# Potential IncRNA regulatory mechanisms in diabetes and its complications

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Potential IncRNA regulatory mechanisms in diabetes and its complications

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ABSTRACT

Long noncoding RNAs (lncRNA) are transcripts longer than 200 nucleotides without protein-coding potential. Though these molecules were initially considered as “junk-products” of transcription without biological meaning, recent research advancements have shown that lncRNA plays an important role not only in cellular processes such as proliferation, differentiation and metabolism, but also in pathological processes of cancers, diabetes, and neurodegenerative diseases. In this review, we focus on the potential regulatory roles of lncRNA in diabetes and diabetic complications.

Key words: lncRNA; diabetes; diabetic complications
1. Introduction

Diabetes mellitus (DM) is the most common metabolic disorder that impacts multiple organ systems in a complicated manner. The global DM epidemics has been rising sharply in recent decades, with an estimation of 387 million patients living with diabetes in 2014 and additional 205 million new patients expected by 2035 (Federation 2014). The widespread DM imposes a heavy economic burden to patients and societies, and is currently recognized as a dominant health threat to the world. This calls for a comprehensive understanding of DM pathophysiology to develop better prevention and treatment remedies. Generally DM is classified into two types: Type 1 diabetes mellitus (T1DM) results from insulin deficiency; and type 2 diabetes mellitus (T2DM) is characterized by insulin resistance, with or without abnormal insulin secretion. Although T2DM is far more prevalent, both types can result in a widespread damage to the macro and microvasculature in different organs and tissues, thus causing macrovascular complications (such as atherosclerosis, hypertension and stroke) and microvascular complications (such as diabetic nephropathy, diabetic retinopathy and diabetic neuropathy) (Forbes and Cooper 2013; Rahman et al. 2007).

Non-coding RNAs are RNAs without traditional RNA function in protein translation, but have emerged as new fundamental regulators of gene expression. These non-coding RNAs may fall into two major categories depending on their sizes: Small non-coding RNAs, of which microRNAs (miRNAs) (~22 nucleotides) represent the best characterized sub-class among them; non-coding RNAs with length greater than 200 nt, are classified as long non-coding RNAs (lncRNAs). For the past 10 years or so, miRNAs have become a hot topic for both basic and clinical scientists in searching for new therapeutic targets and clinical biomarkers. Although the biological function of lncRNAs has only been appreciated over the last few years, researchers have started to actively investigate potential roles of lncRNAs in both human physiological and pathological conditions, including diabetes. In this review we aim to summarize recent advancements on lncRNA functions in diabetes and its complications, and discuss their potential value either as clinical biomarkers or
therapeutic targets for this devastating condition.

2. IncRNAs

As mentioned earlier, IncRNAs are endogenous RNA molecules with lengths greater than 200 nt but without coding function for proteins (Perkel 2013). Depending on their genomic location and sequence orientation to protein-coding genes, IncRNA can be divided into the five subsets: 1) sense; 2) antisense; 3) bidirectional; 4) intronic and (5) intergenic. Yan and Wang (2012) first provided a detailed rationale and explanation regarding IncRNAs classification, which is beyond the scope of our current review (Gingeras 2009; Ponting et al. 2009; Wang and Chang 2011; Yan and Wang 2012).

The functional mechanisms of IncRNAs are still under investigation, which are more complicated than miRNAs simply binding with complementary sequences of specific RNAs. IncRNAs often use their large sizes to form secondary or tertiary structures in achieving their functions. Most IncRNAs reside in cell nucleus working as molecular scaffolds to stabilize nuclear structures or signaling complexes (Gingeras 2009; Pan et al. 2011; Rinn et al. 2007). A few IncRNAs are in the cytoplasm, either, like miRNAs modulating translation, while others act as miRNA decoys which essentially neutralize miRNA actions. More detailed discussion on IncRNA working mechanisms were reviewed by others (Gingeras 2009; Pan et al. 2011; Rinn et al. 2007). Recent studies have indicated that IncRNAs play an important role in numerous biological processes, such as X chromosome inactivation, dosage compensation, genomic imprinting, chromatin modification and remodeling, cell cycle, telomere biology, and also in human pathological processes (Kelley et al. 1999; Kertesz et al. 2010; Khorkova et al. 2015; Lee and Bartolomei 2013; Zhu et al. 2013), include diabetes, which we will focus on in this review.

3. Islet IncRNAs and their implications in DM

Pancreatic β cells are highly specialized endocrine cells located within the islets of Langerhans in the pancreas that function primarily to produce, store and secrete insulin in response to glucose stimulation. Loss
of β cell identity or function contributes to the pathogenesis of both T1D and T2D. Recently, researchers showed that IncRNA mediated biological processes in islet cells, such as β cell differentiation and proliferation, insulin biosynthesis and secretion (summarized in Table 1). Moran et al. uncovered a high-confidence set of 1128 human islet-cell genes by transcriptome mapping, with 55% of intergenic IncRNAs and 40% of antisense IncRNAs being islet-specific (Moran et al. 2012). Ku et al. identified over 1000 long intergenic ncRNAs (lincRNAs) in mouse islet by RNA-seq, most of which are β-cell-specific. Among them, lincRNA-XLOC_019089 was detected only in β-cell tissue and located in an antisense position to the pancreatic and duodenal homeobox 1 (Pdx1) locus (Ku et al. 2012). Bramswig et al. further discovered 12 β-cell-specific and 5 α-cell-specific IncRNA transcripts using ChIP sequencing and RNA sequencing analyses (Bramswig et al. 2013). Most recently, by deep RNA-seq of purified human β-cells in 11 cadaveric healthy islets, 132 lincRNAs were found over-expressed in these cells as compared to the whole islets while 148 IncRNAs were over-expressed in β-cells versus non-β ones (Nica et al. 2013). The restricted distribution of massive beta cell IncRNAs suggests that they may perform highly β-cell-specific tasks such as regulating the epigenetic landscape and pattern of gene expression that determine β-cell identity.

Intriguingly, islet IncRNAs often map proximal to islet-enriched/specific genes that play a role in β-cell function, development and transcription (Ku et al. 2012; Moran et al. 2012). Using qPCR method, Moran et al. showed that there exists a stage-specific activation of IncRNAs during β-cell maturation (Moran et al. 2012). All 13 β-cell-selective IncRNAs except 1 were silent or expressed at low levels in human embryonic pancreatic progenitors but later became active in adult mature islets. They observed similar results in a human embryonic stem-cell (hES) differentiation model: Half of the identified 12 IncRNAs were silent or expressed at extremely low levels throughout in vitro differentiation process but were activated during in vivo maturation procedures. This demonstrates that islet IncRNAs are an integral component of β cell differentiation and maturation program, and suggests that abnormal expression of β-cell-specific IncRNAs
may impact diabetes pathophysiology. Moran et al. found that KCNQ1 overlapping transcript-1 (KCNQ1OT1) is significantly increased in islets from T2D patients while the expression of HI-LNC45 was significantly decreased (Moran et al. 2012). Further analysis of 55 T2D susceptibility loci showed that 9 loci contained islet lncRNAs within 150 kb of the reported lead SNP, and among them, 6 have been directly correlated to β-cell dysfunction. Notably, representative islet lncRNA-HI-LNC25 was found to be a potential regulator of GLIS family zinc finger 3 (GLIS3), which seems more associated with T2D incidence (Barrett et al. 2009; Cho et al. 2012; Dupuis et al. 2010; Moran et al. 2012). Therefore, islet lncRNAs may serve as diabetes biomarkers. In addition, islet lncRNAs and their nearby protein-coding genes are usually located near islet-selective cluster of open chromatin regulatory elements (COREs), suggesting potential co-regulatory mechanisms between lncRNAs and their adjacent coding genes (Moran et al. 2012). For example, Fadista et al. identified islet lincRNA LOC283177 was strongly co-expressed with MAP-kinase activating death domain (MADD), synaptotagmin 11 (SYT11), and paired box 6 (PAX6), which regulate proinsulin synthesis, insulin exocytosis, and pancreatic islets development, respectively (Andersson et al. 2012; Fadista et al. 2014; Gosmain et al. 2012; Huyghe et al. 2013). Taken together, reported studies suggest strong correlations for lncRNAs in regulating β cell identity and function in the context of DM pathophysiology, which warrants further vigorous investigation on their functional consequences.

4. lncRNAs and adipogenesis

Obesity is a strong predictor of risk for metabolic disorders such as dyslipidemia, hyperglycemia and diabetes (Grundy 2004; Schienkiewitz et al. 2006). Adipocytes are an integral regulator of glucose homeostasis, and play a critical role in energy balance as the fuel reservoir of body. They also work as endocrine cells, secreting hormones and cytokines that impact cellular functions both locally and the body as a whole (Rosen and Spiegelman 2006). Adipogenesis is a complex process that is highly regulated by
multiple transcription factors, cofactors, cell-cycle regulator as well as signaling intermediates from numerous pathways (Gesta et al. 2007; Gregoire et al. 1998; Rangwala and Lazar 2000; Rosen and MacDougald 2006). Recently, IncRNAs are emerging as important regulators in diverse biological processes including adipocyte differentiation (Dinger et al. 2008; Guttman et al. 2011). Specifically, Xu et al. (Xu et al. 2010) first identified IncRNA- steroid receptor RNA activator (SRA), a transcriptional coactivator of peroxisome proliferator-activated receptor gamma (PPARγ), promoted adipocyte differentiation and improved insulin-stimulated glucose uptake in adipocytes. They further showed that SRA-/- mice remained lean on a high fat diet (HFD), with decreased expression of adipocyte marker genes and inflammation genes, and improved insulin sensitivity, suggesting that SRA might be a potential therapeutic target against obesity and T2D (Liu et al. 2014). Using qRT-PCR, Sun et al. (Sun et al. 2013) found 175 IncRNAs that were specifically regulated during white and brown adipogenesis. Among them, 26 IncRNAs were up-regulated and exhibited adipose-enriched expression patterns. To investigate whether these IncRNAs are functionally important for adipogenesis, Lei et al. further used RNAi-mediated loss of function approaches and identified 10 Inc-RAP-n (IncRNAs regulated in adipogenesis) important in regulating adipogenetic transcriptional networks(Sun et al. 2013). You et al. adopted a high-throughput microarray screening method to explore differentially expressed IncRNAs during brown adipose cell differentiation, by examining the genomic context, gene ontology (GO) enrichment of their associated protein-coding genes and pathway analysis. They discovered that three IncRNAs( Gm15051, Tmem189 and Cebpd) were associated with their flanking coding genes Homeobox protein Hox-A1 (Hoxa1), CCAAT-enhancer-binding protein β and δ (C/EBPβ and C/EBPδ), respectively, which indicates IncRNAs may play potential roles in brown adipose cell differentiation (You et al. 2015b). Divoux et al. found that IncRNA HOTAIR was expressed in gluteal but not in abdominal subcutaneous adipose tissue and may regulate key processes in adipocyte differentiation by positively regulating the expression of PPARγ and lipoprotein lipase (Divoux et al. 2014). An antisense
lncRNA, PU.1-AS, was revealed to promote adipogenesis through preventing PU.1 mRNA translation via forming PU.1 mRNA/PU.1-AS lncRNA duplex in mice and porcine preadipocytes (Pang et al. 2013; Wei et al. 2015). In addition, Zhao et al found a novel lncRNA, brown fat lncRNA 1 (Blnc1), which formed a feed forward ribonucleoprotein transcriptional complex with transcription factor early B cell factor 2 (EBF2) to direct adipogenesis toward thermogenic phenotype (Zhao et al. 2014). Together these studies have demonstrated that lncRNAs play important roles in regulating adipocyte differentiation, which may provide novel insights in diabetes therapy.

5. lncRNAs in regulating glucose and lipid metabolism

Consistent hyperglycemia is the predominant trait of diabetes and inflicts great damages and complications to multiple organs (such as diabetic nephropathy, diabetic neuropathy, diabetic retinopathy). Meanwhile, accumulation of excess lipids in white adipose tissue (WAT) leads to low-grade inflammation, and induces insulin resistance in obese individuals (Glass and Olefsky 2012; Saltiel and Kahn 2001). Thus, dysregulation of glucose and lipid metabolism plays a major role in the pathophysiological development of insulin resistance and diabetes. Regarding lncRNA regulation of glucose and lipid metabolism in adipocytes, Xu et al. (Xu et al. 2010) first reported that SRA, a lncRNA, promotes insulin-stimulated glucose uptake through co-activating PPARγ which leads to increased phosphorylation of downstream targets Akt and Forkhead box protein O1 (FOXO1) in adipocytes. Furthermore, the same group demonstrated that global knock-out of SRA protected mice against HFD-induced obesity and improved the whole body glucose tolerance in these animals (Liu et al. 2014). In addition, lncRNAs were found to regulate glucose and lipid metabolism in certain cancer cells. For example, lncRNA CRNDE was validated to be down-regulated by the MAPK and PI3K arms of the insulin/IGF signaling pathway in CRC (colorectal cancer cells); and the elevated levels of CRNDE nuclear transcripts in CRC cells increase glucose metabolism, lactate secretion and lipid synthesis, yet decrease lipid catabolism (Ellis et al. 2014). Another lncRNA UCA1 was discovered to promote glucose
consumption and lactate production through the mTOR–STAT3–miR143–HK2 pathway in cancer cells (Li et al. 2014). In addition to targeting multiple metabolic processes (glucose plus lipids), there are lncRNAs solely involving in the regulation of lipid metabolism. Hu et al. (Hu et al. 2014) reported that an Ox-LDL-induced lincRNA–DYNLRB2-2, was able to promote ABCA1-mediated cholesterol efflux and inhibit inflammation through GPR119/GLP-1R, in THP-1 macrophage derived foam cells. Moreover, the upregulation of GPR119 by DYNLRB2-2 led to decreased lipid and serum inflammatory cytokine levels in apoE−/− mice, indicating an essential role of lincRNA DYNLRB2-2 in regulating cholesterol homeostasis (Hu et al. 2014). Most recently Li et al. identified a liver-specific triglyceride regulator lncRNA (lncLSTR) to regulate systemic lipid metabolism in mice (Li et al. 2015). They showed that lncLSTR modulates an FXR/apoC2/PLP pathway through regulation of TDP-43/Cyp8b1, a key component driving triglycerides (TG) clearance. Further in vivo experiment demonstrated that lncLSTR depletion accelerates ApoC2 expression and LPL activities, and enhances plasma TG clearance, and finally leads to significantly decreased plasma TG level (Li et al. 2015). This exciting study suggests that lncLSTR may be a therapeutic target for metabolic disorders. In addition, knockdown of SRA in HeLa cells led to a sharp reduction in solute carrier family 2 (facilitated glucose transporter) member 3 (SLC2A3), as well as insulin induced gene 1 (INSIG1) and ATP-binding cassette sub-family A member 1 (ABCA1), which are important in mediating cholesterol synthesis and transport (Foulds et al. 2010). Therefore, lncRNAs may represent a new direction in treating glucose and lipid dysfunction in diabetes.

6. lncRNAs in regulation of insulin secretion and sensitivity

Insulin is the only glucose-dropping hormone produced by islet β cells. Absolute or relative insulin deficiency is the key etiology of diabetes. Thus current agents used in diabetes treatment often focus on promoting insulin secretion and/or insulin sensitivity. Recent studies discovered several lncRNAs able to regulate insulin secretion and sensitivity. For instance, Xu et al. reported that SRA has a positive effect on
promoting insulin sensitivity and insulin-stimulated glucose uptake in adipocytes (Xu et al. 2010). The underlying mechanisms seem partially due to the ability of SRA to regulate the expression of various factors influential to insulin sensitivity: for example, SRA overexpression in ST2 adipocytes suppressed the expression of negative regulators of insulin sensitivity such as suppressor of cytokine signaling (SOCS)-1 and -3 while promoting the expression of positive regulators such as SH3 domain containing 1 (Sorbs1) (Xu et al. 2010). Further, the authors demonstrated that SRA is able to enhance insulin functional action (glucose uptake) via Akt and FOXO1 signaling pathways: elevated SRA increased insulin-stimulated glucose uptake, which was correlated to increased insulin-stimulated phosphorylation of Akt and FOXO1; in contrast, stably knockdown SRA using a lentiviral system resulted in inhibition of both insulin-stimulated glucose uptake and insulin-stimulated phosphorylation of Akt and FOXO1(Xu et al. 2010). Another islet-enriched IncRNA TUG1 was reported to be involved in the regulation of insulin secretion. Yin et al. found that down-regulation of IncRNA TUG1 increased islet β-cell apoptosis and reduced insulin secretion in both in vitro and in vivo conditions(Yin et al. 2015). Knockdown of IncRNA TUG1 in Min-6 cells led to reduced mRNA levels of transcription factors related insulin synthesis /secretion such as pancreatic and duodenal homeobox 1 (Pdx1), neurogenic differentiation 1 (NeuroD1), fibrosarcoma oncogene homolog A (MafA) and glucose transporter 2 (GLUT2) (Yin et al. 2015). In addition, researchers also identified that maternally expressed mouse gene 3 (Meg3) is a novel IncRNA regulator of insulin synthesis and secretion in pancreatic β-cells. Knockdown of Meg3 reduced insulin production via inhibiting key transcription factor expression including Pdx-1 and MafA (You et al. 2015a). So far it appears that different IncRNAs may target similar factors in order to achieve regulation of insulin secretion as mentioned above. Together these studies imply a potential therapeutical role for IncRNAs in enhancing insulin secretion and sensitivity.

7. IncRNAs and Diabetic Retinopathy

Diabetic Retinopathy (DR) is a severe diabetic complication, representing one of the leading causes of
blindness (Yau et al. 2012). Epidemiologic studies and clinical trials showed that the major risk factors for DR are hyperglycemia, hypertension, dyslipidemia (Klein 2007). Recently, researchers are examining the potential involvement of lncRNAs in the pathophysiological development of diabetic retinopathy. Yan et al found that 303 lncRNAs were aberrantly expressed in the retinas of early DR patients, among which 214 were down-regulated while 89 others up-regulated (Yan et al. 2014). The corresponding lncRNAs-co-expressed mRNAs are related to MAPK signaling pathway, complement and coagulation cascades, chemokine signaling pathway, pyruvate metabolism pathway, and the axon guidance signaling pathway (Yan et al. 2014). Particularly important, the axon guidance signaling pathway is essential for the retinal angiogenesis and axon guidance during development and is involved in the pathogenesis of ocular neurodegeneration (Campochiaro 2013; Lange et al. 2012). In addition, metastasis-associated lung adenocarcinoma transcript-1 (MALAT1), a highly conserved lncRNA, was found to be strongly up-regulated in the retinas of STZ-induced diabetic mice, in RF/6A cell model of hyperglycemia, as well as in the fibrovascular membranes and aqueous humor collection of DR patients. Bioinformatics analysis showed that MALAT1 could interact with NF-κB (Yan et al. 2014). It remains to be determined whether MALAT1 regulates NF-κB signaling to achieve its biological effects. It also requires more research to confirm whether MALAT1 could be a target in developing novel diagnostic and therapeutic tools for DR, as it is only reported by a single study (Lange et al. 2012).

8. lncRNAs and diabetic nephropathy

Diabetic nephropathy (DN) is a chronic kidney disease characterized by glomerular microvascular impairment (Yagi et al. 2015). It features excessive accumulation of extracellular matrix (ECM) and mesangial expansion in glomeruli, resulting in impaired glomerular filtration. A plethora of studies showed that increased transforming growth factor-beta1 (TGF-β) in renal cells contributes to DN progress (Reeves
and Andreoli 2000; Sharma and Ziyadeh 1995; Yamamoto et al. 1993). Long-term treatment with anti-TGF-β antibody improved glomerular filtration rates in experimental DN (Ziyadeh et al. 2000). An early study showed that TGF-β activated Akt via promoting the expression of miR-216a and miR-217 along with their host lncRNA RP23 in mesangial cells (MC), which led to mesangial cell proliferation and hypertrophy (Kato et al. 2009). Similarly in these cells, TGF-β also induced the expression of miR-192 together with its host lncRNA - CJ241444, which led to Akt and p300 activation resulting in mesangial hypertrophy (Kato et al. 2013). In addition, increased MALAT1 was found in the kidneys of diabetic mice and can be induced by hyperglycemia stimulation (Puthanveetil et al. 2015). It was found that MALAT1 activated serum amyloid antigen 3(SAA3) to regulate glucose-induced inflammatory cytokine production and oxidative stress process, both of which damage endothelial stability (Puthanveetil et al. 2015).

Another key lncRNA, plasmacytoma variant translocation 1 (PVT1), was first identified as a candidate gene for end-stage renal disease (ESRD) in type-2 diabetes (Hanson et al. 2007). Subsequently PVT1 was also found in a tight association with ESRD in type-1 diabetes, expressing abundantly in renal cells such as mesangial, cortical epithelial, epithelial, and proximal tubule cells (Millis et al. 2007). Further functional studies revealed that PVT1 may act as a regulator of ECM gene expression. High glucose stimulation elevated both PVT1 and ECM proteins levels in mesangial cells, and PVT1 small interfering RNA attenuated the expression of key ECM proteins such as FN1 and COL4A1 via both TGFB1-dependent and independent mechanism (Alvarez and DiStefano 2011). It appears that PVT1 targets TGFB1 and plasminogen activator inhibitor-1 (PAI-1), two key regulators of ECM accumulation in the glomeruli (Alvarez and DiStefano 2011). Further study confirmed this PVT1 function: Over-expressing PVT1 significantly increased the levels of TGFB1, PAI-1, FN1 mRNA and protein, while knockdown of PVT1 led to the decreased expression of these molecules (Alvarez et al. 2013). Therefore, PVT1 is a mediator of extracellular matrix accumulation in the kidney and a key gene in determining susceptibility to DN. Taken together, these reports demonstrated
that lncRNAs play an important role in the pathogenesis of diabetic nephropathy.

9. lncRNAs and diabetic vascular complications

Many diabetic complications are associated with either microvascular or macrovascular impairments, resulting in diabetic neuropathy, retinopathy, nephropathy, cardiovascular and peripheral vascular diseases (Cade 2008). These vascular complications often display impaired angiogenesis features (Duh and Aiello 1999; Hammes et al. 2011). Though few lncRNAs have been directly linked to diabetic vascular complications, a number of diabetic-related lncRNAs has also been shown to independently regulate angiogenesis. For example, MALAT1, a putative diabetic-related lncRNA mentioned above, appeared to modulate proangiogenic response in endothelial cells: both siRNA-induced silencing and pharmacological inhibition of MALAT1 suppressed vascular growth in vivo (Michalik et al. 2014). In addition, novel lncRNAs have been recently identified to regulate angiogenesis. Smooth muscle and endothelial cell-enriched migration/differentiation-associated lncRNA (SENCR), a vascular cell-enriched lncRNA, was first reported in human coronary artery smooth muscle cells (Bell et al. 2014). Further investigation showed that SENCr stabilizes vascular smooth muscle cell (VSMC) contractile phenotype and inhibits VSMC migration (Bell et al. 2014). Since hyperglycemia-induced growth of VSMCs is a characteristic feature of diabetic cardiovascular complications (Marrero et al. 2005), one may wonder whether SENCr plays any role in the process. Finally, Wu et al. reported that lincRNA-p21 repressed the proliferation of both VSMCs and macrophages and also induced their apoptosis through the p53 signalling pathway (Wu et al. 2014). This raises the question whether lincRNA-p21 might play a role in diabetic vascular complications or associated inflammation. Other than MALAT1, which was shown to regulate inflammatory cytokine production and oxidative stress process by activating SAA3 in endothelial cells (Puthanveetil et al. 2015), we have not found any more concrete experimental data regarding lincRNAs in diabetic vascular complications and simply present several potential leads for investigators to consider.
10. Conclusion

At present, more and more lncRNAs are identified, yet the functions and working mechanisms of the majority lncRNAs are still unclear. The lncRNA study in the diabetes field is in its infancy. Recent works have clearly shown that lncRNAs play an important role in adipogenesis, beta cell function and the development of insulin resistance. These new advancements suggest lncRNAs could serve both as promising new diagnostic markers and as therapeutic targets for diabetes and its complications. It is clearly an exciting new direction in diabetes research.

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The authors declare no conflicts of interest.
References


## Table 1 LncRNAs implicated in the pathophysiological development of diabetes

<table>
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<tr>
<th>LncRNAs</th>
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<th>Types</th>
<th>Target Gene</th>
<th>Function</th>
<th>References</th>
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<tr>
<td>HI-LNC25</td>
<td>Chr 20 (human)</td>
<td>Intergenic</td>
<td>GLIS3</td>
<td>HI-LNC25 positively regulates GLIS3 mRNA, which contains both T1D and T2D risk variants</td>
<td>Moran et al. 2012</td>
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<tr>
<td>LOC283177</td>
<td>Chr 11 (human)</td>
<td>Intergenic</td>
<td>?</td>
<td>XLOC_019089 is strongly co-expressed with SYT11, MADD and PAX6 to regulate the production and secretion of insulin</td>
<td>Fadista et al. 2014</td>
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<td>SRA</td>
<td>Chr 18 (mouse)</td>
<td>?</td>
<td>PPARγ, p21Cip1 and p27Kip1, etc.</td>
<td>SRA promotes adipogenesis through transcriptionally co-activating PPARγ, promoting S-phase entry and regulating adipocyte cycle-related genes</td>
<td>Liu et al. 2014; Xu et al. 2010</td>
</tr>
<tr>
<td>SRA</td>
<td>Chr 18 (mouse)</td>
<td>?</td>
<td>pAkt, GLUT3 and SLC2A3</td>
<td>SRA increases insulin-stimulated glucose uptake in vitro; SRA gene knock-out improves glucose tolerance in HFD-fed Mice</td>
<td>Foulds et al. 2010; Liu et al. 2014; Xu et al. 2010</td>
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<tr>
<td>SRA</td>
<td>Chr 18 (mouse)</td>
<td>?</td>
<td>pAkt, TNFα</td>
<td>In vitro and in vivo knockout of SRA improves insulin sensitivity, probably through up-regulating the insulin signaling pathway and down-regulating TNFα signaling</td>
<td>Liu et al. 2014; Xu et al. 2010</td>
</tr>
<tr>
<td>HOTAIR</td>
<td>Chr 18 (mouse)</td>
<td>?</td>
<td>PPARγ, LPL</td>
<td>HOTAIR promotes adipogenesis through regulating key adipogenic genes PPARγ and LPL</td>
<td>Divoux et al. 2014</td>
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<tr>
<td>PU.1 AS</td>
<td>Chr 2 (mouse) &amp; Chr 2 (pig)</td>
<td>Antisense</td>
<td>PU.1</td>
<td>PU.1 AS promotes adipogenesis through preventing PU.1 mRNA translation via forming PU.1 mRNA/PU.1 AS lncRNA duplex</td>
<td>Pang et al. 2013; Wei et al. 2015</td>
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<tr>
<td>Blnc1</td>
<td>Chr 14 (mouse)</td>
<td>Intergenic</td>
<td>EBF2</td>
<td>Blnc1 forms a feedforward regulatory loop with EBF2 that directs adipogenesis toward thermogenesis</td>
<td>Zhao et al. 2014</td>
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<td>lncRNA</td>
<td>Chromosome</td>
<td>Status</td>
<td>Gene</td>
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<td>Reference</td>
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<tr>
<td>CRNDE</td>
<td>Chr 16 (human)</td>
<td>Intergenic</td>
<td>?</td>
<td>CRNDE is a downstream target of both PI3K/Akt/mTOR and Raf/MAPK pathway and regulates genes involved in central metabolism</td>
<td>Ellis et al. 2014</td>
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<td>UCA1</td>
<td>Chr 19 (human)</td>
<td>?</td>
<td>HK2</td>
<td>UCA1 promotes glucose consumption and lactate production through the mTOR–STAT3/miR143–HK2 pathway in cancer cells</td>
<td>Li et al. 2014</td>
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<td>lincRNA-DYNLRB2-2</td>
<td>Chr 16 (human)</td>
<td>Intergenic</td>
<td>GPR119</td>
<td>LincRNA-DYNLRB2-2 modulates GPR119/GLP-1R/ABCA1-dependent signal transduction pathway to regulate cholesterol homeostasis</td>
<td>Hu et al. 2014</td>
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<td>IncLSTR</td>
<td>Chr 1 (mouse)</td>
<td>?</td>
<td>ApoC2</td>
<td>IncLSTR modulates the FXR/apoC2/PLP pathway through regulation of TDP-43/Cyp8b1 to maintain systemic lipid homeostasis</td>
<td>Li et al. 2015</td>
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<td>TUG1</td>
<td>Chr 1 (mouse)</td>
<td>?</td>
<td>?</td>
<td>Downregulation of lncRNA TUG1 expression increased apoptosis and reduced insulin secretion in islet β cells both in vitro and in vivo</td>
<td>Yin et al. 2015</td>
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<tr>
<td>Meg3</td>
<td>Chr 12 (mouse)</td>
<td>?</td>
<td>Pdx-1, MafA</td>
<td>Meg3 regulates beta cells identity and function via affecting insulin production and cell apoptosis</td>
<td>You et al. 2016</td>
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Table 2. Potential lncRNAs involved in diabetic complications

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<td>MALAT1</td>
<td>Chr 11 (mouse)</td>
<td>Intergenic</td>
<td>CPNL1</td>
<td>MALAT1 is potential biomarker of DR: significantly up-regulated in RF/6A cell model of hyperglycemia, in the aqueous humor samples and fibrovascular membranes of diabetic patients</td>
<td>Lange et al. 2012; Yamamoto et al. 1993</td>
</tr>
<tr>
<td>MALAT1</td>
<td>Chr 11 (mouse)</td>
<td>?</td>
<td>SAA3</td>
<td>MALAT1 regulates glucose-induced inflammatory changes and oxidative stress via SAA3 in the kidney of diabetic mice</td>
<td>Hammes et al. 2011</td>
</tr>
<tr>
<td>PVT1</td>
<td>Chr 8 (human)</td>
<td>?</td>
<td>FN1, COL4A1, TGFB1 and PAI-1</td>
<td>PVT1 is associated with ESRD in both type 1 and type 2 diabetes, probably through mediating extracellular matrix accumulation in the kidney</td>
<td>Bell et al. 2014; Marrero et al. 2005; Michalik et al. 2014; Wu et al. 2014</td>
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