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Role of microRNAs in Metabolic Diseases

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ABSTRACT

MicroRNAs regulate a number of processes by controlling the gene expression at the post-transcriptional level. These small, non-coding RNA molecules play an important role in predisposition to metabolic diseases by maintaining glucose, lipid, and cholesterol metabolism. miRNAs are synthesized as double-stranded RNA, the two strands are separated to produce functional single-stranded miRNAs. The miRNAs are part of a large silencing complex called RNA-induced silencing complex (RISC). miRNAs regulate adipogenesis, the accumulation and droplet size of triacylglycerols, and PPAR gene expression. Dysfunction or higher expression of certain miRNAs (e.g., miR-222) silences the glucose transporter mRNAs resulting in a decrease in the surface receptors for glucose uptake hence predisposing to diabetes. miR-222 has also been reported to increase insulin resistance. Certain miRNAs are upregulated in obese mice as well as obese humans including miR143-145, miR29a, etc. The most important regulatory miRNA for lipid metabolism is miR-122, in addition, miR-33a and miR-33b exert their effect through sterol regulatory element binding proteins. The naturally occurring miRNAs can be silenced by chemically modified anti-miRNA oligonucleotides (AMOs) to alter their cellular expression levels. Another therapeutic oligonucleotide type called miRNA sponges compete with miRNAs for binding sites on the target mRNAs. The nuclease-resistant locked nucleic acids (LNAs) can also reduce the expression of certain miRNAs and have been shown to reduce cholesterol levels in mice. In conclusion, miRNAs appear to be faithful therapeutic targets for altering the gene expression of many target genes involved in lipid and fat metabolism in the future.

1. INTRODUCTION

The adipogenesis is the maturation of adipocytes from precursor cells known as pre-adipocytes. The adipocytes store fats and their development is controlled by different transcription factors. Hypoxia in adipocytes leads to dysfunction of adipose tissues. The functional impairment leads to the development of obesity and associated diseases

(Meissburger *et al.*, 2011; Trayhurn, 2013; Kawai *et al.*, 2021). MicroRNAs (miRNAs) are non-coding RNAs which regulate the gene expression. miRNAs inhibit the translation by degrading the mRNAs. These are very small molecules consisting of ~21 nucleotide base pairs (Esteller, 2011; Nemeth *et al.*, 2023). miRNAs perform important roles in maintaining homeostasis of cholesterol,

glucose, and lipids metabolism, and insulin sensitivity (Li *et al.*, 2013). The obesity-associated diseases emerge when the regulatory functions of miRNAs are interrupted (Heneghan *et al.*, 2010; Improtacaria *et al.*, 2023). The purpose of this review is to examine the role of various types of miRNAs in the development of obesity and its associated diseases.

1.1 miRNAs Biogenesis and Functions

miRNAs have a specific role in different biological processes as gene expression regulators of cell differentiation and elimination (Carthew, 2006; Jiao *et al.*, 2021). The downregulation of miRNAs is responsible for the development of different metabolic disorders. The transcription of miRNA by RNA polymerase II or III is the first step leading to the generation of (pri-miRNA) primary miRNA (Bartel, 2004). The processing of pri-miRNAs takes place within the nucleus by class II RNase III (Drosha), hence precursor miRNAs (pre-miRNAs) are generated (Han *et*

al., 2004). The exportin-5 protein binds with and transports pre-miRNAs from the nucleus to the cytoplasm. In the cytoplasm, the Dicer enzyme cleaves pre-miRNAs leading to the formation of ~22 nucleotide base pairs of double-stranded miRNAs. These double strands of miRNAs are separated by Argonaute (AGO) protein and a functional copy of miRNA is taken up by RNA-induced silencing complex (RISC) to suppress the target region on mRNA (Bohnsack *et al.*, 2004; Frédérick and Simard, 2022). The role of miRNAs has been studied intensively in plants and animals as the post-transcriptional gene regulators that suppress or degrade the mRNA (Carrington and Ambros, 2003). RISC is directed by miRNA first to silence and then degrade the mRNA target (Valencia-Sanchez *et al.*, 2006; Frédérick and Simard, 2022). The inhibition of translation depends on the miRNA-mediated disruption of the eIF4F complex. The RNA helicase eIF4A2 is responsible for the suppression of translation followed by mRNA degradation (Wilczynska and Bushell, 2015; Naineni *et al.*, 2023) (Figure 1).

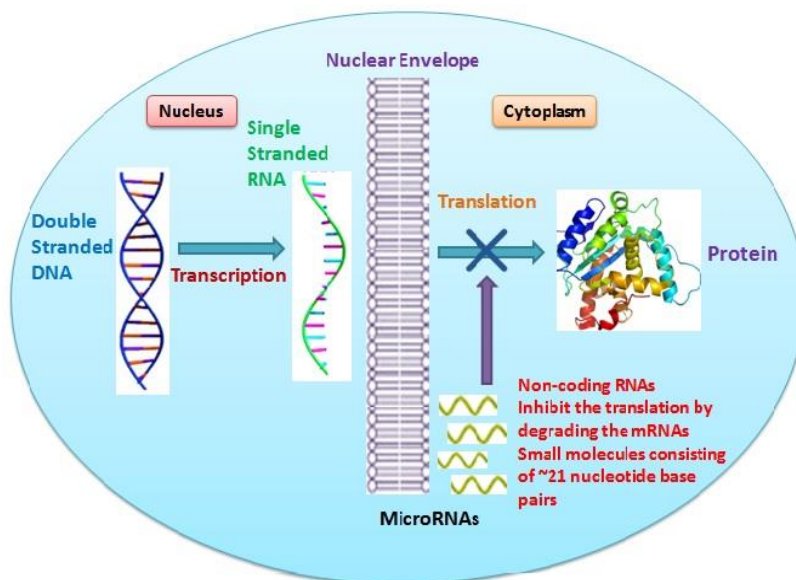


Figure 1. miRNA in Biogenesis and Function



1.2 Role of miRNAs in Adipogenesis

The adipogenesis is induced by transcription factor peroxisome proliferator-activated receptor (PPAR) (Ehsan and Hasnain, 2017). PPAR γ 2 induces sterol regulatory element binding protein (SREBP1) which induces adipocyte proliferation and lipogenesis. SREBP1 induces lipoprotein lipase and fatty acid synthase leading to fatty acid synthesis. The increased rate of fat synthesis and storage in the adipocytes causes dysfunction of glucose and lipid metabolism (Kim *et al.*, 2017).

Several types of miRNAs are activated during adipocyte proliferation. The overexpression of miRNA378/378* in pre-adipocyte 3T3-L1 and bone-marrow derivative ST2 cell lines is found to be associated with the increased lipid droplet size and accumulation of triacylglycerol (Kim *et al.*, 2017; Moreno-Navarrete and Fernández-Real, 2017). The expression levels of miRNAs in subcutaneous adipose tissue were analyzed in a study including obese and non-obese adults. The dysfunction of miRNA-519d lowers the levels of PPAR α in obese individuals. The decreasing expression levels of miR-130 have been found to be associated with the increase in adipocyte differentiation (Figure 2) (Lorente-Cebrián *et al.*, 2019).

The suppression of PPAR expression is accomplished by miR-130 binding with the 3'UTR of mRNA. Similarly, miRNA-103 and miRNA-143 become active during adipogenesis and enhance the process (Parra *et al.*, 2010; Engin and Engin, 2022). The correlation of miRNA expression with the factors associated with obesity was investigated in a study. The samples of subcutaneous and abdominal adipose tissues were taken from glucose-tolerant and type 2 diabetic individuals. Significant proportions of miRNA were found expressed in both types of adipose tissues (Herrera *et al.*, 2010). The expression of miR-17-5p, miR-132, miR-134, miR-181a, miR-27a, miR-30e, miR-140, miR-147, miR-155, miR-197, and miR-210 was found to be associated with adipose dysfunction leading to type 2 diabetes (Klötting *et al.*, 2009; Heo *et al.*, 2022). The existing data show that the expression of miR-375 takes place after the initiation of adipocyte differentiation. The overall process has been observed in 3T3-L1 differentiation where the higher levels of miR-375 are found along with the higher PPAR γ 2 levels. The miR-375 suppression results in a decrease in adipogenesis (Klötting *et al.*, 2009; Heo *et al.*, 2022).

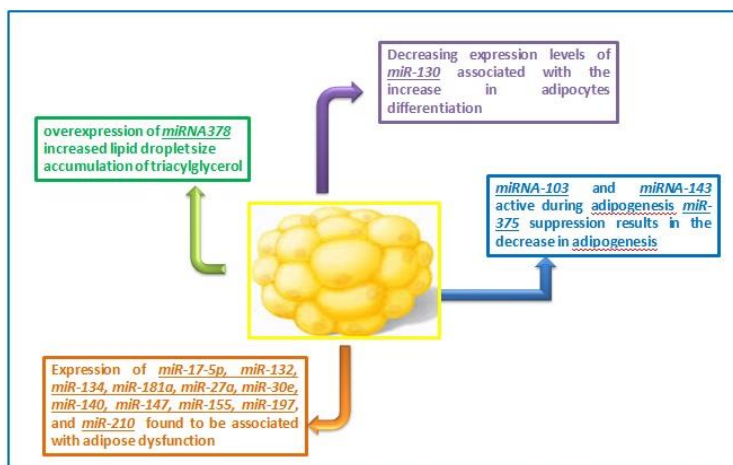


Figure 2. Role of miRNAs in Adipogenesis



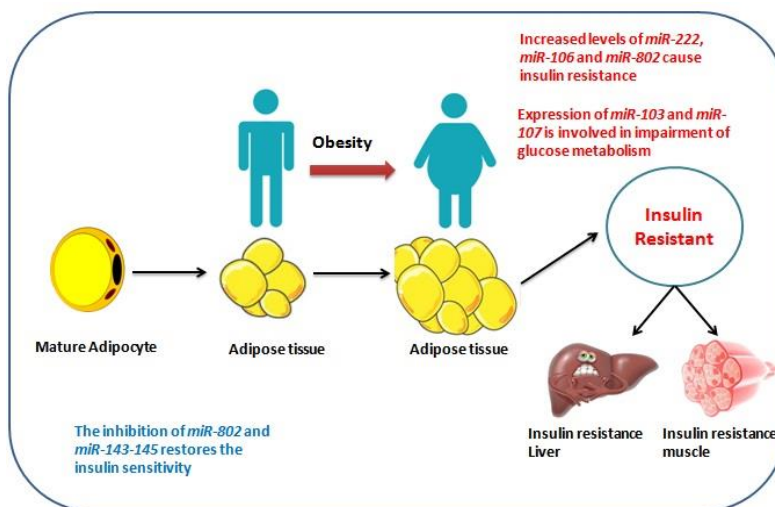


Figure 3. Role of miRNAs in Glucose Metabolism

1.3 Role of miRNAs in Glucose Metabolism

The expression of miRNAs in diabetic and expecting women shows that miR-222 up-regulation is associated with the reduction in glucose transporter 4 (GLUT4) proteins (Deiuliis, 2016; Ibarra *et al.*, 2018). The increased levels of miR-222 in 3T3-L1 adipocytes cause suppression of insulin-sensitive receptors which results in insulin resistance (Shi *et al.*, 2014). Insulin resistance in obese patients develops due to dysfunction in glucose homeostasis. The upregulation of miR-802 in the liver is associated with insulin resistance in obese humans and mice (Kornfeld *et al.*, 2013). The suppression of hepatocyte nuclear factor 1 β by miR-802 results in increased liver gluconeogenesis. The inhibition of miR-802 restores the insulin sensitivity (Kornfeld *et al.*, 2013).

Mitofusin2 (Mfn2) is the protein involved in muscle glucose metabolism and insulin regulation. Mfn2 mRNA is the target of miR-106 mediated posttranscriptional inhibition which leads to insulin resistance and impairment of energy metabolism (Duarte *et al.*, 2015). The suppression of miR-106 is the

therapeutic way to restore insulin sensitivity and energy metabolism in muscles (Rached *et al.*, 2014). Sirtuin-1 (SIRT) is a transcription factor involved in glucose homeostasis in the hepatocytes (Frescas *et al.*, 2005; Mortuza *et al.*, 2013). The 3' untranslated region (3'UTR) of Sirtuin-1 mRNA is suppressed by miR-181a leading to the decreased SIRT levels in the hepatocytes. Diabetic patients have been observed with increased levels of miR-181a. The anti-miR-181a inactivates the miR-181a and restores the insulin sensitivity in the hepatocytes (Cao *et al.*, 2016) (Figure 3).

The upregulation of miR-143 in obese mice is responsible for the suppression of oxysterol-binding-protein-related protein 8 (ORP8). The suppression of ORP8 results in insulin resistance. The mice lacking miR-143-145 are found to be insulin-sensitive (Chen *et al.*, 2012). The Let-7 miRNAs control glucose levels in various tissues but when tested in mice, their overexpression causes insulin resistance. The suppression of Let-7 by anti-miRNAs proves effective in the cure of insulin resistance associated with obesity (Frost and Olson, 2011; Zhu *et al.*, 2011). The miRNA expression of miR-103 and miR-107 is



involved in impairment of glucose metabolism in obese mice. The silencing of miR-103 and miR-107 is associated with the activation of caveolin-1 which regulates insulin signaling and glucose metabolism (Trajkovski *et al.*, 2011). The expression of miR-29a is increased and results in reduced insulin signaling in the hepatocytes (Yang *et al.*, 2014). The miR-29a causes the suppression of phosphoinositide-3-kinase (PI3K) and insulin activity in the hepatocytes is halted (Pandey *et al.*, 2011).

Role of miRNAs in Lipid Metabolism

Dyslipidemia is a severe consequence of elevated cholesterol and triglycerides in the bloodstream which leads to the development of metabolic syndrome and obesity-associated diseases (Vaziri, 2006). The first identified micro-RNA which accounts for 70% of liver miRNAs is miR-122 known to be involved in the regulation of lipid metabolism (Wen and Friedman, 2012). The downregulation of miR-122 by RNA silencing is found to be associated with the cholesterol and triglyceride levels in the bloodstream (Boehm and Slack, 2006; Mirzaei *et al.*, 2023). The genes encoding sterol regulatory element-binding proteins (SREBPs) encompass miR-33a and miR-33b in the introns (Gerin *et al.*, 2010). SREBPs regulate lipid metabolism as miR-33a and miR-33b suppress the adenosine triphosphate-binding cassette transporter A1 (ABCA1) involved in lipoprotein and cholesterol synthesis.

The downregulation of miR-33a and miR-33b activates the ABCA1 which causes increased synthesis of lipoproteins and cholesterol (Najafi-Shoushtari *et al.*, 2010). The lipid homeostasis is also established by miR-223 mediated suppression of BI receptor involved in lipoproteins uptake and inactivation of 3-hydroxy-3-methylglutaryl-CoA synthase 1 and methylsterol monooxygenase 1 involved in cholesterol synthesis (Goedeke and Fernández-

Hernando, 2012; Rotllan *et al.*, 2016). The downregulation of miR-223 also activates ABCA1 which leads to the accumulation of lipoproteins in cells and increased efflux of cholesterol in the bloodstream (Rottiers and Näär, 2012; Chistiakov *et al.*, 2017). The miR-27a mediates regulation of transcription factors involved in lipogenesis such as retinoid X receptor α (RXR α) and lipid transporter ATP-binding cassette subfamily A member 1. The inactivation of miR-27a during hepatitis C virus infection causes increased lipids accumulation and replication of viral particles (Novák *et al.*, 2015).

The lipid biosynthesis is halted by miR-27b mediated suppression of PPAR γ 1 but when exposed to lipopolysaccharides (LPS) the miR-27b inactivation leads to PPAR γ 1 mediated lipid biosynthesis (Jennewein, 2010). The antisense RNA for miR-21 was introduced to human hepatoma cell line 7 (HuH7) to determine the effect on PPAR α mediated lipogenesis. The inactivation of miR-21 resulted in higher PPAR α protein levels (Shimizu *et al.*, 2010). The role of miR-21 as a negative regulator is very crucial in lipid buildup stimulated by lipopolysaccharides. The overexpression of miR-21 causes a decrease in lipid biosynthesis (Wong *et al.*, 2013). Sirtuin 1 (SIRT1) and fibroblast growth factor 21 (FGF21) are the transcriptional factors involved in brown fat synthesis. Brown fat is involved in energy production by uncoupled respiration thus preventing obesity. The overexpression of miR-34a causes obesity by suppression of SIRT1 and FGF21 (Chau *et al.*, 2010).

miRNAs as Therapeutic Target to Treat Obesity

The credit for making advances in miRNA-associated research goes to Ambros and Ruvkun who in 1993 were successful in establishing that the lin-4 gene causes an



increase in miRNA levels (Lee *et al.*, 1993). The role of miRNAs in association with different diseases has been studied well in various animal and human models of inflammatory and metabolic diseases (Lu *et al.*, 2008; Rottiers and Näär, 2012). The silencing of miRNAs involves various strategies but mostly the anti-miRNAs are utilized as antisense RNA fragments. These therapeutic nucleic acids referred to as anti-miRNA oligonucleotides (AMOs) are chemically modified RNA molecules that bind specifically to the miRNAs in vivo and reduce their cellular expression levels (Shah and Calin, 2014). Similarly, the inhibitors termed microRNA sponges are the competitive RNA fragments transcribed from animal cells that bind to the specific miRNA sites (Ebert and Sharp, 2010).

The locked nucleic acid (LNA) molecules are conformational modifications of RNAs that are stable against nucleases and have been effectively utilized as therapeutic agents in metabolic disorders (Petersen *et al.*, 2000; Petersen *et al.*, 2001). Recently the LNA29 has been observed to reduce the miR-29 levels thereby decreasing the lipids biosynthesis and cholesterol levels in mice (Kurtz *et al.*, 2015). The applicability of LNA24 was also tested in a study in mice and miR-24 expression was effectively reduced in the liver. The introduction of LNA24 is responsible for the expression of insulin-induced gene 1 (Insig1) which causes inactivation of transcription factors involved in lipids biosynthesis (Kurtz *et al.*, 2015; Sethupathy, 2016). The mice affected with diabetic nephropathy were subjected to LNA192 administration which resulted in the decreased expression of miR-192 (known to be associated with the disease) (Putta *et al.*, 2012; Sethupathy, 2016). The suppression of miR-192 was found to be promising in decreasing renal fibrosis and proteinuria (Putta *et al.*, 2012). The suppression of p53, miR-216a, miR-217, and miR-200 is also observed in the renal cortex of

diabetic mice when treated with LNA192 (Putta *et al.*, 2012; Gluba-Sagr *et al.*, 2023).

Conclusion

There are many factors, behavioral, environmental as well as genetic that play together and contribute to the predisposition to complex, multifactorial diseases including obesity, dyslipidemia, diabetes, hypertension, cardiovascular diseases, etc. In the quest for the genetic culprits and to find an appropriate way that control the expression of up/downregulated genes in these less understood diseases, miRNAs have emerged as a good therapeutic target. The number of miRNA species identified so far is in the hundreds and the list is still growing. In the future, the use of miRNAs as targets for the regulation of gene expression may result in an easy and accessible treatment for many multifactorial, heterogeneous metabolic diseases.

Conflict of Interest

The authors declare no conflict of interest.

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