, thereby affecting the treatment efficacy and prognosis of patients (Table 4).

### 4.1. Proteins

#### 4.1.1. Yin-yang 1 (YY1)

YY1, categorized as a transcription factor, is a widely expressed protein that can activate and inhibit transcription through interactions with other transcription factors and cofactors.<sup>111</sup> In GSCs, YY1 is highly expressed and actively interacts with the promoter region of SUMO-specific protease 1 (SENPI) to promote its transcription. Subsequently, SENPI activates METTL3 catalytic function, augmenting site-specific m6A deposition on MYC transcripts and ultimately amplifying the self-renewal abilities and tumorigenicity of GSCs.<sup>112</sup> Another study found that YY1 interacts with CDK9 and other transcription elongation factors (such as bromodomain-containing protein 4 [BRD4, AF4/FMR2 family member 4 [AFF4, and TRIM28) to form specific transcription elongation complexes that regulate the transcription elongation process in GSCs.<sup>113</sup> Further experiments found that targeting the YY1-CDK9 complex disrupts its normal function, leading to the downregulation of METTL3 and YTHDF2, ultimately resulting in a reduction in m6A modification level, which activates interferon response and enhances antitumor immune response to GSCs.<sup>113</sup>

#### 4.1.2. R-2-hydroxyglutarate (R-2HG)

R-2HG is a metabolite generated by mutant isocitrate dehydrogenase (IDH) enzymes in tumor cells.<sup>114</sup> It mediates the conversion of  $\alpha$ -ketoglutaric acid to 2HG, and subsequently, the buildup of 2HG results in DNA hypermethylation by inhibiting key histone demethylases.<sup>115</sup> In GBM, R-2HG exerts its antitumor activity by targeting the FTO/m6A/MYC/CCAAT/enhancer-binding protein alpha (CEBPA) signaling pathway.<sup>116</sup> Specifically, R-2HG inhibits FTO, thereby increasing the abundance of intracellular m6A RNA modification, which further destabilizes the MYC and CEBPA transcripts, resulting in the downregulation of their expression.<sup>117</sup> The decrease in CEBPA reduces cell growth, and the reduction of MYC results in the downregulation of the MYC signaling pathway, ultimately inhibiting the expansion of the cancer cell population.<sup>117</sup>

#### 4.1.3. c-MYC

The c-MYC proto-oncogene protein, an integral part of the MYC family, is essential for regulating cell cycle progression, proliferation, apoptosis, and cell transformation.<sup>118</sup> Li *et al.*<sup>119</sup> revealed that c-MYC is an upstream regulator of YTHDF1, while ferredoxin 1 (FDX1) is a downstream target of YTHDF1. High levels of c-MYC enhance FDX1

Table 4. The role of molecules regulating the m6A methylation process in glioma

Molecules	Role in glioma	Related mechanism	Experimental samples	Biological outcomes	References
Protein					
YY1	Promote	YY1 → SENP1 ↑ → METTL3 functional activity ↑ → MYC ↑	GSCs in nude mice, GSCs cultured <i>in vitro</i>	Self-renewal capacity ↑ Tumorigenicity ↑	112
	Promote	YY1-CDK9 ↓ → METTL3, YTHDF2 ↓ → Interferon response ↑	GSCs (e.g., GSC1517, GSC23)	Proliferation ↑ Self-renewal capacity ↑ Antitumor immune response ↓	113
R-2HG	Inhibit	R-2HG → FTO/m6A/MYC/CEBPA pathway ↓	GBM cell line of wild type <i>IDH1/2</i> (e.g., U87, GAMG, T98G)	Proliferation ↓ Drug resistance ↓	116,117
C-MYC	Promote	C-MYC → YTHDF1 ↑ → FDX1 ↑	A172, U251	Proliferation ↑ Invasion ↑ Cuproptosis ↓ Mitophagy ↓	119
EGFR	Promote	EGFR → YTHDF2 ↑ → LXRα, HIVEP2 ↓	GSCs (e.g., GSC11, GSC7-2), GBM (LN229, U87, U251 and T98G)	Proliferation ↑ Invasion ↑ Cholesterol accumulation ↑	122
	Promote	EGFR → ALKBH5 nuclear retention ↑ → GCLM ↑	GSC1919, MES20	Ferroptosis ↓ Proliferation ↑	123,124
SRSF7	Promote	SRSF7 → METTL3 targeted recruitment ↑ → PBK ↑	U87, LN229	Proliferation ↑ Invasion ↑	125
PDGF	Promote	PDGF → EGR1 ↑ → METTL3 ↑ → OPTN ↓	GSC1919, GSC20	Self-renewal capacity ↑ Proliferation ↑ Mitophagy ↓	126,127
EZH2	Promote	EZH2 → miR-454-3p ↓ → YTHDF2 ↑ → PTEN ↓	A172, nude mice	M2 macrophage polarization ability ↑ Immune evasion ↑ Proliferation ↑	129,131
JMJD1C	Inhibit	JMJD1C → miR-302a ↑ → METTL3 ↓ → SOCS2 ↑	LN-229, U251, nude mice	M1 macrophage polarization ability ↑ Proliferation ↓	133,134
LATS2	Promote	LATS2 → Phosphorylated ALKBH5 in nucleus ↑ → LATS2 stability ↑	TPC1115, GL261	Self-renewal capacity ↑ Proliferation ↑ Invasion ↑ EMT ↑	135
p53	Promote	Mutant p53/SVIL/MLL1 complex → YTHDF2 ↑ → CDKN2B, SPOCK2 ↓	LFS iPSC-derived astrocytes, LN2308	Cancer transformation and proliferation ↑ Stem cell-like properties ↑	136
SETD2	Promote	SETD2 → METTL3, METTL14, WTAP ↑	LN229	Proliferation ↑ Metastatic potential ↑ Colony-forming ability ↑	138
LncRNA					
SNAI3-AS1	Inhibit	SNAI3-AS1 → Binding of SND1 and <i>NRF2</i> mRNA ↓ → <i>NRF2</i> ↓	U87MG, U251, A172	Ferroptosis ↑ Proliferation ↓ Invasion ↓ Metastatic potential ↓	139,140
AF127577.4	Inhibit	AF127577.4-ORF → Interaction between ERK2 and METTL3 ↓ → p-ERK ↓ → METTL3 ↓	LN229, U251	Proliferation ↓	142
JPX	Promote	JPX → Targeted binding ability of FTO ↑ → PDK1 ↑	LN229, U251	Aerobic glycolysis ↑ Proliferation ↑ TMZ resistance ↑ DNA damage repair ↑ Apoptosis ↓	143
miRNA					
miR-145	Promote	miR-145 ↑ → FTO/AGO1/ILF3/ miR-145 complex ↑ → Demethylation mediated by FTO ↑ → CLIP3 ↑	GBM1, GBM2, GBM3	Stem cell-like properties ↓ Overall translation efficiency ↑	144,145

(Cont'd...)



Table 4. (Continued)

Molecules	Role in glioma	Related mechanism	Experimental samples	Biological outcomes	References
miR-1208	Inhibit	miR-1208→METTL3 ↓ → NUP214 ↓ → p-Smad2/3 nuclear transport ↓ → TGF-β signaling pathway ↓	U251, U373	Proliferation ↓ Invasion ↓ Apoptosis ↑	146,147
miR-200c-3p	Promote	miR-200c-3p→ZC3H13 ↓ → DUSP9 ↓ → ERK1/2 phosphorylation ↑ → M2 polarization of microglia ↑	BG5, BG7	Tumor growth ↑ M2 polarization of microglia ↑ Neuronal activity and extracellular vesicle release ↑	148

Abbreviations: AGO1: Argonaute RISC catalytic component 1; ALKBH5: AlkB homolog 5, RNA demethylase; CDK9: Cyclin-dependent kinase 9; CDKN2B: Cyclin-dependent kinase inhibitor 2B; CEBPA: CCAAT/enhancer-binding protein alpha; CLIP3: CAP-GLY domain-containing linker protein 3; DUSP9: Dual specificity phosphatase 9; EGFR: Epidermal growth factor receptor; EGR1: Early growth response 1; EMT: Epithelial-mesenchymal transition; ERK2: Extracellular signal-regulated kinase 2; EZH2: Enhancer of zeste homolog 2; FDX1: Ferredoxin 1; FTO: Fat mass and obesity-associated protein; GCLM: Glutamate-cysteine ligase modifier subunit; HIVP2: Human immunodeficiency virus type I enhancer binding protein 2; ILF3: Interleukin enhancer binding factor 3; JMJD1C: Jumonji domain-containing 1C; LATS2: Large tumor suppressor kinase 2; LXRα: Liver X receptor alpha; METTL: Methyltransferase-like protein; MLL1: Mixed-lineage leukemia 1; NRF2: Nuclear factor erythroid 2-related factor 2; NUP214: Nucleoporin 214; OPTN: Optineurin; PBK: PDZ-binding kinase; PDGF: Platelet-derived growth factor; PDK1: Pyruvate dehydrogenase kinase 1; PTEN: Phosphatase and tensin homolog; R-2HG: R-2-hydroxyglutarate; SENP1: SUMO-specific peptidase 1; SETD2: SET domain containing 2; SOCS2: Suppressor of cytokine signaling 2; SPOCK2: Secreted protein acidic and rich in cysteine-related modular calcium-binding 2; SRSF7: Serine/arginine-rich splicing factor 7; SVIL: Supravillin; TGF-β: Transforming growth factor beta; TMZ: Temozolomide; WTAP: Wilms tumor 1-associated protein; YTHDF: YTH domain family proteins; YY1: Yin yang 1; ZC3H13: Zinc finger CCCH-type containing 13.

expression through the upregulation of YTHDF1, which in turn maintains the proper function of the respiratory chain by modulating the tricarboxylic acid cycle. This impedes the occurrence of mitophagy and fosters the malignant phenotype of A172 and U251.

#### 4.1.4. Epidermal growth factor receptor (EGFR)

As a prototypical receptor tyrosine kinase (EGFR; ~170 kDa) undergoes ligand-induced dimerization through its extracellular domain, transmembrane  $\alpha$ -helix, and intracellular kinase domain to initiate downstream oncogenic signaling. It belongs to the ErbB/HER receptor tyrosine kinase family, and like other members of this family, it plays a pivotal role in cell signaling and regulation.<sup>120</sup> In pathological contexts such as glioma, notably GBM, numerous alterations in the *EGFR* gene, encompassing amplifications, deletions, and single-nucleotide polymorphisms, have been detected.<sup>121</sup> For example, research has found that EGFR promotes the overexpression of YTHDF2 in GBM and GSCs through the EGFR/SRC/extracellular signal-regulated kinase (ERK) signaling pathway. YTHDF2 binds to and mediates the attenuation of m6A-modified mRNA, thereby downregulating liver X receptor alpha (LXR $\alpha$ ) and human immunodeficiency virus Type I enhancer-binding protein 2 (HIVP2) to promote tumorigenesis in GBM and GSCs.<sup>122</sup> Furthermore, EGFR signaling interferes with the nuclear export of ALKBH5,<sup>123</sup> promoting its demethylase activity, which attenuates the decay of *GCLM* mRNA mediated by YTHDF2, leading to increased synthesis of glutamate-cysteine ligase modifier subunit (GCLM).<sup>124</sup> In the biosynthetic process of glutathione, GCLM is involved

in the first rate-limiting step. The antioxidant function of glutathione inhibits ferroptosis in GSC1919 and MES20.

#### 4.1.5. SRSF7

In the context of GBM cell lines, including U87 and LN229, an upregulation of the serine/arginine-rich splicing factor 7 (SRSF7) has been observed, enhancing the expression of PDZ-binding kinase (PBK). This mechanism requires sequence-specific m6A deposition by METTL3 on *PBK* transcripts, enabling IGF2BP2 binding through its KH domains to stabilize the mRNA via 3' untranslated region (UTR) protection, thereby amplifying the oncogenic phenotype.<sup>125</sup> As a cell cycle-regulated Ser/Thr kinase, PBK overexpression acts as an oncogenic driver to promote tumor progression by enhancing cell proliferation and invasive capacity, particularly in GBM, where it correlates with a poor prognosis.<sup>125</sup>

#### 4.1.6. Platelet-derived growth factor (PDGF)

In GSCs, PDGF upregulates the expression of METTL3 by targeting the transcription factor early growth response 1.<sup>126</sup> METTL3 subsequently modifies the mRNA of the mitochondrial autophagy regulator optineurin (OPTN) through m6A, thereby promoting the degradation of *OPTN* mRNA.<sup>127</sup> The reduction in OPTN expression level results in the inhibition of mitochondrial autophagy in GSCs, thereby promoting the maintenance of cancer stem cells.<sup>126</sup>

#### 4.1.7. Enhancer of zeste homolog 2 (EZH2)

Within the glioma microenvironment, tumor-associated macrophages represent a significant immune cell population.

These macrophages exist primarily in two functionally distinct polarized states: The classically activated (M1-like) subtype, which exhibits antitumor properties and inhibits glioma progression, and the alternatively activated (M2-like) subtype, which displays protumor functions and promotes tumor growth and development.<sup>128</sup> Notably, EZH2 is a key mediator of macrophage activation, and its overexpression is associated with M2 macrophage polarization.<sup>129</sup> Moreover, studies have indicated that EZH2 functions as an oncogene in GBM, promoting cellular proliferation, accelerating cell cycle progression, and concurrently suppressing apoptotic pathways.<sup>130</sup> In A172, EZH2 exerts its protumor effects at least partially by regulating macrophage polarization, specifically by repressing the expression of miR-454-3p, thereby enhancing YTHDF2's ability to interact with *PTEN* mRNA. This interaction leads to a decline in phosphatase and tensin homolog (PTEN) levels. Since PTEN impedes the conversion of macrophages toward the M2 phenotype in the tumor microenvironment, the downregulation of PTEN favors the polarization of monocytes toward M2 macrophages, ultimately promoting A172 growth and immune evasion.<sup>129,131</sup>

#### 4.1.8. Jumonji domain-containing 1C (JMJD1C)

Acting as a histone demethylase specific for H3K9, JMJD1C<sup>132</sup> specifically enhances miR-302a expression through the catalytic removal of the H3K9me1 epigenetic mark located within the miR-302a promoter region.<sup>133</sup> Subsequently, miR-302a inhibits METTL3, suppressing its m6A modification function and consequently promoting the content of suppressor of cytokine signaling 2 (SOCS2). Notably, the SOCS protein family occupies a pivotal position in regulating the polarization of macrophages; thus, the increase in SOCS2 promotes M1 macrophage polarization, which in turn inhibits LN-229 and U251 development.<sup>133,134</sup>

#### 4.1.9. Large tumor suppressor kinase 2 (LATS2)

In glioma patients, the elevated expression of LATS2 and the increased phosphorylation level of ALKBH5 are correlated with the heightened malignancy of tumors. Research has demonstrated that LATS2 can phosphorylate ALKBH5, which prevents the nuclear export of ALKBH5 and enhances its protein stability. In addition, phosphorylated ALKBH5 in the nucleus directs the m6A demethylation of *LATS2* mRNA, preserving its structural integrity and stability.<sup>135</sup> Further experiments confirmed that the lack of LATS2 or ALKBH5 phosphorylation disrupts the ability of GSCs to undergo self-renewal and undermines their tumorigenic potential, indicating that the interaction between LATS2 and ALKBH5 serves as a facilitator of tumor progression in glioma.<sup>135</sup>

#### 4.1.10. p53

Research has found that in patients with *p53*-mutant glioma, mutant p53 specifically upregulates the expression of YTHDF2 by forming a complex with supervillin (SVIL) and mixed-lineage leukemia protein 1. Subsequently, the m6A modification facilitated by YTHDF2 triggers the downregulation of tumor suppressor gene expression, inducing cancerous reprogramming.<sup>136</sup> This is an important mechanism for the oncogenic function of mutant p53.

#### 4.1.11. SET domain-containing 2 (SETD2)

SETD2 is the only histone H3 lysine 36 trimethylation (H3K36me3) trimethylase in eukaryotic cells, and it functions as an inhibitor of cancer development in numerous cancer types.<sup>137</sup> Interestingly, the deposition of m6A in RNA is guided by H3K36me3, and there is a notable positive association between the expression level of SETD2 and m6A-modifying enzymes.<sup>137,138</sup> Therefore, the upregulation of SETD2 results in a comprehensive increase in m6A levels within cellular mRNA and is crucial for the development of LN229.

In the regulatory network of glioma, proteins act as crucial regulators that directly or indirectly influence the m6A modification process, thereby exerting profound impacts on the biological behavior of glioma. To date, several studies have demonstrated that various proteins are key players linking m6A modification to glioma, with a majority of these proteins showing a primary tendency to promote glioma progression. However, the specific mechanisms by which certain proteins modulate m6A modification and glioma remain unclear. Elucidating the precise interaction modes between these proteins and m6A modification, as well as how they collectively regulate the initiation and progression of glioma, will not only help more accurately delineate glioma's molecular mechanisms but also potentially offer mechanistic strategies for precise glioma therapeutics.

### 4.2. LncRNAs

#### 4.2.1. lncRNA *SNAI3-AS1*

*Staphylococcal* nuclease domain-containing protein 1 (SND1) is a well-known RBP that has recently garnered attention for its role as a recognizer or reader of the m6A modification.<sup>139</sup> Specifically, according to Zheng *et al.*,<sup>140</sup> lncRNA *SNAI3-AS1* competitively interacts with SND1, thereby impairing the m6A-dependent recognition of *NRF2* mRNA by SND1. This disruption results in diminished stability of the *NRF2* transcript. As a key orchestrator of antioxidant defenses, the transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) activates a broad array of cytoprotective genes. This transcriptional program

is essential for counteracting oxidative stress and prevents detrimental outcomes, including lipid peroxidation and the iron-dependent form of cell death known as ferroptosis.<sup>141</sup> Consequently, the reduction of NRF2 expression by SNAI3-AS1 promotes ferroptosis in U87, U251, and A172, thereby exerting antitumor activity.<sup>140</sup>

#### 4.2.2. *LncRNA AF127577.4*

In LN229 and U251, the lncRNA AF127577.4 encodes the endogenous micropeptide AF127577.4-ORF.<sup>142</sup> The latter binds to METTL3, leading to a reduction in the interaction between ERK2 and METTL3. This weakens the effect of ERK phosphorylation on METTL3, resulting in decreased stability and content of METTL3.<sup>142</sup> METTL3 has been considered to facilitate the advancement of LN229 and U251; therefore, reduced intracellular METTL3 may diminish overall m6A abundance, inhibiting the proliferation ability of LN229 and U251.

#### 4.2.3. *LncRNA JPX*

In LN229 and U251, just proximal to XIST (*JPX*) promotes the stability of PDK1 by facilitating the FTO-catalyzed demethylation of *PDK1* mRNA, subsequently increasing PDK1 expression.<sup>143</sup> As a rate-limiting enzyme in glycolysis, upregulated PDK1 promotes aerobic glycolysis in tumors, manifested as increased glucose uptake, lactate production, and ATP generation. Further research found that high levels of PDK1 also partially relieve the chemosensitivity to TMZ induced by *JPX* knockdown, suggesting that *JPX* can promote GBM resistance to TMZ through the FTO/PDK1 axis.<sup>143</sup>

### 4.3. miRNAs

#### 4.3.1. *miR-145*

During the differentiation of GSCs into DGCs, miR-145 is significantly upregulated, and it induces the binding of FTO to *CLIP3* mRNA, thereby increasing the nascent translation of *CLIP3* in cells.<sup>144</sup> *CLIP3* is a tumor suppressor gene, and its downregulation can lead to increased translocation of glucose transporter 3 to the cell membrane, thereby enhancing the glycolytic activity and stem-like properties of cancerous cells.<sup>145</sup> Therefore, the impact of miR-145-mediated loss of m6A modification on the nascent translation of *CLIP3* offers a fresh viewpoint and a promising avenue for therapeutic strategies in the treatment of GBM.<sup>144</sup>

#### 4.3.2. *miR-1208*

In a research by Zhan *et al.*,<sup>146</sup> it was unveiled that miR-1208 represses METTL3 expression by specifically binding to the 3' UTR of *METTL3* mRNA. In turn, reduced METTL3 destabilizes *NUP214* mRNA, lowering *NUP214*

expression. Nucleoporin 214 (NUP214) is a constituent of the nuclear pore complex. It plays a vital role in the nuclear export of proteins and mRNA.<sup>147</sup> Furthermore, NUP214 serves as a crucial modulator of the transforming growth factor-beta (TGF- $\beta$ ) signaling cascade. Its decreased content suppresses TGF- $\beta$  signaling, thereby inhibiting the malignant progression of U251 and U373.<sup>146</sup>

#### 4.3.3. *miR-200c-3p*

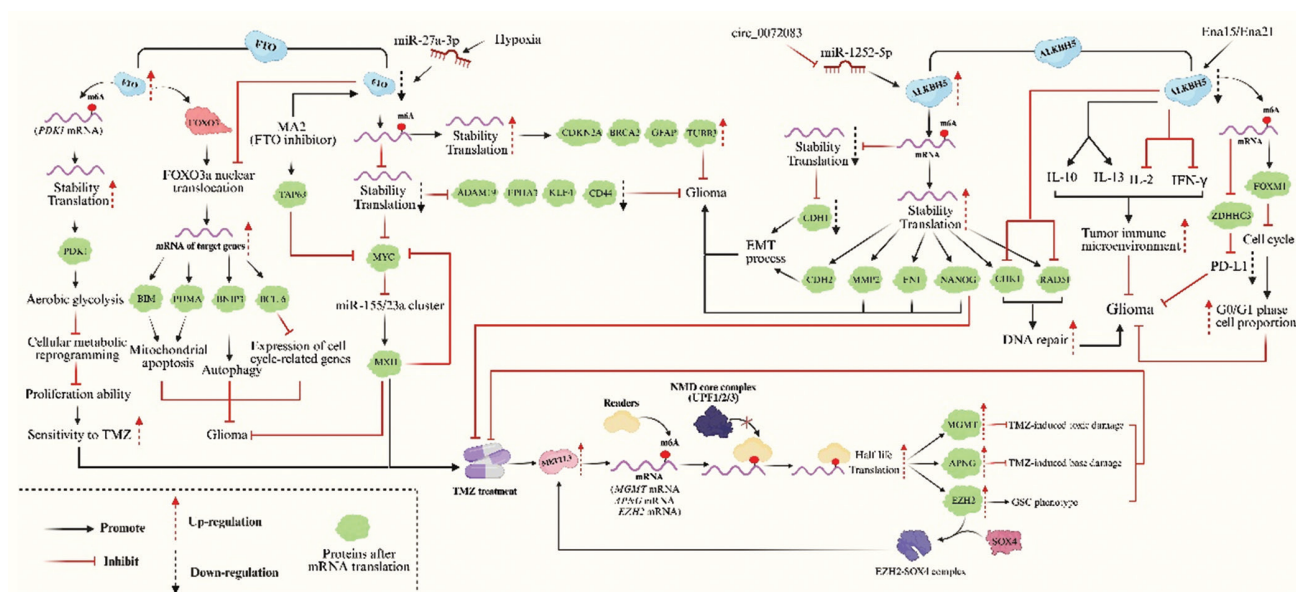
Under hypoxic conditions, BG5 and BG7 cells increase neuronal activity, promoting the release of miR-200c-3p-containing exosomes. In microglia, miR-200c-3p reduces the m6A methylation of *DUSP9* mRNA by downregulating the expression of *ZC3H13*.<sup>148</sup> Functioning as a repressor of the ERK pathway, decreased dual specificity phosphatase 9 (*DUSP9*) expression gives rise to heightened phosphorylation of ERK1/2, thereby triggering the activation of the ERK signaling pathway.<sup>149</sup> Activation of ERK induces M2 polarization of microglia, ultimately fostering the proliferation of BG5 and BG7.<sup>148</sup>

It is evident that in comparison to proteins, a multitude of other molecules with the potential to influence m6A in glioma remain largely unexamined. Furthermore, current research is often constrained by the limited diversity and quantity of experimental samples. The heterogeneity of diseases such as glioma, coupled with inter-individual variations in gene expression, makes it difficult for studies based on single or a few samples to comprehensively reflect the true regulatory landscape of m6A modification. Therefore, to gain a more profound understanding of m6A, researchers need to expand the variety and quantity of experimental samples, striving to encompass a broader spectrum of genetic backgrounds and disease subtypes. Such efforts will facilitate the discovery of additional molecular structures that influence m6A and further elucidate their roles in diseases such as glioma, ultimately providing novel perspectives and strategies for disease diagnosis and treatment.

## 5. Effects of m6A modification on the therapeutic effect of GBM

Glioblastoma is widely recognized as the most lethal subtype of glioma.<sup>7</sup> At present, after maximal surgical resection, radiation therapy combined with TMZ is widely considered the recommended therapeutic approach for newly diagnosed GBM cases.<sup>150</sup> GSCs are the core factor underlying the recurrence of GBM and the failure of TMZ treatment. Endowed with stem cell properties such as self-renewal, GSCs inherently exhibit robust chemoresistance.<sup>151</sup> The significant function of m6A-regulated genes in glioma provides new emerging biomarkers and therapeutic targets for GBM diagnosis and therapy (Figure 3).<sup>152</sup>





**Figure 3.** M6A modification affects the therapeutic effect of glioblastoma (GBM). GBM stem cells (GSCs) are the core cause of GBM recurrence and temozolomide (TMZ) treatment failure, and m6A regulatory genes are potential diagnostic and therapeutic targets.<sup>151,152</sup> Methyltransferase-like protein 3 promotes TMZ resistance by enhancing the m6A modification of genes, such as *MGMT* and *APNG*, thereby forming a positive feedback loop.<sup>27,153,154</sup> Fat mass and obesity-associated protein has a tumor-suppressive effect,<sup>155</sup> and its inhibitor meclofenamic acid 2, can inhibit GSC stemness and enhance TMZ efficacy.<sup>7,156,157</sup> Elevated AlkB homolog 5, RNA demethylase promotes GBM invasion and TMZ resistance, while its silencing or inhibition with Ena15 and Ena21 can suppress cell growth and improve antitumor immunity as well as the efficacy of anti-PD-1 therapy.<sup>156,159-161</sup> Image created using BioRender.com. Tyt (2025) <https://biorender.com/mfoccom>. Abbreviation: EMT: Epithelial-mesenchymal transition.

The *MGMT* and *ANPG* genes are two critical DNA repair genes. After TMZ treatment, the overexpression of *METTL3* significantly enhances m6A methylation and the mRNA levels of *MGMT* and *APNG*, leading to increased resistance of U87 and U251 to TMZ.<sup>153</sup> At the same time, TMZ can increase *METTL3* expression mediated by *SOX4*, then *METTL3* stabilizes the mRNA of histone modification genes (such as *EZH2*) by inhibiting the nonsense-mediated mRNA decay process, thereby regulating histone modification states. More importantly, *EZH2* forms a complex with *SOX4* to regulate *METTL3* expression in an H3K27ac-mediated fashion, creating a positive feedback loop. Therefore, *EZH2* is instrumental in mediating resistance to TMZ therapy in U87 and U251 and is indispensable for maintaining the GSC phenotype.<sup>27,154</sup>

In terms of tumor suppression, FTO can promote the nuclear translocation of forkhead box protein O3a (FOXO3a) and increase the transcription level of its downstream target genes, exerting an antitumor effect in U251 and LN229 by influencing processes such as programmed cell death and proliferation.<sup>155</sup> Regarding drug resistance, FTO can affect the inhibitory effect of TMZ on glioma cells (e.g., U87, U251, LN229).<sup>27</sup> Meclofenamic acid (MA) or its ethyl ester form (MA2) is identified as a specific FTO inhibitor.<sup>156</sup> Treating GSCs with MA2

can inhibit tumorigenesis induced by GSCs and extend the survival duration of mice that have undergone GSC transplantation.<sup>157</sup> Besides, MA2 can downregulate *MYC*, inhibiting U87, U251, and A172 proliferation through the *MYC*-miR-155/23a cluster-*MXI1* feedback loop. Based on the aforementioned research, the researchers speculate that the combination of MA2 and TMZ can enhance the efficacy of TMZ in killing U87, U251, and A172 cells.<sup>7</sup>

In U87, the upregulation of *ALKBH5* enhances invasiveness by regulating the expression of cadherin (*CDH1*), *CDH2*, matrix metalloproteinase-2, and fibronectin 1.<sup>158</sup> In U251, U87, and their TMZ-resistant subtypes, the expression of exosomal circ\_0072083 is significantly increased. circ\_0072083 can upregulate *ALKBH5* expression via competitive engagement with miR-1252-5p and increases the stability of *NANOG* mRNA through the demethylation effect of *ALKBH5*, thereby bolstering the resistance of glioma cells to TMZ.<sup>159</sup> Silencing *ALKBH5* in U87, U251, and GL261 leads to an augmentation in the number of tumor-infiltrating cells, enhancing the antitumor immune response. Simultaneously, the lack of *ALKBH5* impairs the stability of *ZDHHC3* mRNA, which accelerates the degradation of programmed cell death 1 ligand 1 (PD-L1), thereby enhancing the therapeutic effectiveness of anti-PD-1



immunotherapy.<sup>160</sup> GSCs can cause recurrence of GBM, and homologous recombination (HR) is the preferred repair pathway for GSCs.<sup>156</sup> In GSCs (e.g., GC1, GC2), overexpression of ALKBH5 promotes the invasive capacity and resistance to radiotherapy of GSCs by inducing the expression of HR-related genes. Conversely, low levels of ALKBH5 increase the sensitivity of GSCs to radiotherapy and inhibit their invasive capacity.<sup>156</sup> Ena15 and Ena21, two recently discovered inhibitors that exhibit selectivity toward ALKBH5, demonstrate respective inhibition rates of 74% and 53% against this enzyme.<sup>161</sup> These two inhibitors exert their effect by inducing a halt in the cell cycle progression at the G0/G1 phase, leading to a decrease in the cellular population within the S phase. It has been shown that they exert dose-dependent growth inhibition in four GBM cell lines (LN229, KNS81, U87, and U251).<sup>161</sup>

In summary, m6A modification significantly affects the efficacy of therapeutic interventions targeting glioma. The development of inhibitors or agonists that target m6A methyltransferases or demethylases to modulate m6A modification in glioma cells may emerge as an innovative treatment strategy for glioma. Moreover, the combined application of m6A modification-based therapies with other treatment modalities has the potential to yield even better therapeutic outcomes. Through thorough investigation and a comprehensive understanding of the fundamental molecular mechanisms, new strategies and insights for the precise treatment of glioma are expected to be provided.

## 6. Discussion

The high incidence, mortality rate, and complications of glioma have severely threatened human health and quality of life. Therefore, the paramount significance of preventing, promptly detecting, and swiftly treating glioma cannot be overstated.

The m6A modification exerts a sophisticated regulatory influence in glioma. Research to date consistently demonstrates that m6A modification is critically involved in glioma initiation, progression, and malignant transformation, with this modification dynamically orchestrated by methyltransferase (writer), demethylase (eraser), and methyl-binding protein (reader). These three protein groups modulate the proliferation and invasive potential of glioma cells through different mechanisms. Meanwhile, non-coding RNAs (such as miRNA and lncRNA), upstream signaling proteins, and other cellular components can also affect the m6A modification process, thereby exerting corresponding impacts on the progression of glioma. On the other hand, the intricate modification of m6A shows remarkable

potential in improving glioma prognosis, offering a novel avenue for treatment strategies.

However, there are some conflicting studies on the regulatory role of m6A modification in the occurrence, development, and treatment of glioma, which is closely related to the multidimensional nature of cell-line selection, experimental condition settings, and regulatory networks. Taking core regulatory molecules as an example, METTL3 exhibits antitumor effects in specific cell backgrounds by regulating *VPS25* mRNA, *circDLC1*, and *miR-27b-3p* through m6A modification. When it modifies oncogene mRNAs, such as *MGMT* and *EZH2*, or tumor-promoting lncRNAs, such as *MALAT1* and *HOTAIRM1*, it enhances the tumor-promoting effect in more malignant scenarios. This conflict is not experimental bias but is determined by the functional properties of target molecules, heterogeneity of glioma molecular subtypes (such as IDH status), and cellular metabolic characteristics (such as aerobic glycolysis dependence), suggesting that the function of METTL3 needs to be comprehensively judged by specific regulatory networks and tumor microenvironment. Its dual role also provides a segmented approach for precise targeted therapy.

The controversy surrounding the function of another core molecule, FTO, is equally significant. Some studies have shown that FTO can inhibit the proliferation of U251 and LN229 cells and enhance their sensitivity to TMZ by promoting FOXO3a nuclear translocation and downstream apoptosis gene expression.<sup>155</sup> In contrast, other studies have shown that FTO can promote TMZ resistance in U87 and A172 cells by enhancing MYC mRNA stability and activating metabolic reprogramming pathways.<sup>7</sup> The core reason for this conflict lies in the specificity of FTO-targeted genes. As an m6A demethylase, the function of FTO depends on downstream-bound mRNA substrates. When FTO acts on FOXO3a, it exerts antitumor effects by regulating the apoptotic pathway. When targeting oncogenes such as *MYC* and *PDK1*, drug resistance is promoted by enhancing cell proliferation and metabolic adaptability. In addition, differences in the cellular microenvironment exacerbate functional divergence. Under hypoxic conditions, the upregulation of *miR-27a-3p* inhibits FTO expression, while low FTO expression promotes drug resistance by suppressing the FOXO3a pathway. In normoxic or FTO overexpression scenarios, its regulation of MYC and PDK1 is dominant, exhibiting a pro-cancer effect. This bidirectionality is not contradictory, but a typical manifestation of m6A modification of “substrate-dependent function,” suggesting that the role of FTO needs to be comprehensively judged by combining specific regulatory networks with the tumor microenvironment.

The dual role of METTL3 and FTO is not a “functional contradiction” on its own, but an inevitable result of the combined effects of glioma heterogeneity and regulatory network complexity. Simply defining m6A regulatory factors as promoting cancer or inhibiting cancer is overly simplistic and ignores the influence of cellular background, molecular subtypes, and microenvironment, making it difficult to directly translate into clinical plans. From a clinical translation perspective, this conflict provides a breakthrough for precise treatment: in the future, by detecting the molecular characteristics of glioma (such as IDH status and MGMT/FOXO3a expression profile) and microenvironmental indicators (such as hypoxia markers), the functional dominant direction of factors such as METTL3 and FTO can be determined, and personalized treatment plans can be matched for patients. The core challenge of current research is how to accurately match the molecular mechanisms of basic research with the individual characteristics of clinical patients, which should also be a key breakthrough direction for future research.

## 7. Challenges and prospects

Based on the complex regulatory role and transformation potential of m6A modification in glioma, current research still faces several urgent problems that need to be solved. In the future, breakthroughs from multiple dimensions are needed to promote clinical applications.

### 7.1. Core challenges currently faced

#### 7.1.1. Differences between detection techniques and experimental standards

There are multiple methods for detecting m6A modification levels (such as methylated RNA immunoprecipitation sequencing and ultra-high-performance liquid chromatography-tandem mass spectrometry). The sensitivity and specificity differences of different methods may lead to bias in the quantitative results of modification levels. Meanwhile, some studies have not clearly controlled for tumor microenvironment factors, such as hypoxia and nutrient deficiency, which further exacerbate the conflicting results between studies.

#### 7.1.2. Redundancy and compensation mechanism of the regulatory network

The “writer-eraser-reader” system has complex cross-regulation, and single-molecule intervention is easily compensated for by other pathways. For example, after inhibiting METTL3, the body may maintain m6A modification levels by upregulating other methyltransferases (such as METTL14), leading to poor therapeutic effects. Additionally, m6A modification interferes with epigenetic regulation, such as DNA

methylation and histone modification, and its synergistic mechanism has not been fully elucidated, which increases the difficulty of targeted intervention.

#### 7.1.3. Disconnect between clinical samples and basic research

Most mechanism studies are based on conventional cell lines, such as U87 and U251. In contrast, clinical glioma samples have significant individual heterogeneity, such as variations in tumor microenvironment composition and immune cell infiltration ratios. The “ideal mechanism” validated in cell lines may fail in clinical samples due to microenvironment differences, resulting in a low success rate of translating basic research results into clinical practice.

#### 7.1.4. Insufficient knowledge on the specificity and safety of targeted drugs

Existing m6A modification-related inhibitors (such as FTO inhibitor MA2 and ALKBH5 inhibitor Ena15) often have off-target effects, which may affect the m6A modification balance of normal cells and cause adverse reactions. Meanwhile, there is a lack of highly specific drugs targeting specific molecular subtypes of glioma.

### 7.2. Future research and application directions

#### 7.2.1. Establish a multidimensional detection system

Future studies can integrate genomics, transcriptomics, metabolomics, and radiomics technologies to construct a comprehensive detection platform that includes molecular subtypes (IDH, 1p/19q status, etc.), target molecule expression profiles (MGMT, FOXO3a, etc.), and microenvironment indicators (hypoxia, immune infiltration, etc.), developing standardized quantitative thresholds to provide a basis for clinical screening of suitable treatment populations.

#### 7.2.2. Analyze the collaborative and compensatory mechanisms of regulatory networks

Using single-cell sequencing, spatial transcriptomics, and other technologies to systematically draw m6A modification maps of different molecular subtypes of glioma, future studies should clarify the cross-regulatory relationships within the writer-eraser-reader system and the interference mechanisms between m6A modification and other epigenetic regulations. It is also recommended to develop a joint-targeted strategy for key compensatory pathways to improve treatment efficacy.

#### 7.2.3. Strengthen the mechanism research driven by clinical samples

Expanding the clinical sample queue and increasing the *in vitro* culture of clinical samples can make mechanistic

research more closely related to clinical practice. At the same time, prospective clinical studies should be conducted to validate the predictive value of m6A-modified molecular typing for treatment response, thereby promoting the translation of basic research findings into clinical guidelines.

#### **7.2.4. Focus on the key role of m6A modification in glioblastoma stem cells**

The GSCs are the core of glioma recurrence and drug resistance. Therefore, it is necessary to further explore the unique mechanisms of m6A modification in GSC stemness maintenance, DNA repair, and immune escape, ultimately developing targeted strategies for GSCs.

#### **7.2.5. Develop highly specific, personalized, targeted drugs**

Designing highly specific m6A-modified enzyme inhibitors, exploring the combination of inhibitors with chemotherapy/immunotherapy, and utilizing the dual effects of m6A modification on regulating tumor cell sensitivity and the immune microenvironment may enhance comprehensive therapeutic efficacy.

In summary, m6A modification, as the core hub of epigenetic transcriptome regulation in glioma, forms a complex regulatory network by targeting different RNA molecules, combining them with tumor molecular subtypes and microenvironment characteristics. It not only provides new targets and ideas for the precision treatment of glioma but also highlights the multiple challenges in current research, including technical standardization, mechanism analysis, clinical translation, and drug development. In the future, by establishing a multidimensional standardized detection system, analyzing the collaborative and compensatory mechanisms of regulatory networks, strengthening the research paradigm driven by clinical samples, focusing on the unique regulatory laws of GSCs, and developing highly specific personalized drugs, it is expected to break through existing bottlenecks; transform the basic research results related to m6A modification into clinical diagnostic tools and treatment plans; provide breakthroughs for improving the prognosis of glioma patients, thereby reducing recurrence and mortality rates; and promote glioma treatment into a new stage of precision and individualization.

## **8. Conclusion**

As one of the core epitranscriptomic modifications in eukaryotes, m6A modification is deeply involved in the entire process of glioma initiation and progression through a dynamic regulatory network composed of

methyltransferases, demethylases, and m6A-binding proteins. This modification can target multiple RNA subtypes, such as mRNAs, lncRNAs, circRNAs, and miRNAs. By regulating their stability, translational efficiency, or splicing processing, m6A modification affects key metabolic processes, including ferroptosis and glycolysis, as well as signaling pathways such as NF- $\kappa$ B, Wnt/ $\beta$ -catenin, and Hippo, ultimately modulating the malignant phenotypes of glioma cells, including proliferation, invasion, and cancer stem cell self-renewal. Meanwhile, upstream regulatory molecules (including proteins, lncRNAs, and miRNAs) can indirectly participate in glioma progression by regulating the expression or activity of m6A-related enzymes, ultimately forming a multi-layered and complex regulatory network.

Notably, m6A modification has a significant impact on the clinical treatment of glioma. Regulating the methylation levels of genes such as *MGMT* and *FOXM1* significantly affects the sensitivity of glioma to TMZ, serving as a key determinant of patients' prognosis. It is worth noting that the oncogenic or tumor-suppressive effects of m6A regulatory factors depend on the characteristics of target RNAs, glioma molecular subtypes, and the tumor microenvironment. At present, inhibitors targeting m6A-related enzymes have shown potential to enhance chemotherapy sensitivity, offering a promising new direction for clinical treatment.

Future research should further clarify the synergistic effects and compensatory mechanisms of m6A regulatory networks, addressing issues including the standardization of detection techniques and heterogeneity between basic research and clinical samples. At the same time, it is necessary to promote the development of highly specific targeted drugs and optimize the combination strategy of m6A-targeted therapy with chemotherapy/immunotherapy. With the advancement of research, m6A modification is expected to become an important biomarker for glioma molecular typing and prognosis evaluation, offering a novel approach to overcoming the bottleneck of traditional treatment and improving patients' survival and prognosis.

## **Acknowledgments**

None.

## **Funding**

This work was supported by the Medical Science and Technology Program of Henan Province (no. JQRC2025017, no. SBGJ202502086, and no. SBGJ202502084), the Key Scientific Research Program for Universities of Henan Province (no. 26A320003), the Key Science and Technology

Program of Henan Province in China (no. 242102310274), the Open Project Research of the First Affiliated Hospital of Henan University (no. KFZD25005), the Program for Innovative Talents of Science and Technology in Henan Province (no. 23HASTIT043), the China Postdoctoral Science Foundation (no. 2024M750782), the Youth Promotion Project of Zhongzhou Laboratory for Integrative Biology (no. 2024TS0202), and the Open Project of The First Affiliated Hospital of Henan University (no. KFMS25004).

## Conflict of interest

Shuangyu Lv is an Editorial Board Member of this journal, but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

## Author contributions

**Conceptualization:** Ying Wang, Shuangyu Lv

**Visualization:** Jingjing Li, Xiaoguang Zhang

**Writing—original draft:** Jingjing Li, Xiaoguang Zhang, Yaoyao Wang, Chen Dong, Haotian Li

**Writing—review & editing:** Ying Wang, Shuangyu Lv, Jingjing Li

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Availability of data

Not applicable.

## References

1. Zhao K, Li W, Yang Y, *et al.* Comprehensive analysis of m6A/m5C/m1A-related gene expression, immune infiltration, and sensitivity of antineoplastic drugs in glioma. *Front Immunol.* 2022;13:955848.  
doi: 10.3389/fimmu.2022.955848
2. Pan T, Wu F, Li L, *et al.* The role m(6)A RNA methylation is CNS development and glioma pathogenesis. *Mol Brain.* 2021;14(1):119.  
doi: 10.1186/s13041-021-00831-5
3. Louis DN, Perry A, Wesseling P, *et al.* The 2021 WHO classification of tumors of the central nervous system: A summary. *Neuro Oncol.* 2021;23(8):1231-1251.  
doi: 10.1093/neuonc/noab106
4. Smith HL, Wadhwani N, Horbinski C. Major features of the 2021 WHO classification of CNS tumors. *Neurotherapeutics.* 2022;19(6):1691-1704.  
doi: 10.1007/s13311-022-01249-0
5. Bale TA, Rosenblum MK. The 2021 WHO classification of tumors of the central nervous system: An update on pediatric low-grade gliomas and glioneuronal tumors. *Brain Pathol.* 2022;32(4):e13060.  
doi: 10.1111/bpa.13060
6. Wen PY, Packer RJ. The 2021 WHO classification of tumors of the central nervous system: Clinical implications. *Neuro Oncol.* 2021;23(8):1215-1217.  
doi: 10.1093/neuonc/noab120
7. Xiao L, Li X, Mu Z, *et al.* FTO inhibition enhances the antitumor effect of temozolomide by targeting MYC-miR-155/23a cluster-MXI1 feedback circuit in glioma. *Cancer Res.* 2020;80(18):3945-3958.  
doi: 10.1158/0008-5472.CAN-20-0132
8. Yang L, Huang Z, Deng Y, *et al.* Characterization of the m6A/m1A/m5C/m7G-related regulators on the prognosis and immune microenvironment of glioma by integrated analysis of scRNA-seq and bulk RNA-seq data. *J Gene Med.* 2024;26(2):e3666.  
doi: 10.1002/jgm.3666
9. Casile M, Thivat E, Giraudet F, *et al.* Non-invasive intracranial pressure monitoring for high-grade gliomas patients treated with radiotherapy: Results of the GMaPIC trial. *Front Oncol.* 2024;14:1302977.  
doi: 10.3389/fonc.2024.1302977
10. Jahanshahi A, Salarinejad S, Oraee-Yazdani S, *et al.* Gliomatosis cerebri with blindness: A case report with literature review. *Radiol Case Rep.* 2023;18(9):2884-2894.  
doi: 10.1016/j.radcr.2023.05.037
11. Rilinger RG, Guo L, Sharma A, *et al.* Tumor-related epilepsy in high-grade glioma: A large series survival analysis. *J Neurooncol.* 2024;170(1):153-160.  
doi: 10.1007/s11060-024-04787-z
12. Ueno T, Ballard RE, Shuer LM, Yost WT, Cantrell JH, Hargens AR. Intracranial pressure dynamics during simulated microgravity using a new noninvasive ultrasonic technique. *J Gravit Physiol.* 1998;5(1):P39-P40.
13. Kivioja T, Posti JP, Sipila J, *et al.* Motor dysfunction as a primary symptom predicts poor outcome: Multicenter study of glioma symptoms. *Front Oncol.* 2023;13:1305725.  
doi: 10.3389/fonc.2023.1305725
14. Tuzesi A, Hallal S, Satgunaseelan L, Buckland ME, Alexander KL. Understanding the epitranscriptome for



- avant-garde brain tumour diagnostics. *Cancers (Basel)*. 2023;15(4):1232.  
doi: 10.3390/cancers15041232
15. Li F, Zhang C, Zhang G. m6A RNA methylation controls proliferation of human glioma cells by influencing cell apoptosis. *Cytogenet Genome Res*. 2019;159(3):119-125.  
doi: 10.1159/000499062
  16. Zhang M, Yang C, Dong W, Zhao Y, Chen N, Gao C. Expression patterns and prognostic role of m6A RNA methylation regulators in non-small cell lung cancer. *Cell Mol Biol (Noisy-le-grand)*. 2024;70(2):67-72.  
doi: 10.14715/cmb/2024.70.2.11
  17. Tao N, Wen T, Li T, Luan L, Pan H, Wang Y. Interaction between m6A methylation and noncoding RNA in glioma. *Cell Death Discov*. 2022;8(1):283.  
doi: 10.1038/s41420-022-01075-5
  18. Long S, Yan Y, Xu H, *et al*. Insights into the regulatory role of RNA methylation modifications in glioma. *J Transl Med*. 2023;21(1):810.  
doi: 10.1186/s12967-023-04653-y
  19. Deng X, Su R, Feng X, Wei M, Chen J. Role of N6-methyladenosine modification in cancer. *Curr Opin Genet Dev*. 2018;48:1-7.  
doi: 10.1016/j.gde.2017.10.005
  20. Huang AZ, Delaidelli A, Sorensen PH. RNA modifications in brain tumorigenesis. *Acta Neuropathol Commun*. 2020;8(1):64.  
doi: 10.1186/s40478-020-00941-6
  21. Jiang T, Zhang X, Xu W. [The roles of N(6)-methyladenosine modification and its regulators in male reproduction]. N(6)-甲基腺嘌呤修饰及其调控因子在男性生殖中的作用. *Sichuan Da Xue Xue Bao Yi Xue Ban*. 2024;55(3):527-534.  
doi: 10.12182/20240560103
  22. Yen YP, Chen JA. The m6A epitranscriptome on neural development and degeneration. *J Biomed Sci*. 2021;28(1):40.  
doi: 10.1186/s12929-021-00734-6
  23. Wang J, Sha Y, Sun T. m6A modifications play crucial roles in glial cell development and brain tumorigenesis. *Front Oncol*. 2021;11:611660.  
doi: 10.3389/fonc.2021.611660
  24. Zheng J, Wang X, Qiu Y, *et al*. Identification of critical m<sup>6</sup>A RNA methylation regulators with prognostic value in lower-grade glioma. *Biomed Res Int*. 2021;2021:9959212.  
doi: 10.1155/2021/9959212
  25. Xie GS, Richard HT. m<sup>6</sup>A mRNA modifications in glioblastoma: Emerging prognostic biomarkers and therapeutic targets. *Cancers (Basel)*. 2024;16(4):727.  
doi: 10.3390/cancers16040727
  26. Xu Z, Jiang J, Wang S. The critical role of RNA m6A methylation in gliomas: Targeting the hallmarks of cancer. *Cell Mol Neurobiol*. 2023;43(5):1697-1718.  
doi: 10.1007/s10571-022-01283-8
  27. Yan Y, Wei W, Long S, *et al*. The role of RNA modification in the generation of acquired drug resistance in glioma. *Front Genet*. 2022;13:1032286.  
doi: 10.3389/fgene.2022.1032286
  28. Lv J, Xing L, Zhong X, Li K, Liu M, Du K. Role of N6-methyladenosine modification in central nervous system diseases and related therapeutic agents. *Biomed Pharmacother*. 2023;162:114583.  
doi: 10.1016/j.biopha.2023.114583
  29. Du B, Wang P, Wei L, *et al*. Unraveling the independent role of METTL3 in m6A modification and tumor progression in esophageal squamous cell carcinoma. *Sci Rep*. 2024;14(1):15398.  
doi: 10.1038/s41598-024-64517-3
  30. Horiuchi K, Kawamura T, Hamakubo T. Wilms' tumor 1-associating protein complex regulates alternative splicing and polyadenylation at potential G-quadruplex-forming splice site sequences. *J Biol Chem*. 2021;297(5):101248.  
doi: 10.1016/j.jbc.2021.101248
  31. Deacon S, Walker L, Radhi M, Smith S. The regulation of m6A modification in glioblastoma: Functional mechanisms and therapeutic approaches. *Cancers (Basel)*. 2023;15(13):3307.  
doi: 10.3390/cancers15133307
  32. Marcinkowski M, Pilzys T, Garbicz D, *et al*. Human and *Arabidopsis* alpha-ketoglutarate-dependent dioxygenase homolog proteins-New players in important regulatory processes. *IUBMB Life*. 2020;72(6):1126-1144.  
doi: 10.1002/iub.2276
  33. Wang T, Kong S, Tao M, Ju S. The potential role of RNA N6-methyladenosine in Cancer progression. *Mol Cancer*. 2020;19(1):88.  
doi: 10.1186/s12943-020-01204-7
  34. Liao J, Wei Y, Liang J, *et al*. Insight into the structure, physiological function, and role in cancer of m6A readers-YTH domain-containing proteins. *Cell Death Discov*. 2022;8(1):137.  
doi: 10.1038/s41420-022-00947-0
  35. Piperi C, Markouli M, Gargalionis AN, Papavassiliou KA, Papavassiliou AG. Deciphering glioma epitranscriptome: Focus on RNA modifications. *Oncogene*. 2023;42(28):2197-2206.  
doi: 10.1038/s41388-023-02746-y
  36. Fan Y, Yan D, Ma L, *et al*. ALKBH5 is a prognostic factor and promotes the angiogenesis of glioblastoma. *Sci*

- Rep.* 2024;14(1):1303.  
doi: 10.1038/s41598-024-51994-9
37. Jiang X, Liu B, Nie Z, *et al.* The role of m6A modification in the biological functions and diseases. *Signal Transduct Target Ther.* 2021;6(1):74.  
doi: 10.1038/s41392-020-00450-x
  38. Zaccara S, Ries RJ, Jaffrey SR. Reading, writing and erasing mRNA methylation. *Nat Rev Mol Cell Biol.* 2019;20(10):608-624.  
doi: 10.1038/s41580-019-0168-5
  39. Li W, Liang L, Liu S, Yi H, Zhou Y. FSP1: A key regulator of ferroptosis. *Trends Mol Med.* 2023;29(9):753-764.  
doi: 10.1016/j.molmed.2023.05.013
  40. Bu C, Hu S, Yu J, *et al.* Fear stress promotes glioma progression through inhibition of ferroptosis by enhancing FSP1 stability. *Clin Transl Oncol.* 2023;25(5):1378-1388.  
doi: 10.1007/s12094-022-03032-1
  41. Stockwell BR, Jiang X, Gu W. Emerging mechanisms and disease relevance of ferroptosis. *Trends Cell Biol.* 2020;30(6):478-490.  
doi: 10.1016/j.tcb.2020.02.009
  42. Xue Q, Yan D, Chen X, *et al.* Copper-dependent autophagic degradation of GPX4 drives ferroptosis. *Autophagy.* 2023;19(7):1982-1996.  
doi: 10.1080/15548627.2023.2165323
  43. Deng L, Di Y, Chen C, *et al.* Depletion of the N(6)-Methyladenosine (m6A) reader protein IGF2BP3 induces ferroptosis in glioma by modulating the expression of GPX4. *Cell Death Dis.* 2024;15(3):181.  
doi: 10.1038/s41419-024-06486-z
  44. Sarbanes SL, Blomen VA, Lam E, *et al.* E3 ubiquitin ligase Mindbomb 1 facilitates nuclear delivery of adenovirus genomes. *Proc Natl Acad Sci USA.* 2021;118(1):e2015794118.  
doi: 10.1073/pnas.2015794118
  45. Dai W, Tian R, Yu L, *et al.* Overcoming therapeutic resistance in oncolytic herpes virotherapy by targeting IGF2BP3-induced NETosis in malignant glioma. *Nat Commun.* 2024;15(1):131.  
doi: 10.1038/s41467-023-44576-2
  46. Kemuriyama K, An J, Motoyama S, *et al.* Squamous cell carcinoma-derived G-CSF promotes tumor growth and metastasis in mice through neutrophil recruitment and tumor cell proliferation, associated with poor prognosis of the patients. *Genes Cells.* 2023;28(8):573-584.  
doi: 10.1111/gtc.13051
  47. Zha C, Meng X, Li L, *et al.* Neutrophil extracellular traps mediate the crosstalk between glioma progression and the tumor microenvironment via the HMGB1/RAGE/IL-8 axis. *Cancer Biol Med.* 2020;17(1):154-168.  
doi: 10.20892/j.issn.2095-3941.2019.0353
  48. Zhang S, Guo M, Liu Q, Liu J, Cui Y. Neutrophil extracellular traps induce a hypercoagulable state in glioma. *Immun Inflamm Dis.* 2021;9(4):1383-1393.  
doi: 10.1002/iid3.488
  49. Duffy MJ, O'grady S, Tang M, Crown J. MYC as a target for cancer treatment. *Cancer Treat Rev.* 2021;94:102154.  
doi: 10.1016/j.ctrv.2021.102154
  50. Lee TC, Ziff EB. Mxi1 is a repressor of the c-Myc promoter and reverses activation by USF. *J Biol Chem.* 1999;274(2):595-606.  
doi: 10.1074/jbc.274.2.595
  51. Dixit D, Prager BC, Gimble RC, *et al.* The RNA m6A reader YTHDF2 maintains oncogene expression and is a targetable dependency in glioblastoma stem cells. *Cancer Discov.* 2021;11(2):480-499.  
doi: 10.1158/2159-8290.CD-20-0331
  52. Wang YB, Tan B, Mu R, *et al.* Ubiquitin-associated domain-containing ubiquitin regulatory X (UBX) protein UBXN1 is a negative regulator of nuclear factor kappaB (NF-kappaB) signaling. *J Biol Chem.* 2015;290(16):10395-405.  
doi: 10.1074/jbc.M114.631689
  53. Chai RC, Chang YZ, Chang X, *et al.* YTHDF2 facilitates UBXN1 mRNA decay by recognizing METTL3-mediated m(6)A modification to activate NF-kappaB and promote the malignant progression of glioma. *J Hematol Oncol.* 2021;14(1):109.  
doi: 10.1186/s13045-021-01124-z
  54. Zanconato F, Cordenonsi M, Piccolo S. YAP/TAZ at the roots of cancer. *Cancer Cell.* 2016;29(6):783-803.  
doi: 10.1016/j.ccell.2016.05.005
  55. Riley SE, Feng Y, Hansen CG. Hippo-Yap/Taz signalling in zebrafish regeneration. *NPJ Regen Med.* 2022;7(1):9.  
doi: 10.1038/s41536-022-00209-8
  56. Yang J, Wu X, Wang J, *et al.* Feedforward loop between IMP1 and YAP/TAZ promotes tumorigenesis and malignant progression in glioblastoma. *Cancer Sci.* 2023;114(5):2053-2062.  
doi: 10.1111/cas.15636
  57. Masliantsev K, Karayan-Tapon L, Guichet PO. Hippo signaling pathway in gliomas. *Cells.* 2021;10(1):184.  
doi: 10.3390/cells10010184
  58. Xu X, Chen Y, Wang X, Mu X. Role of Hippo/YAP signaling in irradiation-induced glioma cell apoptosis. *Cancer Manag Res.* 2019;11:7577-7585.  
doi: 10.2147/CMAR.S210825

59. Chen W, Li Y, Ruan GX, *et al.* Adenosine deaminase acting on RNA-1 is essential for early B lymphopoiesis. *Cell Rep.* 2022;41(8):111687.  
doi: 10.1016/j.celrep.2022.111687
60. Chen J, Jin J, Jiang J, Wang Y. Adenosine deaminase acting on RNA 1 (ADAR1) as crucial regulators in cardiovascular diseases: Structures, pathogenesis, and potential therapeutic approach. *Front Pharmacol.* 2023;14:1194884.  
doi: 10.3389/fphar.2023.1194884
61. Liu H, Weng J. A comprehensive bioinformatic analysis of cyclin-dependent kinase 2 (CDK2) in glioma. *Gene.* 2022;822:146325.  
doi: 10.1016/j.gene.2022.146325
62. Tassinari V, Cesarini V, Tomaselli S, *et al.* ADAR1 is a new target of METTL3 and plays a pro-oncogenic role in glioblastoma by an editing-independent mechanism. *Genome Biol.* 2021;22(1):51.  
doi: 10.1186/s13059-021-02271-9
63. Kelleher FC, O'sullivan H. FOXM1 in sarcoma: Role in cell cycle, pluripotency genes and stem cell pathways. *Oncotarget.* 2016;7(27):42792-42804.  
doi: 10.18632/oncotarget.8669
64. Zhang S, Zhao BS, Zhou A, *et al.* m6A demethylase ALKBH5 maintains tumorigenicity of glioblastoma stem-like cells by sustaining FOXM1 expression and cell proliferation program. *Cancer Cell.* 2017;31(4):591-606.e6.  
doi: 10.1016/j.ccell.2017.02.013
65. Guo L, Wu Z. FOXM1-mediated NUF2 expression confers temozolomide resistance to human glioma cells by regulating autophagy via the PI3K/AKT/mTOR signaling pathway. *Neuropathology.* 2022;42(5):430-446.  
doi: 10.1111/neup.12824
66. Zhang L, Mao Y, Mao Q, *et al.* FLOT1 promotes tumor development, induces epithelial-mesenchymal transition, and modulates the cell cycle by regulating the Erk/Akt signaling pathway in lung adenocarcinoma. *Thorac Cancer.* 2019;10(4):909-917.  
doi: 10.1111/1759-7714.13027
67. Wang R, Chen Z, Zhang Y, *et al.* Flotillin-1 is a prognostic biomarker for glioblastoma and promotes cancer development through enhancing invasion and altering tumour microenvironment. *J Cell Mol Med.* 2023;27(3):392-402.  
doi: 10.1111/jcmm.17660
68. Song T, Hu Z, Zeng C, Luo H, Liu J. FLOT1, stabilized by WTAP/IGF2BP2 mediated N6-methyladenosine modification, predicts poor prognosis and promotes growth and invasion in gliomas. *Heliyon.* 2023;9(6):e16280.  
doi: 10.1016/j.heliyon.2023.e16280
69. Patra KC, Hay N. The pentose phosphate pathway and cancer. *Trends Biochem Sci.* 2014;39(8):347-54.  
doi: 10.1016/j.tibs.2014.06.005
70. Liu B, Fu X, Du Y, *et al.* Pan-cancer analysis of G6PD carcinogenesis in human tumors. *Carcinogenesis.* 2023;44(6):525-534.  
doi: 10.1093/carcin/bgad043
71. Liu Z, Chen Y, Wang L, Ji S. ALKBH5 promotes the proliferation of glioma cells via enhancing the mRNA stability of G6PD. *Neurochem Res.* 2021;46(11):3003-3011.  
doi: 10.1007/s11064-021-03408-9
72. Zhang J, Liu B, Xu C, *et al.* Cholesterol homeostasis confers glioma malignancy triggered by hnRNPA2B1-dependent regulation of SREBP2 and LDLR. *Neuro Oncol.* 2024;26(4):684-700.  
doi: 10.1093/neuonc/noad233
73. Chen JJ, Lu TZ, Wang T, *et al.* The m6A reader HNRNPC promotes glioma progression by enhancing the stability of IRAK1 mRNA through the MAPK pathway. *Cell Death Dis.* 2024;15(6):390.  
doi: 10.1038/s41419-024-06736-0
74. Zhu X, Yang H, Zhang M, *et al.* YTHDC1-mediated VPS25 regulates cell cycle by targeting JAK-STAT signaling in human glioma cells. *Cancer Cell Int.* 2021;21(1):645.  
doi: 10.1186/s12935-021-02304-0
75. Xu X, Liang Y, Gareev I, *et al.* LncRNA as potential biomarker and therapeutic target in glioma. *Mol Biol Rep.* 2023;50(1):841-851.  
doi: 10.1007/s11033-022-08056-y
76. Chang YZ, Chai RC, Pang B, *et al.* METTL3 enhances the stability of MALAT1 with the assistance of HuR via m6A modification and activates NF-kappaB to promote the malignant progression of IDH-wildtype glioma. *Cancer Lett.* 2021;511:36-46.  
doi: 10.1016/j.canlet.2021.04.020
77. Voce DJ, Bernal GM, Wu L, *et al.* Temozolomide treatment induces lncRNA MALAT1 in an NF-kappaB and p53 codependent manner in glioblastoma. *Cancer Res.* 2019;79(10):2536-2548.  
doi: 10.1158/0008-5472.CAN-18-2170
78. Didonato JA, Mercurio F, Karin M. NF-kappaB and the link between inflammation and cancer. *Immunol Rev.* 2012;246(1):379-400.  
doi: 10.1111/j.1600-065X.2012.01099.x
79. Wu Z, Lin Y, Wei N. N6-methyladenosine-modified HOTAIRM1 promotes vasculogenic mimicry formation in glioma. *Cancer Sci.* 2023;114(1):129-141.  
doi: 10.1111/cas.15578

80. Wu Z, Wei N. METTL3-mediated HOTAIRM1 promotes vasculogenic mimicry contributionsn glioma via regulating IGFBP2 expression. *J Transl Med*. 2023;21(1):855.  
doi: 10.1186/s12967-023-04624-3
81. Cai H, Liu W, Liu X, *et al*. Advances and prospects of vasculogenic mimicry in glioma: A potential new therapeutic target? *Onco Targets Ther*. 2020;13:4473-4483.  
doi: 10.2147/OTT.S247855
82. Chen YS, Chen ZP. Vasculogenic mimicry: A novel target for glioma therapy. *Chin J Cancer*. 2014;33(2):74-79.  
doi: 10.5732/cjc.012.10292
83. Nam KH, Lee BL, Park JH, *et al*. Caveolin 1 expression correlates with poor prognosis and focal adhesion kinase expression in gastric cancer. *Pathobiology*. 2013;80(2):87-94.  
doi: 10.1159/000341685
84. Zhu X, Wu X, Yang H, *et al*. m6A-mediated upregulation of LINC01003 regulates cell migration by targeting the CAV1/FAK signaling pathway in glioma. *Biol Direct*. 2023;18(1):27.  
doi: 10.1186/s13062-023-00386-6
85. Chen H, Duo Y, Hu B, *et al*. PICT-1 triggers a pro-death autophagy through inhibiting rRNA transcription and AKT/mTOR/p70S6K signaling pathway. *Oncotarget*. 2016;7(48):78747-78763.  
doi: 10.18632/oncotarget.12288
86. Yuan Y, Li D, Yu F, Kang X, Xu H, Zhang P. Effects of Akt/mTOR/p70S6K signaling pathway regulation on neuron remodeling caused by translocation repair. *Front Neurosci*. 2020;14:565870.  
doi: 10.3389/fnins.2020.565870
87. Zhang K, Zhang J, Han L, Pu P, Kang C. Wnt/beta-catenin signaling in glioma. *J Neuroimmune Pharmacol*. 2012;7(4):740-749.  
doi: 10.1007/s11481-012-9359-y
88. Wu X, Fu M, Ge C, *et al*. m6A-mediated upregulation of lncRNA CHASERR promotes the progression of glioma by modulating the miR-6893-3p/TRIM14 axis. *Mol Neurobiol*. 2024;61(8):5418-5440.  
doi: 10.1007/s12035-023-03911-w
89. Li B, Zhao R, Qiu W, *et al*. The N(6)-methyladenosine-mediated lncRNA WEE2-AS1 promotes glioblastoma progression by stabilizing RPN2. *Theranostics*. 2022;12(14):6363-6379.  
doi: 10.7150/thno.74600
90. Ji X, Liu Z, Gao J, *et al*. N(6)-methyladenosine-modified lncRNA LINREP promotes glioblastoma progression by recruiting the PTBP1/HuR complex. *Cell Death Differ*. 2023;30(1):54-68.  
doi: 10.1038/s41418-022-01045-5
91. Cheung HC, Hai T, Zhu W, *et al*. Splicing factors PTBP1 and PTBP2 promote proliferation and migration of glioma cell lines. *Brain*. 2009;132(Pt 8):2277-2288.  
doi: 10.1093/brain/awp153
92. Zhao R, Li B, Zhang S, *et al*. The N6-methyladenosine-modified pseudogene HSPA7 correlates with the tumor microenvironment and predicts the response to immune checkpoint therapy in glioblastoma. *Front Immunol*. 2021;12:653711.  
doi: 10.3389/fimmu.2021.653711
93. Zhang Y, Zhu Y, Zhang Y, Liu Z, Zhao X. YTHDF1 promotes the viability and selfrenewal of glioma stem cells by enhancing LINC00900 stability. *Int J Oncol*. 2024;64(5):53.  
doi: 10.3892/ijo.2024.5641
94. Yin J, Ding F, Cheng Z, *et al*. METTL3-mediated m6A modification of LINC00839 maintains glioma stem cells and radiation resistance by activating Wnt/beta-catenin signaling. *Cell Death Dis*. 2023;14(7):417.  
doi: 10.1038/s41419-023-05933-7
95. Yan Y, Luo A, Liu S, *et al*. METTL3-mediated LINC00475 alternative splicing promotes glioma progression by inducing mitochondrial fission. *Research (Wash D C)*. 2024;7:0324.  
doi: 10.34133/research.0324
96. Gao Y, Gao J, Lin F, *et al*. CircRNAs in tumor radioresistance. *Biomolecules*. 2022;12(11):1586.  
doi: 10.3390/biom12111586
97. Zhou WY, Cai ZR, Liu J, Wang DS, Ju HQ, Xu RH. Circular RNA: Metabolism, functions and interactions with proteins. *Mol Cancer*. 2020;19(1):172.  
doi: 10.1186/s12943-020-01286-3
98. Chen J, Chen T, Zhu Y, *et al*. circPTN sponges miR-145-5p/ miR-330-5p to promote proliferation and stemness in glioma. *J Exp Clin Cancer Res*. 2019;38(1):398.  
doi: 10.1186/s13046-019-1376-8
99. Zhang Y, Geng X, Xu J, *et al*. Identification and characterization of N6-methyladenosine modification of circRNAs in glioblastoma. *J Cell Mol Med*. 2021;25(15):7204-7217.  
doi: 10.1111/jcmm.16750
100. Sun W, Zhou H, Han X, Hou L, Xue X. Circular RNA: A novel type of biomarker for glioma (Review). *Mol Med Rep*. 2021;24(2):602.  
doi: 10.3892/mmr.2021.12240
101. Liao Y, Qiu X, Liu J, Zhang Z, Liu B, Jin C. The role of m6A-modified CircEPHB4 in glioma pathogenesis: Insights into cancer stemness metastasis. *Ann Clin Transl Neurol*. 2023;10(10):1749-1767.  
doi: 10.1002/acn3.51864



102. Mittal V. Epithelial mesenchymal transition in tumor metastasis. *Annu Rev Pathol*. 2018;13:395-412.  
doi: 10.1146/annurev-pathol-020117-043854
103. Zhang S, Zhang P, Wu A, *et al*. Downregulated M6A modification and expression of circRNA\_103239 promoted the progression of glioma by regulating the miR-182-5p/MTSS1 signalling pathway. *J Cancer*. 2023;14(18):3508-3520.  
doi: 10.7150/jca.85320
104. Wu Q, Yin X, Zhao W, Xu W, Chen L. Molecular mechanism of m6A methylation of circDLC1 mediated by RNA methyltransferase METTL3 in the malignant proliferation of glioma cells. *Cell Death Discov*. 2022;8(1):229.  
doi: 10.1038/s41420-022-00979-6
105. Lu TX, Rothenberg ME. MicroRNA. *J Allergy Clin Immunol*. 2018;141(4):1202-1207.  
doi: 10.1016/j.jaci.2017.08.034
106. Wang BC, Ma J. Role of MicroRNAs in malignant glioma. *Chin Med J (Engl)*. 2015;128(9):1238-1244.  
doi: 10.4103/0366-6999.156141
107. Zhang S, Zhao S, Qi Y, *et al*. SPI1-induced downregulation of FTO promotes GBM progression by regulating pri-miR-10a processing in an m6A-dependent manner. *Mol Ther Nucleic Acids*. 2022;27:699-717.  
doi: 10.1016/j.omtn.2021.12.035
108. Zhao N, Zhang J, Zhao Q, Chen C, Wang H. Mechanisms of long non-coding RNAs in biological characteristics and aerobic glycolysis of glioma. *Int J Mol Sci*. 2021;22(20):11197.  
doi: 10.3390/ijms222011197
109. Kawano Y, Sasano T, Arima Y, *et al*. A novel PDK1 inhibitor, JX06, inhibits glycolysis and induces apoptosis in multiple myeloma cells. *Biochem Biophys Res Commun*. 2022;587:153-159.  
doi: 10.1016/j.bbrc.2021.11.102
110. Ruan C, Zhang Y, Zhou J, Tan H, Bao Y. Role of METTL3 in aerobic glycolysis of glioma by regulating m6A/miR-27b-3p/PDK1. *J Environ Pathol Toxicol Oncol*. 2023;42(4):31-45.  
doi: 10.1615/JEnvironPatholToxicolOncol.2023046521
111. Agarwal N, Theodorescu D. The role of transcription factor YY1 in the biology of cancer. *Crit Rev Oncog*. 2017;22(1-2):13-21.  
doi: 10.1615/CritRevOncog.2017021071
112. You J, Tao B, Peng L, *et al*. Transcription factor YY1 mediates self-renewal of glioblastoma stem cells through regulation of the SENP1/METTL3/MYC axis. *Cancer Gene Ther*. 2023;30(5):683-693.  
doi: 10.1038/s41417-022-00580-0
113. Qiu Z, Zhao L, Shen JZ, *et al*. Transcription elongation machinery is a druggable dependency and potentiates immunotherapy in glioblastoma stem cells. *Cancer Discov*. 2022;12(2):502-521.  
doi: 10.1158/2159-8290.CD-20-1848
114. Qing Y, Dong L, Gao L, *et al*. R-2-hydroxyglutarate attenuates aerobic glycolysis in leukemia by targeting the FTO/m(6)A/PFKP/LDHB axis. *Mol Cell*. 2021;81(5):922-939.e9.  
doi: 10.1016/j.molcel.2020.12.026
115. Richardson LG, Choi BD, Curry WT. (R)-2-hydroxyglutarate drives immune quiescence in the tumor microenvironment of IDH-mutant gliomas. *Transl Cancer Res*. 2019;8(Suppl 2):S167-S170.  
doi: 10.21037/tcr.2019.01.08
116. Su R, Dong L, Li C, *et al*. R-2HG exhibits anti-tumor activity by targeting FTO/m(6)A/MYC/CEBPA signaling. *Cell*. 2018;172(1-2):90-105.e23.  
doi: 10.1016/j.cell.2017.11.031
117. R-2HG targets FTO to increase m6A levels and suppress tumor growth. *Cancer Discov*. 2018;8(2):137.  
doi: 10.1158/2159-8290.CD-RW2017-240
118. Gao FY, Li XT, Xu K, Wang RT, Guan XX. c-MYC mediates the crosstalk between breast cancer cells and tumor microenvironment. *Cell Commun Signal*. 2023;21(1):28.  
doi: 10.1186/s12964-023-01043-1
119. Guowei L, Xiufang L, Qianqian X, Yanping J. The FDX1 methylation regulatory mechanism in the malignant phenotype of glioma. *Genomics*. 2023;115(2):110601.  
doi: 10.1016/j.ygeno.2023.110601
120. Ciftci HI, Radwan MO, Sever B, *et al*. EGFR-targeted pentacyclic triterpene analogues for glioma therapy. *Int J Mol Sci*. 2021;22(20):10945.  
doi: 10.3390/ijms222010945
121. Saadeh FS, Mahfouz R, Assi HI. EGFR as a clinical marker in glioblastomas and other gliomas. *Int J Biol Markers*. 2018;33(1):22-32.  
doi: 10.5301/ijbm.5000301
122. Fang R, Chen X, Zhang S, *et al*. EGFR/SRC/ERK-stabilized YTHDF2 promotes cholesterol dysregulation and invasive growth of glioblastoma. *Nat Commun*. 2021;12(1):177.  
doi: 10.1038/s41467-020-20379-7
123. Gencel-Augusto J, Bivona TG. Unlocking the EGFR-mediated epitranscriptome: A pathway to novel therapies. *Mol Cell*. 2023;83(23):4199-4201.  
doi: 10.1016/j.molcel.2023.10.044
124. Lv D, Zhong C, Dixit D, *et al*. EGFR promotes ALKBH5 nuclear retention to attenuate N6-methyladenosine and protect against ferroptosis in glioblastoma. *Mol Cell*. 2023;83(23):4334-4351.e7.

- doi: 10.1016/j.molcel.2023.10.025
125. Cun Y, An S, Zheng H, *et al.* Specific regulation of m6A by SRSF7 promotes the progression of glioblastoma. *Genomics Proteomics Bioinformatics*. 2023;21(4):707-728.  
doi: 10.1016/j.gpb.2021.11.001
  126. Lv D, Gimple RC, Zhong C, *et al.* PDGF signaling inhibits mitophagy in glioblastoma stem cells through N(6)-methyladenosine. *Dev Cell*. 2022;57(12):1466-1481.e6.  
doi: 10.1016/j.devcel.2022.05.007
  127. Lv D, Yang K, Rich JN. Growth factor receptor signaling induces mitophagy through epitranscriptomic regulation. *Autophagy*. 2023;19(3):1034-1035.  
doi: 10.1080/15548627.2022.2114765
  128. Ren J, Xu B, Ren J, *et al.* The importance of M1-and M2-polarized macrophages in glioma and as potential treatment targets. *Brain Sci*. 2023;13(9):1466-1481.e6.  
doi: 10.3390/brainsci13091269
  129. Qi B, Yang C, Zhu Z, Chen H. EZH2-inhibited MicroRNA-454-3p promotes M2 macrophage polarization in glioma. *Front Cell Dev Biol*. 2020;8:574940.  
doi: 10.3389/fcell.2020.574940
  130. Zhou X, Chen H, Hu Y, *et al.* Enhancer of zeste homolog 2 promotes renal fibrosis after acute kidney injury by inducing epithelial-mesenchymal transition and activation of M2 macrophage polarization. *Cell Death Dis*. 2023;14(4):253.  
doi: 10.1038/s41419-023-05782-4
  131. Li N, Qin JF, Han X, *et al.* miR-21a negatively modulates tumor suppressor genes PTEN and miR-200c and further promotes the transformation of M2 macrophages. *Immunol Cell Biol*. 2018;96(1):68-80.  
doi: 10.1111/imcb.1016
  132. Lynch JR, Salik B, Connerty P, *et al.* JMJD1C-mediated metabolic dysregulation contributes to HOXA9-dependent leukemogenesis. *Leukemia*. 2019;33(6):1400-1410.  
doi: 10.1038/s41375-018-0354-z
  133. Zhong C, Tao B, Yang F, *et al.* Histone demethylase JMJD1C promotes the polarization of M1 macrophages to prevent glioma by upregulating miR-302a. *Clin Transl Med*. 2021;11(9):e424.  
doi: 10.1002/ctm2.424
  134. Li L, Chen X, Lv M, *et al.* Effect of platycodon grandiflorus polysaccharide on M1 polarization induced by autophagy degradation of SOCS1/2 proteins in 3D4/21 Cells. *Front Immunol*. 2022;13:934084.  
doi: 10.3389/fimmu.2022.934084
  135. Cao L, Han R, Zhao Y, *et al.* A LATS2 and ALKBH5 positive feedback loop supports their oncogenic roles. *Cell Rep*. 2024;43(4):114032.  
doi: 10.1016/j.celrep.2024.114032
  136. Xu A, Liu M, Huang MF, *et al.* Rewired m6A epitranscriptomic networks link mutant p53 to neoplastic transformation. *Nat Commun*. 2023;14(1):1694.  
doi: 10.1038/s41467-023-37398-9
  137. Kumari S, Muthusamy S. SETD2 as a regulator of N6-methyladenosine RNA methylation and modifiers in cancer. *Eur J Cancer Prev*. 2020;29(6):556-564.  
doi: 10.1097/CEJ.0000000000000587
  138. Kumari S, Singh M, Kumar S, Muthuswamy S. SETD2 controls m6A modification of transcriptome and regulates the molecular oncogenesis of glioma. *Med Oncol*. 2023;40(9):249.  
doi: 10.1007/s12032-023-02121-7
  139. Li R, Li S, Shen L, *et al.* SNHG1, interacting with SND1, contributes to sorafenib resistance of liver cancer cells by increasing m6A-mediated SLC7A11 expression and promoting aerobic glycolysis. *Environ Toxicol*. 2024;39(3):1269-1282.  
doi: 10.1002/tox.24014
  140. Zheng J, Zhang Q, Zhao Z, *et al.* Epigenetically silenced lncRNA SNAI3-AS1 promotes ferroptosis in glioma via perturbing the m6A-dependent recognition of Nrf2 mRNA mediated by SND1. *J Exp Clin Cancer Res*. 2023;42(1):127.  
doi: 10.1186/s13046-023-02684-3
  141. Dodson M, Castro-Portuguez R, Zhang DD. NRF2 plays a critical role in mitigating lipid peroxidation and ferroptosis. *Redox Biol*. 2019;23:101107.  
doi: 10.1016/j.redox.2019.101107
  142. Du B, Zhang Z, Jia L, *et al.* Micropeptide AF127577.4-ORF hidden in a lncRNA diminishes glioblastoma cell proliferation via the modulation of ERK2/METTL3 interaction. *Sci Rep*. 2024;14(1):12090.  
doi: 10.1038/s41598-024-62710-y
  143. Li XD, Wang MJ, Zheng JL, Wu YH, Wang X, Jiang XB. Long noncoding RNA just proximal to X-inactive specific transcript facilitates aerobic glycolysis and temozolomide chemoresistance by promoting stability of PDK1 mRNA in an m6A-dependent manner in glioblastoma multiforme cells. *Cancer Sci*. 2021;112(11):4543-4552.  
doi: 10.1111/cas.15072
  144. Zepecki JP, Karambizi D, Fajardo JE, *et al.* miRNA-mediated loss of m6A increases nascent translation in glioblastoma. *PLoS Genet*. 2021;17(3):e1009086.  
doi: 10.1371/journal.pgen.1009086
  145. Kang H, Lee S, Kim K, *et al.* Downregulated CLIP3 induces radioresistance by enhancing stemness and glycolytic flux in glioblastoma. *J Exp Clin Cancer Res*. 2021;40(1):282.

- doi: 10.1186/s13046-021-02077-4
146. Zhan Y, Song Y, Qiao W, *et al.* Focused ultrasound combined with miR-1208-equipped exosomes inhibits malignant progression of glioma. *Br J Cancer*. 2023;129(7):1083-1094.  
doi: 10.1038/s41416-023-02393-w
  147. Mendes A, Fahrenkrog B. NUP214 in leukemia: It's more than transport. *Cells*. 2019;8(1):76.  
doi: 10.3390/cells8010076
  148. Guo X, Qiu W, Li B, *et al.* Hypoxia-induced neuronal activity in glioma patients polarizes microglia by potentiating RNA m6A demethylation. *Clin Cancer Res*. 2024;30(6):1160-1174.  
doi: 10.1158/1078-0432.CCR-23-0430
  149. Wu F, Lv T, Chen G, *et al.* Epigenetic silencing of DUSP9 induces the proliferation of human gastric cancer by activating JNK signaling. *Oncol Rep*. 2015;34(1):121-128.  
doi: 10.3892/or.2015.3998
  150. Hashemi M, Etemad S, Rezaei S, *et al.* Progress in targeting PTEN/PI3K/Akt axis in glioblastoma therapy: Revisiting molecular interactions. *Biomed Pharmacother*. 2023;158:114204.  
doi: 10.1016/j.biopha.2022.114204
  151. Shi J, Zhang P, Dong X, *et al.* METTL3 knockdown promotes temozolomide sensitivity of glioma stem cells via decreasing MGMT and APNG mRNA stability. *Cell Death Discov*. 2023;9(1):22.  
doi: 10.1038/s41420-023-01327-y
  152. Zhang G, Zheng P, Lv Y, Shi Z, Shi F. m6A regulatory gene-mediated methylation modification in glioma survival prediction. *Front Genet*. 2022;13:873764.  
doi: 10.3389/fgene.2022.873764
  153. Shi J, Chen G, Dong X, *et al.* METTL3 promotes the resistance of glioma to temozolomide via increasing MGMT and ANPG in a m6A dependent manner. *Front Oncol*. 2021;11:702983.  
doi: 10.3389/fonc.2021.702983
  154. Li F, Chen S, Yu J, *et al.* Interplay of m6A and histone modifications contributes to temozolomide resistance in glioblastoma. *Clin Transl Med*. 2021;11(9):e553.  
doi: 10.1002/ctm2.553
  155. Du P, Meng L, Liao X, *et al.* The miR-27a-3p/FTO axis modifies hypoxia-induced malignant behaviors of glioma cells. *Acta Biochim Biophys Sin (Shanghai)*. 2023;55(1):103-116.  
doi: 10.3724/abbs.2023002
  156. Kowalski-Chauvel A, Lacore MG, Arnauduc F, *et al.* The m6A RNA demethylase ALKBH5 promotes radioresistance and invasion capability of glioma stem Cells. *Cancers (Basel)*. 2020;13(1):40.  
doi: 10.3390/cancers13010040
  157. Cui Q, Shi H, Ye P, *et al.* m6A RNA methylation regulates the self-renewal and tumorigenesis of glioblastoma stem cells. *Cell Rep*. 2017;18(11):2622-2634.  
doi: 10.1016/j.celrep.2017.02.059
  158. Tao M, Li X, He L, *et al.* Decreased RNA m6A methylation enhances the process of the epithelial mesenchymal transition and vasculogenic mimicry in glioblastoma. *Am J Cancer Res*. 2022;12(2):893-906.
  159. Ding C, Yi X, Chen X, *et al.* Warburg effect-promoted exosomal circ\_0072083 releasing up-regulates NANGO expression through multiple pathways and enhances temozolomide resistance in glioma. *J Exp Clin Cancer Res*. 2021;40(1):164.  
doi: 10.1186/s13046-021-01942-6
  160. Tang W, Xu N, Zhou J, *et al.* ALKBH5 promotes PD-L1-mediated immune escape through m6A modification of ZDHHC3 in glioma. *Cell Death Discov*. 2022;8(1):497.  
doi: 10.1038/s41420-022-01286-w
  161. Takahashi H, Hase H, Yoshida T, *et al.* Discovery of two novel ALKBH5 selective inhibitors that exhibit uncompetitive or competitive type and suppress the growth activity of glioblastoma multiforme. *Chem Biol Drug Des*. 2022;100(1):1-12.  
doi: 10.1111/cbdd.14051