Research Progress on the Role of N6-Methyladenosine in the Development of Diabetes

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Abstract: N6-methyladenosine (m6A) is a key RNA modification widely found in eukaryotic mRNA, regulating RNA stability, translation, splicing, and degradation. Recent studies highlight its critical role in diabetes development by modulating insulin signaling, islet β-cell function, immune response, and lipid metabolism. Additionally, m6A modification contributes to diabetic complications, such as retinopathy and nephropathy, by influencing gene expression. Advances in technology have led to the identification of numerous diabetes-related genes targeted by m6A, opening new therapeutic possibilities. Understanding the molecular mechanisms of m6A in different diabetes types may aid in precision medicine approaches. This review explores the potential of targeting m6A modification for early intervention and treatment, providing novel insights into diabetes management. Future research on m6A's role in diabetes pathogenesis and complications will enhance our ability to develop innovative therapeutic strategies, improving outcomes for diabetic patients.

1 INTRODUCTION

Diabetes mellitus, especially type 2 diabetes mellitus (T2DM), has become one of the major public health problems in the world, and its incidence continues to increase. According to the World Health Organization (WHO), there are more than 400 million people with diabetes worldwide, and this number is still increasing (Zhang et al. 2022). Diabetes not only affects the quality of life of patients, but also leads to a variety of serious complications such as cardiovascular disease, kidney disease, retinopathy, which brings huge social and economic burden (Tomic et al. 2022). Therefore, in-depth study of the pathogenesis of diabetes and search for new therapeutic targets and effective intervention strategies are of great significance to reduce the global burden of disease. In recent years, m6A (N6-methyladenosine), as an important post-transcriptional modification of RNA, has gradually attracted wide attention. m6A modification is the addition of a methyl group at the sixth position of the nitrogen atom of adenosine molecule. This modification plays an important role in gene expression by regulating RNA stability, translation, splicing and degradation. The regulation of m6A modification is accomplished by a series of 'write' (e.g. METTL3, METTL14), 'erase' (e.g. FTO, ALKBH5) and 'read' (e.g. YTHDF1, YTHDF2, etc.) proteins (Wang et al. 2023). It is involved in cell differentiation, proliferation, metabolic regulation and immune response in physiological processes, and plays a key role in a variety of pathological states, especially in metabolic diseases such as cancer, cardiovascular disease and diabetes. m6A modification is closely related to the occurrence and development of diabetes by regulating insulin signaling, β-cell function, glucose metabolism and inflammatory response (Liu et al. 2023).

Although several studies have explored the role of N6-methyladenosine (m6A) modification in diabetes, its precise mechanisms remain unclear. In particular, how m6A influences different types of diabetes, diabetic complications, and various cell types is not yet fully understood. A comprehensive review and analysis of existing literature on m6A modification in diabetes is crucial for advancing our knowledge of the disease at a molecular level. Understanding its specific functions in insulin signaling, β-cell function, immune regulation, and metabolic pathways may help uncover new therapeutic targets. Furthermore, m6A modification appears to play a role in the progression of diabetic

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complications such as retinopathy and nephropathy by regulating gene expression. Investigating these mechanisms in greater detail could provide new insights into disease pathology and potential treatment strategies. As research in this field progresses, targeting m6A modification may pave the way for precision medicine approaches, enabling more effective and personalized diabetes treatments. By systematically summarizing current findings and identifying gaps in knowledge, future studies can focus on unraveling the complexities of m6A in diabetes, ultimately leading to innovative therapeutic advancements. Continued exploration of this modification holds promise for improving early intervention and treatment outcomes in diabetic patients.

2 THE ROLE OF M6A MODIFICATIONS IN THE PATHOGENESIS OF DIABETES MELLITUS

2.1 The Regulation of the Insulin Signaling Pathway by m6A Modification

The N6-methyladenosine (m6A) modification of mRNA has been proposed to play a vital role in the progression of type 2 diabetes (T2D) (De Jesus et al. 2019). In Li's research, it was discovered that m6A modification is related to the regulation of the insulin signaling pathway (Li et al. 2023). KEGG enrichment analysis revealed that the downregulated MP-DEGs were primarily enriched in the insulin signaling, IR, and AMPK signaling pathways. Additional studies have shown that AMPK plays a major role in regulating cellular energy balance. Therefore, the results found by Li's team indicate that the development of IR and T2D may be regulated by these metabolism-related proteins through their interference with the insulin signaling pathway or energy balance.

2.2 The Role of m6A Modification in Pancreatic β-Cell Function

The role of m6A modification in islet β-cell function has been investigated (Regué et al. 2021). In that study, researchers discovered that deletion of IMP2 in pancreatic β-cells leads to reduced compensatory β-cell proliferation and function. Mechanistically, IMP2 directly binds to Pdx1 mRNA and stimulates its translation in an m6A-dependent manner. Furthermore, IMP2 orchestrates the IGF2-AKT-GSK3β-PDX1 signaling pathway to stabilize PDX1 polypeptides. In human EndoC-βH1 cells, overexpression of IMP2 enhances cell proliferation, PDX1 protein levels, and insulin secretion. Another study illustrated that m6A methylation is essential for β-cell maturation and maintenance of their physiological function (Zhou et al. 2022). The relationship between METTL3-mediated m6A RNA methylation and H2O2-induced pancreatic β-cell apoptosis was also demonstrated. It was shown that H2O2 induces β-cell apoptosis by reducing METTL3 expression, while exenatide, which targets METTL3, restores m6A levels, thereby reversing H2O2-induced β-cell injury.

2.3 The Relationship between m6A Modification and Metabolic Regulation

The relationship between m6A modification and metabolic regulation has been analyzed (Zhang et al. 2021). In patients with type 2 diabetes (T2D), glucose levels play a crucial role in the dynamic regulation of N6-methyladenosine (m6A) modification. Specifically, elevated glucose levels can simultaneously reduce the mRNA expression of FTO, an important m6A demethylase, while increasing the expression of key methyltransferases, including METTL3, METTL14, and WTAP. These enzymes are responsible for catalyzing m6A methylation, which affects RNA stability, translation, and overall gene expression. The simultaneous decrease in FTO and increase in methyltransferases contribute to altered m6A patterns, ultimately impacting insulin signaling and metabolic processes. These molecular changes are critical in maintaining glucose homeostasis in T2D patients, influencing β-cell function and systemic glucose metabolism. Understanding the regulatory effects of glucose on m6A modification may provide new insights into diabetes progression and potential therapeutic strategies. Further research into this dynamic interplay could lead to the development of targeted treatments for better glycemic control in T2D patients.

3 THE RELATIONSHIP BETWEEN M6A MODIFICATION AND DIABETIC COMPLICATIONS

3.1 The Relationship between m6A Modification and Diabetic Retinopathy

The relationship between m6Amodification and diabetic retinopathy has been analyzed (Kumari et al. 2021). Researchers discovered that m6ARNA modification exerts its effects through its writer, reader, and eraser proteins. Although limited research has been conducted on the role of m6ARNA modification in diabetic retinopathy (DR), its involvement in inflammation, oxidative stress, angiogenesis, various coding and non-coding RNAs, neurogenesis, diabetes, and its risk factors, as well as other molecular pathways, suggests that it is a potential candidate for targeting the study and control of DR progression and pathogenesis. Another study also delved deeply into the relationship between m6Amodification and diabetic complications (Benak et al. 2023). In retinal pigment epithelium (RPE) cells, high-glucose conditions downregulated the expression of METTL3 at both the transcript and protein levels. Further experiments showed that METTL3 overexpression alleviated the cytotoxic effects of high glucose on RPE cells, while METTL3 depletion had the opposite effect. Conversely, diabetic stress induced upregulation of METTL3 and a subsequent increase in m6Alevels in human retinal pericytes and mouse retinas. Specific depletion of METTL3 in pericytes suppressed diabetes-induced pericyte dysfunction and vascular complications in vivo. A recent study demonstrated downregulation of METTL3 in vitreous humor samples from patients with DR, in a mouse model of DR, and in high glucose-induced human retinal microvascular endothelial cells.

3.2 The Relationship between m6A Modification and Diabetic Nephropathy

The relationship between m6Amodification and diabetic nephropathy (DN) was investigated by a research team (Wan et al. 2022). They analyzed the m6Acontent in the urine of patients with DN and found that m6Alevels were significantly lower in patients with DN compared to those with normal glucose tolerance (NGT) and patients with type 2 diabetes mellitus (T2DM). The team further explored the changes in m6Alevels across different stages of DN progression and discovered that m6Alevels continued to decrease as DN worsened, closely correlating with the presence of DN. They also found that m6Alevels decreased gradually with the progression of DN, highlighting its close association with the pathological process of DN. Urinary m6Alevels were negatively correlated with pancreatic islet and renal function indices, suggesting that m6Ais a potential independent risk factor for DN and is linked to diabetic kidney dysfunction.

3.3 The Relationship between m6A Modification and Diabetic Cardiovascular Complications

The relationship between m6Amodification and cardiovascular complications in diabetes has been analyzed (Qin et al. 2020). m6Amethylation is present across different species and plays a fundamental role in cardiac biological processes and the pathogenesis of cardiovascular diseases (CVD). An increasing number of studies have uncovered the dysregulation of m6Amethylation as a hallmark of CVD development. m6Amodification can either promote or inhibit the development of CVD by regulating the levels of targeted m6A-modified mRNAs. Dysregulation of methyltransferases, demethylases, and m6A-binding proteins has been shown to contribute to the onset and progression of CVD.

4 M6A MODIFICATION AS A NEW THERAPEUTIC TARGET FOR DIABETES

4.1 Therapeutic Strategies Targeting m6A 'Writer' Enzymes

Therapeutic strategies targeting m6A 'writer' enzymes, such as METTL3 and METTL14, have been analyzed (Qiu et al. 2023). The methyltransferase complex is composed of METTL3 and METTL14. METTL3, which contains an active methyltransferase domain, transfers a methyl group from S-adenosylmethionine to the adenosine residue on the substrate. METTL14, a critical component, supports METTL3 in recognizing RNA substrates.

The m6Amodification site is particularly localized at the beginning of the 3'untranslated region, near the stop codon, and is typically embedded within the consensus motif 5'-RRACH-3'. The METTL3-METTL14 heterodimer binds to WTAP, which acts as an adaptor protein interacting with the methyltransferases, even though it lacks catalytic methylation activity.

4.2 Therapeutic Strategies Targeting m6A 'Eraser' Enzymes

Therapeutic strategies targeting m6A 'eraser' enzymes, such as FTO and ALKBH5, have been discussed (Zhang et al. 2021). FTO plays a key role in RNA methylation modifications, including cap m6Am and m1A, with varying efficiency. Its subcellular localization influences substrate specificity. In the nucleus, FTO preferentially demethylates internal m6A in poly(A) RNA, m6A and m6Am in small nuclear RNA (snRNA), and m1A in transfer RNA (tRNA). In the cytoplasm, it demethylates both internal m6A and cap m6Am in poly(A) RNA, as well as m1A in tRNA. The crystal structure of FTO bound to 6mA-modified single-stranded DNA (ssDNA) reveals the molecular basis for its recognition and catalytic demethylation of different substrates. This structural insight demonstrates that N6-methyladenine is the most favorable nucleobase substrate for FTO. Understanding FTO's role in RNA modifications and its substrate specificity provides valuable insights into its function in gene regulation and cellular processes, which may have implications for various diseases, including diabetes.

4.3 m6A Modification and the Application of Small Molecule Drugs

The application of m6Amodification in combination with diabetes drugs has been investigated (Zhou et al. 2024). Zhou's team explored the potential role of metformin in m6Amodification in NIT-1 cells by quantifying the m6Acontent in these cells. They found that treatment with H2O2 led to a significant reduction in m6Amethylation levels compared to cells treated with metformin. Additionally, the mRNA expressions of the m6Amethyltransferases METTL3 and METTL14 were decreased in NIT-1 cells treated with H2O2, while no noticeable changes were observed in the mRNA levels of the m6Ademethylases FTO and ALKBH5. Interestingly, metformin treatment increased the degree of m6Amethylation in the H2O2-treated group and partially restored the mRNA expression of METTL14, although it did not significantly impact the mRNA levels of METTL3 or FTO. Furthermore, Western blot analysis demonstrated that metformin treatment enhanced the protein level of METTL14.

5 RESEARCH PROGRESS AND CHALLENGES

5.1 Complexity and Context-Dependent Effects of m6A

One of the most significant challenges in studying m6A modifications is their complex and context-dependent effects. The consequences of m6A modification can vary depending on the specific RNA molecule, cell type, and physiological condition. For example, in pancreatic β-cells, m6A has been shown to regulate insulin mRNA stability and translation efficiency, but its effects can differ under conditions of hyperglycemia or insulin resistance. Understanding the precise role of m6A in different metabolic tissues and disease states is essential but remains a significant challenge due to the dynamic nature of this modification (Shi et al. 2019).

5.2 Lack of Specific and Potent Small Molecule Modulators

While some small molecule inhibitors and activators of m6A regulators have been identified, their specificity and potency remain major limitations. Many currently available inhibitors, such as Rhein (an FTO inhibitor) and STM2457 (a METTL3 inhibitor), exhibit off-target effects that may lead to unwanted metabolic disturbances. Additionally, the development of highly selective small molecules targeting specific m6A-modifying enzymes without affecting other RNA modifications is still in its early stages (Gu et al. 2020).

5.3 Limited Understanding of m6A Regulatory Networks in Diabetes

The interplay between m6A modifications and key metabolic pathways in diabetes remains poorly understood. Although m6A modifications regulate mRNA stability, splicing, and translation, how these processes interact with insulin signaling pathways,

glucose metabolism, and inflammatory responses is still being explored. Moreover, the roles of m6A readers (e.g., YTHDF1, YTHDF2) in mediating downstream effects are not fully elucidated, making it challenging to design targeted therapeutic interventions (Du et al. 2022).

5.4 Technical Limitations in m6A Detection and Quantification

Despite advancements in m6A sequencing technologies (e.g., MeRIP-seq, m6A-CLIP), challenges remain in accurately mapping m6A modifications at single-nucleotide resolution. Many current methods have limited sensitivity and specificity, making it difficult to distinguish functionally relevant m6A sites from background noise. Furthermore, the requirement for large amounts of RNA and the complexity of bioinformatics analysis hinder widespread adoption in clinical and translational research (Motorin et al. 2023).

5.5 Safety and Long-Term Effects of m6A-Targeting Therapies

The long-term effects of modulating m6A modifications are still not fully understood. Given that m6A plays a vital role in various physiological processes such as cell differentiation, immune responses, and neuronal function, any therapeutic intervention targeting m6A pathways requires careful evaluation for potential side effects. m6A modifications regulate gene expression, RNA stability, and protein synthesis, all of which are essential for normal cellular functions. Therefore, disrupting m6A homeostasis could have unintended consequences. For instance, it may impair immune function, leading to increased susceptibility to infections or autoimmune diseases. Additionally, alterations in m6A regulation could elevate cancer risk by influencing the expression of oncogenes or tumor suppressor genes. Furthermore, m6A dysfunction during development may result in abnormalities in cell differentiation and tissue formation, potentially causing developmental defects. As research progresses, it is crucial to understand the full scope of m6A's impact on health and disease. Long-term safety studies will be necessary before m6A-targeted therapies can be widely used, ensuring their benefits outweigh potential risks (Faraj et al. 2023).

6 FUTURE RESEARCH DIERECTION

6.1 Development of Highly Selective Small Molecule Modulators

Future research should prioritize the design of highly selective and potent small molecule inhibitors or activators of m6A-related enzymes. By leveraging structure-based drug design and high-throughput screening techniques, researchers can identify novel compounds with enhanced specificity, minimizing off-target effects. These approaches could enable the development of therapeutic agents that precisely modulate m6A pathways, offering new treatment options for diseases associated with m6A dysregulation, such as cancer, diabetes, and neurological disorders. Additionally, the development of targeted drug delivery systems, including nanoparticle-based strategies, could improve the therapeutic efficacy of m6A modulators by ensuring more localized action and reducing systemic toxicity. Such systems would allow for the precise delivery of these compounds to specific tissues or cell types, maximizing their beneficial effects while minimizing potential side effects. Ultimately, these advancements could lead to safer, more effective therapies for conditions driven by abnormal m6A regulation, offering promising new avenues for precision medicine (Deng et al. 2022).

6.2 Comprehensive Mapping of m6A Regulatory Networks

To fully understand the role of m6A in diabetes, researchers must map its entire regulatory network across key metabolic tissues, including the pancreas, liver, adipose tissue, and skeletal muscle. These tissues play essential roles in glucose metabolism and insulin signaling, making them critical for studying diabetes progression. Advanced techniques, such as single-cell RNA sequencing combined with m6A profiling, offer powerful tools to investigate cell-type-specific m6A modifications. These approaches can provide deeper insights into how m6A dynamically regulates gene expression in different tissues, influencing insulin production, glucose uptake, and lipid metabolism. By identifying the specific roles of m6A in various cell types, researchers can uncover new mechanisms underlying diabetes development and its complications. Understanding these regulatory pathways may lead to

novel therapeutic strategies targeting m6A modifications to improve diabetes management. Future studies focusing on tissue-specific m6A patterns could pave the way for precision medicine approaches in diabetes treatment (Zhang et al. 2019).

7 CONCLUSION

N6-methyladenosine (m6A) is a key post-transcriptional RNA modification widely found in eukaryotic mRNA, influencing RNA stability, translation, splicing, and degradation. Recent research highlights its significant role in diabetes, particularly type 2 diabetes (T2D), by regulating insulin signaling, islet β-cell function, immune response, and lipid metabolism. However, despite growing evidence, the precise mechanisms of m6A in diabetes and its complications remain unclear, especially its effects across different diabetes types, cell types, and complications such as diabetic retinopathy and nephropathy. Glucose levels dynamically regulate m6A modification in T2D patients. High glucose concentrations lead to reduced expression of FTO, a key m6A demethylase, while simultaneously increasing the expression of METTL3, METTL14, and WTAP, the primary methyltransferases involved in m6A modification. These molecular changes significantly affect insulin signaling and metabolic pathways, contributing to glucose homeostasis and diabetes progression. Advances in technology have identified numerous diabetes-related genes targeted by m6A, offering promising therapeutic opportunities. Given the complexity of m6A's involvement in diabetes, systematically reviewing and summarizing existing studies can deepen our understanding of its molecular mechanisms. A better grasp of how m6A modifications regulate key genes could pave the way for precision treatments aimed at improving diabetes management. As research progresses, targeting m6A-related pathways may provide novel intervention strategies, enhancing therapeutic outcomes for diabetic patients. Exploring this modification in greater depth could lead to more effective, personalized treatment approaches. Future studies should focus on elucidating the specific roles of m6A in different diabetes subtypes and complications. By bridging current knowledge gaps, researchers can develop innovative therapies based on m6A modifications, potentially revolutionizing early intervention and treatment strategies for diabetes and its related complications.

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