



Long non-coding RNAs in diabetes and diabetic cardiomyopathy

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Abstract: Diabetes is a kind of metabolic disorder characterized by hyperglycemia, which is caused by defects in insulin secretion. Diabetic cardiomyopathy (DCM) is a cardiovascular complication of diabetes and leads to heart failure eventually. Long non-coding RNAs (lncRNAs) are RNAs longer than 200 nucleotides without protein-coding function. Here we reviewed the role of lncRNAs in the pathological processes of diabetes as well as DCM and revealed the significance of lncRNAs as therapeutic targets for diabetes and diabetes-associated complications.

Keywords: Diabetes; diabetic cardiomyopathy (DCM); long non-coding RNAs (lncRNAs)

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Introduction

Diabetes affects 425 million people worldwide according to the data of 2017. Diabetes is affecting more and more people nowadays because of increasing population of aging and obesity, sedentary lifestyles, and unhealthy eating habits. Diabetes can be divided into 2 types according to the pathogenesis. Type 1 diabetes (T1DM) is mainly caused by dysfunction of the islet and insulin secretion while type 2 diabetes (T2DM) is more attributed to the impaired insulin sensitivity in insulin-targeted tissues (1-3). DCM, defined as myocardial dysfunction occurring in diabetic patients without coronary artery disease, hypertension or valvular heart disease, is one of the important cardiovascular complications of diabetes, leading to heart failure and increased mortality (4). In recent years, more and more studies are focusing on the molecular mechanisms underlying diabetic cardiomyopathy (DCM).

Long non-coding RNAs (lncRNAs) are defined as RNAs longer than 200 nucleotides without protein-coding function. lncRNAs regulate gene expression via various ways. For example, they can directly act on the genomic DNA to regulate its expression. In addition, they

can interact with proteins such as transcription factors and RNA-binding proteins, thus indirectly regulating gene transcription. Moreover, they can play as competing endogenous RNAs to sponge microRNA (miRNAs, miRs) and regulate the miRNA targets (5).

lncRNAs have been shown to play a role in many tissues and many diseases, regulating various physiological and pathological processes. This review aims to describe the role of lncRNAs in diabetes and DCM reported in recent 5 years. In detail, we will discuss the changes of lncRNA expression in insulin secretion, insulin resistance and DCM, as well as the underlying mechanisms.

lncRNAs regulate β -cell function and insulin secretion

The pancreatic β -cell and its endocrine product insulin play a central role in glucose metabolism and the pathogenesis of diabetes. Although genome-wide association studies (GWASs) had identified many common genetic variants in lncRNAs associated with diabetes in the early 2010s (6-8), there were few studies to date investigating the association between lncRNAs and β -cell function until recent 5 years.

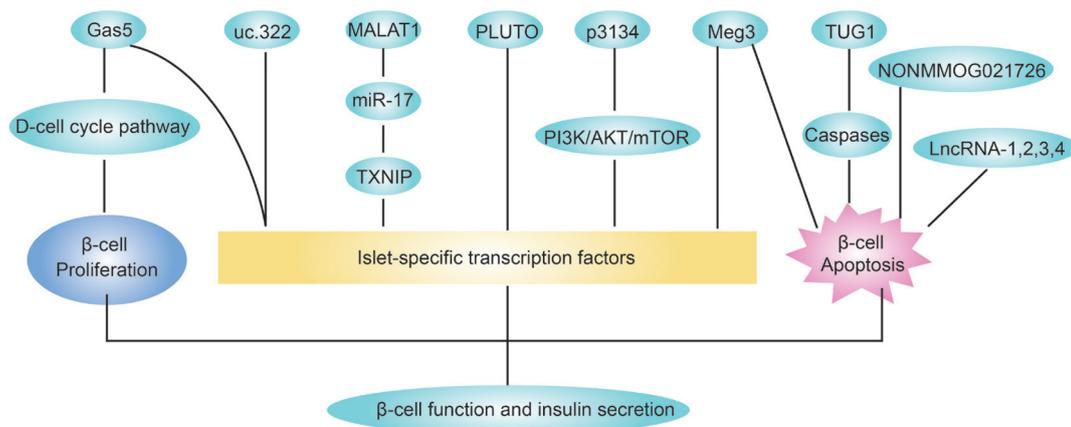


Figure 1 LncRNAs regulate β -cell function and insulin secretion.

Along with the growing studies about lncRNA functions in recent years, more and more researchers have focused on the role of lncRNAs in insulin secretion (*Figure 1*).

LncRNA TUG1 was highly expressed in the mouse pancreas compared to other tissues, implying that TUG1 is a pancreatic specific lncRNA and plays an important role in β -cell function. Downregulation of TUG1 caused β -cells apoptosis both *in vivo* and *in vitro* via caspase pathway. TUG1 expression was inhibited by high glucose and inhibition of TUG1 induces impairment of GSIS (glucose-stimulated insulin secretion) in Min6 cells. Furthermore, TUG1 inhibition in normal mice also reduced insulin secretion. Though TUG1 showed a significant association with insulin secretion, the underlying mechanism was not clarified in that study (9).

Similar to TUG1, lncRNA Meg3 expression was also dynamically regulated by glucose. Inhibition of Meg3 caused β -cell apoptosis and impaired insulin synthesis and secretion in normal mice. Suppression of Meg3 in Min6 cells decreased insulin synthesis by downregulating Pdx1 and MafA (10). Pdx1 plays an important role in pancreas development and adult β -cell function while MafA was specifically expressed in mature β -cells, which are both islet-specific transcription factors and coordinately stimulate insulin synthesis by stimulating the insulin gene promoter in response to elevated blood glucose (11). It was also observed that Meg3 was primarily localized in the nucleus and bound to EZH2 via trimethylation of H3K27 in the Rad21, Smc3, and Sin3 α promoter, and in turn suppressed the expression of these transcription factors, which upregulated the expression of MafA, thus promoting the synthesis of insulin *in vivo* and *in vitro* (12). EZH2 is a methyltransferase belonging to

the core component of the polycomb repressive complex-2 (PRC2), which is responsible for the trimethylation of H3K27 (13). EZH2 also interacted with Meg3 in mouse embryonic stem cells (14,15).

Besides TUG1 and Meg3, lncRNA Gas5 was also relatively high expressed in mouse pancreas and decreased in T2DM mouse models, dynamically regulated by glucose and affecting GSIG. In addition to Pdx1 and MafA, GLUT2 was also reduced in Gas5-knockdown cell line and primary islet. GLUT2 is a glucose transporter essential for activating glucose-sensitive genes and inactivation of GLUT2 leads to impaired GSIS (16). Moreover, inhibition of Gas5 could result in cell cycle G1 arrest and suppress proliferation in Min6 β -cell lines via downregulating D-cell cycle protein pathways (17).

Like the above lncRNAs, lncRNA p3134 also enhances insulin synthesis and secretion via upregulation of islet-specific transcription factors (Pdx1, MafA and GLUT2) both *in vitro* and *in vivo*. But p3134 is mainly expressed in adipose tissue and circulating exosomes secreted by islet β -cells. Additionally, TCF7L2, which was mapped to established T2D susceptibility genes, was increased by p3134 in Min6 cells and obese mice (18). Variants of TCF7L2 was correlated with impaired GSIS in humans and selective deletion of TCF7L2 *in vitro* induced β -cell apoptosis (19). Furthermore, PI3K/Akt/mTOR insulin signaling pathway also mediated the protection of p3134 on pancreatic islet-specific transcription factors and β -cell function in obese mice (20).

LncRNA PLUTO was restrictedly expressed in human pancreatic β -cells and PLUTO was also observed to regulate Pdx1 by affecting local 3D chromatin structure

Table 1 LncRNAs engaged in insulin resistance in insulin-targeted tissues

Tissue	LncRNA	Downstream targets	Function
Liver	H19	Hnf4a	Hepatic glucose production
	MALAT1	JNK/IRS-1/AKT	ROS generation in liver and pancreas
		nuclear SREBP-1c	Hepatic lipid accumulation
	Meg3	Foxo1	Hepatic gluconeogenesis and glycogen synthesis
	Risa	Akt & Gsk3 β	Hepatic autophagy
	LncSHGL	CaM/PI3K/Akt/mTOR/SREBP-1c	Hepatic gluconeogenic and lipogenic gene expression
Skeletal muscle	Gomafu	miR-139/Foxo1	Hepatic gluconeogenesis
	H19	let-7/Insr & Lpl	Glucose regulation in muscle
Adipose tissue	Blnc1	Proinflammatory cytokine signaling	Adipose tissue inflammation and fibrosis

and transcription of Pdx1. PLUTO and Pdx1 were both downregulated in islets from donors with T2DM or impaired glucose tolerance, implying that PLUTO is engaged in the pathophysiology of insulin secretion (21).

LncRNA uc.322 overexpression also increased the insulin transcription factors (Pdx1 and Foxo1) and insulin secretion. LncRNA uc.322 was located in the exon region of the *SOX6* gene and positively regulated *SOX6* expression, which promoted the proliferation and differentiation of pancreatic islet cells (22). LncRNA MALAT1 was found increased in CSE (cigarette smoke extract)-treated Min6 cells. CSE suppressed the production of insulin by increasing MALAT1 and decreasing miR-17/TXNIP pathway (23).

On the other hand, lncRNAs associated with inflammation may also play roles in pancreatic function. LncRNAs (lncRNA-1,2,3,4) regulated by proinflammatory cytokines were increased with the development of insulinitis in non-obese diabetic (NOD) mice and increased β -cell apoptosis, suggesting that they may contribute to cytokine-mediated β -cell dysfunction occurring in the initial phases of T1DM (24). Duodenum lncRNAs also participated in pancreatic secretion and inflammatory processes during the duodenal-jejunal bypass (DJB) operation, which could improve glycemic level, implying that bypass of the duodenum may initiate insulin secretion and attenuate inflammation (25).

LncRNAs in glucose metabolism and insulin resistance

Insulin resistance means the failure of target tissues to

respond adequately to circulating insulin, finally leading to hyperglycemia and glucose metabolism disorders in insulin-targeted tissues. Insulin resistance in the liver cells is characterized by impaired glycogen synthesis and increased glucose production. Insulin resistance in the skeletal muscle and adipose tissue is manifested as reduced glucose uptake and consumption. Until now, most studies are regard to lncRNAs engaged in insulin resistance in the liver, especially in the liver of obese T2DM (Table 1).

Liver

Excessive hepatic glucose production (HGP) contributes significantly to the hyperglycemia of T2DM. Liver-specific H19 overexpression promotes HGP, hyperglycemia, and insulin resistance, while H19 depletion enhances insulin-dependent suppression of HGP. Further genome-wide methylation and transcriptome analyses showed that H19 knockdown altered promoter methylation of *Hnf4a*, which is a gluconeogenic transcription factor in hepatic cells (26).

Similar to H19, lncRNA *Meg3* overexpression also increased hepatic gluconeogenesis and suppressed insulin-stimulated glycogen synthesis in primary hepatocytes via increasing *Foxo1* expression. *Meg3* expression was enhanced by high fat through histone acetylation in hepatocytes while *Meg3* interference could improve glucose tolerance and glycogen content in obese mice (27).

LncSHGL (lncRNA suppressor of hepatic gluconeogenesis and lipogenesis) and its human homologous lncRNA B4GALT1-AS1 were reduced in the livers of obese mice and patients with fatty liver disease. LncSHGL overexpression repressed gluconeogenic and lipogenic

gene expression, thus improving hyperglycemia, insulin resistance, and steatosis in obese diabetic mice. Whereas lncSHGL inhibition exerted the opposite effects in normal mouse livers, promoting fasting hyperglycemia and lipid deposition. Moreover, lncSHGL recruited heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1) to enhance the CaM/PI3K/Akt pathway and repress the mTOR/SREBP-1c pathway independent of calcium and insulin in hepatocytes, playing as an insulin-independent suppressor of hepatic gluconeogenesis and lipogenesis (28).

Besides the above, hepatic lncRNA Gomafu was also associated with gluconeogenesis in both obese and normal mice. Knockdown of Gomafu improved insulin sensitivity in obese mice while overexpression of it led to an increase of fasting blood glucose level in lean mice. Further mechanism research showed that in the obese mouse liver, Gomafu was upregulated by NF- κ B, sponged miR-139 and then increased Foxo1 expression, finally inducing inappropriate activation of gluconeogenesis (29).

Although no evidence showed that MALAT1 was engaged in gluconeogenesis and glycogen synthesis, it was extensively studied in insulin resistance. Downregulation of MALAT1 prevented hepatic lipid accumulation and insulin resistance both *in vivo* and *in vitro* by decreasing nuclear SREBP-1c protein (30). MALAT1 ablation attenuated ROS generation in liver and pancreas, thus improving ROS-induced insulin resistance via inhibiting JNK activity and the subsequent activation of IRS-1 and phosphorylation of Akt. Meanwhile, MALAT1 ablation sensitized insulin response to fast-refeeding and hyperglycemia both in MALAT1 null mice and in isolated MALAT1 null islets, implying MALAT1 is an important therapeutic target for T2DM (31).

Altered autophagic activity is implicated in the progression of obesity to T2DM through impaired β -cell function and development of insulin resistance. A lncRNA named Risa was identified as a regulator of insulin sensitivity and autophagy. Knocking down Risa alleviated insulin resistance via enhancing hepatic autophagy in both normal and obese mice while overexpression of Risa in primary hepatocytes or C2C12 myotubes induces insulin resistance via suppressing insulin-stimulated phosphorylation of Akt and Gsk3 β (32).

Skeletal muscle

H19 was downregulated in skeletal muscle of both human subjects with T2DM and insulin resistant mice as compared

to healthy controls, implying that H19 is associated with insulin resistance in skeletal muscle. *In vitro* experiments showed that H19 depletion impaired insulin sensitivity of muscle cells via activating let-7, which in turn inhibited key metabolic genes such as Insr and Lpl. On the other hand, let-7 targeted H19 for degradation during acute hyperinsulinemia in non-diabetic muscle, illustrating a double-negative feedback loop between H19 and let-7 that contributes to glucose regulation in muscle (33).

Adipose tissue

Blnc1 is upregulated in fats from obese mice and fat-specific inactivation of Blnc1 exacerbates adipose tissue inflammation and fibrosis, leading to insulin resistance and hepatic steatosis, while overexpression of Blnc1 in adipose tissue preserves systemic metabolic homeostasis. Mechanistically, Blnc1 attenuated proinflammatory cytokine signaling and promoted fuel storage in adipocytes through its protein partner Zbtb7b (34).

LncRNA and DCM

Insulin resistance in cardiomyocytes induces decreased mitochondrial glucose utilization and enhanced fatty acid uptake, resulting in triacylglycerol and cytotoxic lipid species accumulating as well as lipid metabolic gene reconstruction in the cardiomyocyte, which is recognized to precede the onset of left ventricular dysfunction of DCM (35). Role of lncRNAs in DCM has been explored in recent years and it is observed that lncRNAs affected multiple pathological processes associated with heart failure in DCM (Figure 2).

LncRNA MALAT1 was the firstly lncRNA reported to be associated with DCM. MALAT1 was upregulated in the dilated and failure diabetic heart. Moreover, MALAT1 knockdown reduced inflammatory cytokine concentration (TNF- α , IL-1 β and IL-6) in the diabetic myocardium, suggesting that MALAT1 might be involved in the inflammatory process of DCM (36). Downregulation of MALAT1 was also proved to markedly reduce cardiomyocyte apoptosis in diabetic rats (37).

Similar to MALAT1, lncRNA MIAT was also upregulated in the myocardium of diabetic rats and MIAT knockdown improved cardiac structure and function in DCM. Mechanically, MIAT played as a competing endogenous RNA to sponge miR-22-3p, subsequently upregulating DAPK2 and consequently leading to

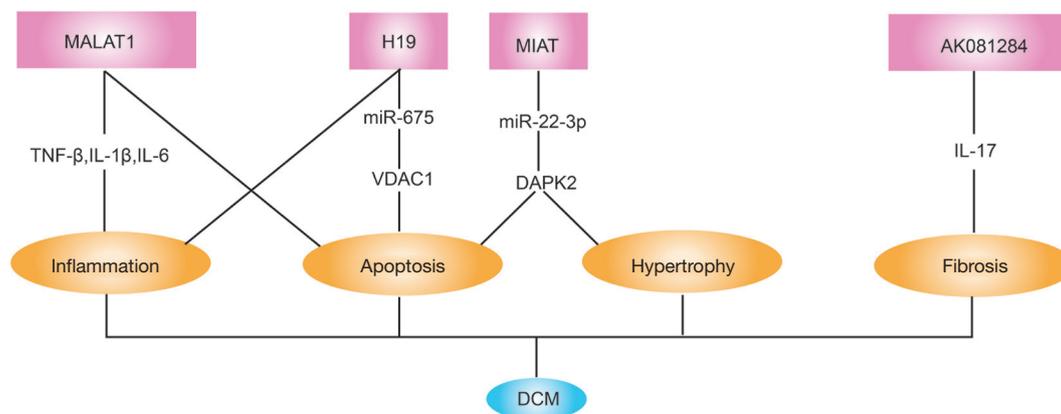


Figure 2 LncRNAs regulate various pathological processes of DCM. DCM, diabetic cardiomyopathy.

hypertrophy and apoptosis of cardiomyocytes exposure to hyperglycemia (38).

On the contrary to MALAT1 and MIAT, lncRNA H19 was downregulated in the myocardium of diabetic rats while overexpression of H19 alleviated inflammation and oxidative stress in DCM and improved structure and function of the diabetic hearts. *In vitro* experiments further revealed that high glucose could induce primary cardiomyocyte apoptosis by regulating H19/miR-675/VDAC1 pathway (39). VDAC1 belongs to the mitochondrial porin family and is recognized as a key protein in the process of mitochondria-mediated apoptosis (40,41).

LncRNA-AK081284 was upregulated in high glucose-treated cardiac fibroblasts and knockdown of AK081284 abolished high glucose induced collagen production. Furthermore, reverse experiments indicated that the regulation of high glucose on AK081284 was mediated by IL-17 pathway (42).

Besides the above, circulating lncRNAs LIPCAR, MIAT and SENCR were identified as biomarkers of left ventricular diastolic function and remodeling in T2DM patients by RT-PCR screening (43). LncRNA Neat1 was found downregulated in diabetic Akita hearts by microarray and next generation sequencing though the underlying mechanism is unclear (44).

Conclusions

As we know, lncRNAs play an important role in gene regulation, thus engaged in the pathogenesis of various diseases. In this review, we summarized the frontier researches regarding the role of lncRNAs in diabetes and DCM, which is a severe complication of diabetes. In detail,

lncRNAs are engaged in β -cell proliferation, apoptosis and insulin secretion in the islet, as well as insulin resistance in the insulin-targeted tissues and multiple pathological processes concerning DCM, implying that lncRNAs are important therapeutic targets for diabetes and DCM.

It is worth mentioning that several lncRNAs engaged in insulin secretion or insulin resistance are also engaged in DCM, in keeping with the opinion that DCM is attributed to inappropriate fuel uptake in the cardiomyocyte, prompting that lncRNAs concerning diabetes may also play roles in diseases induced by metabolism disorder. Despite, more efforts are in need to investigate the role of lncRNAs in the onset of DCM and ventricular remodeling of the diabetic heart. It is also meaningful to explore the role of lncRNAs as biomarkers for DCM diagnosis and prognosis prediction.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/ncrj.2018.09.02>). The authors have no conflicts of interest to declare.

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