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

Yuliang Zhang,[1,2] Wenjie Chen,[3] Xiwang Zheng,[1,2] Yujia Guo,[1,2] Jimin Cao,[4] Yu Zhang,[4,5] Shuxin Wen,[3] Wei Gao,[1,2,4,6,7] and Yongyan Wu[1,2,4,6,8]

[1]Shanxi Key Laboratory of Otorhinolaryngology Head and Neck Cancer, First Hospital of Shanxi Medical University, No. 85, South Jiefang Road, Taiyuan 030001, Shanxi, China; [2]Shanxi Province Clinical Medical Research Center for Precision Medicine of Head and Neck Cancer, First Hospital of Shanxi Medical University, Taiyuan 030001, Shanxi, China; [3]Department of Otolaryngology Head & Neck Surgery, Shanxi Bethune Hospital, Taiyuan 030032, Shanxi, China; [4]Key Laboratory of Cellular Physiology, Ministry of Education, Shanxi Medical University, Taiyuan 030001, Shanxi, China; [5]Department of Physiology, Shanxi Medical University, Taiyuan 030001, Shanxi, China; [6]Department of Otolaryngology Head & Neck Surgery, First Hospital of Shanxi Medical University, Taiyuan 030001, Shanxi, China; [7]Department of Cell Biology and Genetics, Basic Medical School of Shanxi Medical University, Taiyuan 030001, Shanxi, China; [8]Department of Biochemistry & Molecular Biology, Shanxi Medical University, Taiyuan 030001, Shanxi, China

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^7-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 (NAFLD), hypertension, atherosclerosis, chronic kidney disease, cardiovascular disease, 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]
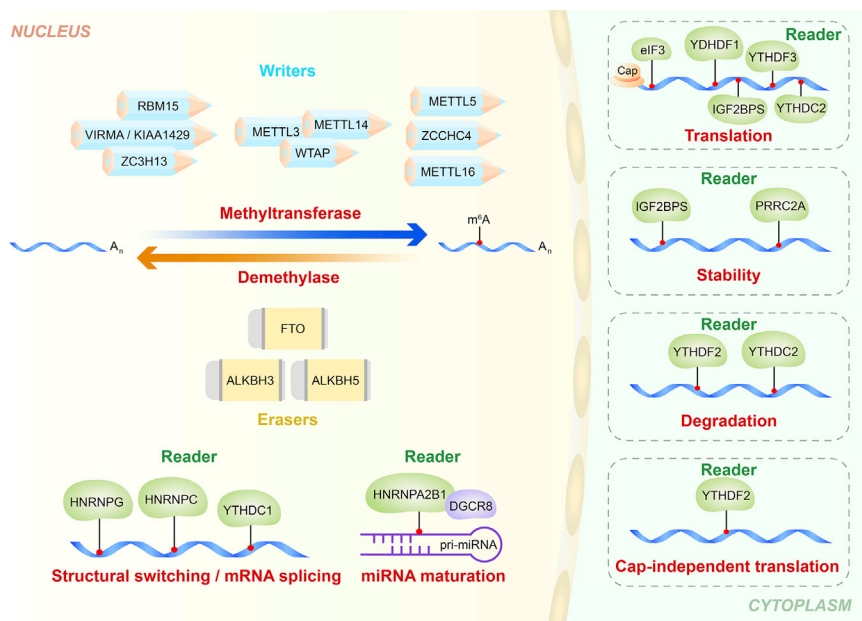
In this review, we summarize the recent progress in the study on the role and molecular mechanisms of m^{6}A RNA modification in diseases associated with metabolism.

Figure 1. Mechanisms of m⁶A RNA modification

m^{6}A methylation is catalyzed by the writer enzyme complex, which includes METTL3, METTL5, METTL14, METTL16, WTAP, RBM15, VIRMA/KIAA1429, ZC3H13, and ZCCHC4. The m^{6}A modification is removed by the demethylase action of FTO, ALKBH3, and ALKBH5. Reader proteins recognize m^{6}A 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.

MECHANISMS OF m⁶A RNA MODIFICATION

Regulators of m^{6}A RNA modification can be classified into three types: writers, erasers, and readers. These enzymatic proteins are implicated in installing, removing, or recognizing m^{6}A on mRNAs or ncRNAs, respectively (Figure 1).

Writers comprise m^{6}A methyltransferases, which catalyze m^{6}A modification through a multicomponent methyltransferase complex that co-regulates transfer of methyl groups from *S*-adenosylmethionine to adenine bases in RNA.[18] 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 m^{6}A methyltransferase associated (VIRMA, also known as KIAA1429), zinc finger CCCH-type containing 13 (ZC3H13), and zinc finger CCHC-type containing 4 (ZCCHC4). METTL3 was the first protein to be identified as an "m^{6}A writer."[19,20] METTL14 structurally supports METTL3, and they form the core methyltransferase complex for m^{6}A modification.[21] WTAP stabilizes the core complex and facilitates m^{6}A by recruiting the complex to nuclear speckles.[22] RBM15 promotes binding of METTL3 and WTAP, thus guiding the two proteins to their target sites.[20,23] VIRMA mainly promotes mRNA methylation modifications near the 3′ UTR and stop codon regions.[24] Alternatively, ZC3H13 and CBLL1 control nuclear m^{6}A methylation by combining with other cofactors such as WTAP.[25] Recent studies report that ZCCHC4 is a methyltransferase involved in modification of the 28S rRNA.[26,27] 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.[28] In addition, METTL16 can function alone and catalyze m^{6}A on U6 snRNA,

precursor (pre-)mRNAs, and ncRNAs.[29,30] METTL5 is implicated in 18S rRNA m^{6}A modification (Table 1).[31]

Erasers comprise m^{6}A demethylases, which remove m^{6}A methyl groups from RNA. Three m^{6}A demethylases have been reported, including fat mass and obesity-associated protein (FTO) and ALKB homologs ALKBH5 and ALKBH3.[32,34,45] The demethylation process involves oxidation of m^{6}A to form N^6-hydroxymethyladenosine (hm^{6}A), conversion of the hm^{6}A to N^6-formyladenosine (f^{6}A), and finally conversion of f^{6}A to adenosine. FTO was the first protein to be identified as an "m^{6}A eraser," and it catalyzes m^{6}A demethylation.[32] ALKBH5 was the second RNA demethylase to be reported, and it reverses m^{6}A modifications.[33] In addition, FTO can mediate m^{6}Am (N^6,2′-*O*-dimethyladenosine) demethylation. However, ALKBH5 is an m^{6}A-specific demethylase in mRNA.[46] Recently, Chen et al.[47] reported that ALKBH3 plays a role as a demethylase of m^{6}A modifications, and that ALKBH3 preferentially modifies tRNA over mRNA or rRNA (Table 1).[34]

m^{6}A readers comprise the YTH domain-containing family (YTHDF1, YTHDF2, YTHDF3, YTHDC1, and YTHDC2),[37,38,48,49] the heterogeneous nuclear ribonucleoprotein (HNRNP) family (HNRNPA2B1, HNRNPC, and HNRNPG),[39–41,50] insulin-like growth factor 2 mRNA-binding proteins (IGF2BP1, IGF2BP2, and IGF2BP3),[42] eukaryotic initiation factor eIF3,[43,51] and proline-rich coiled-coil protein PRRC2A.[44] YTHDF1 interacts with initiation factors, thus promoting RNA translation initiation in cytosol.[52] YTHDF2 regulates RNA degradation by binding to m^{6}A-modified mRNA.[36] YTHDF3 promotes translation by enhancing protein synthesis together with YTHDF1 and regulates mRNA decay mediated by YTHDF2.[35,53] Furthermore, YTHDF1 and YTHDF2 recognize m^{6}A-modified circRNAs and modulate circRNA expression.[54,55] YTHDC1 can affect subcellular localization of circRNA in an m^{6}A-dependent manner.[56] Furthermore, IGF2BP1–IGF2BP3 enhance stability and translation of the target mRNAs by recognizing m^{6}A modifications.[42] HNRNPA2B1 recognizes primary (pri-) miRNA m^{6}A marks and interacts with DiGeorge syndrome critical

Table 1. Role of regulators in m⁶A RNA modification

Regulator	Function	Reference
m⁶A writers		
METTL3	catalyzes m⁶A modification	[19]
METTL14	helps METTL3 to recognize the substrate	[21]
WTAP	contributes to localization of the METTL3-METTL14 heterodimer to the nuclear speckle	[22]
RBM15	binds the m⁶A-methylation complex and recruits it to specific sites in RNA	[20,23]
VIRMA/KIAA1429	VIRMA recruits the catalytic core components METTL3/METTL14/WTAP to guide methylation of a particular region	[24]
ZC3H13	anchors WTAP to the mRNA-binding factor in the nucleus	[25]
ZCCHC4	methylates human 28S rRNA and also interacts with a subset of mRNAs	[26,27]
METTL16	catalyzes m⁶A modification U6 snRNA and pre-mRNAs and ncRNAs independently	[28,29]
METTL5	promotes 18S rRNA m⁶A modification with TRMT112	[31]
m⁶A erasers		
FTO	catalyzes m⁶A demethylation	[32]
ALKBH5	reverses m⁶A modifications oxidatively	[33]
ALKBH3	removes m⁶A modification on tRNA	[34]
m⁶A readers		
YTHDF1	increases mRNA translation efficiency	[35]
YTHDF2	promotes mRNA degradation	[36]
YTHDF3	enhances translation and degradation by interacting with YTHDF1 and YTHDF2	[35]
YTHDC1	contributes to RNA splicing and export	[37]
YTHDC2	enhances translation of target RNA and decreases abundance of target RNA	[38]
HNRNPA2B1	mediates mRNA splicing and primary microRNA processing	[39]
HNRNPC	affects abundance and alternative splicing of target mRNAs	[40]
HNRNPG	regulates transcriptome-wide alternative splicing	[41]
IGF2BPs	enhances mRNA stability and translation	[42]
eIF3	enhances mRNA translation	[43]
PRRC2A	stabilizes Olig2 mRNA	[44]

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.[39] Wu et al.[44] 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).[57,58] Transcriptome-wide distribution of m⁶A is profiled by methylated RNA immunoprecipitation followed by high-throughput sequencing (MeRIP-seq or m⁶A-seq).[6] 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.[59] 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.[60] Recent studies developed antibody-free methods for global m⁶A detection, including MAZTER-seq,[61] DART-seq (deamination adjacent to RNA modification targets),[62] and m⁶A-SEAL (an m⁶A selective chemical labeling method).[63]

Advances in CRISPR-based genome engineering allow determination of the functional role of changing the m⁶A modification site in many organisms.[64] Furthermore, Zhou et al.[65] 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,

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	type 2 diabetes	[70]
METTL3	suppresses hepatic insulin sensitivity through m^{6}A modification of FASN (fatty acid synthetase) mRNA and promoting fatty acid metabolism	type 2 diabetes	[72]
METTL14	knockdown of METTL14 decreases β cell mass and insulin secretion, eventually resulting in glucose intolerance	type 2 diabetes	[74]
METTL14	knockdown of METTL14 in β cells decreases AKT phosphorylation and PDX1 protein levels, resulting in a decrease in insulin secretion	type 2 diabetes	[75]

and the pentose phosphate pathway. T2D is a complex metabolic disease characterized by hyperglycemia and dyslipidemia.[66] 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 WTAP methyltransferases. Forkhead box O1 (FOXO1) and glucose-6-phosphatase catalytic subunit 1 (G6PC) are key regulators in glucose homeostasis.[67,68] Diacylglycerol O-acyltransferase 2 (DGAT2) is required for synthesis and storage of intracellular triglycerides, which play a central role in lipid accumulation.[69] Notably, a high expression level of FTO induces mRNA expression of FOXO1, G6PC, and DGAT2, resulting in abnormal glucose and lipid metabolism.[70,71] 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 modification of fatty acid synthase (FASN) mRNA by m^{6}A and promotion of fatty acid metabolism.[72] METTL3 is downregulated under inflammatory and oxidative stress conditions. Deletion of METTL3 induces islet β cell failure and hyperglycemia.[73] 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.[74] 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.[75] 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).

ROLE OF m^{6}A MODIFICATION IN LIPID METABOLISM-RELATED DISEASES

Lipid metabolism is a complex physiological process that is associated with nutrient adjustment, hormone regulation, and homeostasis, and it involves multiple molecular factors and signaling pathways.[76] Abnormal lipid metabolism is implicated in several diseases,[71] with recent studies reporting that m^{6}A modification plays a role in this relationship.

Low METTL3 activity in cell cultures decreases m^{6}A modification of the peroxisome proliferator-activated receptor (PPAR)α gene, thus increasing its mRNA expression and extending the life of transcripts, which ultimately reduces lipid accumulation. Analysis shows that YTHDF2 binds to PPARα mRNA, thus mediating its stability and regulates lipid metabolism.[77] The zinc finger protein 217 (Zfp217) 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 PPARγ, lipoprotein lipase, and adiponectin in mouse embryonic fibroblasts.[78] 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.[79] For m^{6}A erasers, FTO enhances expression of JAK2 and promotes phosphorylation of STAT3, thus enhancing transcription of C/EBPβ implicated in early stages of adipocyte differentiation. Alternatively, YTHDF2 accelerates decay of JAK2 mRNA and attenuates JAK2-STAT3-C/EBPβ signaling.[80] RUNX1 partner transcriptional co-repressor 1 (RUNX1T1) is a regulator of adipogenesis.[81] FTO controls splicing of RUNX1T1 exons by regulating m^{6}A levels of its transcripts, thus regulating adipogenesis.[82] Angiopoietin-like 4 (ANGPTL4) plays a role in the regulation of triglyceride clearance from the blood serum and in lipid metabolism.[83] FTO binds to ANGPTL4 mRNA and promotes its translation, thus enhancing intracellular lipolysis in mouse adipocytes.[84] 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).[87,88] Several studies report that m^{6}A modification is involved in the development of obesity. The m^{6}A writers WTAP, METTL3, and METTL14 promote cell cycle transition in mitotic clonal expansion; however, these methyltransferases are negatively correlated with adipogenesis.[89,90] 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.[91–95] In addition, FTO promotes adipogenesis by repressing the Wnt/β-catenin signaling pathway in porcine intramuscular preadipocytes.[96]

However, several studies report that m^{6}A writers, erasers, and readers do not work alone. For example, FTO increases expression of

Table 3. Functions of m⁶A RNA modification in lipid metabolism

Regulators	Function	Mechanism	Reference
METTL3	METTL3 decreases PPARα m⁶A abundance and increases PPARα mRNA half-life and expression, reducing lipid accumulation	mRNA stability	77
YTHDF2/FTO	promotes adipose differentiation	gene expression	78
YTHDF1	YTHDF1 promotes mitochondrial carrier homology 2 (MTCH2) translation to regulate adipogenesis	translation	79
FTO/YTHDF2	FTO enhances expression of JAK2 and YTHDF2 directly targets JAK2 and accelerates mRNA decay	gene expression, mRNA decay	80
FTO	FTO controls splicing of RUNX1T1 mRNA by regulating m⁶A levels, regulating adipogenesis	mRNA splicing	82
FTO	FTO binds to Angptl4 to encode an adipokine that stimulates intracellular lipolysis in adipocytes	translation	84
ime4Δ	ime4Δ (yeast m⁶A methyltransferase gene deletion) cells showed a significant decrease in expression of the key genes involved in peroxisomal β-oxidation in yeast	gene expression	85
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	86

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 m⁶A-modified mRNAs.[97] Moreover, FTO regulates adipogenesis by controlling cell cycle progression in an m⁶A-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 m⁶A-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 *de novo* lipogenesis, fatty acid uptake and oxidation, and triglyceride transport.[103,104] Previous studies report that development of NAFLD is highly correlated with m⁶A alteration.[105] m⁶A modification is associated with fat accumulation both *in vivo* and *in vitro*. The m⁶A eraser FTO decreases mitochondrial content and increases triglyceride deposition by downregulating overall m⁶A levels. FTO activity is essential for fat metabolism in hepatocytes, indicating the importance of RNA modification in fat deposition.[106] FTO is implicated in hepatic oxidative stress and lipid deposition, which participate in the development of NAFLD.[107] Curcumin, the active ingredient in dietary turmeric, affects mRNA expression of the m⁶A writers METTL3 and METTL14 in weaned piglets. Analysis showed that increased m⁶A methylation levels alleviate lipopolysaccharide-induced liver injury and reverses

disruption of lipid metabolism in the liver.[108] In another study, knockdown of METTL3 or YTHDF2 increases expression of PPARα mRNA and reduces lipid accumulation.[77] In summary, m⁶A modulators are potential therapeutic targets for NAFLD.

Osteoporosis is a common bone metabolic disease in older populations.[109] Recent studies report that m⁶A modification is involved in development of osteoporosis.[110,111] Conditional knockout of the m⁶A writer METTL3 in bone marrow mesenchymal stem cells in mice decreases bone mass with low osteogenic potential, and it increases marrow adiposity associated with enhanced adipogenic potential by reducing m⁶A methylation levels.[111] METTL3 knockdown in porcine bone marrow stem cells promotes adipogenesis and adipogenic differentiation by targeting the JAK1/STAT5/C/EBPβ pathway in an m⁶A-YTHDF2-dependent manner.[112] Upregulation of the m⁶A eraser FTO by growth differentiation factor 11 promotes differentiation of bone marrow mesenchymal stem cells into adipocytes and osteoblasts through demethylation of *PPARγ* (Table 4).[110]

Dysregulated fatty acid metabolism is associated with insulin resistance in diabetes.[113] Recent studies report that m⁶A modification is involved in fatty acid metabolism. For instance, Xie et al.[72] reported that the m⁶A writer METTL3 increases m⁶A 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. m⁶A 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 m⁶A 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 m⁶A methylation in peroxisomal biology (Table 3).[85]

ROLE OF m⁶A MODIFICATION IN CANCER METABOLIC REPROGRAMING

Reprogramming metabolism is an important feature of cancer pathogenesis.[114] Cancer cells activate or inhibit metabolic pathways such

Table 4. Functions of m⁶A RNA modification in lipid metabolism-related human diseases

m⁶A regulators	Function	Disease	Reference
WTAP			
METTL3	WTAP, METTL3, and METTL14 are negatively related to adipogenesis	obesity	[89]
METTL14			
FTO	FTO alleles and some SNPs are positively associated with obesity	obesity	[91,93–95]
FTO	promotes adipogenesis by repressing the Wnt/β-catenin signaling pathway in porcine intramuscular preadipocytes	obesity	[96]
FTO	increases the autophagy-related protein expression of ATG5/ATG7 and weaken the formation of autophagosomes, thereby inhibiting autophagy and adipogenesis	obesity	[97]
FTO/YTHDF2	FTO 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]
METTL3	downregulates CCND1 and inhibits adipogenesis	obesity	[100]
FTO	downregulates overall m⁶A levels and decreases mitochondrial content and triglyceride deposition	NAFLD	[106]
FTO	associates with hepatic oxidative stress and lipid deposition	NAFLD	[107]
METTL3/METTL14	Increases m⁶A methylation level, thus improving lipopolysaccharide-induced liver injury and hepatic lipid metabolism disruption in the liver of piglets	NAFLD	[108]
METTL3/YTHDF2	knockdown of METTL3 or YTHDF2 increases the expression of PPARα mRNA, thereby decreasing lipid accumulation	NAFLD	[77]
METTL3/YTHDF2	deletion of METTL3 promotes adipogenesis and adipogenic differentiation by targeting the JAK1/STAT5/C/EBPβ pathway via an m⁶A-YTHDF2-dependent manner	osteoporosis	[112]
FTO	promotes the differentiation of adipocyte and osteoblasts from bone marrow mesenchymal stem cells via GDF11	osteoporosis	[110]
METTL3	increases the m⁶A methylated level of fatty acid synthase (Fasn), thereby promoting fatty acid metabolism and enhancing hepatic insulin sensitivity	type 2 diabetes	[72]

as aerobic glycolysis (also known as the Warburg effect),[115] disordered lipid metabolism,[116] and glutamine-dependent anaplerosis to accelerate cell proliferation.[117] Recent studies report that m⁶A modification plays an important role in regulation of metabolic reprogramming of cancer.

m⁶A 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.[118] In colorectal cancer (CRC), the m⁶A 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.[119] Moreover, WTAP enhances stability of HK2 mRNA by binding with the 3′ UTR m⁶A site in gastric cancer.[120] Casein kinase 2 (CK2) is associated with glycolysis, and CK2α is an essential catalytic subunit of the holoenzyme. In bladder cancer, ALKBH5 specifically recognizes the m⁶A sites of the 3′ UTR in CK2α mRNA and reduces its stability, thus inhibiting cell glycolysis and proliferation.[121] Furthermore, FTO triggers m⁶A demethylation of PKM2 mRNA and accelerates its translation, thus promoting hepatocellular carcinoma tumorigenesis.[122] 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.[86] YTHDF2 weakens EGFR mRNA stability in an m⁶A-dependent manner and inhibits the MEK/ERK pathway, consequently impeding cell proliferation.[123] METTL3 enhances translation of IKBKB and RELA and activates the nuclear factor κB (NF-κB)

pathway, thus promoting bladder cancer progression.[124] METTL14 overexpression inactivates the phosphatidylinositol 3-kinase (PI3K)/Akt pathway in high glucose-treated HK2 cells through PTEN-affected, HDAC5-mediated epithelial-to-mesenchymal transition (EMT) of renal tubular cells in diabetic kidney disease.[125] YTHDF2 binds directly to the m⁶A modification site in the 3′ UTR of 6-phosphogluconate dehydrogenase (6PGD) gene, thus promoting 6PGD mRNA translation in lung cancer cells.[126] Moreover, Li et al.[127] reported that m⁶A modification of the 5′ UTR region of PDK4 upregulates its translation, elongation, and mRNA stability by binding with the YTHDF1/eEF-2 complex and IGF2BP3, thus enhancing tumor growth and progression of cervical and liver cancers (Table 5). These studies indicate that m⁶A modification plays an important role in glucose metabolism by modulating glycolytic enzymes or associated signaling pathways.

m⁶A 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.[133] METTL3 promotes stability of lncRNA LINC00958 and activates the miR-3619-5p/HDGF axis, thus inducing lipogenesis in HCC. In addition, LINC00958 affects the expression of sterol regulatory element binding transcription factor 1 (SREBP1), FASN, stearoyl-co-enzyme A (CoA) desaturase (SCD1), and acetyl-CoA carboxylase 1 (ACC1), which are implicated in lipogenesis.[128] FTO increases lipid accumulation by activating the SREBP1c/CIDEC signaling pathway in an m⁶A-dependent manner in liver hepatocellular carcinoma

Table 5. Functions of m⁶A RNA modification in metabolic reprogramming of cancer

m⁶A regulators	Molecules	Function	Reference
Glucose metabolism			
METTL3	HK2, GLUT1	METTL3 interacts with the 3′ UTR regions of HK2 and GLUT1 mRNA and enhances its stability, thereby activating the glycolysis pathway	[119]
ALKBH5	CK2α	ALKBH5 specifically recognizes the m⁶A sites of the 3′ UTR in CK2α mRNA and reduces its stability to inhibit cell glycolysis and proliferation	[121]
FTO	PKM2	FTO triggers the m⁶A demethylation of PKM2 mRNA and accelerates its translation, thus promoting hepatocellular carcinoma tumorigenesis	[122]
YTHDF1	Wnt signaling	YTHDF1 facilitates the translation of the Wnt signaling effectors TCF7L2 and TCF4, which are required for the maintenance of intestinal stem cells during regeneration and tumorigenesis	[86]
YTHDF2	MEK/ERK	YTHDF2 weakens EGFR mRNA stability in an m⁶A-dependent manner and thus impairs the MEK/ERK pathway and consequently impedes cell proliferation and growth	[123]
METTL3	NF-κB pathway	METTL3 enhances the translation of IKBKB and RELA and activates NF-κB pathway to promote bladder cancer progression	[124]
METTL14	PI3K/Akt	METTL14 overexpression inactivates the PI3K/Akt pathway in high glucose-treated HK2 cells via PTEN-regulated HDAC5-mediated EMT of renal tubular cells in diabetic kidney disease	[125]
YTHDF2	6PGD	YTHDF2 binds directly to the m⁶A modification site in the 3′ UTR of the 6-phosphogluconate dehydrogenase (6PGD) gene to promote 6PGD mRNA translation in lung cancer cells	[126]
Lipid metabolism			
METTL3	miR-3619-5p/HDGF	METTL3 promotes the stability of lncRNA LINC00958 and activates the miR-3619-5p/HDGF axis to facilitate lipogenesis in HCC	[128]
FTO	SREBP1c/CIDEC	FTO increases lipid accumulation by activating the SREBP1c/CIDEC signaling pathway in an m⁶A-dependent manner in HepG2 cells	[129]
Glutamine metabolism			
FTO, ALKBH5	D2-HG	FTO and ALKBH5 are α-KG-dependent dioxygenases that are competitively inhibited by structurally related metabolite D-2-hydorxyglutarate (D2-HG), leading to abnormal expression of isocitrate dehydrogenase 1 or 2 (IDH1/2)-mutant tumors	[130,131]
YTHDF1	GLS1	YTHDF1 accelerates GLS1 translation, a key enzyme of glutamine metabolism, and promotes colon cancer development	[132]

HepG2 cells (Table 5).[129] 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.[134,135] Glutamine, the most abundant free amino acid, participates in several of pathways in energy generation, macromolecular synthesis, and signal transmission in cancer cells by donating its nitrogen and carbon atoms.[136] Glutamine can be converted into α-KG to replenish the tricarboxylic acid (TCA) cycle through glutamate dehydrogenase (GLUD1) or transaminases.[137] FTO and ALKBH5 are α-KG-dependent dioxygenases and are competitively inhibited by the structurally related metabolite, D-2-hydorxyglutarate (D2-HG), leading to accumulation in isocitrate dehydrogenase 1 or 2 (IDH1/2) mutant tumors.[130,131] In addition, YTHDF1 accelerates glutaminase GLS1 translation, a key enzyme in glutamine metabolism, therefore promoting development of colon cancers (Table 5).[132] These findings imply that m⁶A modification affects glutamine metabolism, resulting in cancer pathogenesis; however-

er, further studies should explore the role of glutamine metabolism of development of different cancers. Moreover, mores 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 lncRNA participates in progression of metabolic diseases.[138] In turn, metabolites and metabolic pathways are involved in regulation of m⁶A RNA modification; for example, TCA cycle
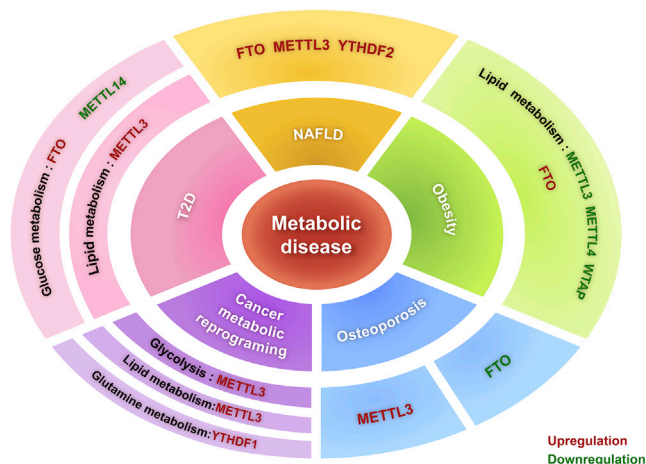
Figure 2. Role of m^{6}A regulators in human metabolic diseases

Obesity mainly involves dysregulation of lipid metabolism, in which the expression of METTL3, METTL14, and WTAP are downregulated, while FTO is upregulated. In T2D, the expression of METTL14 is downregulated and FTO is upregulated in glucose metabolism, with increased expression of METTL3 in fatty acid metabolism. Metabolic disruption in human cancers mainly involves glycolysis and RNA metabolism. High METTL3 activates glycolysis to promote cancer development. The expression of FTO, METTL3, and YTHDF2 are high in the process of NAFLD. In osteoporosis, METTL3 expression is high, while FTO is low.

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 need to urgently explore and develop disease-specific therapeutic targets.[17,140] 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 m^{6}A levels and affect fat formation.[99,142–144] MO-I-500 inhibits m^{6}A demethylase activity of FTO and inhibits colony formation of a triple-negative inflammatory breast cancer cell line.[145] Meclofenamic acid, a nonsteroidal anti-inflammatory drug, selectively inhibits FTO and inhibits GBM cell growth and survival.[146] R-2HG, a major metabolic product of mutant IDH1/2, inhibits FTO activity, thus inhibiting leukemic cell growth/survival and leukemia progression.[147] A more potent FTO inhibitor, FB23-2, inhibits acute myeloid leukemia (AML) progression in xenotransplanted mice.[148] In addition, IOX3, an inhibitor of hypoxia-inducible factor prolyl hydroxylases, can be used to treat immune-related diseases caused by the m^{6}A eraser ALKBH5.[45,149] The methylation inhibitors cycloleucine and S-adenosylhomocysteine can be used to reduce m^{6}A levels,[106,150] whereas a methyl donor, betaine, increases m^{6}A levels.[151]

Resistance to chemoradiotherapy is a major challenge in tumor therapy. m^{6}A 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 m^{6}A modification is related to development of the immune system. Silencing of METTL3 inhibits interleukin (IL)-7 signaling in CD4$^+$ T cells. METTL3-mediated m^{6}A 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 m^{6}A regulators can be combined with anti-PD-1/PD-L1 inhibitors to improve anticancer immunotherapy. The relationship between m^{6}A RNA modification and metabolism should be further explored. Therefore, use of m^{6}A 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 m^{6}A modifications in the cecum and the liver, which affect metabolism, inflammation, and antimicrobial responses in mice.[156] Molecular interactions among human gut microbiota, m^{6}A methylation, and metabolic diseases should be explored in the future.

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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