**Name of Journal:** *World Journal of Diabetes*

**Manuscript NO:** 86880

**Manuscript Type:** MINIREVIEWS

**Molecular mechanisms of noncoding RNA and epigenetic regulation in obesity with consequent diabetes mellitus development**

Guo YC *et al*. Epigenetic pathogenesis in obesity with DM

Yi-Chen Guo, Hao-Di Cao, Xiao-Fen Lian, Pei-Xian Wu, Fan Zhang, Hua Zhang, Dong-Hui Lu

**Yi-Chen Guo, Xiao-Fen Lian, Pei-Xian Wu, Fan Zhang, Dong-Hui Lu,** Department of Endocrinology, Peking University Shenzhen Hospital, Shenzhen 518036, Guangdong Province, China

**Yi-Chen Guo, Hao-Di Cao, Hua Zhang,** Department of Endocrinology, Zhujiang Hospital of Southern Medical University, Guangzhou 510282, Guangdong Province, China

**Author contributions:** Guo YC and Cao HD contributed equally to this work; Guo YC, Cao HD, Lian XF, Wu PX, Zhang F, Zhang H, and Lu DH designed the research; Cao HD and Lian XF contributed analytic tools and specifically visualization; Guo YC analyzed the data and wrote the manuscript; Wu PX, Zhang F, Zhang H, and Lu DH edited and reviewed the manuscript; and all authors have read and approve the final manuscript.

**Supported by** the Shenzhen Science and Technology Innovation Committee Projects, No. JCYJ20170816105416349; Shenzhen High-level Hospital Construction Fund; and Shenzhen Key Medical Discipline Construction Fund, No. SZXK010.

**Corresponding author: Dong-Hui Lu, MD, Chief Physician,** Department of Endocrinology, Peking University Shenzhen Hospital, No. 1120 Lianhua Road, Futian District, Shenzhen 518036, Guangdong Province, China. ludongh@sina.com

**Received:** July 12, 2023

**Revised:** August 26, 2023

**Accepted:** September 27, 2023

**Published online:** November 15, 2023

**Abstract**

Diabetes mellitus (DM) and obesity have become two of the most prevalent and challenging diseases worldwide, with increasing incidence and serious complications. Recent studies have shown that noncoding RNA (ncRNA) and epigenetic regulation play crucial roles in the pathogenesis of DM complicated by obesity. Identification of the involvement of ncRNA and epigenetic regulation in the pathogenesis of diabetes with obesity has opened new avenues of investigation. Targeting these mechanisms with small molecules or RNA-based therapies may provide a more precise and effective approach to diabetes treatment than traditional therapies. In this review, we discuss the molecular mechanisms of ncRNA and epigenetic regulation and their potential therapeutic targets, and the research prospects for DM complicated with obesity.

**Key Words:** Diabetes mellitus; Obesity; Noncoding RNA; Epigenetic regulation; Insulin resistance

**©The** **Author(s) 2023.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation**: Guo YC, Cao HD, Lian XF, Wu PX, Zhang F, Zhang H, Lu DH. Molecular mechanisms of noncoding RNA and epigenetic regulation in obesity with consequent diabetes mellitus development. *World J Diabetes* 2023; 14(11): 1621-1631

**URL**: https://www.wjgnet.com/1948-9358/full/v14/i11/1621.htm

**DOI**: https://dx.doi.org/10.4239/wjd.v14.i11.1621

**Core Tip:** Non-coding RNA (ncRNA) and epigenetic regulation play crucial roles in the pathogenesis of diabetes mellitus complicated by obesity. Identification of the involvement of ncRNA and epigenetic regulation in the pathogenesis of diabetes with obesity has opened new avenues. Targeting these mechanisms with small molecules or RNA-based therapies may provide a more precise and effective approach to diabetes treatment than traditional therapies.

**INTRODUCTION**

The combination of diabetes mellitus (DM) and obesity has become a global health concern due to the high prevalence and serious consequences of these conditions. The pathogenesis of DM combined with obesity is complex and involves multiple mechanisms, including insulin resistance (IR), chronic inflammation, and adipokine dysregulation[1,2].

IR is a key factor in the development of both obesity and type 2 DM (T2DM)[3,4]. Adipose tissue, particularly visceral adipose tissue, produces a range of hormones, cytokines, and chemokines, collectively known as adipokines. In obesity, adipose tissue expands and produces increased amounts of proinflammatory adipokines, such as leptin, as well as decreased amounts of anti-inflammatory adipokines, such as adiponectin[5]. This leads to chronic inflammation, which exacerbates IR. Obesity and diabetes are associated with alterations in the gut microbiome, which can contribute to the pathogenesis of both conditions[6,7]. The gut microbiota of obese and diabetic individuals is distinct from that of healthy individuals, with reduced microbial diversity and altered microbial composition.

While the exact mechanisms underlying the development of DM complicated with obesity are still not fully understood, emerging evidence suggests that epigenetic modifications and noncoding RNA (ncRNA) play a critical role in its pathogenesis[8]. Epigenetic regulation refers to the modification of gene expression without changes to the underlying DNA sequence[9]. These modified activities can have a significant impact on gene expression and cellular function. Additionally, several genes are linked to an increased risk of developing these conditions, including genes involved in adipogenesis, lipid metabolism, and insulin signaling. Compounded obesity in DM is a multifactorial disorder that involves complicated interplay among genetic, environmental and lifestyle factors. It is vital to establish effective strategies for the prevention and treatment of these disorders by understanding these mechanisms.

ncRNAs, particularly microRNA (miRNA) and long noncoding RNA (lncRNA), have been shown to play critical roles in the development and progression of DM. Dysregulation of miRNA expression can lead to impaired glucose metabolism and IR[10]. For example, miRNA-29 regulates insulin signaling by targeting the insulin receptor substrate-1 (*IRS-1*) gene[11]. In obese mice, miRNA-29 expression is decreased, leading to increased *IRS-1* expression and improved insulin sensitivity[11]. Similarly, miRNA-223 has been shown to regulate glucose uptake by targeting GLUT4, a glucose transporter protein. lncRNA has also been implicated in the pathogenesis of DM[12]. In addition, lncRNA MEG3 controls insulin secretion by modulating gene expression involved in insulin synthesis and secretion[13]. lncRNA taurine-upregulated gene 1 regulates the proliferation and differentiation of pancreatic beta cells, which are responsible for insulin production[14].

DNA methylation can alter gene expression patterns. The promoter region of the insulin gene is hypermethylated in patients with T2DM, leading to decreased insulin production[15]. Similarly, the promoter region of the adiponectin gene is hypomethylated in obese individuals, leading to increased adiponectin expression and improved insulin sensitivity[16]. The augmentation of gene expression is linked to histone acetylation, whereas histone methylation may either stimulate or hinder gene expression, contingent on the location and extent of methylation[17].

Emerging evidence suggests that epigenetic modifications and ncRNA play a critical role in the development and progression of DM complicated with obesity (Figure 1). Dysregulation of miRNA and lncRNA expression, as well as altered DNA methylation and histone modifications, can lead to impaired glucose metabolism and IR[18]. Although much is still unknown about the mechanisms underlying these epigenetic changes, identification of these modifications as potential therapeutic targets offers new hope for the prevention and treatment of DM. Future research should elucidate the role of epigenetic regulation and ncRNA in diabetes pathogenesis and develop effective therapies targeting these pathways. The aim of this review is to explore the molecular mechanisms of ncRNAs and epigenetic regulation in the pathogenesis of DM complicated by obesity. We intend to discuss the potential therapeutic targets associated with these mechanisms and highlight the research prospects for DM complicated with obesity.

**MOLECULAR MECHANISMS OF ncRNA IN THE PATHOGENESIS OF DM COMPLICATED WITH OBESITY**

***Role of lncRNAs***

**lncRNAs in obesity and DM:** The utilization of cutting-edge bioinformatic techniques has facilitated the identification of lncRNAs associated with obesity and adipocyte differentiation[19]. Investigations of gain-of-function and loss-of-function have both strongly pointed to the pivotal participation of lncRNAs in adipogenesis. To date, various lncRNAs have been examined in a range of models and they are potent modulators of diverse genetic pathways linked to white adipose tissue (WAT) compartmentalization and activity[20].

The first adipogenesis-related lncRNA was a steroid receptor RNA activator (SRA), which acts as a coactivator of peroxisome proliferator-activated receptor (PPAR)γ[21]. Among the lncRNAs involved in adipogenesis, ASMER-1 and ASMER-2 are upregulated in subcutaneous adipose tissue (ScAT) and are linked to adipocyte-specific metabolism and IR[20]. Several lncRNAs have roles in adipogenesis (the formation of fat cells), lipolysis (the breakdown of fat), and adiponectin secretion in human adipocytes (fat cells). ADNCR is an endogenous competitive RNA for miR-204, and overexpression of SIRT-1 inhibits adipocyte differentiation and impairs the PPARγ pathway *in vitro*. Finally, HOTAIR is implicated in preadipocyte differentiation[20,22-26].

Brown adipose tissue (BAT) is a specialized form of adipose tissue that is mainly responsible for thermogenesis and energy expenditure. It is characterized by the presence of uncoupling protein 1 (UCP1), leading to increased energy expenditure and weight loss[27,28]. Recent studies have identified several lncRNAs that are involved in BAT regulation, including brown fat lncRNA1 (Blnc1) and H19[25,29]. Research has indicated that Blnc1 plays a role in regulating thermogenic genes, resulting in an increase in the expression of UCP1 and mitochondrial genes[30]. Conversely, H19 has been found to have an inverse correlation with body mass index (BMI) and a positive correlation with browning markers. H19 is involved in modulating adipogenesis, oxidative metabolism, and mitochondrial respiration in BAT. Thus, the manipulation of lncRNA expression shows promise as a therapeutic approach for metabolic diseases. This could involve enhancing BAT activity or inducing browning in WAT[31]. Various studies have suggested the potential of different lncRNAs as biomarkers for diagnosing and managing obesity. For example, Sun *et al*[32] found reduced expression of three lncRNAs in obese but not in lean subjects. The expression of these lncRNAs was inversely correlated with waist-to-hip ratio, BMI and fasting plasma insulin levels. lncRNA-p19461 was upregulated following weight loss due to a 12-wk diet, suggesting that bariatric interventions could manage expressed lncRNA profiles. Alterations in the expression levels of lncRNAs were found following bariatric surgery in animals, particularly those engaged in digestive, absorptive and inflammatory pathways.

While the potential of lncRNAs as therapeutic targets for obesity management is promising, several challenges need to be addressed before their clinical application. One major challenge is the lack of understanding of the precise molecular mechanisms underlying the regulation of lncRNA expression in different tissues and under different physiological conditions[33]. The delivery of lncRNA-based therapeutics to specific tissues remains a major hurdle due to their large size and potential off-target effects[33,34]. Therefore, additional investigation is required to uncover the molecular pathways involved in the regulation of lncRNA and to develop delivery methods that can specifically target tissues while minimizing off-target effects.

**lncRNAs in DM:** In animal models and human islets, dysregulation of lncRNAs is engaged in various stages of insulin secretion and is implicated in the progression of IR[35,36] (Table 1). In addition, the genes that encode them are located near islet-specific chromatin domains that contain genes involved in β-cell function modulation[37]. The specific functions and action mechanisms of these lncRNAs are still not fully understood[36].

In T2DM, metabolic syndrome and low-level high-density lipoprotein, a decline in MALAT1 expression was found, along with overexpressed H19 in patients with worse glycemic control than those with glycated hemoglobin concentration < 7%[38]. Additionally, MALAT1 is related to angiogenesis in diabetic eyes and kidneys. A few dysregulated lncRNAs in diabetic subjects are positively correlated with transcriptional markers of IR, impaired glucose control, and aging. These lncRNAs were apparently relevant to DM, even after correction[39]. Newly diagnosed diabetic patients exhibited similar results, indicating that dysregulated lncRNAs control IR and inflammation, ultimately resulting in disrupted glucose homeostasis[40].

The role of lncRNAs in both microvascular and macrovascular complications of DM has been investigated. A widely studied lncRNA associated with diabetic complications is ANRIL, which is considered a potential biomarker[41,42]. Another is MALAT1 in association with elevated production of reactive oxygen species and proinflammatory cytokines, contributing to endothelial lesions in the microvasculature[35,41].

Dysregulation of specific genes has been identified in renal biopsies affected by diabetic nephropathy. Additionally, a study of diabetic patients with chronic complications found downregulation of CASC2 in the serum and renal tissue of DM patients with chronic kidney disease when compared to healthy controls[36,43]. Both MIAT and MALAT1 were found to be over-regulated in renal specimens from diabetic subjects and in animal models[36]. The effect of lncRNAs in diabetic patients with peripheral neuropathy has also been investigated. Specifically, NONRATT021972 was shown to be increased in T2DM subjects with exacerbated symptoms connected to neuralgia, together with an increase in tumor necrosis factor (TNF)-α levels. Furthermore, siRNA-NONRATT021972 alleviated neuropathic pain by decreasing TNF-α in rats, resulting in decreased blood glucose and inflammation, which paved the way for potential therapies of neuropathic pain[44]. MALAT1 is over-expressed in gastrointestinal spasms and in T2DM sufferers with signs related to gastric spasms, and its impact is likely associated with smooth muscle cells.

**Function of miRNAs in DM with obesity:** miRNAs prevent the translation of mRNA into protein, leading to mRNA degradation or translational repression. miRNAs have been shown to regulate various cellular processes. Dysregulated miRNA has been implicated in metabolic disorders, such as in obesity (Table 2).

The pathogenesis of metabolic diseases has been linked to the expression of various miRNAs. Kunej *et al*[45] found that 221 of the 1736 Loci associated with obesity coincided with miRNAs. It has been reported that miRNAs can modulate pathways that control adipogenesis[46,47], which is impaired in obesity. Consequently, miRNA dysregulation could be involved in metabolic processes that contribute to obesity[48,49].

**miRNA-375:** The islet-specific miRNA-375 is expressed at high levels in pancreatic islets and regulates insulin secretion by modulating gene expression. The impact of miRNA-375 on glucose-stimulated insulin secretion (GSIS) and insulin gene transcription was investigated by Poy *et al*[50], who found that its overexpression suppressed GSIS and reduced insulin gene transcription, whereas its downregulation resulted in increased insulin secretion. This study confirmed the crucial role of miRNA-375 in the development of T2DM, as demonstrated by its higher expression in the pancreas of T2DM patients compared to healthy individuals. Dysregulation of miRNA-375 was observed 5 years prior to the start of T2DM and in prediabetes, indicating its potential use in the prediction and prevention of high-risk populations[51].

**miRNA-130b:** In prepubertal obesity, some miRNAs may become deregulated, as evidenced by a study which showed that the expression of miRNA-130b in plasma was upregulated and directly correlated with BMI and other indicators of obesity in children.

**miRNA-200 family:** The miRNA-200 family can contribute to protection against beta-cell apoptosis and dedifferentiation *in vitro*[52]. miRNA-200c is one of the most highly expressed miRNAs in beta cells, and partially protects against oxidative stress-induced beta-cell apoptosis, suggesting that the miRNA-200 family is essential in diabetes pathophysiology[53].

**miRNA-7:** Human islets are enriched in another miRNA named miRNA-7, which adversely modulates GSIS by restricting the expression of genes participating in the integration of insulin granules within the plasma membrane and the SNARE proteins[54]. The levels of hsa-miRNA-7-1-3p were reduced in pancreatic islets of individuals with T2DM compared to nondiabetic donors. The expression levels of hsa-miRNA-7-3-5p were increased in T2DM pancreatic islets[55].

**miRNA-184:** miRNA-184 is one of the miRNAs predominantly expressed in beta cells of pancreatic islets, regulating insulin secretion and beta-cell proliferation during IR[56]. Knockout of miRNA-184 in beta cells has been shown to increase their proliferation, resulting in improved insulin secretion following glucose stimulation. Blocking miRNA-184 in rat and human islets has been demonstrated to protect beta cells from apoptosis induced by prolonged exposure to proinflammatory cytokines and/or fatty acids.

***Circular RNAs in obesity and DM***

**Role of circular RNAs:** Adipose tissue is a complex and metabolically active organ, playing an essential role in energy storage and homeostasis. Adipocytes are the primary cell type in adipose tissue, and their differentiation and function are tightly regulated by multiple molecular mechanisms. In recent years, the role of circular RNAs (circRNAs) in adipose tissue has gained significant attention.

circRNA expression in carboxy-terminal region, prediabetic and T2DM patients showed 411 downregulated and 78 upregulated circRNAs[57]. Notably, 220 circRNAs demonstrated differential expression, including 107 upregulated and 113 downregulated circRNAs[58]. Of particular interest were the ci-INS and ci-Ins2 Lariats, derived from human INS and mouse Ins2, respectively in beta cells[59].

**EPIGENETIC REGULATION AND ITS ROLE IN THE PATHOGENESIS OF DM COMPLICATED WITH OBESITY**

Genetic variation is a crucial factor in the regulation of DNA methylation[60]. As methylated DNA predominantly arises on cytosine nucleotides after a guanine, it is evident additions or deletions of variants of cytosine-guanine dinucleotides(CG dinucleotides) affect the likelihood of methylated DNA at the loci[61]. Remarkably, roughly one-fourth of single nucleotide polymorphisms (SNPs) add or delete CpG site[62].

The presence of an SNP in NDUFB6 Led to the emergence of a CpG site that in turn affected DNA methylation and gene expression in human skeletal muscle, particularly age-related gene expression[63]. Although genetic variations can directly impact DNA methylation, it remains unclear whether they can affect methylation in more remote sites and, if so, what the underlying mechanism would be. The extent to which this phenomenon is widespread throughout the genome and its potential contribution to clinical phenotypes remain uncertain. Another study identified that nearly half of the genetic variations associated with diabetes introduce or remove a CpG site[64].

In 2014, a study extended previous research and provided a whole-genome description of genetic and epigenetically variations in human pancreatic islets[63]. Numerous *cis*- and *trans*-SNP–CpG pairs were determined, even though the machinery of the latter is still unclear[65]. Additionally, causal inference test established a catalytic interaction between SNPs, DNA methylation and genetic expression of annotated HLA regions highly correlated with type 1 DM[66]. More than 100000 DNA metylation quantitative trait loci (mQTLs) were identified by GWASs, which were linked to adipose-tissue gene expression, BMI, and insulin levels[67,68].

**RESEARCH PROSPECTS**

***ncRNAs as early diagnostic markers***

ncRNAs are involved in the development of both diabetes and obesity and may be potential early diagnostic markers for these conditions. miRNAs are small ncRNAs that play important roles in post-transcriptional gene regulation. These miRNAs are dysregulated in both DM and obesity and may serve as potential early diagnostic markers for these conditions[69]. For example, miRNA-126 has been shown to be downregulated in obese individuals and may serve as a potential early diagnostic marker in obesity[70]. Similarly, miRNA-375 has been shown to be upregulated in individuals with T2DM and may serve as a potential early diagnostic marker for this condition[71].

lncRNAs are longer ncRNAs that also play important roles in gene regulation, suggesting that lncRNAs are involved in the development of both diabetes and obesity and may serve as potential early diagnostic markers[19]. The lncRNAs HOTAIR and H19 have been shown to be upregulated in individuals with T2DM and may be early diagnostic markers[72,73].

circRNAs are a class of ncRNAs that form covalently closed circular RNA molecules, which have recently been observed in the dysregulation in both DM and obesity and may be early diagnostic markers[74]. For example, circRNA-000911 has been shown to be downregulated in individuals with T2DM, and may serve as a potential early diagnostic marker[75]. Similarly, serum and exosome circRNA-0000907 and circRNA-0057362 have been shown to be upregulated in patients with diabetic foot ulcer (DFU), indicating that they may have a potential role as early diagnostic markers for DFU[11].

ncRNAs have emerged as potential early diagnostic markers for both DM and obesity. Early diagnosis and management of DM and obesity are crucial to prevent complications and improve outcomes. Therefore, the identification of novel early diagnostic markers for these conditions is of utmost importance. ncRNAs may serve as valuable tools in this regard and may help improve patient outcomes. Therefore, further research is needed to validate the potential of ncRNAs in early diagnosis.

***Possible treatment targets for DM with obesity***

miRNAs are one of the best-studied classes of ncRNAs, and they have been implicated in the regulation of glucose homeostasis and insulin sensitivity. It was shown that miRNA-29a regulates insulin signaling by targeting IRS1 in adipocytes[76]. Additionally, miRNA-103 and miRNA-107 have been shown to promote IR by targeting the insulin receptor and GLUT4, respectively[77]. Another lncRNA, NEAT1, has been shown to regulate the expression of genes involved in the inhibition of high glucose-induced diabetic retinopathy[78]. Furthermore, S961-treated mouse sera reproduced beta-cell replication in pancreatic islets in an E2F1-dependent way, indicating that IR-induced adipocyte proliferation signaling activates E2F1 and is a potential target for promoting beta-cell compensation[79].

Epigenetic regulation has also emerged as an important contributor to the pathogenesis of DM with obesity. DNA methylation regulates motifs involved in glucose homeostasis and insulin signaling[80]. Histone modifications regulate the expression of key genes in the insulin signaling pathway[81].

In addition, lncRNAs are newly emerging and promising biomarkers, so we summarize the shared lncRNAs in both obesity and DM in order to provide further information (Table 3).

Identification of the pathogenesis of DM with obesity has opened new avenues. Targeting these mechanisms with small molecules or RNA-based therapies may provide a more precise and effective approach to DM treatment than traditional therapies. For example, miRNA-based therapies have already been tested in preclinical models of DM, with promising results.

**CONCLUSION**

The pathogenesis of DM complicated with obesity involves complex molecular mechanisms, including ncRNA and epigenetic regulation. Understanding the roles of ncRNA and epigenetic regulation in the pathogenesis of DM complicated with obesity provides new insights into the development of novel therapeutic targets and strategies. Future research should focus on exploring the potential of ncRNA and epigenetic regulation as biomarkers for diagnosis and prognosis, as well as precision medicine and personalized treatment strategies.

**REFERENCES**

1 **Chobot A**, Górowska-Kowolik K, Sokołowska M, Jarosz-Chobot P. Obesity and diabetes-Not only a simple link between two epidemics. *Diabetes Metab Res Rev* 2018; **34**: e3042 [PMID: 29931823 DOI: 10.1002/dmrr.3042]

2 **Barb D**, Repetto EM, Stokes ME, Shankar SS, Cusi K. Type 2 diabetes mellitus increases the risk of hepatic fibrosis in individuals with obesity and nonalcoholic fatty liver disease. *Obesity (Silver Spring)* 2021; **29**: 1950-1960 [PMID: 34553836 DOI: 10.1002/oby.23263]

3 **Kahn SE**, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 2006; **444**: 840-846 [PMID: 17167471 DOI: 10.1038/nature05482]

4 **Malone JI**, Hansen BC. Does obesity cause type 2 diabetes mellitus (T2DM)? Or is it the opposite? *Pediatr Diabetes* 2019; **20**: 5-9 [PMID: 30311716 DOI: 10.1111/pedi.12787]

5 **Czaja-Stolc S**, Potrykus M, Stankiewicz M, Kaska Ł, Małgorzewicz S. Pro-Inflammatory Profile of Adipokines in Obesity Contributes to Pathogenesis, Nutritional Disorders, and Cardiovascular Risk in Chronic Kidney Disease. *Nutrients* 2022; **14** [PMID: 35406070 DOI: 10.3390/nu14071457]

6 **de Vos WM**, Tilg H, Van Hul M, Cani PD. Gut microbiome and health: mechanistic insights. *Gut* 2022; **71**: 1020-1032 [PMID: 35105664 DOI: 10.1136/gutjnl-2021-326789]

7 **Singer-Englar T**, Barlow G, Mathur R. Obesity, diabetes, and the gut microbiome: an updated review. *Expert Rev Gastroenterol Hepatol* 2019; **13**: 3-15 [PMID: 30791839 DOI: 10.1080/17474124.2019.1543023]

8 **Formichi C**, Nigi L, Grieco GE, Maccora C, Fignani D, Brusco N, Licata G, Sebastiani G, Dotta F. Non-Coding RNAs: Novel Players in Insulin Resistance and Related Diseases. *Int J Mol Sci* 2021; **22** [PMID: 34299336 DOI: 10.3390/ijms22147716]

9 **Ling C**, Rönn T. Epigenetics in Human Obesity and Type 2 Diabetes. *Cell Metab* 2019; **29**: 1028-1044 [PMID: 30982733 DOI: 10.1016/j.cmet.2019.03.009]

10 **Kiran S**, Kumar V, Kumar S, Price RL, Singh UP. Adipocyte, Immune Cells, and miRNA Crosstalk: A Novel Regulator of Metabolic Dysfunction and Obesity. *Cells* 2021; **10** [PMID: 33923175 DOI: 10.3390/cells10051004]

11 **Yang WM**, Jeong HJ, Park SY, Lee W. Induction of miR-29a by saturated fatty acids impairs insulin signaling and glucose uptake through translational repression of *IRS-1* in myocytes. *FEBS Lett* 2014; **588**: 2170-2176 [PMID: 24844433 DOI: 10.1016/j.febslet.2014.05.011]

12 **Zhang X**, Xue XC, Wang Y, Cao FF, You J, Uzan G, Peng B, Zhang DH. Celastrol Reverses Palmitic Acid-Induced Insulin Resistance in HepG2 Cells *via* Restoring the miR-223 and GLUT4 Pathway. *Can J Diabetes* 2019; **43**: 165-172 [PMID: 30287053 DOI: 10.1016/j.jcjd.2018.07.002]

13 **Li X**, Bai C, Wang H, Wan T, Li Y. LncRNA MEG3 regulates autophagy and pyroptosis *via* FOXO1 in pancreatic β-cells. *Cell Signal* 2022; **92**: 110247 [PMID: 35101568 DOI: 10.1016/j.cellsig.2022.110247]

14 **Yin DD**, Zhang EB, You LH, Wang N, Wang LT, Jin FY, Zhu YN, Cao LH, Yuan QX, De W, Tang W. Downregulation of lncRNA TUG1 affects apoptosis and insulin secretion in mouse pancreatic β cells. *Cell Physiol Biochem* 2015; **35**: 1892-1904 [PMID: 25871529 DOI: 10.1159/000373999]

15 **Kim AY**, Park YJ, Pan X, Shin KC, Kwak SH, Bassas AF, Sallam RM, Park KS, Alfadda AA, Xu A, Kim JB. Obesity-induced DNA hypermethylation of the adiponectin gene mediates insulin resistance. *Nat Commun* 2015; **6**: 7585 [PMID: 26139044 DOI: 10.1038/ncomms8585]

16 **Ou XH**, Zhu CC, Sun SC. Effects of obesity and diabetes on the epigenetic modification of mammalian gametes. *J Cell Physiol* 2019; **234**: 7847-7855 [PMID: 30536398 DOI: 10.1002/jcp.27847]

17 **Sankar A**, Mohammad F, Sundaramurthy AK, Wang H, Lerdrup M, Tatar T, Helin K. Histone editing elucidates the functional roles of H3K27 methylation and acetylation in mammals. *Nat Genet* 2022; **54**: 754-760 [PMID: 35668298 DOI: 10.1038/s41588-022-01091-2]

18 **Ling C**, Bacos K, Rönn T. Epigenetics of type 2 diabetes mellitus and weight change - a tool for precision medicine? *Nat Rev Endocrinol* 2022; **18**: 433-448 [PMID: 35513492 DOI: 10.1038/s41574-022-00671-w]

19 **Rey F**, Urrata V, Gilardini L, Bertoli S, Calcaterra V, Zuccotti GV, Cancello R, Carelli S. Role of long non-coding RNAs in adipogenesis: State of the art and implications in obesity and obesity-associated diseases. *Obes Rev* 2021; **22**: e13203 [PMID: 33443301 DOI: 10.1111/obr.13203]

20 **Gao H**, Kerr A, Jiao H, Hon CC, Rydén M, Dahlman I, Arner P. Long Non-Coding RNAs Associated with Metabolic Traits in Human White Adipose Tissue. *EBioMedicine* 2018; **30**: 248-260 [PMID: 29580841 DOI: 10.1016/j.ebiom.2018.03.010]

21 **Chawla A**, Schwarz EJ, Dimaculangan DD, Lazar MA. Peroxisome proliferator-activated receptor (PPAR) gamma: adipose-predominant expression and induction early in adipocyte differentiation. *Endocrinology* 1994; **135**: 798-800 [PMID: 8033830 DOI: 10.1210/endo.135.2.8033830]

22 **Giroud M**, Scheideler M. Long Non-Coding RNAs in Metabolic Organs and Energy Homeostasis. *Int J Mol Sci* 2017; **18** [PMID: 29189723 DOI: 10.3390/ijms18122578]

23 **Li M**, Sun X, Cai H, Sun Y, Plath M, Li C, Lan X, Lei C, Lin F, Bai Y, Chen H. Long non-coding RNA ADNCR suppresses adipogenic differentiation by targeting miR-204. *Biochim Biophys Acta* 2016; **1859**: 871-882 [PMID: 27156885 DOI: 10.1016/j.bbagrm.2016.05.003]

24 **Huang Y**, Zheng Y, Jin C, Li X, Jia L, Li W. Long Non-coding RNA H19 Inhibits Adipocyte Differentiation of Bone Marrow Mesenchymal Stem Cells through Epigenetic Modulation of Histone Deacetylases. *Sci Rep* 2016; **6**: 28897 [PMID: 27349231 DOI: 10.1038/srep28897]

25 **Squillaro T**, Peluso G, Galderisi U, Di Bernardo G. Long non-coding RNAs in regulation of adipogenesis and adipose tissue function. *Elife* 2020; **9** [PMID: 32730204 DOI: 10.7554/eLife.59053]

26 **Divoux A**, Karastergiou K, Xie H, Guo W, Perera RJ, Fried SK, Smith SR. Identification of a novel lncRNA in gluteal adipose tissue and evidence for its positive effect on preadipocyte differentiation. *Obesity (Silver Spring)* 2014; **22**: 1781-1785 [PMID: 24862299 DOI: 10.1002/oby.20793]

27 **Lorente-Cebrián S**, González-Muniesa P, Milagro FI, Martínez JA. MicroRNAs and other non-coding RNAs in adipose tissue and obesity: emerging roles as biomarkers and therapeutic targets. *Clin Sci (Lond)* 2019; **133**: 23-40 [PMID: 30606812 DOI: 10.1042/CS20180890]

28 **Zhao XY**, Li S, Wang GX, Yu Q, Lin JD. A long noncoding RNA transcriptional regulatory circuit drives thermogenic adipocyte differentiation. *Mol Cell* 2014; **55**: 372-382 [PMID: 25002143 DOI: 10.1016/j.molcel.2014.06.004]

29 **Schmidt E**, Dhaouadi I, Gaziano I, Oliverio M, Klemm P, Awazawa M, Mitterer G, Fernandez-Rebollo E, Pradas-Juni M, Wagner W, Hammerschmidt P, Loureiro R, Kiefer C, Hansmeier NR, Khani S, Bergami M, Heine M, Ntini E, Frommolt P, Zentis P, Ørom UA, Heeren J, Blüher M, Bilban M, Kornfeld JW. LincRNA H19 protects from dietary obesity by constraining expression of monoallelic genes in brown fat. *Nat Commun* 2018; **9**: 3622 [PMID: 30190464 DOI: 10.1038/s41467-018-05933-8]

30 **Mi L**, Zhao XY, Li S, Yang G, Lin JD. Conserved function of the long noncoding RNA Blnc1 in brown adipocyte differentiation. *Mol Metab* 2017; **6**: 101-110 [PMID: 28123941 DOI: 10.1016/j.molmet.2016.10.010]

31 **Knoll M**, Lodish HF, Sun L. Long non-coding RNAs as regulators of the endocrine system. *Nat Rev Endocrinol* 2015; **11**: 151-160 [PMID: 25560704 DOI: 10.1038/nrendo.2014.229]

32 **Sun J**, Ruan Y, Wang M, Chen R, Yu N, Sun L, Liu T, Chen H. Differentially expressed circulating LncRNAs and mRNA identified by microarray analysis in obese patients. *Sci Rep* 2016; **6**: 35421 [PMID: 27767123 DOI: 10.1038/srep35421]

33 **Izquierdo AG**, Crujeiras AB. Obesity-Related Epigenetic Changes After Bariatric Surgery. *Front Endocrinol (Lausanne)* 2019; **10**: 232 [PMID: 31040824 DOI: 10.3389/fendo.2019.00232]

34 **Liang Y**, Yu B, Wang Y, Qiao Z, Cao T, Zhang P. Duodenal long noncoding RNAs are associated with glycemic control after bariatric surgery in high-fat diet-induced diabetic mice. *Surg Obes Relat Dis* 2017; **13**: 1212-1226 [PMID: 28366671 DOI: 10.1016/j.soard.2017.02.010]

35 **De Rosa S**, Arcidiacono B, Chiefari E, Brunetti A, Indolfi C, Foti DP. Type 2 Diabetes Mellitus and Cardiovascular Disease: Genetic and Epigenetic Links. *Front Endocrinol (Lausanne)* 2018; **9**: 2 [PMID: 29387042 DOI: 10.3389/fendo.2018.00002]

36 **Guo J**, Liu Z, Gong R. Long noncoding RNA: an emerging player in diabetes and diabetic kidney disease. *Clin Sci (Lond)* 2019; **133**: 1321-1339 [PMID: 31221822 DOI: 10.1042/CS20190372]

37 **Goyal N**, Kesharwani D, Datta M. Lnc-ing non-coding RNAs with metabolism and diabetes: roles of lncRNAs. *Cell Mol Life Sci* 2018; **75**: 1827-1837 [PMID: 29387902 DOI: 10.1007/s00018-018-2760-9]

38 **Tello-Flores VA**, Valladares-Salgado A, Ramírez-Vargas MA, Cruz M, Del-Moral-Hernández O, Cahua-Pablo JÁ, Ramírez M, Hernández-Sotelo D, Armenta-Solis A, Flores-Alfaro E. Altered levels of MALAT1 and H19 derived from serum or serum exosomes associated with type-2 diabetes. *Noncoding RNA Res* 2020; **5**: 71-76 [PMID: 32346662 DOI: 10.1016/j.ncrna.2020.03.001]

39 **Sathishkumar C**, Prabu P, Mohan V, Balasubramanyam M. Linking a role of lncRNAs (long non-coding RNAs) with insulin resistance, accelerated senescence, and inflammation in patients with type 2 diabetes. *Hum Genomics* 2018; **12**: 41 [PMID: 30139387 DOI: 10.1186/s40246-018-0173-3]

40 **Wang X**, Chang X, Zhang P, Fan L, Zhou T, Sun K. Aberrant Expression of Long Non-Coding RNAs in Newly Diagnosed Type 2 Diabetes Indicates Potential Roles in Chronic Inflammation and Insulin Resistance. *Cell Physiol Biochem* 2017; **43**: 2367-2378 [PMID: 29073614 DOI: 10.1159/000484388]

41 **Tang N**, Jiang S, Yang Y, Liu S, Ponnusamy M, Xin H, Yu T. Noncoding RNAs as therapeutic targets in atherosclerosis with diabetes mellitus. *Cardiovasc Ther* 2018; **36**: e12436 [PMID: 29797660 DOI: 10.1111/1755-5922.12436]

42 **Zhang L**, Wang YM. Expression and function of lncRNA ANRIL in a mouse model of acute myocardial infarction combined with type 2 diabetes mellitus. *J Chin Med Assoc* 2019; **82**: 685-692 [PMID: 31469688 DOI: 10.1097/JCMA.0000000000000182]

43 **Wang L**, Su N, Zhang Y, Wang G. Clinical Significance of Serum lncRNA Cancer Susceptibility Candidate 2 (CASC2) for Chronic Renal Failure in Patients with Type 2 Diabetes. *Med Sci Monit* 2018; **24**: 6079-6084 [PMID: 30171178 DOI: 10.12659/MSM.909510]

44**Yu W**, Zhao GQ, Cao RJ, Zhu ZH, Li K. LncRNA NONRATT021972 Was Associated with Neuropathic Pain Scoring in Patients with Type 2 Diabetes. *Behav Neurol* 2017; **2017**: 2941297 [PMID: 28928602 DOI: 10.1155/2017/2941297]

45 **Kunej T**, Jevsinek Skok D, Zorc M, Ogrinc A, Michal JJ, Kovac M, Jiang Z. Obesity gene atlas in mammals. *J Genomics* 2013; **1**: 45-55 [PMID: 25031655 DOI: 10.7150/jgen.3996]

46 **Klöting N**, Berthold S, Kovacs P, Schön MR, Fasshauer M, Ruschke K, Stumvoll M, Blüher M. MicroRNA expression in human omental and subcutaneous adipose tissue. *PLoS One* 2009; **4**: e4699 [PMID: 19259271 DOI: 10.1371/journal.pone.0004699]

47 **Ortega FJ**, Moreno-Navarrete JM, Pardo G, Sabater M, Hummel M, Ferrer A, Rodriguez-Hermosa JI, Ruiz B, Ricart W, Peral B, Fernández-Real JM. MiRNA expression profile of human subcutaneous adipose and during adipocyte differentiation. *PLoS One* 2010; **5**: e9022 [PMID: 20126310 DOI: 10.1371/journal.pone.0009022]

48 **Kim Y**, Kim OK. Potential Roles of Adipocyte Extracellular Vesicle-Derived miRNAs in Obesity-Mediated Insulin Resistance. *Adv Nutr* 2021; **12**: 566-574 [PMID: 32879940 DOI: 10.1093/advances/nmaa105]

49 **Lee EK**, Lee MJ, Abdelmohsen K, Kim W, Kim MM, Srikantan S, Martindale JL, Hutchison ER, Kim HH, Marasa BS, Selimyan R, Egan JM, Smith SR, Fried SK, Gorospe M. miR-130 suppresses adipogenesis by inhibiting peroxisome proliferator-activated receptor gamma expression. *Mol Cell Biol* 2011; **31**: 626-638 [PMID: 21135128 DOI: 10.1128/MCB.00894-10]

50 **Poy MN**, Eliasson L, Krutzfeldt J, Kuwajima S, Ma X, Macdonald PE, Pfeffer S, Tuschl T, Rajewsky N, Rorsman P, Stoffel M. A pancreatic islet-specific microRNA regulates insulin secretion. *Nature* 2004; **432**: 226-230 [PMID: 15538371 DOI: 10.1038/nature03076]

51**Jiménez-Lucena R**, Camargo A, Alcalá-Diaz JF, Romero-Baldonado C, Luque RM, van Ommen B, Delgado-Lista J, Ordovás JM, Pérez-Martínez P, Rangel-Zúñiga OA, López-Miranda J. A plasma circulating miRNAs profile predicts type 2 diabetes mellitus and prediabetes: from the CORDIOPREV study. *Exp Mol Med* 2018; **50**: 1-12 [PMID: 30598522 DOI: 10.1038/s12276-018-0194-y]

52 **Sebastiani G**, Grieco GE, Brusco N, Ventriglia G, Formichi C, Marselli L, Marchetti P, Dotta F. MicroRNA Expression Analysis of In Vitro Dedifferentiated Human Pancreatic Islet Cells Reveals the Activation of the Pluripotency-Related MicroRNA Cluster miR-302s. *Int J Mol Sci* 2018; **19** [PMID: 29649109 DOI: 10.3390/ijms19041170]

53 **Belgardt BF**, Ahmed K, Spranger M, Latreille M, Denzler R, Kondratiuk N, von Meyenn F, Villena FN, Herrmanns K, Bosco D, Kerr-Conte J, Pattou F, Rülicke T, Stoffel M. The microRNA-200 family regulates pancreatic beta cell survival in type 2 diabetes. *Nat Med* 2015; **21**: 619-627 [PMID: 25985365 DOI: 10.1038/nm.3862]

54 **Latreille M**, Hausser J, Stützer I, Zhang Q, Hastoy B, Gargani S, Kerr-Conte J, Pattou F, Zavolan M, Esguerra JL, Eliasson L, Rülicke T, Rorsman P, Stoffel M. MicroRNA-7a regulates pancreatic β cell function. *J Clin Invest* 2014; **124**: 2722-2735 [PMID: 24789908 DOI: 10.1172/JCI73066]

55 **Nesca V**, Guay C, Jacovetti C, Menoud V, Peyot ML, Laybutt DR, Prentki M, Regazzi R. Identification of particular groups of microRNAs that positively or negatively impact on beta cell function in obese models of type 2 diabetes. *Diabetologia* 2013; **56**: 2203-2212 [PMID: 23842730 DOI: 10.1007/s00125-013-2993-y]

56 **Tattikota SG**, Rathjen T, McAnulty SJ, Wessels HH, Akerman I, van de Bunt M, Hausser J, Esguerra JL, Musahl A, Pandey AK, You X, Chen W, Herrera PL, Johnson PR, O'Carroll D, Eliasson L, Zavolan M, Gloyn AL, Ferrer J, Shalom-Feuerstein R, Aberdam D, Poy MN. Argonaute2 mediates compensatory expansion of the pancreatic β cell. *Cell Metab* 2014; **19**: 122-134 [PMID: 24361012 DOI: 10.1016/j.cmet.2013.11.015]

57 **Zhao Z**, Li X, Jian D, Hao P, Rao L, Li M. Hsa\_circ\_0054633 in peripheral blood can be used as a diagnostic biomarker of pre-diabetes and type 2 diabetes mellitus. *Acta Diabetol* 2017; **54**: 237-245 [PMID: 27878383 DOI: 10.1007/s00592-016-0943-0]

58 **Fang Y**, Wang X, Li W, Han J, Jin J, Su F, Zhang J, Huang W, Xiao F, Pan Q, Zou L. Screening of circular RNAs and validation of circANKRD36 associated with inflammation in patients with type 2 diabetes mellitus. *Int J Mol Med* 2018; **42**: 1865-1874 [PMID: 30066828 DOI: 10.3892/ijmm.2018.3783]

59 **Stoll L**, Rodríguez-Trejo A, Guay C, Brozzi F, Bayazit MB, Gattesco S, Menoud V, Sobel J, Marques AC, Venø MT, Esguerra JLS, Barghouth M, Suleiman M, Marselli L, Kjems J, Eliasson L, Renström E, Bouzakri K, Pinget M, Marchetti P, Regazzi R. A circular RNA generated from an intron of the insulin gene controls insulin secretion. *Nat Commun* 2020; **11**: 5611 [PMID: 33154349 DOI: 10.1038/s41467-020-19381-w]

60 **Zhu W**, Shen Y, Liu J, Fei X, Zhang Z, Li M, Chen X, Xu J, Zhu Q, Zhou W, Zhang M, Liu S, Du J. Epigenetic alternations of microRNAs and DNA methylation contribute to gestational diabetes mellitus. *J Cell Mol Med* 2020; **24**: 13899-13912 [PMID: 33085184 DOI: 10.1111/jcmm.15984]

61 **He L**, Huang H, Bradai M, Zhao C, You Y, Ma J, Zhao L, Lozano-Durán R, Zhu JK. DNA methylation-free Arabidopsis reveals crucial roles of DNA methylation in regulating gene expression and development. *Nat Commun* 2022; **13**: 1335 [PMID: 35288562 DOI: 10.1038/s41467-022-28940-2]

62 **Olsson AH**, Volkov P, Bacos K, Dayeh T, Hall E, Nilsson EA, Ladenvall C, Rönn T, Ling C. Genome-wide associations between genetic and epigenetic variation influence mRNA expression and insulin secretion in human pancreatic islets. *PLoS Genet* 2014; **10**: e1004735 [PMID: 25375650 DOI: 10.1371/journal.pgen.1004735]

63 **Rautenberg EK**, Hamzaoui Y, Coletta DK. Mini-review: Mitochondrial DNA methylation in type 2 diabetes and obesity. *Front Endocrinol (Lausanne)* 2022; **13**: 968268 [PMID: 36093112 DOI: 10.3389/fendo.2022.968268]

64 **Shah UJ**, Xie W, Flyvbjerg A, Nolan JJ, Højlund K, Walker M, Relton CL, Elliott HR; RISC consortium. Differential methylation of the type 2 diabetes susceptibility locus KCNQ1 is associated with insulin sensitivity and is predicted by CpG site specific genetic variation. *Diabetes Res Clin Pract* 2019; **148**: 189-199 [PMID: 30641161 DOI: 10.1016/j.diabres.2019.01.008]

65 **Uno Y**, Murayama N, Kato M, Tanaka S, Ohkoshi T, Yamazaki H. Genetic Variants of Glutathione S-Transferase GSTT1 and GSTT2 in Cynomolgus Macaques: Identification of GSTT Substrates and Functionally Relevant Alleles. *Chem Res Toxicol* 2018; **31**: 1086-1091 [PMID: 30169019 DOI: 10.1021/acs.chemrestox.8b00198]

66 **Volkov P**, Olsson AH, Gillberg L, Jørgensen SW, Brøns C, Eriksson KF, Groop L, Jansson PA, Nilsson E, Rönn T, Vaag A, Ling C. A Genome-Wide mQTL Analysis in Human Adipose Tissue Identifies Genetic Variants Associated with DNA Methylation, Gene Expression and Metabolic Traits. *PLoS One* 2016; **11**: e0157776 [PMID: 27322064 DOI: 10.1371/journal.pone.0157776]

67 **Walaszczyk E**, Luijten M, Spijkerman AMW, Bonder MJ, Lutgers HL, Snieder H, Wolffenbuttel BHR, van Vliet-Ostaptchouk JV. DNA methylation markers associated with type 2 diabetes, fasting glucose and HbA(1c) levels: a systematic review and replication in a case-control sample of the Lifelines study. *Diabetologia* 2018; **61**: 354-368 [PMID: 29164275 DOI: 10.1007/s00125-017-4497-7]

68 **Shvangiradze TA**, Bondarenko IZ, Troshina EA, Shestakova MV. [MiRNAs in the diagnosis of cardiovascular diseases associated with type 2 diabetes mellitus and obesity]. *Ter Arkh* 2016; **88**: 87-92 [PMID: 28635856 DOI: 10.17116/terarkh201688687-92]

69 **López-Armas GC**, Yessenbekova A, González-Castañeda RE, Arellano-Arteaga KJ, Guerra-Librero A, Ablaikhanova N, Florido J, Escames G, Acuña-Castroviejo D, Rusanova I. Role of c-miR-21, c-miR-126, Redox Status, and Inflammatory Conditions as Potential Predictors of Vascular Damage in T2DM Patients. *Antioxidants (Basel)* 2022; **11** [PMID: 36139749 DOI: 10.3390/antiox11091675]

70 **Li X**. MiR-375, a microRNA related to diabetes. *Gene* 2014; **533**: 1-4 [PMID: 24120394 DOI: 10.1016/j.gene.2013.09.105]

71 **Wang H**, Xia Y, Zhang Y. Diagnostic significance of serum lncRNA HOTAIR and its predictive value for the development of chronic complications in patients with type 2 diabetes mellitus. *Diabetol Metab Syndr* 2021; **13**: 97 [PMID: 34496971 DOI: 10.1186/s13098-021-00719-3]

72 **Costa-Júnior JM**, Ferreira SM, Kurauti MA, Bernstein DL, Ruano EG, Kameswaran V, Schug J, Freitas-Dias R, Zoppi CC, Boschero AC, Oliveira CAM, Santos GJ, Carneiro EM, Kaestner KH. Paternal Exercise Improves the Metabolic Health of Offspring *via* Epigenetic Modulation of the Germline. *Int J Mol Sci* 2021; **23** [PMID: 35008427 DOI: 10.3390/ijms23010001]

73 **Zhang YP**, Ye SZ, Li YX, Chen JL, Zhang YS. Research Advances in the Roles of Circular RNAs in Pathophysiology and Early Diagnosis of Gestational Diabetes Mellitus. *Front Cell Dev Biol* 2021; **9**: 739511 [PMID: 35059395 DOI: 10.3389/fcell.2021.739511]

74 **Ren S**, Lin P, Wang J, Yu H, Lv T, Sun L, Du G. Circular RNAs: Promising Molecular Biomarkers of Human Aging-Related Diseases *via* Functioning as an miRNA Sponge. *Mol Ther Methods Clin Dev* 2020; **18**: 215-229 [PMID: 32637451 DOI: 10.1016/j.omtm.2020.05.027]

75 **Chen ZJ**, Shi XJ, Fu LJ, Liu J, Shi K, Zhang WB, Su PK. Serum and exosomal hsa\_circ\_0000907 and hsa\_circ\_0057362 as novel biomarkers in the early diagnosis of diabetic foot ulcer. *Eur Rev Med Pharmacol Sci* 2020; **24**: 8117-8126 [PMID: 32767340 DOI: 10.26355/eurrev\_202008\_22498]

76 **Behrooz M**, Hajjarzadeh S, Kahroba H, Ostadrahimi A, Bastami M. Expression pattern of miR-193a, miR122, miR155, miR-15a, and miR146a in peripheral blood mononuclear cells of children with obesity and their relation to some metabolic and inflammatory biomarkers. *BMC Pediatr* 2023; **23**: 95 [PMID: 36859176 DOI: 10.1186/s12887-023-03867-9]

77 **Chen Q**, Xi X, Ma J, Wang X, Xia Y, Wang X, Deng Y, Li Y. The mechanism by which crocetin regulates the lncRNA NEAT1/miR-125b-5p/SOX7 molecular axis to inhibit high glucose-induced diabetic retinopathy. *Exp Eye Res* 2022; **222**: 109157 [PMID: 35718188 DOI: 10.1016/j.exer.2022.109157]

78 **Shirakawa J**, Togashi Y, Basile G, Okuyama T, Inoue R, Fernandez M, Kyohara M, De Jesus DF, Goto N, Zhang W, Tsuno T, Kin T, Pan H, Dreyfuss JM, Shapiro AMJ, Yi P, Terauchi Y, Kulkarni RN. E2F1 transcription factor mediates a link between fat and islets to promote β cell proliferation in response to acute insulin resistance. *Cell Rep* 2022; **41**: 111436 [PMID: 36198264 DOI: 10.1016/j.celrep.2022.111436]

79 **Liu J**, Carnero-Montoro E, van Dongen J, Lent S, Nedeljkovic I, Ligthart S, Tsai PC, Martin TC, Mandaviya PR, Jansen R, Peters MJ, Duijts L, Jaddoe VWV, Tiemeier H, Felix JF, Willemsen G, de Geus EJC, Chu AY, Levy D, Hwang SJ, Bressler J, Gondalia R, Salfati EL, Herder C, Hidalgo BA, Tanaka T, Moore AZ, Lemaitre RN, Jhun MA, Smith JA, Sotoodehnia N, Bandinelli S, Ferrucci L, Arnett DK, Grallert H, Assimes TL, Hou L, Baccarelli A, Whitsel EA, van Dijk KW, Amin N, Uitterlinden AG, Sijbrands EJG, Franco OH, Dehghan A, Spector TD, Dupuis J, Hivert MF, Rotter JI, Meigs JB, Pankow JS, van Meurs JBJ, Isaacs A, Boomsma DI, Bell JT, Demirkan A, van Duijn CM. An integrative cross-omics analysis of DNA methylation sites of glucose and insulin homeostasis. *Nat Commun* 2019; **10**: 2581 [PMID: 31197173 DOI: 10.1038/s41467-019-10487-4]

80 **Liu D**, Yang KY, Chan VW, Ye W, Chong CCN, Wang CC, Wang H, Zhou B, Cheng KKY, Lui KO. YY1 Regulates Glucose Homeostasis Through Controlling Insulin Transcription in Pancreatic β-Cells. *Diabetes* 2022; **71**: 961-977 [PMID: 35113157 DOI: 10.2337/db21-0695]

81 **Ji C**, Guo X. The clinical potential of circulating microRNAs in obesity. *Nat Rev Endocrinol* 2019; **15**: 731-743 [PMID: 31611648 DOI: 10.1038/s41574-019-0260-0]

82 **Zhao XY**, Xiong X, Liu T, Mi L, Peng X, Rui C, Guo L, Li S, Li X, Lin JD. Long noncoding RNA licensing of obesity-linked hepatic lipogenesis and NAFLD pathogenesis. *Nat Commun* 2018; **9**: 2986 [PMID: 30061575 DOI: 10.1038/s41467-018-05383-2]

83 **Wijesinghe SN**, Nicholson T, Tsintzas K, Jones SW. Involvements of long noncoding RNAs in obesity-associated inflammatory diseases. *Obes Rev* 2021; **22**: e13156 [PMID: 33078547 DOI: 10.1111/obr.13156]

84 **Alfaifi M**, Verma AK, Alshahrani MY, Joshi PC, Alkhathami AG, Ahmad I, Hakami AR, Beg MMA. Assessment of Cell-Free Long Non-Coding RNA-H19 and miRNA-29a, miRNA-29b Expression and Severity of Diabetes. *Diabetes Metab Syndr Obes* 2020; **13**: 3727-3737 [PMID: 33116722 DOI: 10.2147/DMSO.S273586]

85 **Guo X**, Wu X, Han Y, Tian E, Cheng J. LncRNA MALAT1 protects cardiomyocytes from isoproterenol-induced apoptosis through sponging miR-558 to enhance ULK1-mediated protective autophagy. *J Cell Physiol* 2019; **234**: 10842-10854 [PMID: 30536615 DOI: 10.1002/jcp.27925]

**Footnotes**

**Conflict-of-interest statement:** The authors have no conflicts of interest to declare.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** July 12, 2023

**First decision:** August 10, 2023

**Article in press:** September 27, 2023

**Specialty type:** Endocrinology and metabolism

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

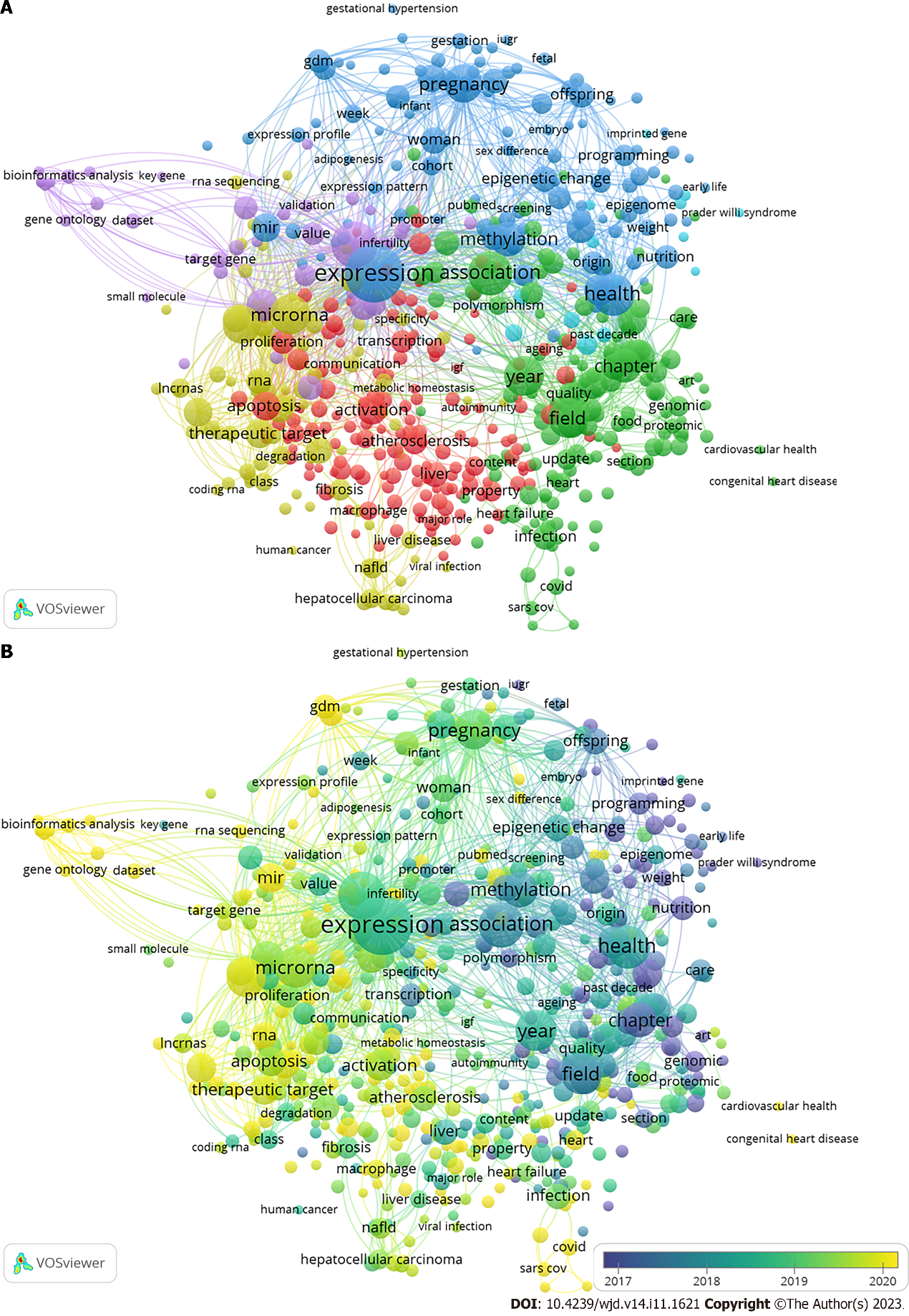
Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Cigrovski Berkovic M, Croatia; Nwabo Kamdje AH, Cameroon **S-Editor:** Chen YL **L-Editor:** A **P-Editor:** Chen YX

**Figure Legends**

****

**Figure 1 Epigenetic modifications and noncoding RNA play a critical role in the development and progression of diabetes mellitus complicated with obesity.** A: Network visualization of the titles and abstracts related to the long noncoding RNAs and epigenetic regulation in the pathogenesis of diabetes mellitus complicated with obesity; B: Overlay visualization of the years of publication on long noncoding RNAs and epigenetic regulation in the pathogenesis of diabetes mellitus complicated with obesity. Different color dots are used to distinct the keywords that have appeared in the publications.

**Table 1 Transcription factors and long noncoding RNAs in insulin resistance**

|  |  |  |
| --- | --- | --- |
| **Factors related to the development of IR** | **Names of lncRNAs** | **Targeted nuclear proteins** |
| Lipogenic activity | H19, MALAT1, MEG3, and MIAT↑ | SREBP-1c, PPARγ, and FoxO1 |
| Gluconeogenesis | MEG3 and H19↑ | CRTC2/CREB, FoxO1, HNF4A and ATF4 |
| Inflammation and oxidative stress | MALAT1 and H19↑ | EZH2 and PRC2 |
| Cellular dysfunction | MEG3, MALAT1 and MIAT↑ | N/A |

lncRNA: Long noncoding RNA; IR: Insulin resistance; SREBP-1c: Sterol reg-ulatory element binding protein-1c; PPARγ: Peroxisome proliferator-activated receptor γ; FoxO1: Forkhead box protein O1; CRTC2/CREB: CREB-regulated transcription coactivator 2; HNF4A: Recombinant hepatocyte nuclear factor 4α; ATF4：Recombinant activating transcription factor 4; EZH2: Enhancer of zeste homolog 2; N/A: Not applicant.

**Table 2 Circulating microRNA in obesity**

|  |  |  |
| --- | --- | --- |
| **Tissue or organs** | **Names of miRNAs** | **Targeted genes** |
| Adipocytic tissue | miR-155, miR-27a, and miR-34a | *SOCS1*, *PPARγ* |
| Liver | miR-99b and miR-155 | *FGF21*, *PPARγ* |
| Muscle | miR-27a, miR-155, and miR-130b | *PPARγ*, *PGC1α* |
| Pancreas | miR-132 and miR-92a | *BTG2*, *PTBP1* |
| Cardiovascular system | miR-29a, miR-410-5p, and miR-194 | *SMAD7* |

miRNA: microRNA.

**Table 3 The profiles of shared** **long noncoding RNAs in obesity and diabetes mellitus**

|  |  |  |  |
| --- | --- | --- | --- |
| **lncRNA** | **Description** | **Expression in obesity** | **Expression in DM** |
| SRA | Steroid receptor RNA activator | High | Low in patients with type II diabetic cardiovascular disease[74] |
| ASMER-1 | Adipocyte-associated metabolic related lncRNA 1 | High in ScAT | High expression related to IR[20] |
| ASMER-2 | Adipocyte-associated metabolic related lncRNA 2 | High in ScAT | High expression related to IR[20] |
| ADNCR | Adipocyte differentiation-associated lncRNA | Low | Low[23] |
| HOTAIR | HOX antisense intergenic RNA | High | High[71] |
| Blnc1 | Brown fat lncRNA 1 | High in high-fat-diet-fed mice[28] | High in the blood of patients with diabetic nephropathy[82] |
| H19 | LncRNA H19 | Low in obesity-associated inflammatory conditions[83] | Low[84] |
| MALAT1 | Metastasis-associated lung adenocarcinoma transcript 1 | High[85] | High expression in PBMCs from type 2 diabetes patients[39] |

lncRNA: Long noncoding RNA; DM: Diabetes mellitus; ScAT: Subcutaneous adipose tissue; IR: Insulin resistance; PBMC: Peripheral blood mononuclear cell.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +19253991568

**Email:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2023 Baishideng Publishing Group Inc. All rights reserved.**