

REVIEW

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Regulation of m6A methylation in the immune microenvironment in the development of diabetes mellitus

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Abstract

Diabetes mellitus is a widespread metabolic disorder characterized by chronic hyperglycemia, driven primarily by insulin resistance and β -cell dysfunction. N6-methyladenosine (m6A), the most prevalent internal RNA modification in eukaryotes, has emerged as a critical regulator in diabetes pathogenesis. This review outlines how m6A methylation, mediated by writers (METTL3, METTL14), erasers (FTO, ALKBH5), and readers (YTHDFs, IGF2BPs), influences key diabetic processes including β -cell function, lipid metabolism, and insulin resistance. A key focus is on the role of m6A in modulating the immune microenvironment, such as by regulating macrophage polarization and T-cell activity, which contributes to inflammation and disease progression in both type 1 and type 2 diabetes. Furthermore, m6A dysregulation is implicated in multiple diabetic complications. Therapeutic agents, including existing drugs, natural extracts, and specific m6A inhibitors, can modulate m6A levels, highlighting its potential as a therapeutic target. This review synthesizes the evidence linking m6A to diabetes, with an emphasis on immunoregulation, and suggests that targeting m6A pathways offers promise for future treatments.

Keywords Diabetes, m6A, Insulin resistance, B-cell dysfunction, FTO

Introduction

Since the 1960s, over 170 types of Post-translational modifications of RNA have been discovered [1]. N6-methyladenosine (m6A) was first discovered in eukaryotic messenger RNA (mRNA) and viral nuclear RNA during the 1970s, and has been recognized as one of the most prevalent and abundant RNA modifications [2]. The m6A site is mainly located in the RRACH sequence (where R = A or G, H = A, C or U), and it is enriched near

the stop codon, 3' untranslated region (UTR) and long intron [3]. In eukaryotic cells, the methylation of RNA m6A is dynamically regulated by “writers” and “erasers” and recognized by “readers” in various ways [4]. Writers are methyltransferase complexes (MTC) composed of methyltransferase-like 3 (METTL3), methyltransferase-like 14 (METTL14), and many auxiliary subunits [5]. “Erasers”, as the demethylases of RNA, include fat mass and obesity-associated protein (FTO) and ALKB homolog 5 (ALKBH5), can demethylate RNA [6]. Readers are process that m6A recognition proteins (such as the YTH domain family, insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs) and heterogeneous nuclear ribonucleoproteins (HNRNPs)) participate in regulating the circumstance of target transcripts [7–9]. In a large number of studies related to m6A methylation, the imbalance of m6A is associated with many human

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diseases, including obesity, diabetes, heart failure, brain diseases and various cancers [10].

Diabetes is a metabolic disorder which is characterized by chronic hyperglycemia. It is one of the most common and fastest growing diseases in the world. By 2045, diabetes is expected to affect 693 million adults [11]. Among them, insulin resistance (IR) and β -cell dysfunction are the two major pathological characteristics of diabetes. Only when the insulin produced by β -cells is not enough to compensate for insulin resistance, diabetes can occur [12]. The two major features of metabolic syndrome (MetS), insulin resistance and hyperinsulinemia, both lead to the dysfunction of pancreatic β -cells, resulting in ER stress, mitochondrial dysfunction, oxidative stress and inflammation, ultimately leading to cell death [13]. IR is a condition in which the body restricts glucose flux into cells when glucose and free fatty acids (FFA) increase in the blood, thereby preventing nutritional overload and metabolic stress [14]. However, when the feedback circuit between insulin action and insulin secretion operates abnormally, glucose tolerance will be impaired. Because of the existing insulin resistance and the continuous decline of β -cells function, plasma glucose will rise or even exceed the normal range, eventually leading to diabetes [15]. Fat tissue is also closely related to diabetes. It can not only react with hormones and metabolic compounds (such as cortisol, growth hormone and insulin), but also produce and secrete fat factors [16, 17]. The damage of fat function will lead to the interruption of fat storage and energy metabolism, causing metabolic dysfunction and inducing insulin resistance [18], which are important factors to promote the occurrence of diabetes.

m6A plays a critical role in driving the pathogenesis of autoimmune diseases. By regulating the development, activation, migration, and polarization of immune cells, as well as inflammatory pathways, m6A is essential for shaping both innate defense and adaptive immunity. Its involvement has been identified not only in systemic autoimmune diseases such as lupus and rheumatoid arthritis but also in organ-specific disorders including multiple sclerosis and type 1 diabetes [19]. Despite growing evidence linking m6A modification to diabetic pathophysiology, a systematic synthesis of its roles—particularly in reshaping the immune microenvironment—is still lacking. This review summarizes how m6A regulates β -cell function, insulin resistance, and immune cell activity in diabetes, and discusses its therapeutic potential.

The function of m6A in diabetes

Survival and secretion of β -cells

Glucose and other environmental factors regulate m6A methylation in pancreatic β -cells. This methylation plays a critical role in controlling gene expression and

maintaining the normal function of β -cells [20]. One study found that genes with known m6A modifications in pancreatic islets from individuals with type 2 diabetes mellitus (T2DM) are enriched in biological processes relevant to T2DM pathogenesis. This suggests that m6A regulators may participate in modulating gene expression in the pancreatic β -cells of T2DM patients [21]. These regulators are categorized into three groups: “writers” such as METTL3, METTL14, and WTAP; “erasers” including FTO and ALKBH5; and “readers” which involve YTHDF1, YTHDF2, YTHDC1, YTHDC2, IGF2BP2, IGF2BP3, and members of the HNRNP family. Modulation of m6A-related regulators (e.g., METTL3, METTL14, WTAP, YTHDC1) to increase m6A levels confers protection to β -cells against cellular damage and apoptosis, which helps maintain β -cell function.

Autophagy of β -cells

β -cell autophagy serves a protective function, countering challenges such as proinsulin misfolding, insulin secretion defects, and cholesterol-induced ER stress [22]. This protective mechanism is augmented by metformin, which activates AMPK to enhance autophagy and clear accumulated vacuoles, thus inhibiting β -cell apoptosis [23]. Conversely, impaired autophagy induces ER stress, disrupts antigen processing, and increases MHC-I/HLA-I presentation to immune cells. Consequently, β -cells become far more vulnerable to immune-mediated attack and damage [24]. An analysis of perfused human pancreatic islets and hyperglycemic diabetic db/db mice has identified the NR3C1-FTO-m6A-Atg gene axis as the key mediator regulating autophagic flux in pancreatic β -cells. This study demonstrated that excessive and detrimental autophagy, which ultimately promotes diabetes, occurs only under conditions of glycolipid toxicity following the activation of nuclear receptor subfamily 3, group C, member 1 (NR3C1). Furthermore, the research revealed that NR3C1 upregulation increases FTO expression in β -cells. This, in turn, reduces m6A methylation on the mRNAs of four core autophagy-related genes (Atg5, Atg9a, Atg12, and Atg16l2), leading to hyperactivated autophagy and impaired insulin secretion. Pharmacological inhibition of FTO with the small-molecule inhibitor Dac51 in β NR3C1 mice demonstrated a potent therapeutic effect. Within just 2–3 weeks of treatment, the diabetic phenotypes of hyperglycemia and impaired glucose tolerance were dose-dependently alleviated. With prolonged administration, blood glucose levels, glucose tolerance, and serum insulin levels further improved, nearly normalizing to those of the control group [25, 26].

Secretion of β -cells

The methylation of m6A is closely related to the secretion of β -cells. The expression of pancreatic duodenal

homeobox-1 (PDX1) is crucial for integration and regulation of GLP-1R (Glucagon-like peptide-1 receptor)-dependent signaling, which is secreted by α -cell glucagon, as well as essential for the growth, differentiation, and survival of pancreatic beta cells [27]. There is research confirming that m6A methylation controls the insulin/insulin-like growth factor 1 (IGF1)-AKT-PDX1 pathway. By targeting METTL3 or METTL14 to reduce m6A levels, AKT phosphorylation and PDX1 protein levels can be downregulated, leading to cell cycle stand and glucose-stimulated insulin secretion assay (GSIS) damage, thus reproducing human T2D [28]. As a m6A “reader”, the absence of human insulin-like growth factor 2 (IGF2) mRNA binding protein 2 (IMP2) in pancreatic β -cells leads to compensatory decline in β -cell proliferation and function. By directly binding to PDX1 mRNA, IMP2 can promote its translation in an m6A dependent manner. In addition, the deficiency of IMP2 reduces the maintenance of PDX1 peptide stability by downregulating the IGF2-AKT-GSK3 β (glycogen synthase kinase-3 β) - PDX1 pathway, which leads to the damage of insulin secretion [29].

PDX1 suppresses inflammatory signaling through long-range repression of NF- κ B and recruitment of the canonical corepressor SIN3A, thereby protecting β -cells from stress and inflammation. Additionally, it regulates the circadian gene network via CLOCK/BMAL1 regulatory elements to maintain metabolic homeostasis in mature β -cells [30]. PDX1 has further been implicated in chronic inflammation-induced insulin resistance and pancreatic β -cell dysfunction. miR-155, a master regulator of chronic inflammation highly expressed in macrophages, contributes to islet damage through the miR-155-PDX1 axis. Experiments show that targeting PDX1 via miR-155 in islet-resident macrophages impairs β -cell function. In contrast, high-fat diet (HFD) mice treated with a miR-155 sponge lentivirus exhibited increased PDX1 expression and improved β -cell function, while inhibition of miR-155 upregulates PDX1 expression in db/db mouse islets. These results indicate that miR-155-PDX1 axis-mediated islet inflammation suppresses β -cell function by targeting PDX [31]. Beyond its role in inflammation, miR-155 also influences insulin secretion. Under hyperlipidemia-associated endotoxemia, miR-155-5p targets MafB in β -cells, promoting IL-6 expression, which subsequently elevates glucagon-like peptide (GLP) levels and enhances insulin secretion [32].

Methylglyoxal (MG), a major precursor of advanced glycation end products, is elevated in the plasma of patients with type 2 diabetes. MafA, a core regulator of glucose-stimulated insulin secretion (GSIS) and β -cell function, shows reduced expression in pancreatic tissue of MG-induced T2DM rat models [33]. Recent studies indicate that METTL3 can ameliorate MG-induced

insulin secretion dysfunction in pancreatic β -cells by regulating the expression of MafA, which is closely associated with diabetes. In-depth investigation using the β -cell line NIT-1 (neonatal rat insulinoma tumor cell line-1) revealed that METTL3 silencing downregulated m6A levels, mRNA stability, and both mRNA and protein expression of MafA, leading to reduced GSIS indices. MeRIP-qPCR results demonstrated that METTL3 overexpression increased m6A modification on MafA mRNA in MG-treated NIT-1 cells, significantly counteracted MG-induced MafA mRNA decay, and activated insulin transcription [34]. These findings confirm that METTL3 improves MG-induced insulin secretion impairment in β -cells by regulating MafA. Enhancing METTL3 expression to upregulate MafA may represent a novel therapeutic approach for ameliorating MG-induced β -cell dysfunction in diabetes. It is noteworthy that MafA is also involved in islet-related immune responses and influences the progression of type 1 diabetes (T1D). T1D susceptibility genes have been shown to correlate with MAFA expression in human islets [35]. Deficiency of MafA impairs both β -cell and T-cell function, promotes cytokine production in islets, disrupts T-cell activation patterns, and affects the balance of peripheral immune responses against islet autoantigens, leading to local islet inflammation. In MafA-deficient mice, an inflammatory process similar to that observed in T1D occurs, characterized by T-cell accumulation in the pancreas and T-cell-mediated targeting of islets, ultimately resulting in β -cell destruction [36].

Mettl14 plays a crucial role in beta cells. Lacking of Mettl14 leads to cell mortality increases, affecting cell differentiation, reducing beta cell quality and insulin secretion, eventually causing glucose intolerance [37]. Some researchers have studied for transgenic mice lacking Mettl3 and pancreatic explant system, proving that Mettl3 can regulate Hdac1 in the transformation process of endocrine norms in an m6A dependent manner, down regulating the expression of Hdac1 protein, causing abnormal activation of Wnt/Notch signaling pathway and blocking endocrine differentiation, ultimately affecting the formation of endocrine progenitor cell pool [38].

As m6A writer proteins, WTAP and METTL3 are crucial for maintaining islet β -cell function. By stabilizing METTL3, WTAP plays an important role in partially maintaining β -cell function. Furthermore, it is worth noting that other molecular processes may also be involved in the WTAP function in pancreatic beta cells. Upregulation of WTAP or METTL3 maintains beta cell function and helps to reverse hyperglycemia, diabetes and hypoinsulinemia [39].

YTH domain-containing protein 1 (YTHDC1) is a key m6A nuclear reader protein, which is essential of maintaining β -cell function. The down-regulation of YTHDC1

will lead to beta cell failure and diabetes. This may be due to the reduced expression of beta cell specific transcription factors and insulin secretion related genes [40].

Endoplasmic reticulum stress in β -cells

As a core component of the m6A methyltransferase complex, METTL3 deficiency disrupts β -cell identity and insulin secretion while promoting endoplasmic reticulum (ER) stress. In β -cell-specific Mettl3-knockout mice, both Ire1 α and Xbp1—key ER stress markers—were upregulated. METTL3 loss reduced m6A modification on Ire1 α mRNA, whereas METTL3 overexpression suppressed Ire1 α /Xbp1 and restored insulin expression under ER stress conditions [41].

Some studies have shown that beta cells lacking METTL14 can induce diabetes by increasing ER stress. re1 α is a response gene to ER stress, which is modified

by m6A in its last exon and 3' UTR region in mouse insulinoma 6 (MIN6) cells. This further confirms that in β KO islets, both mRNA and protein of Ire1 α and spliced x-box binding protein 1 (XBP-1) are significantly increasing [42]. YTH domain family 2 (YTHDF2) plays an important role in regulating insulin secretion. B-cells lacking YTHDF2 induce glucose intolerance by adjusting insulin secretion and ER stress [43] (Fig. 1).

The maintenance of fat levels

Lipogenesis

Adipose cell differentiation is regulated by multiple mechanisms, among which mitotic clonal expansion (MCE) is a key step. Recent studies have revealed that the decrease in WTAP in mice results in protection against diet induced obesity (DIO), thereby increasing insulin sensitivity. Further research has found that the

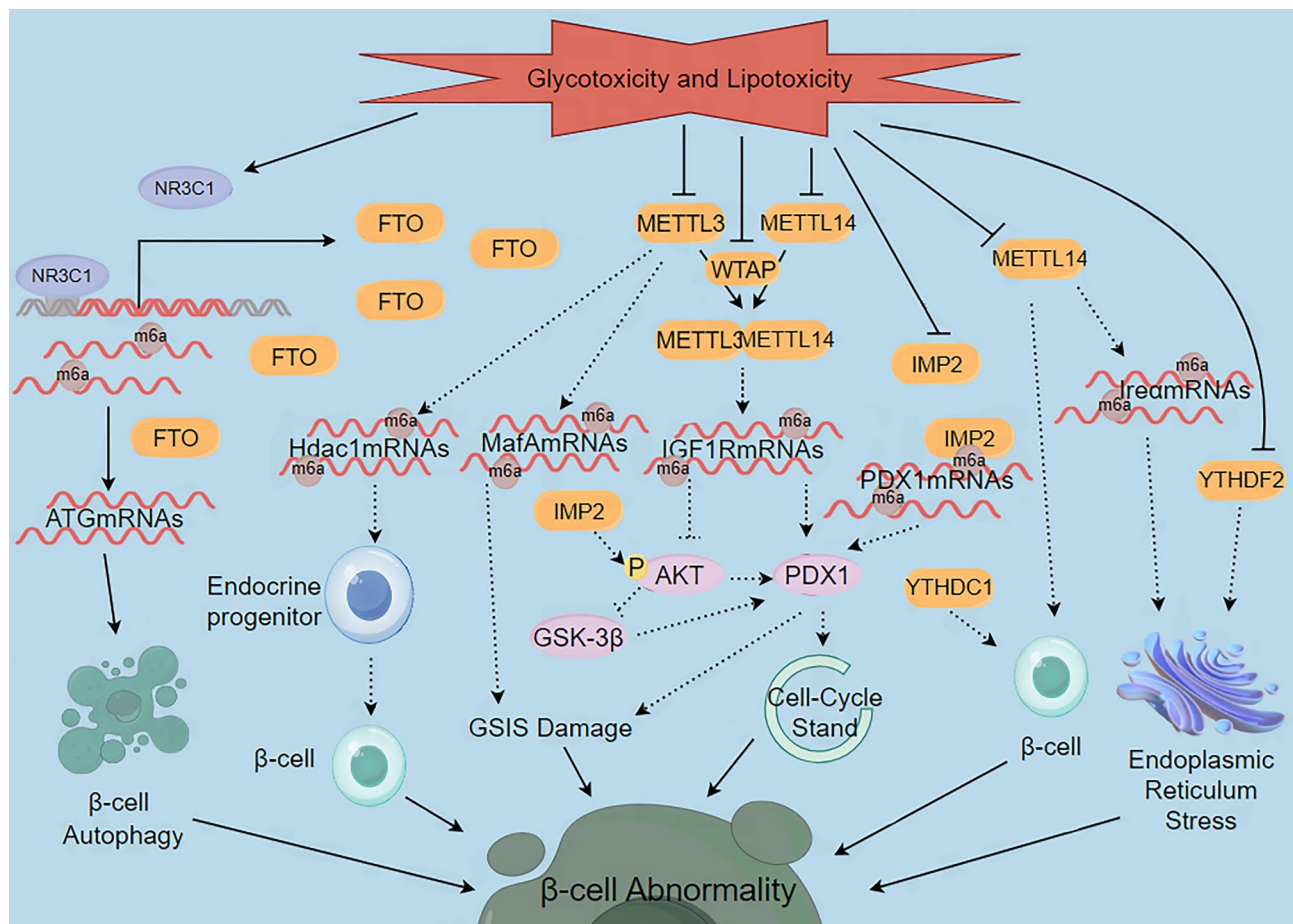


Fig. 1 This figure illustrates the multiple molecular regulatory mechanisms involved in the development of abnormal β -cell function in the context of glycolipotoxicity and lipotoxicity. Glycolipotoxicity enhances the demethylation activity of FTO through upregulation of NR3C1, which demethylates ATG mRNAs (Atg12, Atg5, Atg16l2, and Atg9a), among others, and triggers autophagy in β -cells. Meanwhile, METTL3 and METTL14 perform m6A modification of various mRNAs under WTAP recruitment. However, decreasing the levels of METTL3 and METTL14 can down-regulate AKT phosphorylation and PDX1 protein levels, among which, IMP2 can affect AKT phosphorylation and PDX1 protein levels, which ultimately cause GSIS and Cell - Cycle Stand. In addition, down-regulation of METTL3, METTL14 and YTHDC1 can have direct effects on β -cells through related mechanisms (e.g., reduction of Hdac1 expression), respectively. The inhibited METTL14 and YTHDF2-related pathways induce endoplasmic reticulum stress. The interaction of these factors ultimately leads to β -cell abnormality

downregulation of WTAP may impair the recruitment of METTL3 and METTL14 to mRNA, leading to dysregulation of downstream cell cycle related molecules (including cyclin A2) production, accelerating the cell cycle transition of MCE in adipogenesis, and impairing adipogenesis [44]. After injection of NADPH into both Fto-knockout (with exons 2–4 deleted) and wild-type (WT) mice, a significant decrease in m6A levels was observed in WT mice, whereas no significant change occurred in the knockout mice. This finding confirms that the deletion of Fto blocks the capacity of NADPH to diminish m6A [45]. Regrettably, the study did not succeed in defining the mechanism through which NADP modulates FTO activity, leaving a key question unanswered and highlighting the limitations of the current work. Additional research shows that branched-chain amino acids (BCAA) inhibits the process of MCE by reducing the expression of cell cycle protein-dependent kinase 2 (CDK2) and cell cycle protein A2 (CCNA2) through the coordinated action of G6PD-NADPH-FTO-m6A both internal and external, thereby suppressing lipogenesis. Specifically, dietary BCAA can reduce intracellular NADPH in preadipocytes produced by the pentose phosphate pathway, thus inhibiting FTO expression, increasing m6A levels of CCNA2 and CDK2 mRNA, ultimately causing CCNA2 and CDK2 mRNA decay and blocking the cell cycle [46].

FTO directly targets Atg5 and Atg7 transcripts and promotes their expression in an m6A dependent manner, thereby impacting autophagy and adipogenesis. Pass through in-depth research, it was found that after FTO silencing, transcripts of Atg5 and Atg7 with high m6A levels were captured by YTHDF2, leading to mRNA degradation and reduced protein expression, alleviating autophagy and lipogenesis [47]. FTO inhibits the binding of serine-rich splicing factor 2 (SRSF2) to exon splicing enhancer (ESE) by demethylating m6A RRACHs near ESE, which controls the exon splicing of lipid regulatory factor RUNX1 translocation partner 1 (RUNX1T1) and regulates the expression of RUNX1T1 subtype, thereby contributing to adipogenesis [48]. FTO regulates the proliferation and differentiation of 3T3-L1 cells, which is a pre-adipose cell line, through various mechanisms, including peroxisome proliferator-activated receptor gamma (PPAR γ) and PI3K/ATK signaling [49]. Inhibition of FTO represents a crucial pathway for reducing fat accumulation, concurrently diminishing white adipose tissue (WAT) inflammation and immune cell recruitment. Research on the mechanism by which adipose-derived stem cell (ADSC) exosomes ameliorate obesity and metabolic disorders has revealed that FTO inhibition enables miR-1246 to regulate macrophage polarization, adipogenesis, and the pro-beiging process in WAT. Downregulation of FTO mitigates hypertrophy and hyperplasia of white adipocytes, thereby reducing WAT

inflammation and the recruitment of immune cells. This shift in the inflammatory milieu suppresses M1 macrophage polarization while promoting an M2-dominant phenotype, ultimately enhancing systemic insulin sensitivity [50]. Together, these mechanisms coordinately regulate WAT homeostasis and restore systemic metabolic balance, positioning miR-1246 as a promising therapeutic candidate for obesity and related metabolic disorders. When administered to HFD-induced obese mice, miR-1246 elicited beneficial effects on obesity and metabolic parameters that were equivalent to those achieved with iADSC-EXO treatment [51].

The extracellular signal-regulated kinase (ERK) pathway, a well-established signaling cascade involved in adipogenesis and cell differentiation, is also subject to m6A-mediated regulation [52]. Through the IGF2BP3-MYLK-ERK1/2 regulatory axis, IGF2BP3 inhibits the production of adipocyte in high-fat diet (HFD) mice thereby reducing body weight and insulin resistance. Specifically, insulin-like growth factor 2 mRNA-binding protein 3 (IGF2BP3) enhances the stability of myosin light chain kinase (MYLK) mRNA by binding to its m6A site. Subsequently, MYLK inhibits phosphorylation of the ERK1/2 pathway, thereby blocking adipogenesis and differentiation of Mesenchymal stem cells (MSCs) [53].

Mitochondrial carrier homolog 2 (MTCH2) is an obesity susceptibility gene. There is evidence to suggest that YTHDF1 directly targets the MTCH2 transcript, enhancing the translation of this protein in muscle pre-adipocytes in an m6A dependent manner [54].

Lipolysis

A study has proposed a obesity epigenetic transcriptome reprogramming paradigm centered around METTL14/m6A. The abnormal upregulation of adipose METTL3 and METTL14 by obesity inducing factors induces m6A methylation of adrenoceptor beta 2 (Adrb2), adrenoceptor beta 3 (Adrb3), adipose triglyceride lipase (Atgl), and comparative gene identification-58 (Cgi-58), driving lipocatecholamine resistance and lipolysis inhibition, leading to white adipose tissue (WAT) amplification, obesity progression, and metabolic diseases [55]. Support for this comes from studies on adipocyte-specific Mettl14 knockout (Mettl14 Δ fat) mice, demonstrating that the ablation of Mettl14 attenuates HFD-induced obesity, insulin resistance, glucose intolerance, and NAFLD, alongside increased β -adrenergic signaling and lipolysis in WAT [55]. Angiopoietin-like 4 (Angptl4) is a fat factor that stimulates intracellular fat breakdown. There is research confirming that FTO in adipocytes regulates intracellular lipolysis in adipocytes by upregulating the translation of Angptl4 in adipose tissue, thereby partially regulating body weight. The qPCR analysis revealed significantly elevated Angptl4 mRNA levels in AFO mouse adipose

tissue compared to wild-type mice under both fed and fasted conditions. Adenoviral FTO expression inhibited LPL activity in wild-type mouse adipocytes, an effect abolished in *Angptl4*-deficient mouse adipocytes. Moreover, *Angptl4* adenovirus administration restored body weight, triglyceride levels, and lipolysis in AFO mice after isoproterenol stimulation [56].

In a study investigating the relationship between ANGPTL4 and LPL expression and human obesity, researchers found that obese individuals with abnormal glucose metabolism had significantly higher ANGPTL4 expression levels than obese individuals with normal glucose tolerance. Furthermore, the omental adipose tissue of obese subjects with high ANGPTL4 expression showed signs of inflammation and meta-inflammation,

characterized by upregulation of biomarkers related to cell death, cellular stress, and stromal remodeling. These findings suggest that overexpression of ANGPTL4 in visceral adipose tissue may be associated with local metabolic dysfunction and inflammatory conditions [57] (Fig. 2).

Insulin resistance (IR)

Insulin receptor substrate (IRS)

The established link between IRS dysfunction and insulin resistance is further elucidated by METTL3-mediated m6A methylation of CYP2B6. Elevated CYP2B6 expression, observed in NAFLD patients' livers, impairs IRS phosphorylation and GLUT2 membrane translocation, thereby exacerbating insulin resistance. Notably,

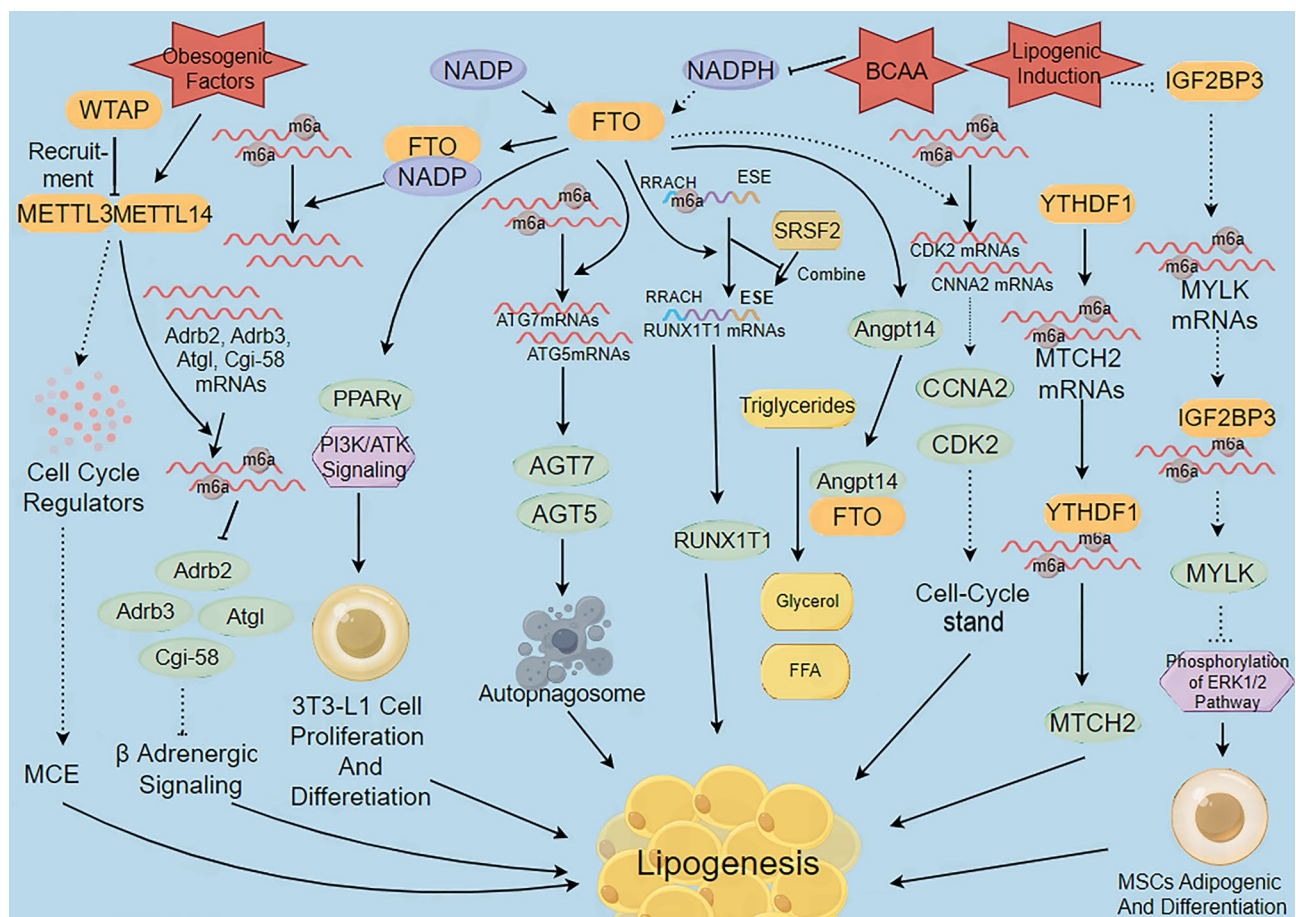


Fig. 2 As shown in Fig. 2, the multilevel molecular network of m6A modifications regulating fat metabolism is demonstrated. Obesogenic Factors (OF) recruit METTL3/METTL14 through WTAP, m6A modification of specific mRNAs (e.g., *Adrb2*, *Adrb3*, etc.), which affects β -adrenergic signaling and the cell cycle transition of MCE in adipogenesis. m6A-modified mRNAs are demethylated by FTO with the involvement of NADP and inhibited by BCAA, thus preventing the expression of FTO and increasing the adipose metabolism of MCE. FTO demethylates the m6A-modified mRNAs with the participation of NADP and inhibits NADPH with the participation of BCAA, thus preventing the expression of FTO, increasing the m6A level of *CDK2* and *CCNA2* mRNAs, causing their decay and stopping the cell cycle. FTO itself can regulate related mRNAs through multiple signaling pathways, such as *RUNX1T1*, *ATG5/ATG7*, *Angptl4*, *PI3K/Akt* signaling, etc., affecting cell autophagy, triglyceride metabolism and other processes, which ultimately lead to adipogenesis. In addition, *YTHDF1* directly targets the *MTCH2* transcript to enhance the translation of this protein, and *IGF2BP3* affects the lipogenic differentiation of MSCs by means of the *IGF2BP3-MYLK-ERK1/2* regulatory axis. Together, these mechanisms constitute a synergistic regulatory network of m6A modification-mediated lipid metabolism disorders

METTL3 knockdown combined with CYP2B6 overexpression significantly attenuates insulin signaling pathway phosphorylation [58].

Adipose Browning

The transplantation of brown adipose tissue (BAT) improves systemic energy metabolism and enhances insulin sensitivity induced by HFD. Brown adipose tissue (BAT) transplantation enhances systemic energy metabolism and insulin sensitivity in high-fat diet (HFD) models. It upregulates fatty acid oxidation genes (e.g., MCAD, PPAR α , PGC1 α , CPT1 β , UCP), reverses HFD-induced physical inactivity, and ameliorates hepatic steatosis and BAT hypertrophy. BAT transplantation also downregulates hepatic PPAR γ 2 and TNF α expression, improves glucose homeostasis, and reduces pro-inflammatory cytokines (IL-6, TNF- α) in white adipose tissue [59]. Stimulating BAT development or expanding BAT pool may be a feasible strategy for treating diabetes.

Studies have shown that FTO deficiency upregulates m6A levels of hypoxia-inducible factor 1 alpha (Hif1 α) mRNA, which is then recognized by YTHDC2, leading to increased mRNA translation and upregulation of Hif1 α protein abundance. Hif1 α activates transcription of thermogenic genes, including peroxisome proliferator-activated receptor gamma coactivator 1-Alpha (Ppargc1a), PR domain containing 16 (Prdm16), and peroxisome proliferator-activated receptor gamma (Pparg), ultimately promoting uncoupling protein-1 (UCP) expression and process of adipose browning [60]. The BAT specific deficiency of Mettl3 inhibits the maturation of BAT in internal by reducing m6A modification and the expression of Prdm16, Pparg, and Ucp1 transcripts, ultimately leading to a significant reduction in adaptive thermogenesis mediated by BAT and promoting obesity which is induced by HFD and systemic insulin resistance [61]. In an in vitro model study targeting the regulation of HIF-1 α to promote m6A modification of SOX2 mRNA and delay wound healing in diabetic foot ulcers, it was found that METTL3 knockdown exhibited an antagonistic effect with HIF-1 α knockdown [62]. These observations suggest that METTL3 may potentially influence HIF-1 α expression or function.

There is experimental evidence that the prostaglandin E2- prostaglandin E2 receptor EP3 subtype (PGE2-EP3) axis controls BAT development through the PKA/ERK/WTAP/ZFP410 pathway. To elaborate, among the four PGE2 receptor isoenzymes (EP1-EP4), EP3 eliminates the inhibition of ERK1/2 mediated by PKA, preventing ubiquitin mediated WTAP degradation. Then, it activates m6A modification mediated by WTAP to stabilize zinc finger protein 410 (Zfp410) mRNA, thus promoting brown gene expression [63].

IMP2 can bind to many mRNAs encoding mitochondrial components both external and internal, and inhibit their steady-state translation rates. It may also be necessary to transport these mRNAs to the vicinity of mitochondria, where their positioning translation can promote mitochondrial co-translation absorption. It has been confirmed that IMP2 can bind to Ucp1 mRNA and inhibit its translation [64] (Table. 1).

Fat acid

FASN catalyzes the final step in the fatty acid (FA) biosynthetic pathway and is considered a key determinant of the maximal capacity for FA synthesis via de novo lipogenesis in tissues, particularly the liver. In patients with NAFLD, hepatic mRNA expression of fructokinase (a key enzyme in fructose metabolism) and FASN is elevated [65]. Studies in aged rats with large adipocytes have also revealed significantly reduced FA synthase activity due to decreased cellular FASN content, leading to impaired FA synthesis and contributing to insulin resistance in these enlarged cells [66]. The endogenous FA biogenesis catalyzed by FASN appears to play an essential role in integrating multiple signaling pathways that regulate lipid metabolism, proliferation, and survival in human epithelial cells. Furthermore, FASN coordinately regulates genes, proteins, and activation states closely associated with the natural progression of insulin-related metabolic disorders. Through regulating glucose-insulin axis, fatty acid synthase (FASN) plays an important role in the pathogenesis of metabolic diseases characterized by insulin resistance [67]. Interestingly, some researchers have found that METTL3 silencing downregulates m6A methylation and total mRNA levels of FASN, thereby improving insulin sensitivity and making a negative impact on fatty acid metabolism [68]. This observation further underscores that METTL3, as a critical m6A regulator, serves an indispensable function in modulating fatty acid metabolism and insulin resistance pathways (Fig. 3) (Table 1).

Complication

Eye (diabetes retinopathy, diabetes cataract)

It has been reported that METTL3 regulates high glucose (HG) induced human lens epithelial cells (HLEC) and then causes diabetes cataract (DC). In detail, METTL3 specifically targets the 3'UTR of intercellular adhesion molecule 1 (ICAM-1) to stabilize mRNA stability and increase its protein expression. When METTL3 is down regulated, it enhances the proliferation of HG induced HLECs (Human lens epithelial cells) and inhibits their apoptosis [69]. Interestingly, in this study, the relationship between ICAM-1 and DC was not explained. On the contrary, some studies showed that diabetes induced endothelial ICAM-1 up-regulated most in the retina. The

Table 1 The metabolic mechanism of m6A methylation

Consequences of action		m6A molecule	Molecules involved	Refer- ence
β-cells	Inhibit autophagy	Upward revision of FTO	NR3C1-FTO-m6A modifications-Atg genes axis 21	[25]
		Downward revision of METTL3 or METTL14	Control insulin/IGF1-AKT-PDX1 pathway	[28]
		Downward revision of METTL3	Modulation of MafA expression ameliorates impaired insulin secretion in MG pancreatic β-cells	[34]
	Inhibit secretion		Down-regulation of Hdac1 protein aberrantly activates the Wnt/Notch signaling pathway, affecting the formation of endocrine progenitor cell pools	[38]
		Upward revision of WTAP	Stabilization of METTL3 partially maintains β-cell function	[39]
		Downward revision of IMP2	Down-regulation of the IGF2-AKT-GSK3β-PDX1 pathway reduces stabilization of PDX1 peptides	[29]
		Downward revision of YTHDC1	Decreased expression of β-cell-specific transcription factors and insulin secretion-related genes	[40]
		Downward revision of Mettl14	Increases cell death rate, affects cell differentiation	[37]
		Downward revision of METTL3	Increased endoplasmic reticulum stress through upregulation of Ire1α and Xbp1	[41]
		Downward revision of METTL14	Increased endoplasmic reticulum stress through upregulation of Ire1α	[42]
	Promote endoplasmic reticulum stress	Downward revision of YTHDF2	Regulation of insulin secretion and ER stress induced glucose intolerance	[43]
		Downward revision of WTAP	Dysregulated production of cell cycle-related molecules including cell cycle protein A2, accelerating the cell cycle transition of MCE in adipogenesis	[44]
fat levels	Promote lipogenesis	Upward revision of FTO	NADP bind to FTO, than promote RNAm6A demethylation and adipogenesis	[45]
			Increase expression of CDK2 and CCNA2 to promote the process of MCE	[46]
	Inhibit lipolysis		Promote the expression of Atg5 and Atg7, and than promote autophagy and lipogenesis	[47]
			Control of exon splicing of the lipidogenic regulator RUNX1T1, thereby regulating RUNX1T1 isoform expression	[48]
			PPARγ and PI3K/ATK signaling regulate	[49]
			suppresse M1 macrophage polarization while promoting an M2-dominant phenotype	[50]
		Upward revision of IGF2BP3	IGF2BP3-MYLK-ERK1/2 regulating axis	[53]
		Upward revision of YTHDF1	Enhanced translation of MTCH2 protein in intramuscular preadipocytes	[54]
		Upward revision of Mettl3 and Mettl14	Induction of m6A methylation of Adrb2, Adrb3, Atgl, and Cgi-58 drives fat catecholamine resistance and lipolysis inhibition	[55]
		Upward revision of FTO	In part through posttranscriptional regulation of Angptl4	[56]
		Upward revision of METTL3	Increased CYP2B6 expression impeded IRS phosphorylation and GLUT2 translocation to the membrane	[58]
		Downward revision of FTO	Up-regulation of HIF1A protein abundance and HIF1A activation of thermogenic gene transcription	[60]
IR	Affect IRS	Downward revision of Mettl3	Reduced expression of Prdm16, Pparg and Ucp1 transcripts and inhibited BAT maturation in vivo	[61]
		Upward revision of WTAP	Stabilizes Zfp410 mRNA, to promote brown gene expression	[63]
	Promote adipose browning	Upward revision of IMP2	bind to Ucp1 mRNA and inhibits its translation	[64]
		Downward revision of Mettl3	downregulates m6A methylation and total mRNA levels of FASN	[68]
	Inhibit fatty acid metabolism			

obvious induction of ICAM-1 on the surface of endothelial cells would lead to the increase of leukocyte adhesion to these endothelial cells, and then lead to retinal microvascular leakage and degradation [70].

Protein kinase C eta (PKC - η), FAT atypical cadherin 4 (FAT4), and platelet-derived growth factor receptor alpha (PDGFRA) play a key role in peri cellular function. Under the stress of diabetes, METTL3 triggers the

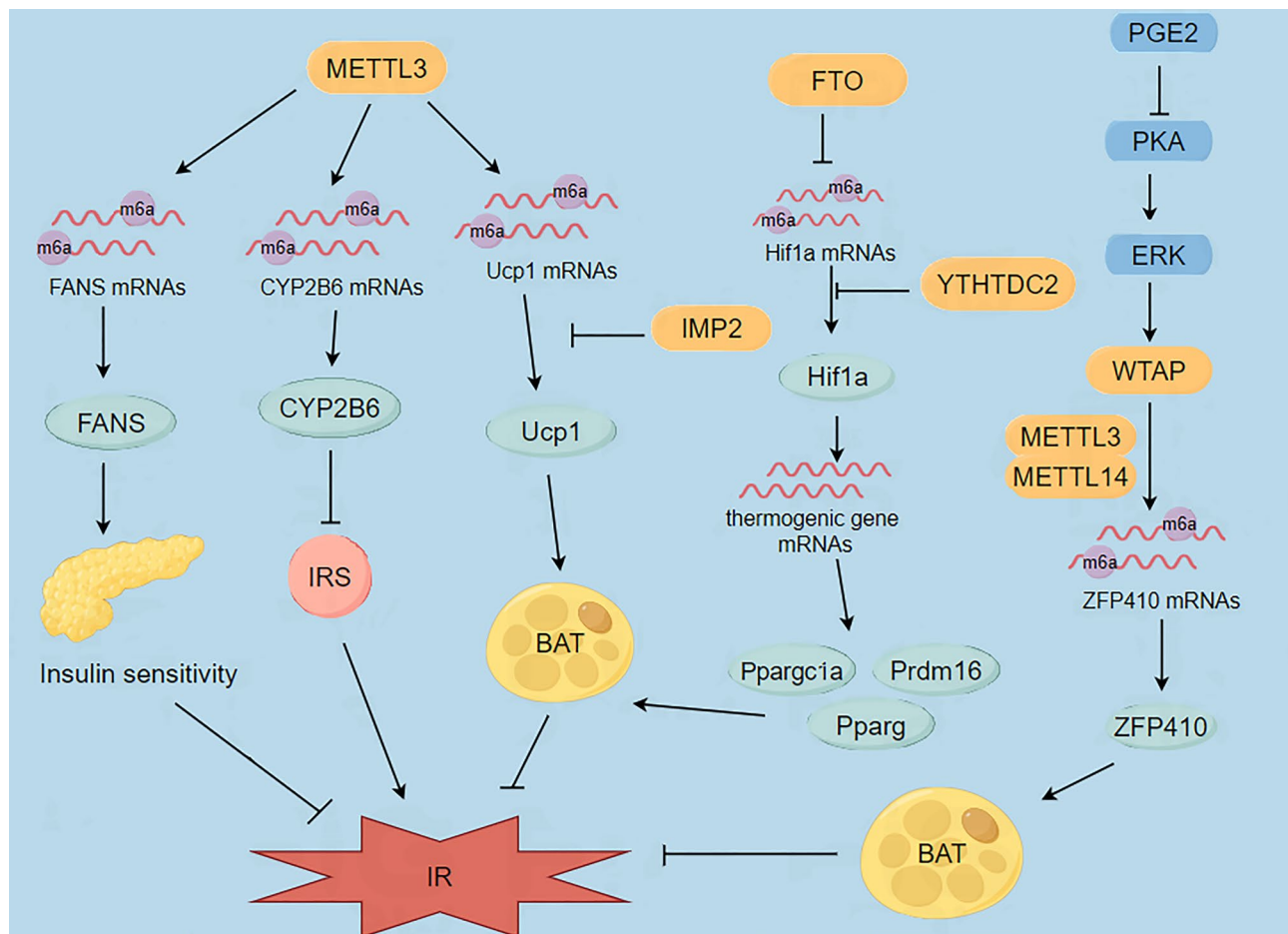


Fig. 3 The figure illustrates the molecular mechanisms related to insulin resistance (IR), focusing on the roles of METTL3, FTO, and other molecules in insulin receptor substrate - related processes, adipose browning, and fatty acid metabolism. In the context of insulin receptor substrate (IRS), METTL3 regulates the m6A methylation of CYP2B6 gene. Overexpression of CYP2B6 inhibits IRS phosphorylation and GLUT2 translocation, accelerating IR. Regarding adipose browning, FTO deficiency increases the m6A levels of Hif1a mRNA, which is recognized by YTHDC2, leading to increased Hif1a protein. Hif1a activates thermogenic genes, promoting adipose browning. METTL3 deficiency in BAT reduces m6A modification and the expression of key genes, decreasing adaptive thermogenesis and promoting IR. The PGE2 - PKA - ERK - WTAP - ZFP410 pathway also controls BAT development, with WTAP - mediated m6A modification stabilizing Zfp410 mRNA. IMP2 can bind to Ucp1 mRNA and inhibit its translation. For fatty acid metabolism, METTL3 silencing downregulates the m6A methylation and total mRNA levels of FASN, improving insulin sensitivity and affecting fatty acid metabolism. The overall network shows how these molecular interactions either promote or inhibit IR through different pathways related to various physiological processes

RNA modification on its downstream mRNA transcripts and coordinates YTHDF2 to bind to the mRNA of m6A modified PKC η , FAT4 and PDGFRA and induce their degradation, ultimately damaging the proliferation and differentiation of pericytes and causing diabetes retinopathy [71].

The retinal pigment epithelium (RPE) cells are the main cells of the retina. A study has found that overexpression of METTL3 alleviates high glucose induced pyroptosis in RPE cells by regulating the miR-25-3p/PTEN/ATK signaling cascade of diGeorge syndrome critical region 8 (DGCR8) [72]. DGCR8 is located in the 22q11.21 region of human chromosome 22 and is classically involved in the synthesis of miRNAs. Its absence increases the risk of immunodeficiency and autoimmune diseases [73].

There are studies claiming that METTL3 regulates endothelial mesenchymal transition in DR through the SNHG7/KHSRP/MKL1 axis. METTL3 enhances the stability of small nucleolar RNA host gene 7 (SNHG7) by installing m6A modification to increase its expression, while SNHG7 binds to KH-type splicing regulatory protein (KHSRP) to downregulate the stability of megakaryoblastic leukemia 1 (MKL1) mRNA. Downregulation of MKL1 inhibits HG induced EndoMT in HRMEC, achieving the goal of preventing EndoMT in DR [74]. Recent research reports have revealed the relationship between ALKBH5 and diabetes retinopathy. In detail, the decrease of ALKBH5 expression leads to the increase of m6A modification level, the decrease of mRNA stability, the acceleration of A20 mRNA degradation, and the decrease of A20 expression, which leads to the increase

of M1 polarization of retinal microglia, and ultimately causes retinal inflammation and participates in the development of diabetes retinopathy [75].

Recently, researchers noticed that lactate mediated histone lactylation histone H3 lysine 18 lactylation (H3K18la) in diabetes promotes the up regulation of FTO in endothelial cells (EC). In depth research has found that upregulated FTO increases CDK2 expression by regulating the stability of CDK2 mRNA. Subsequently, YTHDF2 mediates integrin subunit beta 1 (ITGB1) mRNA instability in an m6A-YTHDF2 dependent manner to inhibit EC proliferation and tube formation, thereby alleviating DR progression [76].

Sirtuin 1 (SIRT1) is a classic regulatory factor for autophagy, inflammation, and cellular aging. Researchers have found that METTL3 mediated m6A modification disrupts the stability of SIRT1 mRNA in a YTHDF2 dependent manner, thereby inducing aging in the human lens epithelial cell line human lens epithelial cell line B3 (HLEB3) [77].

Heart (DCM (diabetes cardiomyopathy))

DCM is closely associated with cardiomyocyte pyroptosis in an NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) dependent manner. Recent research reports indicate that upregulation of METTL14 increases the m6A methylation level of the terminal differentiation-induced non-coding RNA (TINCR) gene, while YTHDF2 mediates the degradation of TINCR, ultimately leading to downregulation of lncRNA TINCR. The downregulation of TINCR will lead to its inability to effectively increase the stability of NLRP3 mRNA and inhibit the activation of NLRP3 apoptosis-related proteins [78].

Db/db mice are mature models of type 2 diabetes, researchers have proposed that overexpression of FTO can improve the cardiac systolic and diastolic function in db/db mice. Based on its experiments, FTO may reduce myocardial fibrosis and hypertrophy by catalyzing the demethylation of m6A on specific mRNA subgroups (such as myocyte enhancer factor 2a (Mef2a), kruppel-like factor 15 (Klf15), B-cell lymphoma 2 like 2 (Bcl2l2), cluster of differentiation 36 (Cd36), and solute carrier family 25 member 33 (Slc25a33)), thereby improving cardiac function [79]. Among them, KLF15 can affect myocardial hypertrophy by inhibiting MEF2 and GATA4 transcription, and can reduce myocardial fibrosis by downregulating the expression of transforming growth factor- β (TGF- β), connective tissue growth factor and myocardin-related transcription factor-A in myocardial fibroblasts [80].

Antisense of IGF2R non-protein coding RNA (Airn) directly binds to IMP2 to exert anti fibrotic effects and inhibit its ubiquitination dependent degradation. In addition, we found that Airn/IMP2 protects p53 mRNA from

m6A degradation, inhibits fibroblast activation, and suppresses cardiac fibrosis by affecting the stability of its target genes, the presence of p53 can enhance the inhibitory effect of Airn on fibroblast activation and cardiac fibrosis to achieve the effect of alleviating diabetic myocardial fibrosis [81].

Kidney (DN (diabetes nephropathy))

Recent research has revealed that METTL3 is overexpressed in type 1 and type 2 diabetic nephropathy, and upregulates the m6A modification level of tissue inhibitor of metalloproteinase 2 (TIMP2) in podocytes through an IGF2BP2 dependent mechanism to enhance its stability. TIMP2 may upregulate the Notch3/4 signaling pathway by inhibiting MT1-MMP (membrane-type 1 - matrix metalloproteinase), mediating DN podocyte inflammation and apoptosis [82].

Recent studies have found that METTL14 can aggravate high glucose induced glomerular endothelial cell injury and diabetes nephropathy by down-regulation of α - klotho via methylation of m6A RNA [83]. There is research confirming that HG - induced p300 promotes WTAP transcription in HK-2 cells through histone H3 lysine 27 (H3K27) acetylation, and WTAP may promote m6A methylation of NLRP3 mRNA, thereby upregulating the levels of NLRP3 inflammasome and pro-caspase-1. The active caspase-1 further lysed gasdermin D (GSDMD) to form GSDMD-N, which contains an N-terminal domain attached to the membrane lipid and forms a pore, resulting in cell pyrolysis [84]. GSDMD-N was active in inducing cell permeability, lysis and release of pro-inflammatory cytokines [85]. Studies in HK-2 cells and db/db mice have demonstrated that WTAP can be knocked down to reduce m6A methylation of NLRP3 mRNA or directly knock out NLRP3, thereby reducing renal tissue cell pyroptosis, restoring renal function, and reducing the release of pro-inflammatory factors [86]. Therefore, WTAP and NLRP3 have broad therapeutic prospects in diabetic nephropathy.

The specific deficiency of SIRT1 podocytes exacerbates proteinuria and podocyte damage in adriamycin (ADR) or DN mice. In this context, some researchers have confirmed that the increase of METTL14 dependent RNA m6A modification downregulates the stability of SIRT1mRNA in damaged podocytes through post transcriptional regulation, aggravating podocyte injury and proteinuria [87]. Recent studies have revealed that FTO regulates the m6A levels, RNA stability, and expression of lncRNA ENST0000436340 in podocytes. ENST0000436340 is likely to act as a protein scaffold to recruit polypyrimidine tract binding protein 1 (PTBP1) to RAS-related protein rab-3B (RAB3B) to promote RAB3B mRNA degradation. Downregulation of RAB3B may lead to cytoskeletal rearrangement, which may result

in glucose transporter 4 (GLUT4) translocation to the plasma membrane being inhibited, leading to insulin resistance, which is an important cause of DK occurrence and progression [88].

There is evidence to suggest that calmodulin-dependent protein kinase I (CAMK1) expression may be associated with DN progression, and starbase software predicts a possible interaction between IGF2BP3 and CAMK1. Based on the above background, some researchers speculate and verify the hypothesis that IGF2BP3 stabilizes CAMK1, inhibits mitochondrial fission, and slows down the DN process. Through this study, we hope to provide new potential molecular targets for the treatment of diabetes neuropathy [89].

The overexpression of METTL14 alleviates histone deacetylase 5 (HDAC5) mediated epithelial mesenchymal transformation (EMT) of renal tubular cells in diabetes nephropathy by enhancing phosphatase and tensin homolog (PTEN) induced inactivation of PI3K/ATK pathway in high glucose treated HK2 cells, and subsequently down-regulation of HDAC5 expression, thus improving the performance and phenotype of diabetes nephropathy [90].

Vascular (diabetes angiopathy)

Some experimental studies have shown the relationship between FTO-TNIP1-NF- κ B network and vascular endothelial changes induced by diabetes. Specifically, overexpression of FTO downregulates the inflammatory core regulatory factor TNIP1, inhibits TNIP1 to physically link A20 with inhibitor of kappa B kinase gamma (IKK γ), and positively regulates A20 mediated IKK γ deubiquitination, thereby inhibiting the action of nuclear factor κ B (NF- κ B). The promoted NF- κ B increases inflammatory cytokines (IL-1 β and IL-18) in an m6A dependent manner, ultimately leading to endothelial dysfunction [91].

In atherosclerosis, m6A methylation upregulates WTAP expression to promote SMC proliferation and migration, while ALKBH5 upregulation in ECs induces cell proliferation and migration involved in germinated angiogenesis, and enhances macrophage activation and differentiation through METTL3 and YTHDF2 [92, 93]. SMC and macrophages play an important role in the formation of atherosclerotic plaques.

In diabetic wounds, elevated glucose levels disrupt autophagy and impede cellular migration and re-epithelialization—a process that is complexly regulated by m6A methylation [94]. The m6A writer METTL3 can modify the lncCCKAR-5 molecule, enhancing the formation of the lncCCKAR-5/LMNA/MKRN2 complex in human umbilical cord mesenchymal stem cells (hUCSCs). This complex subsequently promotes the expression of aging-related genes and ubiquitin-mediated degradation of

LMNA, while inhibiting autophagy processes. These mechanisms collectively impair the wound healing capacity of hUCSCs in diabetic nude mouse models [95].

Liver (nonalcoholic fatty liver disease (NAFLD))

Rubicon (containing a RUN structural domain and a cysteine-rich structural domain) act as a negative regulator of classical autophagy and endosomal transport [96]. An experimental study evidenced that NAFLD lipotoxicity is able to raise the m6A modification level. Specifically speaking, up-regulated METTL3 is directly combined with Rubicon mRNA and mediates m6A modification, after that, YTHDF1 interacts with m6A-tagged Rubicon mRNA promoting its stability and reducing its degradation. Then, with its content increasing, Rubicon inhibits the fusion of autophagosomes with lysosomes and hinders lipid droplets (LDs) clearance, further aggravating NAFLD [97]. With uniquely linked to lipids, insulin could stimulate FTO transcription through a mechanism related to the role of intranuclear insulin receptor beta. By demethylating m6A sites, FTO could enhance the stability of two major lipogenic transcription factors' mRNAs, sterol regulatory element binding transcription factor 1 (SREBF1) and carbohydrate responsive element binding protein (ChREBP) [98].

Dysregulation of triglyceride (TG) homeostasis plays an important role in the pathogenesis of NAFLD [99]. Researchers have found that in obese mice, ectopic overexpression of Ythdc2 in the liver improves hepatic steatosis and insulin resistance. Through further investigation of the mechanism, the researchers concluded that Ythdc2 may bind to mRNAs of adipogenic genes, including sterol regulatory element-binding protein 1c, fatty acid synthase, stearoyl coenzyme A desaturase 1, and acetyl coenzyme A carboxylase 1, and then decrease their mRNA stability and inhibit their gene expression, which ultimately regulate hepatic lipogenesis and TG homeostasis [100]. Some experimentalists have carefully constructed a new NAFLD mouse model, and accordingly, they have found that overexpression of METTL14 and METTL3 binds to the mRNA of ATP citrate lyase (ACLY) and stearoyl-CoA desaturase1 (SCD1), while increases the expression of both proteins. After that, it enhances the synthesis of fatty acid (FA) and the accumulation of lipids, which further enhances the chronic inflammation, apoptosis, and DNA damage, and finally causes the overcompensatory cell proliferation in the liver and the progression of NAFLD and hepatocellular carcinoma (HCC) [101]. Fragile X messenger ribonucleoprotein 1 (FMR1) is the RNA Binding Protein (RBP) gene for FASN. It has been suggested that m6A RNA methylation may recognize RBP of FASN regulates lipid metabolism-related genes induced by high fructose diet (HFrD),

which leads to lipid metabolism disorders and ultimately NAFLD [102].

It was recently studies have confirmed that when circadian rhythms are disrupted, the *Bmal1* gene is downregulated in the liver, leading to the accumulation of ROS. What's more, ROS upregulate *METTL3* to increase mRNA methylation and subsequently causing an increased expression of *YTHDF2*. *YTHDF2* can recognize m6A modified *PPARα* mRNA to inhibit *PPARα* expression, increase *PPARα* m6A abundance and reduce *PPARα* mRNA lifespan and expression, thereby increasing lipid accumulation in cells, leading to oxidative damage, fatty liver and lipid metabolism abnormalities and elevated levels [103]. In another recent study, it was evidence that *IMP2* combines and stabilizes mRNAs of *PPARα* and carnitine palmitoyltransferase 1 A (*CPT1A*), key regulators of hepatic fatty acid oxidation. When the *IMP2* absents, the abundance of these mRNAs was down-regulated, leading to reduced mitochondrial fatty acid oxidation. As time goes by, hepatic triglycerides accumulate in hepatic *IMP2*-deficient mice fed a high-fat diet, eventually appearing elevated circulating triglycerides and mildly elevated blood glucose [104].

Recently, Yvette Simon et al. elegantly demonstrated that animals with a liver-specific overexpression of the insulin-like IGF2 (growth factor 2) mRNA-binding protein p62/*IMP2*-2/*IGF2BP2*-2 exhibit significantly raised levels of chemokine (C-C motif) ligand 2 (*CCL2*) expression when fed a methionine-choline-deficient (MCD) diet which can simulate the full stage of NAFLD [105]. Meanwhile, the *CCL2*/*CCR2* axis critically regulates monocyte/macrophage infiltration in the liver during injury and plays an functionally important role in hepatic inflammation and fibrosis [106]. In addition, some findings confirmed that *MYC* is downwarded in NAFLD and associated with various m6A regulators. Higher *MYC* mRNA levels were associated with higher HDL cholesterol and unsaturated fatty acid ratios, as well as lower fat mass, glucose and transaminase [107]. Taken together, dysregulation of m6A methylation caused steatosis and fibrosis, affecting the occurrence of NAFLD, and *MYC* might be its potential target.

By slowing down weight gain, decreasing lipid accumulation, and increasing insulin sensitivity, it has been proposed that hepatocyte-specific knockdown of *Mettl3* remarkably alleviates HFD-induced metabolic disorders [108]. Based on this, some researchers have further explored and found that absence of *METTL3* in macrophages leads to a significant up-regulation of DNA Damage Inducible Transcript 4 (*DDIT4*) mRNA level, which inhibits ER-triggered cellular stress response and negatively affects the activities of mammalian target of rapamycin (mTOR) and NF-κB signaling pathways,

resulting in attenuating macrophage effector function and improving NAFLD [109].

Skins (Delayed wound healing)

Dysregulation of autophagy accounts for delayed healing of diabetic skin wounds [110]. Sequestosome 1 (*SQSTM1*) is a kind of selective autophagy receptors [111]. One research implied that under diabetic conditions, *YTHDC1* mayne synergize with ELAV like RNA binding protein 1 (*ELAVL1*) to regulate the stability of *SQSTM1* nuclear mRNA in keratinocytes, which raises *SQSTM1* expression to cause autophagic flux and delaying wound healing. In the case of high sugar, *SQSTM1* expression will be inhibited [112].

Recent findings have confirmed that adipose-derived mesenchymal stem cells (ADSC) may be a promising therapeutic modality to promote wound healing in diabetic foot ulcers (DFUs). In detail, through *METTL3*/*IGF2BP2*-m6A pathway-mediated modification of vascular endothelial growth factor C (*VEGF-C*) m6A, ADSCs enhance vascular endothelial growth factor receptor 3 (*VEGFR3*)-mediated lymphangiogenesis and improve wound healing in DFUs [113]. This suggests that ADSCs can be considered as a promising therapeutic strategy to promote DFU wound healing. Ubiquinone oxidoreductase subunit B5 (*NDUFB5*) is related to DFU [114]. After *METTL3*-mediated *NDUFB5* m6A modification, *IGF2BP2* may contribute to *NDUFB5* mRNA stability through recognizing its m6A modification, thereby promoting vascular endothelial *NDUFB5* expression, which ultimately ameliorates advanced glycation end products (AGEs)-mediated DFU [115].

Testicular (Diabetes-induced testicular damage (DITD))

Diabetes induced testicular injury is a common complication of diabetes, characterized by increased apoptosis of spermatogenic cells, low sperm level and motility, and testicular endocrine dysfunction [116]. There are research data elucidating the potential regulatory mechanisms of m6A modification on diabetes-induced testicular damage. *METTL3* overexpression increased the viability of HG-treated GC-1 spg cells and reduced apoptosis, while *METTL3*-mediated m6A modification increased the stability of *TUG1*. However, both *METTL3* and *TUG1* were downregulated in diabetic mice and HG-cultured GC-1 spg cells [117].

Cognitive dysfunction in diabetes

Tau is a primarily neuronal protein. Neurodegeneration induced by tau hyperphosphorylation is strongly associated with cognitive dysfunction in diabetes [118]. In diabetic rats, Tau hyperphosphorylation is typically associated with reduced expression of the m6A demethylase *ALKBH5*. In HN-h cells, elevated glucose levels suppress

the expression of ALKBH5, thereby inhibiting its ability to demethylate m6A residues on Dgkh. This leads to decreased Dgkh levels, which subsequently activate PKC- α in hippocampal neurons. The resulting Dgkh deficiency further promotes tau hyperphosphorylation, ultimately contributing to cognitive dysfunction in diabetes mellitus [119] (Fig. 4).

Curing

In the above studies on the changes of m6A modification in diabetes and its pathogenic mechanism, it is not difficult to find that m⁶A modification, as an important epitranscriptome regulatory mechanism, shows great potential for application in the treatment of diabetes and its complications. From the perspective of therapeutic related research, they can be categorized into three main groups: existing drugs, relevant substances, and inhibitors. Among them, related extract studies are more

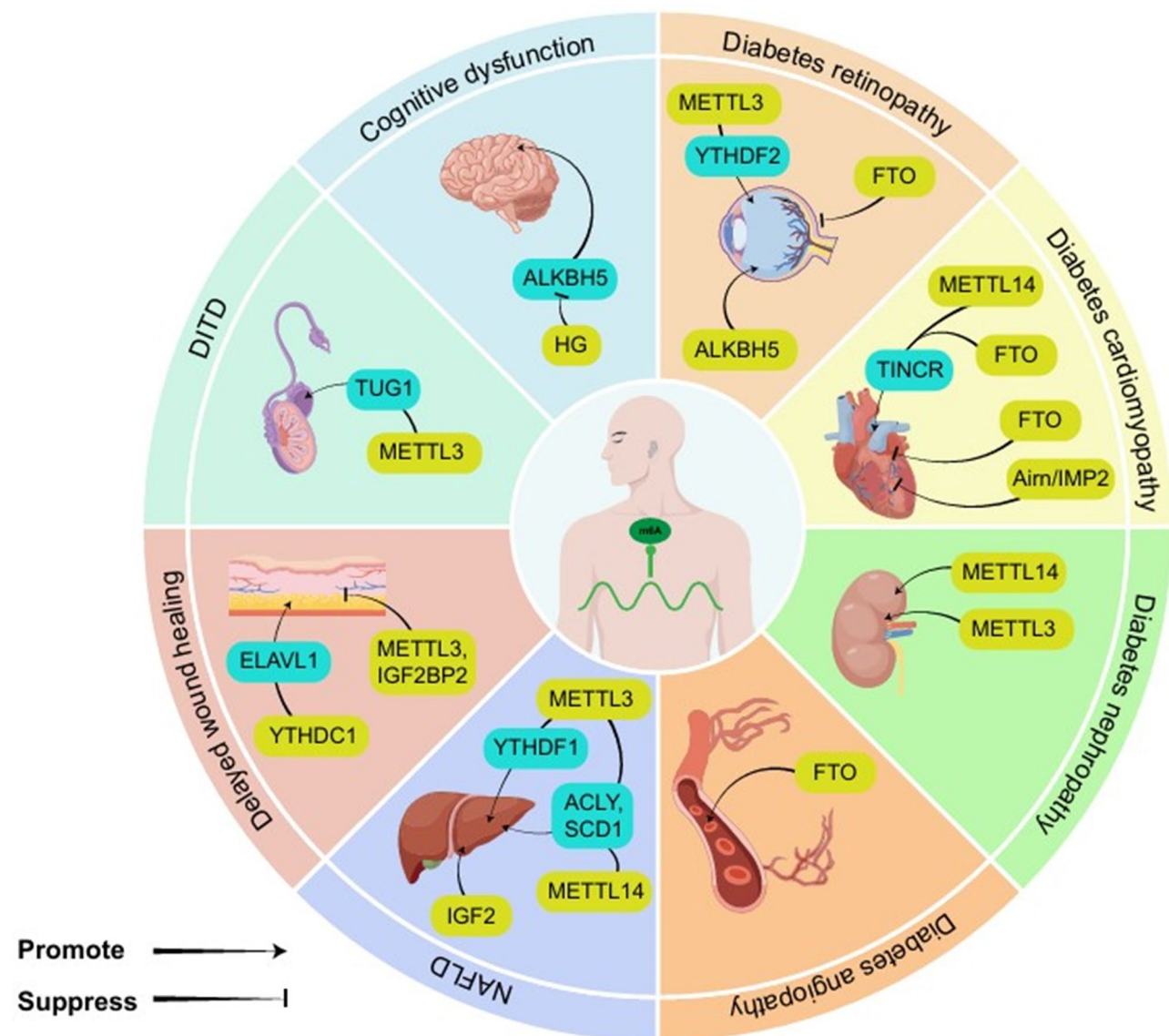


Fig. 4 The figure depicts the relationships between various diabetes - related complications and key molecular regulators. In the eye, METTL3 affects the occurrence and development of diabetic retinopathy by mediating the action of YTHDF2 and jointly participating in the regulation with FTO and ALKBH5. In the heart, METTL14 and FTO are involved in diabetic cardiomyopathy by regulating TINCER. Meanwhile, FTO and Aim/IMP2 can also directly affect the occurrence and development of diabetic cardiomyopathy. In the kidney, METTL3 and METTL14 are associated with diabetes nephropathy. For the vascular system, the FTO-TNIP1-NF - κ B network is linked to diabetes angiopathy. In the liver, multiple molecules such as METTL3, FTO, Ythdc2, and IMP2 play roles in nonalcoholic fatty liver disease. In the skin, YTHDC1, ELAVL1, METTL3, and IGF2BP2 are related to delayed wound healing in diabetes. In the testis, METTL3 is involved in diabetes - induced testicular damage. Regarding cognitive dysfunction in diabetes, ALKBH5, Dgkh, and PKC - α are shown to be related

extensive, while existing drug studies focus on mechanism elucidation to provide theoretical support for clinical applications.

Existing drugs

Metformin

As a first-line drug for diabetes mellitus, metformin, can inhibit the protein expression of FTO and reduce the methylation level of cell cycle protein D1 (CCND1) and CDK2, which leads to the YTHDF2-dependent decay and protein expression. Eventually, MCE was blocked and adipogenesis was inhibited [120].

Exenatide

As an extended-release formulation injected once a week and an exendin-4-based glucagon-like peptide-1 (GLP-1) receptor agonist which was approved for the treatment of type 2 diabetes, exenatide has been proven to reduce blood glucose and lead to modest decreases in body weight, blood pressure, and lipid levels [121]. One of the mechanisms by which excess ROS can impair β -cell function is through reduced levels of two transcriptional factors, Pdx-1 and MafA [122]. It is characterized by a particular sensitivity to oxidative stress due to a low antioxidative defense capacity. An imbalance between a high H₂O₂ (hydrogen peroxide) production capacity and a low inactivation capacity is the central feature of this special vulnerability [123]. From the above, it is clear that METTL3 can affect β -cell insulin secretion by influencing the expression of MafA and Hdac1 [34, 38]. It has been shown that H₂O₂ can reduce the expression of METTL3 and then induce apoptosis in β -cells, however, after the application of exenatide targeting METTL3, can restore its m6A level and finally reverse the H₂O₂-induced β -cell injury [124]. Regrettably, the study did not elaborate on the precise mechanism by which exenatide influences METTL3. It merely demonstrated, through investigations of mouse islets, that exenatide can elevate METTL3 levels. More detailed mechanisms require further investigation.

Rosiglitazone

Rosiglitazone, a thiazolidinedione antidiabetic, improves insulin resistance [125]. Elevated levels of FTO in muscle are a characteristic of type 2 diabetes. According to a study, in muscle, increased FTO expression inhibits insulin-induced PKB phosphorylation in HEK293 cells, thereby affecting insulin signalling pathways, and, rosiglitazone treatment improves insulin sensitivity and reduces FTO expression in patients with type 2 diabetes. It means the growing FTO expression in skeletal muscle of patients with type 2 diabetes can be normalized through thiazolidinedione treatment [126]. A research indicates that there is a certain correlation between FTO

expression and insulin sensitivity [127], however, this study supports the notion that there is no correlation between the two [126]. How rosiglitazone improves insulin sensitivity in the muscles of type 2 diabetes patients via FTO remains to be investigated, but its reduction of FTO expression thereby affecting insulin signalling pathways is well established.

Fufang Zhenzhu Tiaozi (FTZ)

FTZ consists of eight Chinese herbs including Coptidis Rhizoma, Salvia Miltiorrhiza Radix, Notoginseng Radix, Ligustri Lucidi Fructus, Cirsii Japonici Herba, Eucommiae Cortex, Citri Sarcodactylis Fructus and Atractylodes Macrocephala Radix. Citri Sarcodactylis Fructus and Atractylodes Macrocephala Radix, which is one of the patented and clinically approved herbal prescriptions invented by Professor Jiao Guo based on new Traditional Chinese Medicine (TCM) therapeutic strategies [128, 129]. Sirtuins (SIRT), a family of nicotinamide adenine dinucleotide (NAD)-dependent histone deacetylases, consumes one NAD + molecule per deacetylation cycle and has the ability to deacetylate histone and non-histone targets [130, 131]. FTZ can down-regulate YTHDF2 to inhibit the degradation of SIRT3 mRNA, and then increase the expression of SIRT3 to enhance mitochondrial membrane potential and reduce HG/Oxidized Low-Density Lipoprotein (ox-LDL)-induced apoptosis in endothelial cells, as well as enhance the antioxidant capacity in order to reduce cytotoxicity and apoptosis in human umbilical vein endothelial cells (HUVECs) and ultimately change the promotion of atherosclerosis by diabetes mellitus. In diabetic patients, FTZ may be the drug of choice for the clinical treatment of atherosclerosis [129].

Relevant substance

Cinnamaldehyde (CA)

CA, a yellow viscous liquid, constitutes 98% of the essential oil of cinnamon bark, which is first isolated by Dumas and Péligot [132]. CA ameliorates steatosis by affecting METTL3-CYP4F40-mediated fatty acid metabolism. Through promoting METTL3 expression, CA upregulates cytochrome P450 family 4 subfamily f polypeptide 40 (CYP4F40) and increases levels of decanoic acid, gamma-linolenic acid (GLA), arachidonic acid (AA), and docosahexaenoic acid (DPA). After knocking down METTL3, the beneficial effects of CA on steatosis were reversed [133].

Abelmoschus Manihote (TFA)

Gradually, Traditional Chinese Medicine (TCM) has come into our view, and has been suggested to have better therapeutic effects on kidney disease in various studies [134]. One of these is the flowering plant Abelmoschus

manihot (Linn) .Medic. (Mallowaceae), also called Mal-lowaceae Sunset Muskgrass, Sunset Hibiscus or Hibiscus manihot [135]. Cell pyroptosis is a specific kind of lytic programmed cell death where NLRP3 inflammatory vesicles are the most significant initiator. Pyroptosis is closely related to the progression of diabetic kidney disease (DKD), and recent studies have also reported that effective inhibition of renal cell death and attenuated of DKD in in vivo or in vitro models [136, 137]. Some researchers have found that TFA improves HG-induced podocyte pyroptosis and injury with a METTL3-dependent manner and achieves it through regulating the activation of NLRP3 inflammatory vesicles and the phosphate and tension homology (PTEN)/PI3K/ATK signaling pathway [138].

Resveratrol

As a stilbene molecule belonging to the polyphenol family, resveratrol is commonly extracted from many natural plants [139]. Among the three PPAR subtypes α , γ and δ , PPAR α enhances fatty acid catabolism in the liver [52]. It has been demonstrated that METTL3 causes increased expression of YTHDF2, which mediates downstream PPAR α mRNA stabilization in order to regulate hepatic lipid metabolism [103]. At the same time, resveratrol intake can alter the transcriptional level of PPAR α , alleviate the accumulation of hepatic lipids, increase the level of mRNA of m6A methylase and demethylase, up-regulate the expression of YTHDF2, and finally significantly reduce the expression of YTHDF3 mRNA and the level of hepatic m6A [140].

Epigallocatechin gallate (EGCG)

EGCG is the main bioactive compound in green tea [141]. CCNA2 and CDK2 play an essential role in MCE. EGCG decreased the expression of FTO and YTHDF2, which down-regulated their mediated m6A-dependent CCNA2 and CDK2 expression, and finally blocked MCE to inhibit adipogenesis [142]. Adipose tissue can contribute to the development of diabetes [16–18]. Therefore, EGCG may indirectly influence the course of diabetes.

Curcumin

Curcumin is an important bioactive component of turmeric [143]. Curcumin has been shown to exhibit anti-hyperglycemic effects and improve insulin sensitivity, which at least in part, may be attributed to the anti-lipolytic effect as evidenced by attenuating plasma free fatty acids, according to existing studies. It suggests that curcumin may be a beneficial adjunctive therapy for patients with T2DM [144]. But perhaps the part of the mechanism has to do with its inhibition of lipogenesis. Recently, it has been confirmed that curcumin up-regulates the m6A level of TNF receptor-associated factor 4 (TRAF4)

mRNA by decreasing the expression of ALKHB5, while TRAF4 mRNA with higher m6A level will be recognized and bound by YTHDF1, which raises the translation of TRAF4. At this time, TRAF4, a kind of E3 RING ubiquitin ligase, promotes the differentiation of adipocytes through the ubiquitin-proteasome pathway and ultimately inhibit adipogenesis by degrading PPAR γ [145].

Rhein

FTO is closely related to adipogenesis [45–49], fat browning [60], fatty acid mobilization [56], and β -cell autophagy [25]. In the liver, FTO also mediates the adipogenic effects of insulin [98]. So, inhibition of FTO expression and/or activity may provide a new therapeutic approach for the treatment of diabetes and NAFLD. As the most effective compound to inhibit FTO, the natural product rhein can directly bind to FTO and inhibit its demethylase activity, which exhibits good inhibitory activity against intracellular m6A demethylation [146]. What's more, rhein treatment reduces glucose-6-phosphatase (G6PC) mRNA levels in mouse hepatocyte AML12 cells [147]. One study indicates that elevated hepatic FTO participates in regulating hepatic gluconeogenesis genes and ATF4 expression, leading to increased G6pc and Atf4 mRNA levels. Reducing the activity of the hepatic FTO-ATF4 pathway may be beneficial for decreasing hepatic glucose production and improving hyperglycaemia in diabetes [148]. Although it is not clear that the Rhein's useful effects is mediated by inhibition of hepatic FTO, these findings create a new avenue for developing therapeutic interventions by altering hepatic FTO activity. Despite being the first substrate-competitive fatty acid transporter (FTO) inhibitor, Rhein exhibits poor selectivity [149]. Moreover, it has been demonstrated to potentially act as a PPAR γ antagonist, capable of reducing fat mass and improving hyperlipidaemia [150], and glucose tolerance in mice by modulating PPAR γ signalling pathways [150]. I think that conducting the corresponding experimental research presents certain difficulties. Furthermore, Rhein exhibits hepatotoxic and nephrotoxic properties [151].

FTO inhibitor

The FTO inhibitor meclofenamic acid 2 (MA2) inhibited the activation of the ATK pathway and subsequently down-regulated HDAC5 in high glucose-cultured HK2 cells, which attenuates HDAC5-mediated cellular EMT in diabetic nephropathic renal tubular cells, thereby ameliorating the manifestation and phenotype of diabetic nephropathy [90]. MA2 is the ethyl ester form of methylchlorfenidate (MA), which is a highly selective inhibitor of FTO with an IC₅₀ value of 7 μ M as measured by HPLC assay. The structural complex of MA bound to FTO incorporates a portion of NRL, providing additional

Table 2 Therapeutic mechanism of m6A related drugs

Medicines		Mechanisms of action	Consequences of action	Reference
Existin-g drugs	Metformin	Downward revision of FTO	Blocks MCE and inhibits adipogenesis	[120]
	Exenatide	Upward revision of METTL3	Reversal of H2O2-induced β -cell damage	[124]
	Rosiglitazone	Downward revision of FTO	Increase insulin sensitivity in muscles	[126]
	FTZ	Downward revision of YTHDF2	Reducing the promotional effect of diabetes on atherosclerosis	[129]
releava-nt substance	CA	Upward revision of METTL3	Improvement of steatosis	[133]
	TFA	Upward revision of METTL3	Inhibition of renal podocyte pyroptosis and injury	[138]
	Resveratrol	Upward revision of YTHDF2	Alleviates lipid accumulation in the liver	[140]
	Rhein	Downward revision of FTO	Reduction of G6PC mRNA levels in mouse hepatocytes AML12 cells	[147]
	EGCG	Downward revision of FTO and YTHDF2	Inhibits the production of fat	[16–18], [142]
	Curcumin	Downward revision of ALKBH5	Inhibits the production of fat	[145]
	MA2	Downward revision of FTO	Improvement of diabetic nephropathy	[90]
FTO inhibit-or	Dac51		Relief of impaired insulin secretion	[25]
	Entacapone		Improved body weight and glucose tolerance	[155]

interactions between MA and FTO. Consequently, MA fails to inhibit subfamily members possessing this NRL region, including ALKBH2 and ALKBH3. However, ALKBH5 lacks this NRL portion, leading to leakage upon MA binding [152].

Building upon the optimisation of previously reported FTO inhibitors FB23 and FB23-2, the small-molecule compound Dac51 represents a newly developed FTO-specific inhibitor. In vitro experiments demonstrate that Dac51 binds to and stabilises FTO, exhibiting significant inhibitory effects on its demethylating activity with an IC_{50} value of approximately 0.4 μ M [153]. A study indicates that administration of Dac51 for merely 2–3 weeks effectively improve the impaired insulin secretion and impaired glucose tolerance in hyperglycemic β -cell-specific NR3C1 overexpressing mice [25].

Entacapone is an inhibitor of FTO, while the m6A site on the mRNA of the transcription factor forkhead box protein O1 (FOXO1) can be demethylated by FTO leading to upregulate FoxO1 expression [154]. In vivo administration of entacapone to mice reduced body weight and improved glucose tolerance through inducing hepatic gluconeogenesis and adipogenic thermogenesis by the action of FTO-FOXO1 regulatory axis [155]. However, the existing FTO inhibitor entacapone is limited in clinical application due to factors such as low potency and a short plasma elimination half-life [156], and is predominantly used in research settings for the treatment of Parkinson’s disease [157, 158] (Table 2).

Conclusions and prospect

Conclusion

m6A directly or indirectly regulates the development of diabetes mellitus through the regulation of β -cell autophagy, secretion, endoplasmic reticulum stress, participation in adipogenesis and lipolysis, and the influence of insulin resistance. m6A also participates in the

development of several organ pathologies in diabetic patients, such as diabetic retinopathy, diabetic cardiomyopathy, diabetic nephropathy, diabetic vasculopathy, non-alcoholic fatty liver disease, diabetic wound healing, and diabetes-induced testicular damage. Some diabetes medications, such as metformin, exenatide, rosiglitazone, and Fufeng Zhenzhu Dizhi have been found to affect m6A levels during treatment. Some extracts of cinnamonaldehyde, resveratrol, rhubarbic acid, epigallocatechin gallate, and curcumin have also been found to affect m6A levels through various pathways, such as fatty acid metabolism, promotion of m6A methylase expression, inhibition of FTO and intracellular m6A demethylation, and inhibition of adipogenesis. Relevant inhibitors such as MA2, Entacapone and Dac51 can regulate m6A by affecting m6A metabolic pathways such as ATK and FTO-FOXO1. Improving the prognosis of diabetic patients by regulating m6A may be an effective way to treat diabetes. Few studies have definitively demonstrated that a particular drug or extract can be used clinically, with most research remaining at the trial stage. Among these, greater attention has been directed towards downregulating FTO and upregulating METTL3. Moreover, given the intricate diversity of m6A ‘writers,’ ‘erasers,’ and ‘readers,’ few studies have comprehensively considered and investigated the entire m6A system. Presently, research into m6A-related mechanisms remains fragmented and lacks a unified framework. Nevertheless, the influence of m6A on upstream risk factors for diabetes development—such as obesity and insulin resistance—is undeniable. Furthermore, given that most currently identified drugs are extracts, and considering the comprehensive review of m6A-related mechanisms and drug research throughout this paper, m6A regulation may be more appropriately positioned as a preventive strategy or adjunctive measure. For instance, incorporating specific doses of relevant extracts into dietary supplements could be explored.

Prospect

Chronic macrophage-mediated tissue inflammation is a critical mechanism for insulin resistance in obesity [159]. M6A was found to be closely related to macrophage phenotype and dysfunction [160]. It is easy to find that macrophages are associated with reduced insulin sensitivity and also with m6A, but there are no relevant studies linking the three. Among the complications of diabetes, a study has been implied that METTL3 targets the 3' UTR of ICAM-1 to change HG-induced HLEC and thus cause diabetic cataract (DC) [69]. It has a study shown that significant induction of ICAM-1 on the endothelial cell surface can lead to retinal microvascular leakage and degeneration [70]. However, up-to-now, no study has shown that ICAM-1 is associated with DC, and METTL3 regulates ICAM-1. This provided us with two research directions, the relationship between ICAM-1 and DC and the relationship between METTL3 and diabetic retinopathy. Most studies about the relationship between m6A and diabetes have researched at type 2 diabetes but not other types of diabetes. However, m6A has been associated with other types of diabetes. For example, in type 1 diabetes mellitus (T1DM), abnormal immune function is one of the key etiologic factors, however, m6A may be involved in the pathogenesis of T1DM through immune-related pathways [5, 161]. This point was touched upon in the preceding discussion: m6A can influence the immune microenvironment, such as T cells and macrophages, yet no related studies exist in therapeutic contexts. This may well represent a novel avenue for research. It is also a research demonstrating that METTL3 mediates m6A modification of hsa_circ_0072380, a circular RNA (circRNA), to regulate gestational diabetes mellitus (GDM) progression [162]. It even affects the children of GDM mothers, making them more susceptible to metabolic disorders [163]. Downregulation of m6A in the 3'-UTRs and near-stop codons of the coding sequences (CDSs) in placental mRNA may contribute to the pathophysiology of gestational diabetes mellitus [164]. Unfortunately, there is no studies having compared m6A differences across distinct types of diabetes. Only one paper has indicated that elevated FTO levels in muscle tissue constitute a characteristic of type 2 diabetes, unrelated to obesity, systemic insulin resistance, or hyperglycaemia [126].

Diabetes is inextricably linked to m6A. There has been a great deal of research on the mechanisms involved, but there has been a lack of research on related drugs. For example, CA ameliorates steatosis by affecting METTL3-CYP4F40-mediated fatty acid metabolism [133]. Although METTL3 knockdown downregulates CYP4F40, the detailed mechanisms involved remain to be investigated. A study implied that by affecting the expression of YTHDF2, resveratrol can change the transcriptional level of PPAR α and slows lipid accumulation in

the liver [140]. However, in this study, resveratrol significantly altered the levels of METTL3 and YTHDF2, but it was not clear whose expression was specifically affected. As the most potent compound to inhibit FTO, the liver benefits of Rhein are unquestionable, while the effects of FTO on the liver are also evident [98, 146, 147]. Rhein reduces G6PC mRNA levels [147], whereas FTO elevates them [148]. As Rhein is also an inhibitor of FTO [146], it is reasonable to hypothesise that the hepatoprotective effect of rhein (an anthraquinone) may be achieved by suppressing hepatic FTO to lower G6PC mRNA levels. However, no studies have yet confirmed this hypothesis, suggesting this could represent a promising avenue for future research. EGCG may indirectly influence the course of diabetes [16–18, 142]. Regrettably, owing to its chemical instability and poor absorption properties, EGCG has not yet found application in pharmaceutical treatments. Concurrently, it is noteworthy that promising derivatives of EGCG—achieved by introducing fatty acid chains or sugar molecules into its chemical structure to alter solubility, or by blocking the hydroxyl group with various substituents—exhibit superior stability and activity compared to the parent compound, potentially offering novel therapeutic avenues [165].

Abbreviations

AA	Arachidonic Acid
ACLY	ATP Citrate Lyase
ADR	Adriamycin (Doxorubicin)
Adrb2	Adrenoceptor Beta 2
Adrb3	Adrenoceptor Beta 3
ADSC	Adipose-Derived Stem Cell
AGEs	Advanced Glycation End Products
Airm	Antisense of IGF2R non-protein coding RNA
ALKBH5	AlkB Homolog 5
Angptl4	Angiopoietin-like 4
Atg	Autophagy-related
Atgl	Adipose Triglyceride Lipase
BAT	Brown Adipose Tissue
BCAA	Branched-Chain Amino Acids
Bcl2l2	BCL2 Like 2
CA	Cinnamaldehyde
CAMK1	Calcium/Calmodulin Dependent Protein Kinase 1
C-C motif	Chemokine (C-C motif)
CCL2	C-C Motif Chemokine Ligand 2
CCNA2	Cyclin A2
CCND1	Cyclin D1
Cd36	Cluster of Differentiation 36
CDK2	Cyclin-Dependent Kinase 2
CDSs	Coding sequences
Cgi-58	Comparative Gene Identification-58
ChREBP	Carbohydrate Responsive Element Binding Protein
circRNA	Circular RNA
CPT1A	Carnitine Palmitoyltransferase 1 A
CYP2B6	Cytochrome P450 Family 2 Subfamily B Member 6
CYP4F40	Cytochrome P450 Family 4 Subfamily F Member 40
DC	Dendritic Cell
DCM	Dilated Cardiomyopathy
DDIT4	DNA Damage Inducible Transcript 4
DFUs	Diabetic Foot Ulcers
DGCR8	DiGeorge Syndrome Critical Region 8
Dgkh	Diacylglycerol Kinase Eta
DIO	Diet-Induced Obesity
DITD	Drug-Induced Thyroid Dysfunction

DKD	Diabetic Kidney Disease	MT1	Metallothionein 1
DN	Diabetic Nephropathy	MTC	Mitochondrial Transcription
DPA	Docosapentaenoic Acid	MTCH2	Mitochondrial Carrier Homolog 2
EC	Endothelial Cell	mTOR	Mechanistic Target of Rapamycin
EGCG	Epigallocatechin Gallate	MYLK	Myosin Light Chain Kinase
ELAVL1	ELAV-Like RNA Binding Protein 1	NAD	Nicotinamide Adenine Dinucleotide
EMT	Epithelial-Mesenchymal Transition	NADP	Nicotinamide Adenine Dinucleotide Phosphate
ERK	Extracellular Signal-Regulated Kinase	NAFLD	Non-Alcoholic Fatty Liver Disease
ESE	Exonic Splicing Enhancer	NDUFB5	NADH: Ubiquinone Oxidoreductase Subunit B5
FA	Fatty Acid	NF-κB	Nuclear Factor Kappa B
FASN	Fatty Acid Synthase	NIT-1	Mouse insulinoma beta cell line
FAT4	FAT Atypical Cadherin 4	NLRP3	NLR Family Pyrin Domain Containing 3
FFA	Free Fatty Acids	NR3C1	Nuclear Receptor Subfamily 3 Group C Member 1
FMR1	Fragile X Mental Retardation 1	OF	Obese Factor
FOXO1	Forkhead Box O1	ox-LDL	Oxidized Low-Density Lipoprotein
FTO	Fat Mass and Obesity-associated Protein	PDGFRA	Platelet-Derived Growth Factor Receptor Alpha
G6PC	Glucose-6-Phosphatase Catalytic Subunit	PDX1	Pancreatic and Duodenal Homeobox 1
GDM	Gestational Diabetes Mellitus	PGE2-EP3	Prostaglandin E2 Receptor EP3 Subtype
GLA	Gamma-Linolenic Acid	PKC	Protein Kinase C
GLP-1	Glucagon-Like Peptide-1	Ppargc1a	Peroxisome Proliferator Activated Receptor Gamma Coactivator 1 Alpha
GLP-1R	Glucagon-like Peptide-1 Receptor	Pparg	Peroxisome Proliferator Activated Receptor Gamma
GLUT2	Glucose Transporter Type 2	PPARα	Peroxisome Proliferator Activated Receptor Alpha
GLUT4	Glucose Transporter Type 4	PPARγ	Peroxisome Proliferator-Activated Receptor Gamma
GSDMD-N	Gasdermin D N-terminal domain	Prdm16	PR Domain Containing 16
GSIS	Glucose-Stimulated Insulin Secretion	PTBP1	Polypyrimidine Tract Binding Protein 1
GSIS experiments	Glucose-Stimulated Insulin Secretion experiments	PTEN	Phosphatase and Tensin Homolog
GSK3β	Glycogen Synthase Kinase 3 beta	PTEN	Phosphatase and Tensin Homolog
H2O2	Hydrogen Peroxide	RAB3B	RAB3B, member RAS oncogene family
H3K18la	Histone H3 Lysine 18 Lactylation	RBP	Retinol Binding Protein
H3K27	Histone H3 Lysine 27	RPE	Retinal Pigment Epithelium
HCC	Hepatocellular Carcinoma	RUNX1T1	RUNX1 Translocation Partner 1
HDAC5	Histone Deacetylase 5	SCD1	Stearoyl-CoA Desaturase 1
HFD	High-Fat Diet	SIRT	Silent Information Regulator
HFrD	High-Fat and Fructose Diet	SIRT1	Sirtuin 1
HG	High Glucose	Slc25a33	Solute Carrier Family 25 Member 33
Hif1a	Hypoxia Inducible Factor 1 Alpha	SNHG7	Small Nucleolar RNA Host Gene 7
HK-2 cells	Human Kidney 2 cells	SQSTM1	Sequestosome 1
HLEB3	Human Lens Epithelial Cell Line B3	SREBF1	Sterol Regulatory Element Binding Transcription Factor 1
HLEC	Human Lens Epithelial Cell	SRSF1	Serine/Arginine-Rich Splicing Factor 1
HLECs	Human Lens Epithelial Cells	SRSF2	Serine/Arginine-Rich Splicing Factor 2
HNRNPs	Heterogeneous Nuclear Ribonucleoproteins	T1DM	Type 1 Diabetes Mellitus
HUVECs	Human Umbilical Vein Endothelial Cells	T2DM	Type 2 Diabetes Mellitus
ICAM-1	Intercellular Adhesion Molecule 1	TCM	Traditional Chinese Medicine
IGF1	Insulin-like Growth Factor 1	TFA	Trans Fatty Acid
IGF2	Insulin-like Growth Factor 2	TG	Triglycerides
IGF2BP3	Insulin-like Growth Factor 2 mRNA-Binding Protein 3	TIMP2	Tissue Inhibitor of Metalloproteinases 2
IGF2BPs	Insulin-like Growth Factor 2 mRNA-Binding Proteins	TINCR	Terminal Differentiation-Induced Non-Coding RNA
IKKγ	Inhibitor of Nuclear Factor Kappa B Kinase Subunit Gamma	TRAF4	TNF Receptor-Associated Factor 4
IMP2	IGF2 mRNA-binding Protein 2	TUG1	Taurine Upregulated Gene 1
IR	Insulin Resistance	UCP	Uncoupling Protein
IRS	Insulin Receptor Substrate	UTR	Untranslated Region
ITGB1	Integrin Beta 1	VEGF-C	Vascular Endothelial Growth Factor C
KHSRP	KH-Type Splicing Regulatory Protein	VEGFR3	Vascular Endothelial Growth Factor Receptor 3
Klf15	Kruppel-Like Factor 15	WAT	White Adipose Tissue
LDs	Lipid Droplets	WTAP	Wilms Tumor 1-Associating Protein
m6A	N6-methyladenosine	XBP-1	X-box Binding Protein 1
MA2	Malate Dehydrogenase 2	YTHDC1	YTH Domain Containing 1
MafA	V-maf Musculoaponeurotic Fibrosarcoma Oncogene Homolog A	YTHDF2	YTH Domain Family 2
MCD	Methionine-Choline Deficient	Zfp410	Zinc Finger Protein 410
MCE	Mitotic clonal expansion		
Mef2a	Myocyte Enhancer Factor 2 A		
MetS	Metabolic Syndrome		
METTL14	Methyltransferase-like 14		
METTL3	Methyltransferase-like 3		
MG	Methylglyoxal		
MIN6	Mouse insulinoma beta cell line		
MKL1	Megakaryoblastic Leukemia 1		
MMP	Matrix Metalloproteinase		
mRNA	Messenger Ribonucleic Acid		
MSCs	Mesenchymal Stem Cells		

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