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The impact of N6-methyladenosine modification on diabetes and its complications and exploration of potential therapeutic agents

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Abstract: *Diabetes mellitus (DM) is globally recognized as one of the three major chronic noncommunicable diseases. Genetic and environmental factors are key contributors to its onset, with type 2 diabetes (T2D) accounting for 90% of cases. Epigenetics has been demonstrated to participate in T2D pathogenesis, including methylation, acetylation, ubiquitination, and histone modifications. In recent years, research on RNA modifications has intensified, with over 150 distinct modification patterns identified. Among these, m6A modification is the most prevalent, involving the coordinated action of RNA methyltransferases (Writers), RNA demethylases (Erasers), and RNA methyltransferase-reading proteins (Readers) to regulate multiple biological processes in the body. Indeed, an increasing number of therapeutic mechanisms targeting DM have been found to correlate with m6A modification, including traditional Chinese medicine, classic hypoglycemic agents, and novel small-molecule drugs. Furthermore, these interventions have demonstrated efficacy in managing diabetic complications such as diabetic nephropathy. This review focuses on m6A modification within the RNA methylation landscape of diabetes, summarizing current research advances and potential therapeutic strategies targeting m6A modification for improving DM.*

Keywords: *Diabetes, Diabetic Complications, m6A, drug intervention*

1. Introduction

Diabetes is a chronic metabolic disorder characterized by hyperglycemia as its typical pathological feature, ranking among the most prevalent and rapidly increasing disease categories globally. In recent decades, the number of diabetes patients has surged dramatically. According to authoritative statistics, the current global diabetes population has reached 415 million [1], with type 2 diabetes (T2DM) accounting for approximately 90% of all diabetes cases [2]. Research indicates that diabetes is characterized by a prolonged course, difficulty in achieving a cure, and a high disability rate. Most patients require long-term medication to manage their condition, imposing a significant economic burden on their families, particularly in developing countries [3]. Diabetes often involves a series of macrovascular and microvascular complications, which are key factors contributing to mortality. Based on the affected sites, these complications are primarily categorized as diabetic cardiomyopathy, retinopathy, neuropathy, nephropathy, and osteoporosis [4]. The etiology of diabetes is multifactorial, encompassing genetic predisposition, environmental influences, lifestyle habits, autoimmune responses, and chronic psychological stress [5]. Clinical studies indicate that individuals with a positive family history of diabetes exhibit a significantly elevated risk of developing the disease [6]. Consequently, in-depth investigation into the relationship between genetics and the pathogenesis of diabetes is of paramount importance.

Epigenetics studies stable, heritable changes in chromatin that occur without alterations to the DNA sequence. In 1942, British biologist John Waddington first proposed the concept of epigenetics [7]. The

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molecular mechanisms of epigenetics primarily focus on the pre-transcriptional and post-transcriptional stages, with research centered around three major components: DNA, histones, and RNA. Methylation plays a crucial role in all three components [8]. Previously, research on RNA methylation remained relatively stagnant. However, following Nobel laureate T. Lindahl's 2015 discovery of peroxidase-catalyzed oxidative demethylation (a DNA repair mechanism) and subsequent breakthroughs like the identification of FTO [9], interest in RNA methylation research surged dramatically.

2. Major RNA modification types—m6a

A wide variety of chemical modifications exist on RNA molecules, with over 150 distinct modification patterns identified to date [10]. Among these, non-coding RNA methylation and mRNA methylation represent the most prevalent modification forms [8]. Specifically, modification types encompass N6-methyladenosine (m6A), 5-methylcytosine (m5C), N1-methyladenosine (m1A), N7-methylguanosine (m7G), and 3-methylcytosine (m3C), among others [11]. Among these, m6A is the most prevalent modification type, participating in nearly every stage of the RNA life cycle. It is present not only on mRNA but also on ribosomal RNA (rRNA) and transfer RNA (tRNA) [10]. As a crucial modification, m6A methylation was first identified in rat mRNA during the 1970s [12]. Despite this discovery, research in this field remained relatively neglected until 2011. The identification of the obesity-associated protein FTO as an mRNA m6A demethylase revealed the reversibility of m6A modifications, triggering a surge in m6A research interest [13]. Typically, m6A modifications are enriched in the 3′-UTR region near mRNA termination codons and exhibit the conserved RRACH sequence motif (where R represents G or A, and H represents A, C, or U) [14]. The function of m6A modification relies primarily on three types of functional enzymes: methyltransferases (Writers), demethylases (Erasers), and m6A-binding proteins (Readers) [15].

3. Overview of Three m6A Modifying Enzymes and Their Link to Diabetes

3.1 Methyltransferases

The core components encompass “WTAP and the METTL3/METTL14 complex,” which synergistically regulate RNA m6A methylation [16]. WTAP initiates binding to target RNA, subsequently recruiting the METTL3-METTL14 dimer for catalytic activity [17]. WTAP deficiency impairs its ability to recruit the METTL3 subunit, leading to reduced m6A modification levels. The METTL3 subunit (also known as the MT-A70 subunit) comprises two major functional domains: an S-adenosylmethionine (SAM)-binding domain and a catalytic DPPW (Asp-Pro-Pro-Trp) domain [18]. In HeLa cells, defective METTL3 expression reduces m6A levels by approximately 30% [16]. Analysis of METTL3 homologs revealed that METTL14 similarly possesses an S-adenosylmethionine-binding site for m6A formation and a catalytic EPPL domain. Consequently, METTL14 is recognized as another subunit of the m6A methyltransferase complex [19]. These two subunits combine in a 1:1 ratio to form the complex, thereby enhancing their respective catalytic efficiencies [17]. Recent studies confirm that mediating m6A modification of PGC-1α mRNA suppresses arsenic-induced ferroptosis in hepatocytes, thereby treating insulin resistance (IR) [20]. High-fat diets upregulate METTL3 expression in CYP2B6, exacerbating hepatic IR [21]. METTL3 holds promise as a potential therapeutic target for type 2 diabetes [22]. Animal studies further reported elevated METTL3 expression and m6A levels in the livers of high-fat diet (HFD) mice. Specific knockout of METTL3 in mouse hepatocytes significantly improved hepatic IR [23]. Another in vivo study revealed that pancreatic beta cell-specific knockout of METTL14 in mice led to beta cell-specific death, impairing insulin release and ultimately causing diabetes [24].

3.2 Demethylases

Currently, two primary enzymes have been identified that catalyze the demethylation of m6A modifications: FTO and ALKBH5. In the presence of ferrous ions and α-ketoglutarate, FTO oxidizes N6-methyladenosine to N6-hydroxymethyladenosine (hm6A), then further catalyzes the formation of N6-formyladenosine (F6A) and adenosine, ultimately removing the m6A modification [25]. Recent years have witnessed significant advances in FTO research within the diabetes field. Jia G et al. [26]confirmed FTO as a gene associated with obesity and type 2 diabetes (T2DM), while Wu T et al. [27] discovered that inhibiting NR3C1 downregulates FTO expression, thereby reducing autophagy levels in pancreatic β-cells—offering novel therapeutic insights for diabetes. Ren Y et al. [28] also highlighted in a review

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that FTO expression significantly increases during type 2 diabetes (T2DM) rather than type 1 diabetes (T1DM). Reports on ALKBH5 in diabetes are relatively scarce. Nevertheless, Chen T et al. [29] demonstrated its involvement in therapeutic pathways for diabetic retinopathy, while Qu M et al. [30] found that a high-sugar environment reduces ALKBH5 expression, increases m6A modification of DGKH, and ultimately exacerbates diabetic cognitive impairment and hippocampal neuronal apoptosis.

3.3 RNA Methylation Recognition Proteins

The core members comprise a family of proteins containing the YTH domain [31], which includes cytoplasmic proteins YTHDF1 and YTHDF2, as well as the nuclear-localized protein YTHDC1 [32]. Compared to YTHDF1, YTHDF2 exhibits stronger binding affinity for m6A. PAR-CLIP sequencing analysis indicates that these proteins primarily bind to mRNA and certain long non-coding RNAs, with binding sites predominantly located in the 3′UTR regions rich in GAC sequences, showing high overlap with m6A-modified regions [33]. YTHDF1 has been demonstrated to participate in protein translation. Upon binding to m6A-modified mRNA, human YTHDF1 interacts with translation initiation factors eIF and ribosomes, accelerating ribosomal binding and sliding along mRNA to enhance translation efficiency [34]. Unlike the cytoplasmic YTHDF1 and YTHDF2, PAR-CLIP sequencing data indicate that YTHDC1 binds to GGAC sequences [33], and interacts with mRNA splicing factors to regulate mRNA splicing [35]. Compared to RNA methyltransferases and demethylases, direct studies on reading proteins in diabetes are relatively scarce, and even then, they are more prevalent in research on diabetic complications, fully reflecting their close relationship with diabetes. Zheng J et al. identified both YTHDF2 and YTHDF1 as potential therapeutic targets for type 2 diabetes [36].

4. Drug Targeting of m6A Modification Improves Diabetes and Its Complications

Dysfunction of pancreatic beta cells, reduced insulin sensitivity (insulin resistance), excessive fat intake, and gut microbiota dysbiosis are among the multifactorial contributors to diabetes and its complications [37]. Research into the mechanisms of various drug therapies targeting these pathways has also deepened. In recent years, a growing body of research has revealed that multiple drugs can exert anti-diabetic effects and mitigate complications by regulating m6A modification-related enzymes to remodel abnormal methylation pathways.

4.1 Research Progress on Drug-Mediated m6A Modification for Diabetes Management

Novel SGLT2 inhibitors (SGLT2is) such as dapagliflozin reduce systemic glucose levels by decreasing renal glucose reabsorption, thereby improving diabetes management [38]. One study further demonstrated that these agents lower blood glucose in rats by reducing m6A modification of Marcks mRNA mediated by METTL3 [39]. GLP-1 receptor agonists (e.g., semaglutide) achieve glycemic control by glucose-concentration-dependent promotion of insulin secretion and inhibition of glucagon secretion [40]. Research indicates semaglutide improves pancreatic β-cell function via METTL14 signaling to regulate blood glucose [41]. Of course, classic hypoglycemic drugs like metformin have been reported to downregulate FTO expression in adipocytes [42]. Traditional Chinese medicine components and novel small-molecule compounds in modern pharmacology research have also been found to exert antidiabetic effects through the aforementioned pathways. For instance, the METTL3 inhibitor STM2457 improves high-fat diet-induced insulin resistance in mice . (-)-Epigallocatechin 3-gallate has also been demonstrated to inhibit NR3C1, thereby reducing FTO expression and increasing pancreatic β-cell survival, which significantly improves diabetes outcomes [43]. Baicalin regulates METTL3 to lower blood glucose in diabetic mice, thereby reducing their incidence of hepatocellular carcinoma [44]. Lipid accumulation also plays a crucial role in diabetes development. Research indicates that resveratrol can inhibit diabetes onset by regulating METTL3 expression and reducing lipid accumulation in high-fat diet (HFD)-fed mice [45].

4.2 Research Progress on Improving Diabetic Complications through Regulation of m6A Modification

4.2.1 Diabetic Kidney Disease (DKD)

Diabetic kidney disease (DKD) is the most common microvascular complication of diabetes, with mortality rates 3 to 12 times lower in patients with diabetes alone compared to those with diabetic

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nephropathy. A flavonoid compound extracted from Abelmoschus manihot (TFA) can target METTL3-mediated m6A modification of PTEN mRNA, thereby improving podocyte function under high-glucose conditions and alleviating diabetic kidney disease [46]. Renal fibrosis is an inevitable manifestation of advanced DKD. Another report indicates that soy isoflavone (genistein) exerts renal protective effects, potentially by alleviating renal fibrosis and reducing kidney injury through regulating the expression of the demethylase ALKBH5 in Snail [47]. -Tanshinone IIA (Tan-IIA), present in sage root, exerts therapeutic effects in DN by regulating m6A modification of PRLR mRNA via WTAP, thereby inhibiting cell proliferation and fibrosis to ultimately improve DKD [48]. Lumbrokinase, a bioactive protease extracted from Lumbricus rubbellus, exerts its DKD-improving effects by regulating m6a modification of the Snail protein [49].

4.2.2 Diabetes Cognitive Impairment (DCI)

m6A modification is widely distributed in the mammalian hippocampus [50] and participates in synapse-related functional pathways [51]. Furthermore, studies indicate that diabetic patients are more prone to develop DCI than non-diabetic individuals, with a significantly increased likelihood of ultimately progressing to Alzheimer's disease [52]. Another study indicates that an in vivo investigation of m6A modification revealed FB23 (a mature FTO inhibitor) plays a crucial role in DCI development. It increases levels of neurotrophic factors by elevating the expression of the transcription factor STAT3, ultimately rescuing DCI in SAMP8 mice with high-frequency barriers [53]. Additional studies demonstrate that overexpression of either YTHDF1 or YTHDF2 suppresses DCI in mice [54, 55].

In summary, although currently marketed drugs for diabetes and its complications have received limited research attention in the m6A field, it remains undeniable that m6A-modifying enzymes represent potential therapeutic targets for intervening in diabetes and its complications. By regulating the activity of these enzymes, abnormal m6A modification profiles can be controlled [56], thereby improving diabetes and its complications. This offers novel insights at the epigenetic-transcriptomic level for repurposing existing drugs and developing novel hypoglycemic agents. Furthermore, in clinical studies, screening patients' unique m6A modification profiles enables the design of personalized treatment plans.

5. Summary

Overall, RNA methylation occupies a pivotal position in the field of epigenetics, with m6A modification being the most prevalent type of modification. The function of m6A modification primarily relies on the coordinated action of three functional enzymes: Writers (methyltransferases), Erasers (demethylases), and Readers (methylation-recognizing proteins). These enzymes play vital roles in numerous biological processes, including carbohydrate and lipid metabolism. Currently, numerous therapeutic agents targeting diabetes and its complications—including traditional Chinese medicine formulations, conventional hypoglycemic drugs, and novel small-molecule compounds—are exploring m6A modification as a potential mechanism. Some studies have provided preliminary support for this hypothesis. However, among the many diabetes-related targets, the specific m6A modification sites and associated genes require further validation. Moving forward, researchers will address this gap through in-depth investigations, aiming to uncover additional potential mechanisms for diabetes treatment.

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