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Differential Expression and Functional Regulation of MicroRNAs in Type 2 Diabetes Mellitus and Obesity

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Abstract. Type 2 diabetes and obesity are both chronic metabolic diseases that are prevalent in the world. The pathophysiological processes of the two are intertwined with each other, which will form a vicious circle. It also constitutes a significant public health challenge. This review focuses on how microRNA (miRNA) shows differential expression and functional regulation in the context of the coexistence of these two diseases. The article systematically explains the biosynthetic mechanism of miRNA and its multi-dimensional regulatory role in core pathological processes such as insulin resistance, glucose and lipid metabolism disorders, and chronic inflammation. Additionally, this work also reveals the systematic regulatory network characteristics of miRNA in tissues such as liver, adipose tissue and pancreas. Findings show that circulating miRNA has the potential to be used as a biomarker to distinguish between simple obesity and obesity with insulin resistance. miRNA analogs and antagonists also show a certain therapeutic potential in improving metabolic disorders, while weight loss surgery can achieve early metabolic improvement by reversing the characteristic miRNA expression pattern. This review fills some gaps in miRNA research under single metabolic conditions. On the one hand, it clarifies its tissue-specific expression pattern. On the other hand, it also provides some candidate biomarkers for early screening of diseases, and also lays a theoretical foundation for precise multi-target treatment. This also points out a general direction for the personalized prevention and control strategies of metabolic complications.

Keywords: Type 2 Diabetes Mellitus, Obesity, miRNAs, Insulin Resistance, Metabolic Comorbidity.

1. Introduction

Diabetes and obesity have become two of the most serious chronic non-communicable diseases in the world by the 21st century. They have a relatively high incidence and comorbidity rate, and the incidence of the disease is also showing a trend of rejuvenation, which is becoming an urgent public health problem to be solved. These two diseases are not independent of each other. On the contrary, there is a close pathophysiological relationship between them. On the one hand, obesity is not only the most important risk factor for Type 2 diabetes mellitus (T2DM), but also significantly increases the risk of complications such as cardiovascular diseases, non-alcoholic fatty liver and tumors by aggravating insulin resistance (IR), lipid metabolism disorders and chronic inflammation. On the

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other hand, the metabolic pathological changes caused by T2DM, in turn, can promote the abnormal accumulation of fat, thus forming a pathological cycle that promotes each other.

T2DM is a relatively common chronic disease. The global prevalence of this disease has been rising, posing a considerable threat to human health [1]. If taking metabolic disorders as an example, T2DM can essentially be regarded as a dual pathological state. It is characterized by a decrease in insulin sensitivity and insufficient insulin secretion. The insulin sensitivity of the peripheral tissue is reduced, and the insulin secretion capacity of the pancreatic islet β-cells is insufficient. These two problems together destroy the blood glucose homeosisis, thus causing hyperglycemia. They can cause metabolic disorders and organ damage too. Obesity is also a chronic metabolic disorder. It is characterized by pathological expansion of adipose tissue (AT), which is mainly manifested in the abnormal growth of fat cells, which includes hypertrophy and proliferation [2]. AT is not something that is too lazy to move in metabolism. It will secrete many kinds of fat factors, inflammatory mediators and chemokines. Through local and systemic effects, AT can deeply affect energy metabolism, immune homeosis and the function of multiple organs. In this way, it also induces IR, chronic low-degree inflammation, and a variety of metabolic complications. Obesity is a major risk factor for T2DM, and about 85% of T2DM patients have obesity problems [3]. The core mechanism of obesity and T2DM is that the two will interact, eventually forming a vicious circle called "hyperglycemia-hyperinsulinemia-lipid accumulation". Whether it is excessive weight gain or obesity itself, it is regarded as the most important risk factor in the occurrence and development of T2DM at all ages. Considering that obesity has reached the level of global prevalence, the treatment of obesity is quite critical for the prevention and control of T2DM worldwide [4].

The potential mechanism behind the two diseases of T2DM and obesity is still not particularly clear, but recent studies have shown that microRNAs (miRNAs) are involved in the occurrence and development of these diseases. miRNAs are endogenous non-coding single-stranded RNAs in eucaryotic organisms. It will be derived from a relatively long primary transcript, and then getting through a processing step such as precursor intermediate, finally mature into a functional miRNA [5]. These miRNAs are mainly specifically bound to the 3' non-translated region of the target messenger RNA (mRNA) molecule, so that the expression of genes can be regulated at the level after transcription. If miRNA has expression disorder, including abnormal upregulation or downregulation of expression levels, it is closely related to the occurrence and development of many human diseases, such as tumors [6], Alzheimer's disease [7], hypertension [8] and T2DM.

There are indeed some limitations in the existing research work. Most previous studies were only done under a single metabolic condition. In this way, on the one hand, the functional specificity of miRNA regulation in the context of complications was ignored, on the other hand, it also ignored its own clinical significance. Considering this, this review focuses on exploring the differential expression of the core miRNAs and their functional regulation mechanisms in patients with T2DM combined with obesity. This work also clarifies the interaction pathway between glucose and lipid metabolism disorders mediated by miRNA and chronic inflammation. This review summarizes some candidate biomarkers that can be used for early disease screening, and also provides a certain theoretical basis for multi-target precision treatment. In addition, it also integrates those scattered research results together. Firstly, it can guide the future research direction, and secondly, it can promote some strategies in individualized prevention and control of metabolic complications.

2. Pathophysiological mechanisms of T2DM and obesity and connection

There are intertwined pathophysiological processes between T2DM and obesity, and the core problem is the continuous metabolic imbalance. Specifically, the characteristics of T2DM can be

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summarized by two main pathophysiological defects, one is IR, and the other is pancreatic islet β-cell dysfunction [9]. IR will show a decrease in the reactivity of liver, skeletal muscle and AT to insulin signals, which will damage the uptake and utilization of glucose, and then cause hyperglycemia. Pancreatic islet β-cells secrete excessive insulin, resulting in compensatory hyperinsulinemia. However, if this long-term state of excessive secretion continues, it will make the functional failure of β-cells more serious, and eventually it will cause insufficient insulin secretion. β-cells will integrate these signals from glucose, free fatty acids (FFA) and glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide together to regulate insulin secretion in this way. The reason why their function declines is driven by many factors, including glucose toxicity, pancreatic amyloid deposition, and pro-inflammatory signals. In the same period of time, obesity and dyslipidemia will make IR stronger through two pathways of anti-inflammatory effect and ectopic lipid deposition. At the same time, chronic inflammation, endoplasmic reticulum stress and oxidative stress will damage the sensitivity of insulin and the function of β-cells from two directions. In the part of genetic factors, it has a certain impact on the whole pathological process by regulating the renin-angiotensin system, lipid metabolism and inflammatory response. IR and hyperinsulinemia will mainly be shown in the early stage of the disease, while it will slowly develop into β-cell dysfunction in the later stage. If taking too much calories, the fat accumulated in the liver and pancreas will exceed the "individual fat threshold", and it is a key trigger for the development of T2DM [10].

Following the mechanism of T2DM mentioned above, obesity, as a chronic disease characterized by excessive AT or abnormal distribution, is also necessary to discuss it separately. In clinical terms, the definition of obesity is body mass index (BMI $\geq$ 30 kg/m^2), which is generally regarded as a multifactorial disease driven by systemic energy imbalance [11]. Unlike subcutaneous fat, the metabolic activity of fat in the abdominal cavity will be higher. There is an obvious negative correlation between its accumulation and insulin-mediated glucose utilization. For patients with central obesity, if the fat in the abdominal cavity increases, it will weaken the inhibitory effect of insulin on the decomposition of liver glycogen. Excessive FFAs in the blood will induce ectopic lipid deposition, which will further damage the secretory function of pancreatic islet β-cells. This process will increase the output of liver glycogen through substrate competition. On the one hand, it will hinder the clearance of glucose, and on the other hand, it will inhibit the oxidation of glucose and the synthesis of muscle glycogen. At the same time, it will promote glycogenesis and interfere with the activity of insulin receptors and substrates. In this way, the IR and glucose metabolism disorders have been aggravated. The occurrence of obesity is closely related to the imbalance in the regulation of fat volume in the brain-adipose tissue axis. Under normal circumstances, the central nervous system will integrate the signals from intestinal hormones like leptin to maintain the homeosis of body weight through a "setting point" adjustment method, which can offset those abnormal changes in fat volume [12]. The core pathology of obesity is leptin resistance in the end. The brain perceives the relative lack of leptin, but there is no way to compensate for the accumulation of fat by suppressing appetite or increasing energy consumption, which leads to an increase in the set point of fat volume, thus establishing a new weight homeody. Although this process is not driven by subjective factors, it does directly cause immune and metabolic disorders, which will further promote the occurrence and development of metabolic diseases.

There is a close relationship between obesity and T2DM. The pathophysiological processes of these two diseases can be said to be intertwined and promote each other. One of the characteristics of obesity is the accumulation of visceral fat and hypertrophy of fat cells, which will cause hypoxia in AT and bring cell stress. In this way, it will continue to cause chronic low-degree inflammation,

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which in turn prompts fat cells to secrete some pro-inflammatory mediators, such as TNF-α and IL-6 [13]. These mediators will recruit immune cells and activate them, thus driving macrophages in AT and polarizing them from the anti-inflammatory M2 types to the inflammatory M1 types. Once the balance between M1 and M2 is destroyed, a local and systemic inflammatory microenvironment will be formed. This inflammation will further activate the signaling pathway inside the cell, taking c-Jun N-terminal kinase and nuclear factor kappa-B kinase subunit beta inhibitors as an example, it interferes with the transmission of insulin signals through phosphorylation and modification of insulin receptor substrate proteins. At the same time, it will also inhibit the production of fat, promote fat fibrosis and aging-related secretion phenotypes, thus intensifying IR [14]. In addition, the increase in the release of FFAs caused by obesity will induce the ectopic deposition of lipids, which will damage the function of pancreatic islet β-cell on the one hand, and on the other hand, it will disrupt the metabolism of glucose and lipids through substrate competition. If the secretion of fat factors is disordered, it will further aggravate the metabolic and inflammatory disorders. Finally it forms a vicious circle called "obesity-inflammation-IR-T2DM". This cycle will eventually lead to the occurrence and development of T2DM, and it will be accompanied by a progressive decline in the function of pancreatic islet β-cells.

3. Biogenesis and function of miRNAs

Looking down at the pathophysiological mechanisms mentioned above, miRNAs, as key non-coding RNAs with a length of between 18 and 25 nucleotides, has attracted considerable attention. These miRNAs play a core role in the post-transcriptional regulation of gene expression, and are also widely involved in the regulation of physiological metabolism, cell function and the progression of diseases. In the past decade, miRNAs have been confirmed to be an important regulatory factor in metabolic function. In the human genome, there are more than 2,000 miRNAs that have been identified so far, and some of them are tissue-specific [15]. miRNAs will either inhibit the translation process or induce the degradation of mRNAs through complementary binding with the 3' non-translation zone of the target mRNAs. In this way, miRNAs regulate key processes such as glucose metabolism, insulin sensitivity and β-cell survival. For example, miRNAs such as miR-375, miR-29a and miR-103/107 are all regulating the above processes. If these miRNAs are expressed abnormally, they will be closely related to metabolic disorders such as IR and T2DM. The process of biosynthesis of miRNAs involves two aspects: classical pathways and non-classical pathways. In the classical pathway, the miRNA genes will first be transcribed into primary miRNAs, and then processed by the Drosha-DGCR8 complex to become the precursor miRNAs. Afterwards it is transported into the cytoplasm by Exportin-5, and finally cut into mature miRNAs by Dicer enzyme. The non-classical pathway does not depend on Drosha or Dicer enzyme. Some of the sources of precursor miRNAs are tRNAs, snRNAs and other small non-coding RNAs, which will be processed by specific enzymes and then produce mature forms. Additionally, the selective processing in the biosynthesis process will also produce miRNA isoforms (isomiRs). This further enriches the genetic regulation networks [16]. The combination of single-cell RNA sequencing and computational strategies provides new technical support for clarifying the biosynthetic mechanism of miRNAs and isomiRs and the post-transcriptional regulation mode. On the other hand, it also opens up some new ways for the study of disease mechanism and clinical transformation.

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4. miRNAs regulation and biomarker roles in T2DM and obesity

4.1. The functional regulation of miRNAs in T2DM and obesity

miRNA will participate in the pathophysiological process of T2DM and obesity through a multidimensional regulatory network. They all play a central role in glucose metabolism disorders, lipid metabolism disorders, IR, chronic inflammation and multi-organ metabolic coordination. If looking specifically at the regulation of IR, miRNAs can target some key genes in the insulin signaling pathway. Take miR-103 and miR-107 as an example, they weaken the activity of insulin receptor substrates by inhibiting the expression of caveolin-1, while miR-29a inhibits the PI3K/AKT pathway by targeting PIK3R1 [17]. It is worth noting that the expression level of these miRNAs in those patients with obesity combined with T2DM, specifically in their AT and liver, is upregulated. There will be a positive correlation with the HOMA-IR indices. In this way, they may be used as a molecular marker of IR.

In the regulation of lipid metabolism, miRNAs will participate in processes such as fatty acid synthesis and cholesterol metabolism. For example, miR-203a-3p can directly regulate the whole process of lipid metabolism [18]. As a characteristic miRNA target gene, SREBF1 itself is a key transcription factor for maintaining lipid homeosis. When miRNA regulates it, it will cause lipid deposition and dyslipidemia, which will also make the metabolic disorders related to obesity and diabetes more seriously. In the regulation of chronic inflammation, there are some miRNAs, such as miR-30c-2-3p, which can regulate the inflammatory stress response in AT, inducing the generation of fat and the release of inflammatory cytokines [19]. This will promote obesity-related chronic inflammation. thus further aggravating the metabolic imbalance.

From the perspective of multi-tissue coordination, miRNAs form a systematic network between the liver, AT and pancreas. Liver-derived miR-122 will circulate to AT and play a role in regulating lipid storage [20]. The miR-27a secreted by AT will act on the pancreas and have a certain impact on the function of β-cells [21]. As for the miR-375 produced locally by the pancreas, its function is to maintain the homeostas of insulin secretion [22]. These miRNAs will regulate many pathways at the same time. This includes glucose metabolism and β-cell function, which can be used to achieve metabolic control throughout the body. In addition to the above, clinical intervention studies also show that the expression of miRNAs is plastic. Within a week after the weight loss surgery, the expression of those characteristic miRNAs will be reversed, and this change will occur earlier than weight loss. In this way, miRNAs may be working as an early effect molecule that benefits metabolism from surgery. Weight loss surgery can quickly reverse the expression trend of characteristic miRNA. These changes will occur before weight loss and will play a role in metabolic improvement independently of fat factors. Under different surgical methods, the differences between the miRNA expression spectrum also reveal the molecular mechanism behind the surgical relief of T2DM. Some core miRNAs have target genes, such as PIK3R1 and TPI1. These target genes are involved in some key pathways, including insulin signaling pathways, glycolysis and mitochondrial energy metabolism. These genes constitute the core gene network regulated by miRNA in T2DM and obesity, which also provides some important molecular targets for the treatment of disease-specificity.

What is shown in Figure 1 is the specific miRNA regulatory network in the liver, adipose, and pancreatic tissues. It reveals how different miRNAs induce IR, chronic inflammation and abnormal lipid metabolism through synergy, and finally make the whole process of T2DM combined with obesity more seriously. This diagram uses a visual method to summarize the multi-organization regulation mechanisms mentioned above.

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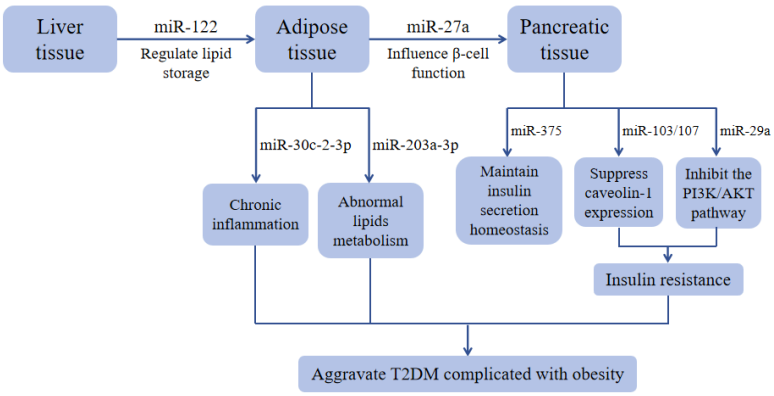

Figure 1. Tissue-specific miRNA regulatory networks in type 2 diabetes complicated with obesity

4.2. Circulating miRNAs as potential biomarkers for T2DM complicated with obesity

Circulating miRNA has a relatively important biomarker value in the clinical diagnosis and management process of T2DM accompanied by obesity. It can be used for early disease detection, risk stratification, therapeutic effect monitoring and complication assessment. When it comes to early risk identification, plasma miR-15a, miR-29a and miR-126 are put together for joint testing [23], which can distinguish between simple obese patients and obese patients with IR. Compared with a single metabolic marker, it shows better predictive efficiency.

In the process of lifestyle intervention and therapeutic effect monitoring, there are some specific plasma miRNA combinations that can reflect the metabolic improvement in real time, which is also conducive to the adjustment of individualized treatment plans. If looking at the treatment monitoring, whether it is lifestyle intervention or drug treatment, there is a relatively obvious correlation between the dynamic changes of those specific miRNAs after completion and the improvement of weight loss and insulin sensitivity. Therefore, they can be used as a supplementary indicator for efficacy evaluation. In addition to the above, some miRNA combinations can also identify cardiovascular complications in obese patients earlier, so that multi-dimensional monitoring of metabolic diseases can be achieved. When it comes to complication prediction, miR-133a and miR-208b are related to myocardial remodeling, while miR-34a and miR-122 can reflect the severity of liver fibrosis. This also supports multi-dimensional risk assessment [24].

Judging from the current situation, there is still a lack of a standardized testing system and a unified combination of biomarkers in this field. The lack of these two things has limited its clinical transformation [25]. As for future research, the following things requires attention. The first is to promote the standardization of miRNA detection technology, the second is to comprehensively verify the stability of the biomarker combination, and the third is to carry out a long-term tracking of the intervention effect. Taking these steps will make circulating miRNA a reliable tool that can be used in the clinical diagnosis and treatment of T2DM with obesity.

5. Therapeutic targeting of miRNAs in T2DM

5.1. Mechanisms and preclinical evidence of miRNAs mimics and antagomirs

miRNA is a key regulatory factor in terms of glucose metabolism, insulin sensitivity and pancreatic islet β-cell function. It is for the reason that miRNA analogs and antagonists are hoped to become effective tools for the treatment of T2DM. The miRNA analogue can restore the activity of

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metabolic protective miRNA, which can also improve insulin signal conduction and blood sugar control in the preclinical T2DM model [26]. On the other hand, antagonists will specifically silence those diabetes-related miRNAs, thus reducing IR and inflammatory reactions in AT [17]. Chemically modified analogues and antagonists have higher stability, and can also achieve targeted delivery to the liver, muscles and AT. On the one hand, these synthetic oligonucleotides help to clarify the miRNA-dependent regulatory network in T2DM, and on the other hand, they can also accelerate the development of new metabolic interventions.

When it comes to optimizing the delivery system, it plays a crucial role in what kind of treatment effect miRNA analogues and antagonists can achieve in the end. The liver-targeted delivery system represented by GalNAc modification is now relatively mature. Lipid nanoparticles and carriers such as exocrine analogues have also shown good application prospects in enhancing nucleic acid stability and improving tissue enrichment efficiency. However, because the technical bottleneck has not been completely broken through, there are still many challenges to accurately target drugs to the pancreas, AT and the central nervous system. This is one of the core problems that restricts the wide application of miRNA therapy in metabolic diseases.

5.2. Prospects and challenges of miRNA-targeted therapy in T2DM complicated with obesity

MiRNA targeted therapy can show considerable potential in the treatment of T2DM combined with obesity by regulating insulin sensitivity, lipid metabolism and AT inflammation [27]. The analogues and antagonists of miRNA can reverse metabolic disorders in the preclinical model and also improve blood sugar control. This also provides some support for future clinical transformation [28]. Preclinical research has confirmed the feasibility of improving glucose metabolism and lipid metabolism. However, due to the existence of various obstacles, it is still facing considerable challenges to transform these research findings into clinical applications. From the perspective of security, there are the following problems. Firstly, the short complementary base pairing of miRNA seed sequences may lead to unexpected mRNA inhibition (off-target effect). Secondly, oligonucleotides after chemical modification may activate the innate immune response. Thirdly, it is not clear what kind of long-term effects these therapies may have on tumor suppressor genes and developmental regulatory genes. In terms of technology, it is necessary to make some breakthroughs in organizational-specific delivery, dose optimization and drug delivery routes. As for the supervision, no miRNA therapy has been approved for the treatment of metabolic diseases, and the relevant review standards and guidelines for the design of clinical trials are still being improved. Taking these aspects into account, it is necessary to further promote the development of chemical modification and targeted delivery systems. On the one hand, it improves the therapeutic effect, and on the other hand, it reduces risks. If miRNA targeted treatment can be optimized through design and strict verification, it may become a new strategy for the treatment of T2DM with obesity.

6. Conclusion and future perspectives

If looking at the disease state of T2DM combined with obesity, the regulation of miRNA will show three core characteristics: multidimensionality, network connectivity and reversibility. miRNAs form a systematic regulatory network in many tissues such as liver, AT and pancreas through targeted insulin signaling pathways, glucose and lipid metabolism pathways, and inflammation-related pathways. Its expression mode can respond to clinical intervention and can undergo reversible changes. In this way, it has become a key molecular bridge between metabolic disorders and chronic inflammation. In addition, circulating miRNA has also shown considerable clinical

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transformation potential in early screening and efficacy monitoring of diseases. However, judging from the current situation, its application still lacks the support of a standardized system, so it has not really reached the stage of clinical application. This review integrates the scattered research results and fills some gaps in the research of miRNA function under single metabolic conditions. It also clarifies the tissue-specific expression mode and core regulatory network of miRNAs under the background of complications, which also provides a unified theoretical framework for subsequent research.

When it comes to the current research on miRNA regulation of T2DM combined with obesity, it actually faces many limitations and challenges. Most of the existing research work relies on cross-sectional analysis. For the causal relationship, there is a lack of long-term longitudinal verification. It is difficult to figure out the time correlation between abnormal miRNA expression and the occurrence or progression of the disease because of this. The standardization of miRNA detection technology is not high enough, and there are also technical problems in the analysis of the source of circular miRNA tissue, coupled with the tissue specificity of the targeted delivery system. These problems come together to limit the comparability and transformation application of the research results. Another point is that the regulatory network between miRNA and mRNA is highly complex and interrelated. If the intervention is aimed at a single miRNA, it is easy to cause the off-target effect. This will hinder the precise regulation of metabolism, and may also bring some safety hazards to clinical treatment.

As for the future research in this field, it requires methodological innovation and paradigm shift. Specifically, firstly, it is necessary to integrate single-cell sequencing, multi-group analysis and longitudinal animal model tracking, so as to clarify the dynamic regulation mechanism and causal relationship of miRNA in the development of complications. The second is to accelerate the standardization of miRNA detection technology, which is also quite critical. This includes determining the threshold of circulating miRNA in clinical application, and developing a highly specific tissue-targeted delivery system to reduce the risk of off-targeting. Speaking of clinical transformation, researchers should explore the combination of biomarkers that can be used for the joint detection of multiple miRNAs, develop multi-target precise intervention strategies based on miRNA, and promote its application to gradually transform from basic research to clinical screening, efficacy monitoring and targeted treatment. After taking these steps, we will finally provide some new molecular tools for the individualized prevention, control and treatment of T2DM combined with obesity, which will also help build a precise medical system for metabolic diseases.

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