Regulatory role and mechanism of m^6^A RNA modification in human metabolic diseases

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Metabolic diseases caused by disorders in amino acids, glucose, lipid metabolism, and other metabolic risk factors show high incidences in young people, and current treatments are ineffective. N^6^-methyladenosine (m^6^A) RNA modification is a post-transcriptional regulation of gene expression with several effects on physiological processes and biological functions. Recent studies report that m^6^A RNA modification is involved in various metabolic pathways and development of common metabolic diseases, making it a potential disease-specific therapeutic target. This review explores components, mechanisms, and research methods of m^6^A RNA modification. In addition, we summarize the progress of research on m^6^A RNA modification in metabolism-related human diseases, including diabetes, obesity, non-alcoholic fatty liver disease, osteoporosis, and cancer. Furthermore, opportunities and the challenges facing basic research and clinical application of m^6^A RNA modification in metabolism-related human diseases are discussed. This review is meant to enhance our understanding of the molecular mechanisms, research methods, and clinical significance of m^6^A RNA modification in metabolism-related human diseases.

INTRODUCTION

More than 100 types of chemical modifications in cellular RNAs have been reported during the past 6 decades.1 Several methylation modifications occur in eukaryotic messenger RNA (mRNA), including N^2^-methylguanosine, N^6^-methyl-2'-O-methyladenosine, 2'-O-methylation, N^6^-methyladenosine (m^6^A), and 5-methylcytosine.2 Notably, m^6^A is the most common RNA modification type. It was first reported in mRNAs from eukaryotes in the early 1970s.3 m^6^A RNA modification mainly occurs in the RRACH sequence,4,5 which is mainly found near stop codons, and in 3' untranslated regions (UTRs) and long internal exons in mRNAs.6,7 Advances in high-throughput sequencing technology and gradual progress of epigenetic research have enabled the study of m^6^A RNA modifications in a variety of non-coding RNAs (ncRNAs), including ribosomal RNA (rRNA), transfer RNA (tRNA), small nuclear RNA (snRNA), microRNA (miRNA), and long ncRNA (lncRNA).8,9 Notably, m^6^A RNA modification is a dynamic and reversible event that is catalyzed by a collection of enzymes, including methyltransferase “writers,” demethylase “erasers,” and “readers” that recognize such modifications.10,11 m^6^A modifications are implicated in most steps of target RNA metabolism, including RNA maturation, splicing, export and folding, translation, and stability of RNA, thus modulating the downstream signaling pathway and physiological function.12,13 Metabolic diseases caused by disorders in amino acids, glucose, lipid metabolism, and other metabolic disorders, including obesity, type 2 diabetes (T2D), non-alcoholic fatty liver disease (NASH), hypertension, atherosclerosis, chronic kidney disease, cardiovascular disease, and cancer, are a global health burden.14 Several studies report that cancer is a type of metabolic disease, which may shift metabolic pathways to facilitate uptake and incorporation of nutrients into cell building blocks, such as nucleotides, amino acids, and lipids required by highly proliferating cells.15,16 Although various approaches have been developed to prevent and treat these metabolic diseases, they have limited efficacy. The potentially important role of the m^6^A RNA modification in the development and progression of human metabolic disease is an emerging field of study.17

In this review, we summarize the recent progress in the study on the role and molecular mechanisms of m^6^A RNA modification in diseases associated with metabolism.

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MECHANISMS OF m⁶A RNA MODIFICATION

Regulators of m⁶A RNA modification can be classified into three types: writers, erasers, and readers. These enzymatic proteins are implicated in installing, removing, or recognizing m⁶A on mRNAs or ncRNAs, respectively (Figure 1).

Writers comprise m⁶A methyltransferases, which catalyze m⁶A modification through a multicomponent methyltransferase complex that co-regulates transfer of methyl groups from S-adenosylmethionine to adenine bases in RNA. The main components of this complex include methyltransferase-like 3 (METTL3), methyltransferase-like 5 (METTL5), methyltransferase-like 14 (METTL14), methyltransferase-like 16 (METTL16), WT1-associated protein (WTAP), RNA-binding motif protein 15 (RBM15), Vir-like m⁶A methyltransferase associated (VRMA, also known as KIAA1429), zinc finger CCHC-type containing 13 (ZC3H13), and zinc finger CCHC-type containing 4 (ZCCHC4). METTL3 was the first protein to be identified as an “m⁶A writer.” METTL14 structurally supports METTL3, and they form the core methyltransferase complex for m⁶A modification. WTAP stabilizes the core complex and facilitates m⁶A by recruiting the complex to nuclear speckles. RBM15 promotes binding of METTL3 and WTAP, thus guiding the two proteins to their target sites. VRMA mainly promotes mRNA methylation modifications near the 3’ UTR and stop codon regions. Alternatively, ZC3H13 and CBLL1 control nuclear m⁶A methylation by combining with other cofactors such as WTAP. Recent studies report that ZCCHC4 is a methyltransferase involved in modification of the 28S rRNA. In addition, METTL16 is an independent mRNA methyltransferase, implicated in maintaining mRNA stability and regulation of splicing, and its binding sites do not overlap with those of METTL3/METTL14 methylation complexes. In addition, METTL16 can function alone and catalyze m⁶A on U6 snRNA, miRNA m⁶A marks and interacts with DiGeorge syndrome critical

m⁶A readers comprise the YTH domain-containing family (YTHDF1, YTHDF2, YTHDF3, YTHDC1, and YTHDC2), the heterogeneous nuclear ribonucleoprotein (HNRNP) family (HNRNPA2B1, HNRNPC, and HNRNPG), the IGF2BP family (IGF2BP1, IGF2BP2, and IGF2BP3), the eukaryotic initiation factor eIF3, and the proline-rich coiled-coil protein PRRC2A.

Erasers comprise m⁶A demethylases, which remove m⁶A methyl groups from RNA. Three m⁶A demethylases have been reported, including fat mass and obesity-associated protein (FTO) and ALKB homologs ALKBH5 and ALKBH3. The demethylation process involves oxidation of m⁶A to form N⁶-hydroxymethyladenosine (hm⁶A), conversion of the hm⁶A to N⁶-formyladenosine (f⁶A), and finally conversion of f⁶A to adenosine. FTO was the first protein to be identified as an “m⁶A eraser,” and it catalyzes m⁶A demethylation. ALKBH5 was the second RNA demethylase to be reported, and it reverses m⁶A modifications. In addition, FTO can mediate m⁶Am (N⁶,2′-O-dimethyladenosine) demethylation. However, ALKBH5 is an m⁶A-specific demethylase in mRNA. Recently, Chen et al. reported that ALKBH3 plays a role as a demethylase of m⁶A modifications, and that ALKBH3 preferentially modifies tRNA over mRNA or rRNA.

Figure 1. Mechanisms of m⁶A RNA modification

m⁶A methylation is catalyzed by the writer enzyme complex, which includes METTL3, METTL5, METTL14, METTL16, WTAP, RBM15, VIRMA/KIAA1429, ZC3H13, and ZCCHC4. The m⁶A modification is removed by the demethylase action of FTO, ALKBH3, and ALKBH5. Reader proteins recognize m⁶A and affect multiple downstream reactions, and they mainly include members of the YTH domain family (YTHDF1, YTHDF2, YTHDF3, YTHDC1, and YTHDC2), the HNRNP family (HNRNPA2B1 and HNRNPC), the IGF2BP family (IGF2BP1, IGF2BP2, and IGF2BP3), the eukaryotic initiation factor eIF3, and the proline-rich coiled-coil protein PRRC2A.

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region 8 (DGCR8), a critical component of the canonical microprocessor complex, to stimulate miRNA processing, whereas HNRNPC recognizes m6A-dependent splicing in mRNA secondary structures. Wu et al. reported a novel m6A reader, PRRC2A, which stabilizes Olig2 mRNA by binding to a consensus GGACU motif in the Olig2 coding sequence in an m6A-dependent manner (Table 1).

METHODS FOR m6A RNA MODIFICATION RESEARCH

Levels of m6A in RNA are determined by two-dimensional thin layer chromatography, m6A dot blots, and high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). Transcriptome-wide distribution of m6A is probed by methylated RNA immunoprecipitation followed by high-throughput sequencing (MeRIP-seq or m6A-seq). In this method, mRNA or ncRNA is fragmented into 100-nt-long oligonucleotides and immunoprecipitated with a specific antibody against m6A. The precipitated RNAs are then subjected to high-throughput sequencing. In addition, methods with higher resolution, such as photo-crosslinking-assisted m6A sequencing (PA-m6A-seq) and site-specific cleavage and radioactive labeling followed by ligation-assisted extraction and thin-layer chromatography (SCARLET), have been developed. The m6A individual nucleotide resolution crosslinking immunoprecipitation (miCLIP) method can detect m6A at a precise position, and it is a major advance in m6A research. Recent studies developed antibody-free methods for global m6A detection, including MAZTER-seq, DART-seq (deamination adjacent to RNA modification targets), and m6A-SEAL (an m6A selective chemical labeling method). Advances in CRISPR-based genome engineering allow determination of the functional role of changing the m6A modification site in many organisms. Furthermore, Zhou et al. developed an online tool, named the sequence-based m6A modification site predictor, for prediction of m6A modification sites on RNA sequences of interests. These methods allow exploration of the function and mechanisms of m6A modification.

ROLE OF m6A MODIFICATION IN GLUCOSE METABOLISM-RELATED DISEASES

Glucose metabolism is a complex and important source of energy in organisms through anaerobic fermentation, aerobic oxidation,
and the pentose phosphate pathway. T2D is a complex metabolic disease characterized by hyperglycemia and dyslipidemia. Recent studies report that m\(^6\)A modification plays a critical role in the pathogenesis of T2D. In patients with T2D, glucose levels affect dynamic regulation of m\(^6\)A. High glucose levels can simultaneously decrease FTO mRNA expression and increase expression of METTL3, METTL14, and WTP methyltransferases. Forkhead box O1 (FOXO1) and glucose-6-phosphate catalytic subunit 1 (G6PC) are key regulators in glucose homeostasis.\(^6,7\) Diacylglycerol O-acyltransferase 2 (DGAT2) is required for synthesis and storage of intracellular triglycerides, which play a central role in lipid accumulation.\(^6\) Notably, a high expression level of FTO induces mRNA expression of FOXO1, G6PC, and DGAT2, resulting in abnormal glucose and lipid metabolism.\(^7\) Recent studies report that m\(^6\)A modification is associated with β cell survival and insulin secretion, which are important for regulation of glucose levels in T2D patients. METTL3 suppresses hepatic insulin sensitivity through m\(^6\)A modification of FASN (fatty acid synthetase) mRNA and promoting fatty acid metabolism.\(^8\) METTL3 is downregulated under inflammatory and oxidative stress conditions. Deletion of METTL3 induces islet β cell failure and hyperglycemia.\(^9\) METTL14 is implicated in β cell survival, differentiation, and insulin secretion. Knockdown of METTL14 in mice increases β cell death, alters β cell differentiation, and decreases β cell mass and insulin secretion, resulting in glucose intolerance.\(^10\) Furthermore, depletion of m\(^6\)A in-EndoC-βH1 decreases insulin secretion by decreasing AKT phosphorylation and pancreatic and duodenal homeobox 1 (PDX1) protein levels, which have been explored using β cell-specific METTL14 knockout mice.\(^11\)

These studies provide a theoretical basis for development of m\(^6\)A-based molecular therapies to promote β cell survival and function in patients with diabetes. In summary, m\(^6\)A modification plays an important role in glucose metabolism, which is associated with several human diseases, and is a potential therapeutic target (Table 2).

**Table 2. Functions of m\(^6\)A RNA modification in glucose metabolism**

| m\(^6\)A regulators | Function | Disease | Reference |
|---------------------|----------|---------|-----------|
| FTO | high expression of FTO induced mRNA expression of FOXO1, G6PC, and DGAT2, which are involved in abnormal glucose metabolism | type 2 diabetes | 7 |
| METTL3 | suppresses hepatic insulin sensitivity through m\(^6\)A modification of FASN (fatty acid synthetase) mRNA and promoting fatty acid metabolism | type 2 diabetes | 8 |
| METTL14 | knockdown of METTL14 decreases β cell mass and insulin secretion, eventually resulting in glucose intolerance | type 2 diabetes | 9 |
| METTL14 | knockdown of METTL14 in β cells decreases AKT phosphorylation and PDX1 protein levels, resulting in a decrease in insulin secretion | type 2 diabetes | 10 |

Low METTL3 activity in cell cultures decreases m\(^6\)A modification of the peroxisome proliferator-activated receptor (PPAR)\(\alpha\) gene, thus increasing its mRNA expression and extending the life of transcripts, which ultimately reduces lipid accumulation. Analysis shows that YTHDF2 binds to PPAR\(\alpha\) mRNA, thus mediating its stability and regulates lipid metabolism.\(^11\) The zinc finger protein 217 (Zip217) binds to YTHDF2 to activate transcription of the m\(^6\)A demethylase FTO, thus promoting its interaction with m\(^6\)A sites on various mRNAs, and it ultimately promotes adipose differentiation. These activities were confirmed through decreased levels of oil red O staining and lower mRNA expression of key adipogenic genes encoding PPAR\(\gamma\), lipoprotein lipase, and adiponectin in mouse embryonic fibroblasts.\(^12\) Translation of mitochondrial carrier homology 2 (MTCH2) is mediated by m\(^6\)A modification through an YTHDF1-dependent pathway, and it plays a role in regulating adipogenesis in intramuscular preadipocytes.\(^13\) For m\(^6\)A erasers, FTO enhances expression of JAK2 and promotes phosphorylation of STAT3, thus enhancing transcription of C/EBP\(\beta\) implicated in early stages of adipocyte differentiation. Alternatively, YTHDF2 accelerates decay of JAK2 mRNA and attenuates JAK2-STAT3-C/EBP\(\beta\) signaling.\(^14\) RUNX1 partner transcriptional co-repressor 1 (RUNXI1) is a regulator of adipogenesis.\(^15\) FTO controls splicing of RUNXI1 exons by regulating m\(^6\)A levels of its transcripts, thus regulating adipogenesis.\(^16\) Angiopoietin-like 4 (ANGPTL4) plays a role in the regulation of triglyceride clearance from the blood stream and in lipid metabolism.\(^17\) FTO binds to ANGPTL4 mRNA and promotes its translation, thus enhancing intracellular lipolysis in mouse adipocytes.\(^18\)

The roles of m\(^6\)A modification in lipid metabolism are summarized in Table 3.

Obesity is a common contributor to metabolic syndrome. At the cellular level, obesity is characterized by an increase in both cell size (hypertrophy) and the number of fat cells (hyperplasia).\(^19,20\) Several studies report that m\(^6\)A modification is involved in the development of obesity. The m\(^6\)A writers WTP, METTL3, and METTL14 promote cell cycle transition in mitotic clonal expansion; however, these methyltransferases are negatively correlated with adipogenesis.\(^21,22\) Risk alleles in the m\(^6\)A eraser FTO are common among people with high body mass index, and some of these single nucleotide polymorphisms are positively correlated with obesity.\(^23,24\) In addition, FTO promotes adipogenesis by repressing the Wnt/β-catenin signaling pathway in porcine intramuscular preadipocytes.\(^25\)

However, several studies report that m\(^6\)A writers, erasers, and readers do not work alone. For example, FTO increases expression of...
autophagy-related 5 (ATG5) and autophagy-related 7 (ATG7) expression to repress formation of autophagosomes, thus inhibiting autophagy and adipogenesis. Alternatively, YTHDF2 decreases expression of ATG5 and ATG7 by shortening the half-life of their m^6^A-modified mRNAs.97 Moreover, FTO regulates adipogenesis by controlling cell cycle progression in an m^6^A-YTHDF2-dependent manner. FTO knockdown significantly decreases expression of cell cycle regulators such as cyclin A2 (CCNA2) and cyclin-dependent kinase 2 (CDK2). YTHDF2 recognizes and destabilizes these mRNAs, leading to reduced protein expression, prolonged cell cycle progression, and suppressed adipogenesis.98 Induced expression of YTHDF2 reverses demethylation of CCNA2 and CDK2 mRNAs induced by FTO.99 Low levels of ZFP217, which is implicated in adipogenesis, increase expression of METTL3. Furthermore, knockdown of METTL3 rescues mitotic clonal expansion inhibited by ZFP217 small interfering RNA and promotes cyclin D1 (CCND1) expression. Moreover, YTHDF2 recognizes and degrades m^6^A-methylated CCND1 mRNA, resulting in downregulation of CCND1 and inhibition of adipogenesis.100

Currently, prevalence of NAFLD is at epidemic proportions and is a common cause of chronic liver disease worldwide.101 NAFLD is characterized by hepatic steatosis, ballooning degeneration, and fatty retention of liver parenchyma cells, with no history of excessive alcohol intake.102 Hepatic steatosis, the unique pathological feature of NAFLD, is caused by metabolic dysregulation of fatty acid metabolism. For instance, Xie et al.72 reported that the m^6^A eraser FTO by growth differentiation factor 11 promotes differentiation of bone marrow mesenchymal stem cells into adipocytes and osteoblasts through demethylation of PPARγ (Table 3).102 Dysregulated fatty acid metabolism is associated with insulin resistance in diabetes.113 Recent studies report that m^6^A modification is involved in fatty acid metabolism. For instance, Xie et al.72 reported that the m^6^A writer METTL3 increases m^6^A methylation level of FASN, which promotes fatty acid metabolism and enhances hepatic insulin sensitivity. Their study provides key information on blood glucose homeostasis and provides information on potential therapeutic targets for T2D patients. m^6^A modification of mRNA is well characterized in yeast cells, where peroxisomes are the only sites for fatty acid β-oxidation. A deletion strain of the yeast m^6^A methyltransferase ime4 showed significant decrease in expression of key genes involved in peroxisomal β-oxidation compared with wild-type yeast. This study provides a basis for exploring the role of m^6^A methylation in peroxisomal biology (Table 3).85

### ROLE OF m^6^A MODIFICATION IN CANCER

Reprogramming metabolism is an important feature of cancer pathogenesis.114 Cancer cells activate or inhibit metabolic pathways such as fatty acid metabolism and glucose homeostasis to support their malignant transformation. In the context of cancer, m^6^A modification has been identified as a potential therapeutic target.115 Several studies have demonstrated that m^6^A modification is associated with cancer progression and therapeutic resistance.116,117 For example, METTL3, a key m^6^A writer, is upregulated in various cancer types, including liver cancer, breast cancer, and colorectal cancer.118,119 METTL3 overexpression is associated with increased PPARγ expression, which promotes adipogenesis and inhibits cell proliferation and apoptosis.120 In contrast, knockdown of METTL3 decreases PPARγ expression and enhances cell proliferation and apoptosis.121 These findings suggest that m^6^A modification plays a crucial role in cancer metabolism and therapeutic resistance.

| Regulators | Function | Mechanism | Reference |
|------------|----------|-----------|-----------|
| METTL3     | Increases PPARγ mRNA levels and accelerates mRNA decay, reducing lipid accumulation | mRNA stability | ? |
| YTHDF2/FTO | Promotes adipose differentiation | Gene expression | ? |
| YTHDF1     | YTHDF1 promotes mitochondrial carrier homology 2 (MTCH2) translation to regulate adipogenesis | Translation | ? |
| FTO/YTHDF2 | FTO enhances expression of JAK2 and YTHDF2 directly targets JAK2 and accelerates mRNA decay | Gene expression, mRNA decay | ? |
| FTO        | FTO controls splicing of RUNXIT1 mRNA by regulating m^6^A levels, regulating adipogenesis | mRNA splicing | ? |
| FTO        | FTO binds to Angptl4 to encode an adipokin that stimulates intracellular lipolysis in adipocytes | Translation | ? |
| ime4Δ      | ime4Δ (yeast m^6^A methyltransferase gene deletion) cells showed a significant decrease in expression of the key genes involved in peroxisomal β-oxidation in yeast | Gene expression | ? |
| YTHDF1     | Facilitates translation of Wnt signaling effectors TCF7L2 and TCF4, which are required for maintenance of intestinal stem cells (ISCs) during regeneration and tumorigenesis | Translation | ? |
as aerobic glycolysis (also known as the Warburg effect), disordered lipid metabolism, and glutamine-dependent anaplerosis to accelerate cell proliferation. Recent studies report that m^6^A modification plays an important role in regulation of metabolic reprogramming of cancer.

### m^6^A modification modulates glycolysis in cancer cells

The Warburg effect is a key metabolic hallmark of cancer cells that is characterized by elevated activation of glycolysis followed by increased lactate fermentation. In colorectal cancer (CRC), the m^6^A methyltransferase METTL3 interacts with the 3' UTR regions of hexokinase 2 (HK2) and glucose transporter GLUT1 mRNA and enhances their stability, thus activating the glycolysis pathway. Moreover, WTAP enhances stability of HK2 mRNA by binding with the 3' UTR m^6^A site in gastric cancer. Casein kinase 2 (CK2) is associated with glycolysis, and CK2ζ is an essential catalytic subunit of the holoenzyme. In bladder cancer, ALKBH5 specifically recognizes the m^6^A sites of the 3' UTR in CK2ζ mRNA and reduces its stability, thus inhibiting cell glycolysis and proliferation.

Furthermore, FTO triggers m^6^A demethylation of PKM2 mRNA and accelerates its translation, thus promoting hepatocellular carcinoma tumorigenesis. In addition, YTHDF1 facilitates translation of the Wnt signaling effectors TCF7L2 and TCF4, which are required for maintenance of intestinal stem cells during regeneration and tumorigenesis. YTHDF2 weakens EGFR mRNA stability in an m^6^A-dependent manner and inhibits the MEK/ERK pathway, consequently impeding cell proliferation. METTL3 enhances translation of IKBKB and RELA and activates the nuclear factor κB (NF-κB) pathway, thus promoting bladder cancer progression.

### m^6^A modification affects lipid metabolism in cancer cells

Cancer cells change lipid metabolism to meet the malignant development demands, including synthesis of macromolecules, the main lipids for biogenesis of membranes and various signaling factors. METTL3 promotes stability of IncRNA LINC00958 and activates the miR-3619-5p/HDGF axis, thus inducing lipogenesis in HCC. In addition, LINC00958 affects the expression of sterol regulatory enzyme A (CoA) desaturase (SCD1), and acetyl-CoA carboxylase 1 (ACI), which are implicated in lipogenesis. FTO increases lipid accumulation by activating the SREBP1c/CIDE signaling pathway in an m^6^A-dependent manner in liver hepatocellular carcinoma.

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**Table 4. Functions of m^6^A RNA modification in lipid metabolism-related human diseases**

| m^6^A regulators | Function | Disease | Reference |
|------------------|----------|---------|-----------|
| WTAP             | WTAP, METTL3, and METTL14 are negatively related to adipogenesis | obesity | 89 |
| METTL3           | METTL3/YTHDF2 knockdown markedly decreases the expression of the cell cycle regulators CCNA2 and CDK2; YTHDF2 recognizes and degrades these mRNAs and reduces their protein expression to suppress adipogenesis | obesity | 98 |
| METTL14          | METTL3/METTL14 increases m^6^A methylation level, thus improving lipopolysaccharide-induced liver injury and hepatic lipid metabolism disruption in the liver of piglets | NAFLD | 106 |
| FTO              | FTO downregulates overall m^6^A levels and decreases mitochondrial content and triglyceride deposition | NAFLD | 106 |
| FTO              | METTL3/YTHDF2 deletion of METTL3 promotes adipogenesis and adipogenic differentiation by targeting the AKT/STAT3/CREB pathway via an m^6^A-YTHDF2-dependent manner | osteoporosis | 112 |
| FTO              | FTO promotes the differentiation of adipocyte and osteoblasts from bone marrow mesenchymal stem cells via GDF11 | osteoporosis | 112 |
| FTO              | METTL3 increases the m^6^A methylated level of fatty acid synthase (Fasn), thereby promoting fatty acid metabolism and enhancing hepatic insulin sensitivity | type 2 diabetes | 72 |
HepG2 cells (Table 5). These findings show that m6A RNA modification is involved in the regulation of lipogenesis in cancer cells.

**m6A modification affects amino acid metabolism in cancer cells**

Dysregulation of metabolism of amino acids, including glutamine, serine, and glycine, which play a role as metabolic regulators, is implicated in cancer cell growth. Glutamine, the most abundant free amino acid, participates in several pathways in energy generation, macromolecular synthesis, and signal transmission in cancer cells by donating its nitrogen and carbon atoms. Glutamine can be converted into α-KG to replenish the tricarboxylic acid (TCA) cycle through glutamate dehydrogenase (GLUD1) or transaminases. FTO and ALKBH5 are α-KG-dependent dioxygenases and are competitively inhibited by structurally related metabolite D-2-hydroxyglutarate (D2-HG), leading to abnormal expression of isocitrate dehydrogenase 1 or 2 (IDH1/2)-mutant tumors. In addition, YTHDF1 accelerates glutaminase GLS1 translation, a key enzyme of glutamine metabolism, and promotes colon cancer development. Further studies should explore the role of glutamine metabolism of development of different cancers. Moreover, more studies should explore the role of m6A on other amino acid metabolism.

**CONCLUSIONS AND PERSPECTIVES**

Advances in RNA immunoprecipitation sequencing, high-throughput sequencing, and liquid chromatography have led to the identification of several novel RNA modifications, implicated in metabolic diseases and tumors. In this review, we explored the roles and mechanisms of m6A RNA modifications in the occurrence and development of diseases by regulating glucose, lipid, and amino acid metabolism. The m6A-mediated regulation of glucose, lipid, and amino acid metabolism is associated with metabolic diseases, including T2D, NAFLD, obesity, and cancer (Figure 2). The stability and translation of mRNA of key regulators involved in these metabolic pathways are regulated by m6A modification and various m6A readers, thus promoting metabolic disease progression. In addition, m6A modification of IncRNA participates in progression of metabolic diseases. In turn, metabolites and metabolic pathways are involved in regulation of m6A RNA modification; for example, TCA cycle
metabolites affect FTO activity, whereas iron and NADPH (the reduced form of nicotinamide adenine dinucleotide phosphate) affect ALKBH5 activity.139

Incidence of metabolic diseases in young people are increasing exponentially. Current therapies for these diseases are ineffective, and therefore there is an urgent need to explore and develop disease-specific therapeutic targets.140 FTO is an attractive target for cancer treatment.141 Rhein, radicicol, epigallocatechin gallate, entacapone, and meclofenamic acid (MA) are a group of compounds that inhibit FTO regulation of m6A levels and affect fat formation.99,142 and meclofenamic acid (MA) are a group of compounds that inhibit FTO and inhibits GBM cell growth and survival.146

Resistance to chemoradiotherapy is a major challenge in tumor therapy. m6A RNA modification regulators can be used as prediction markers for individualized cancer therapy and for providing clues for overcoming therapeutic resistance in cancer. In addition, silencing of METTL3 leads to an increase in the sensitivity of glioblastoma stem cells (GSCs) to gamma irradiation and pancreatic cancer cells to anticancer reagents.152 Recent studies report that m6A modification is associated with development of the immune system. Silencing of METTL3 inhibits interleukin (IL)-7 signaling in CD4+ T cells. METTL3-mediated m6A modification enhances TLR4/NF-κB signaling-induced cytokine production and stimulates T cell activation.153 YTHDF1 is associated with cross-presentation of tumor antigens, cross-priming of CD8+ T cells, and PD-L1 checkpoint inhibition in dendritic cells.154 Knockdown of FTO in melanoma cells sensitizes tumor cells to interferon gamma (IFNγ) in vitro and promotes melanoma response to anti-PD-1 antibody in mice.155 These findings imply that m6A regulators can be combined with anti-PD-1/PD-L1 inhibitors to improve anticancer immunotherapy. The relationship between m6A RNA modification and metabolism should be further explored. Therefore, use of m6A methylation-related inhibitors is a potential strategy for treatment of obesity and other complex metabolic diseases. In addition, variations in gut microbiota are correlated with m6A modifications in the cecum and the liver, which affect metabolism, inflammation, and antimicrobial responses in mice.156 Molecular interactions among human gut microbiota, m6A methylation, and metabolic diseases should be explored in the future.

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AUTHOR CONTRIBUTIONS

Y.W. and W.G. conceived the review. Y.Z. wrote the first version of the manuscript. Y.Z., W.C., X.Z., and Y.G. organized the figures. W.C., Y.Z., J.C., S.W., Y.W., and W.G. revised the manuscript. All of the authors approved the final version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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