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Review Article

Long non-coding RNA-mediated regulation of glucose homeostasis and diabetes

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Abstract: Long non-coding RNAs (lncRNAs) represent an important class of non-coding RNAs that plays key roles in regulating the expression of genes in health and disease. Accumulating genetic, experimental, and epidemiological studies highlight a growing list of lncRNAs that control glucose homeostasis and diabetic pathologies and complications. Through interactions with chromatin, RNA, and protein, lncRNAs modulate chromatin modification, mRNA stability, microRNA activity, and the function of proteins such as transcription factors. This review highlights emerging concepts in lncRNA-mediated control of glucose homeostasis as well as some of the challenges and therapeutic opportunities in the pathogenesis of diabetes and its complications.

Keywords: Long non-coding RNAs, glucose, diabetes

The prevalence of diabetes is increasing rapidly worldwide with more than 90% of the diabetic population affected by type 2 diabetes (T2D). Being diabetic puts patients at a greater risk for cardiovascular diseases. T2D is a multifactorial disease involving genetic, environmental, and behavioral components. In particular, emerging studies have highlighted the importance of genetic factors in the pathogenesis of T2D [1].

Genomic research has greatly improved our understanding of the function of the human genome. Of the 84% of the genome that is transcribed, only 2% codes for proteins, whereas the vast majority is transcribed as non-coding RNAs; these include long non-coding RNAs (lncRNAs), microRNAs, and others [2, 3]. LncRNAs account for much of this pervasive transcription, yet the functions of most lncRNAs remain undiscovered. Nevertheless, the link between genetically controlled expression of large intergenic non-coding RNAs (lincRNAs) and human disease has been established [4, 5]. Many disease-associated genetic variants affect lincRNA expression levels in a tissue-specific manner. GWAS studies have identified a large number of disease-associated single nucleotide polymorphisms. Only a fraction of these variations are located within protein-coding genes, while a majority (93%) maps to non-coding regions [6, 7]. In another study, the authors found that there are about 91,000 genes in the human transcriptome - with 58,000 genes being classified as lncRNAs and 3,900 lncRNAs overlapping with disease-associated gene variants [8]. Indeed, lncRNAs are emerging as critical regulators of tissue physiology and human disease. In this review, the roles of lncRNAs in the regulation of glucose homeostasis and diabetic pathologies are summarized.

Long non-coding RNAs

LncRNAs are non-coding transcripts larger than 200 nucleotides in length without protein-coding capacity [9, 10]. Many lncRNAs have multiple exons and are subjected to alternative splicing to generate isoforms. Compared to protein-coding transcripts, lncRNAs are shorter with fewer exons and are expressed at 10-fold lower levels on average [11-13]. Meanwhile, lncRNAs display a higher degree of tissue- and cell-specific expression [11]. LncRNA sequences also

often contain retrotransposon sequences and tandem repeat elements [14, 15]. Though lncRNAs show little sequence or motif conservation across species [10, 11], this does not imply a lack of function [16]. The conserved secondary structure of lncRNAs confers similar functions to different lncRNAs [16-18].

Based on genomic localization, lncRNAs are categorized into different groups; these include enhancer-related, intergenic, intronic, and antisense lncRNAs. Gene enhancers can be bidirectionally transcribed to give rise to enhancer-related lncRNAs (eRNAs), which participate in many programs of gene activation by targeting chromatin-remodeling complexes to specific promoters [19-21]. eRNAs marked by histone 3 lysine 4 monomethylation (H3K4me1) are 5' capped but generally are not polyadenylated. The genes of lincRNAs are located between two protein-coding genes and at least 5 kilobases away from protein-coding genes [22, 23]. They are typically transcribed by RNA polymerase II, capped, polyadenylated, and characterized by well-defined transcriptional chromatin landmarks such as histone H3-lysine 4 (H3K4) and H3-lysine 36 (H3K36) tri-methylation, H3-lysine 9 (H3K9) acetylation, and CpG DNA methylation. Intronic lncRNAs are transcribed from the introns of protein-coding genes on either the sense or anti-sense strands. Only a few long intronic lncRNAs have been studied in detail to date [24]. Natural antisense transcripts are a subgroup of endogenous lncRNAs that are transcribed from the antisense strands of protein-coding genes and contain complementary sequences to the mature mRNA sequences [25]. As much as 70% of annotated transcription units have antisense transcripts [25-27].

The location of lncRNAs can be nuclear, cytoplasmic, or both. Nuclear lncRNAs exert their functions through different mechanisms; these include: 1) recruiting chromatin modification complexes to specific genomic loci to influence DNA methylation or histone modifications [9, 28]; 2) titrating transcription factors and other proteins away from chromatin; and 3) functioning as transcriptional coactivators [29, 30]. Cytoplasmic lncRNAs can indirectly enhance protein expression by sequestering microRNAs. In particular, lncRNAs can regulate gene expression through base-pairing complementary regions on target RNAs [31].

The role of lncRNAs in regulating glucose homeostasis and diabetic complications

Long noncoding RNA - H19

The mouse and human H19 genes were discovered in 1984 [32] and 1990 [33], respectively. The *H19* gene is imprinted leading to transcription exclusively from the maternal allele [34, 35], and encodes a capped, spliced, and polyadenylated lncRNA [33, 35]. LncRNA H19 functions in both the cytoplasm and nucleus, despite its predominant expression in the cytoplasm. Its mechanisms of action include the following: 1) interacts with methyl-CpG-binding domain protein 1 to inhibit gene transcription by recruiting repressive histone marks [36]; 2) serves as a host gene for miR-675 to allow for rapid inhibition of cell proliferation in response to cellular signals [37]; 3) targets polycomb repressive complex 2 (PRC2) [38]; 4) acts as a molecular sponge for miR-let-7 [39]; and 5) binds to S-adenosylhomocysteinehydrolase and inhibits its functions, thus blocking DNA methylation [40]. The role of H19 in regulating body weight and glucose homeostasis is discussed in detail below.

The genes of H19 and insulin-like growth factor 2 (IGF2) are transcribed from a conserved imprinted gene cluster [35] - with the IGF2 gene located approximately 100 kilobases upstream of H19. H19 is maternally expressed, while IGF2 is paternally expressed. A maternal deletion of H19 disrupts the imprinting of IGF2, and offspring with such a deletion are 27% heavier than those inheriting a deletion from their fathers [41]. Interestingly, fetal disruption of H19 causes significantly higher glucose concentrations during the last trimester in pregnant mice. The study demonstrated that the risk of gestational diabetes mellitus can be influenced by gene variation in the fetal genome [42]. In humans, gene variation in maternally transmitted fetal H19 alleles (rs2071094) is associated with birth weight and other markers of size, but not with significant changes in maternal glucose tolerance in the third trimester of pregnancy [43]. Birth weight is associated with the risk of many chronic diseases in later life [44], but whether H19 participates in the pathogenesis of diabetes and cardiovascular disease by regulating birth weight remains unknown.

H19 regulates glucose homeostasis by acting as a molecular sponge for miR-let-7 [39]. H19 is highly expressed in both human and mouse skeletal muscle, and was shown to be reduced about 5-fold in muscle of both human diabetic subjects and insulin resistant mice [39]. Under physiological conditions, H19 binds to miR-let-7 and prevents it from inhibiting the expression of target genes including the genes of insulin receptor (Insr) and lipoprotein lipase (lpl) [45]. In the setting of diabetes, reduction of H19 increases the bioavailability of miR-let-7, which in turn inhibits the expression of *Insr* and *lpl* [39]. Studies have shown that knockdown of H19 reduces the expression of *Insr* and *lpl* in C3H myotubes, and that co-transfection of miR-let-7 inhibitors with H19 siRNA blocks the effects of H19 knockdown on the expression of miR-let-7 target genes. These findings suggest that in diabetic muscles, miR-let-7 mediates the decreased expression of *Insr* and *lpl* secondary to the reduction of H19. Functionally, knockdown of H19 expression reduces glucose uptake in C3H myotubes. Acute hyperinsulinemia promotes the biogenesis of miR-let-7, mediating H19 destabilization and thus down-regulating H19 expression. Therefore, H19 and miR-let-7 form a double-negative feedback loop that participates in the regulation of glucose homeostasis in muscle cells [39].

The plasmacytoma variant translocation 1 gene

The plasmacytoma variant translocation 1 gene (PVT1) is a long non-coding RNA. Variations of PVT1 are associated with end-stage renal disease attributed to both type 1 diabetes (T1D) and T2D [46, 47]. Diabetic nephropathy is characterized by the excessive accumulation of extracellular matrix in the glomeruli - with mesangial cells contributing significantly to the production of extracellular matrix proteins. PVT1 is expressed in different types of cells in the kidney [47], and its expression is increased by glucose in mesangial cells. Knockdown of PVT1 expression using small interference RNAs is associated with decreases in fibronectin1, collagen type IV alpha 1, transforming growth factor beta 1 (TGF-β1), and plasminogen activator inhibitor-1 (PAI-1) expression at both mRNA and protein levels. Specifically, the reduction in TGF-β1 is less and slower than that of the other three genes in response to PVT1 knockdown. These data indicate that PVT1's contributions to extracellular matrix deposition in the glomeruli are, at least in part, independent of TGF-β1 [48]. Furthermore, studies have demonstrated that PVT1 is a host gene of at least six miRNAs - with miR-1207-5p being the major PVT1-derived miRNA in renal cells. Both glucose and TGF-β1 induce miR-1207-5p expression. In addition, miR-1207-5p overexpression increases the expression of TGF-β1, PAI-1, and fibronectin1 in mesangial cells. These results demonstrate that both miR-1207-5p and its host gene are involved in the complex pathogenesis of diabetic nephropathy [49].

Maternally expressed gene 3

Maternally expressed gene 3 (Meg3) is an imprinted gene that encodes a lncRNA also known as gene trap locus 2. Meg3 expression is decreased in type 1 and type 2 diabetic mice. In Min6 cells and isolated mouse islets, Meg3 expression is also dynamically regulated. Knockdown of Meg3 expression decreases insulin synthesis and secretion by modulating Pancreatic and duodenal homeobox 1 and MafA expression in Min6 cells. Suppression of Meg3 also increases beta cell apoptosis, suggesting a role for Meg3 in maintaining beta cell mass. In addition, inactivation of Meg3 in normal mice has been shown to decrease insulin synthesis and secretion, leading to glucose tolerance [50]. Meanwhile, Meg3 overexpression increases Fox01, G6pc, and Pepck expression and hepatic glucose production and suppresses insulin-stimulated glycogen synthesis in primary hepatocytes. Regarding diabetes, Meg3 knockdown reverses the increase in triglycerides, impairment of glucose homeostasis, and reduction in glycogen content in diabetic mice [51]. Furthermore, the authors found that a high-fat diet enhances expression of Meg3 through histone acetylation in hepatocytes. In humans, GWAS revealed an association between a SNP (rs941576) located in an intron of Meg3 and T1D [52]. In particular, the SNP (rs941576: A>G) with the strongest association with T1D lies within intron 6 of MEG3 in the well-established imprinted DLK1-MEG3 gene region. The authors demonstrated that only paternal transmission of SNP rs941576 alters inherited risk of T1D, and that the variant may influence one of the paternally expressed

imprinted genes in its neighborhood (e.g. DLK1, DIO3) [52].

Myocardial infarction-associated transcript

Myocardial infarction-associated transcript (MIAT) expression was reduced in diabetic rats and in human renal tubular epithelial cell lines (HK-2) exposed to high glucose. MIAT interacts with Nf-E2 related factor 2 and improves its stability, which in turn increases cell viability. This interaction is involved in diabetic nephropathy by regulating proximal convoluted tubule cell viability [53]. LncRNA MIAT was also identified as a susceptible locus for myocardial infarction [54]. MIAT expression is upregulated in the retinas of diabetic rats and patients as well as in endothelial cells cultured in high glucose medium [55]. MIAT knockdown decreases the number of apoptotic cells, alleviates retinal vessel impairment, and ameliorates retinal function. Bioinformatics prediction and experimental results demonstrate that miR-150-5p directly targets MIAT in endothelial cells. In other words, lncRNA MIAT functions as a miR-150-5p sponge in these cells. Consistent with this line of thought, MIAT has been shown to regulate the expression of VEGF - a target gene of miR-150-5p. The interplay between MIAT, miR-150-5p, and VEGF is a critical regulator of endothelial cell function and has implications in diabetes mellitus-induced microvascular dysfunction.

Metastasis associated lung adenocarcinoma transcript 1

LncRNAs are likely involved in the pathogenesis of diabetic retinopathy. In particular, a genetic variation (rs9362054) strongly associated with diabetic retinopathy in Japanese patients resides in an intron of RP1-90L14.1 - the gene of lincRNA metastasis associated lung adenocarcinoma transcript 1 (MALAT1) [56]. Studies have implicated MALAT1 in the pathogenesis of diabetes-related microvascular diseases - specifically, diabetic retinopathy. The expression of MALAT1 is significantly upregulated in the retinas of diabetic mice, high-glucose-treated retinal endothelial cells, and fibrovascular membranes of diabetic patients. MALAT1 knockdown decreases the number of apoptotic retinal cells, alleviates retinal inflammation, and ameliorates retinal function in diabetic rats. Moreover, MALAT1 knockdown decreases the viability of retinal endothelial cells in vitro, reduces endothelial cell migration and tube formation, and prevents the hyperproliferation of retinal endothelial cells through p38 MAPK signaling [57]. MALAT1 has also been shown to affect other cell and tissue types. For example, high-glucose-treated HUVECs and renal tissues from diabetic animals have increased MALAT1 expression along with increased levels of serum amyloid antigen 3 and inflammatory mediators such as tumor necrosis factor alpha and interleukin 6. MALAT1 knockdown prevents these changes in serum amyloid antigen 3 and inflammatory marker expression [58].

The steroid receptor RNA activator

The steroid receptor RNA activator (SRA) was cloned and characterized in 1999 [59]. LncRNA SRA exists in a ribonucleoprotein complex that contains the Steroid receptor coactivator 1, functions as a eukaryotic transcriptional coactivator for steroid hormone receptors, and interacts with either trithorax group or PRC2 to regulate gene expression [59, 60]. It has been found to serve as a coactivator for numerous transcription factors including PPARγ and to promote adipocyte differentiation [61]. In mature adipocytes, SRA increases insulin receptor transcription and expression and leads to increased insulin signaling, at least in part by inhibiting phosphorylation of JNK and p38 MAPK [62]. SRA knockout mice have increased resistance to high fat diet-induced obesity and improved insulin sensitivities, as evidenced by reduced fasting insulin levels and reduced blood glucose levels in response to glucose and insulin tolerance tests [63].

LncRNA E33

The impact of diabetes on genome-wide lncRNA expression has been studied in macrophages. Bioinformatics analyses of RNA-seq data identified 119 RefSeq lncRNAs and 52 novel lncRNAs that are differentially expressed in macrophages isolated from diabetic db/db and control db/+ mice. Specifically, lncRNA E33 expression was significantly upregulated by more than two-fold. In addition, expression of MIR143HG - the human homolog of mouse E33 - has been shown to be increased in monocytes from diabetic patients. Both mouse lncRNA

E33 and human MIR143HG are host genes for miRNAs miR-143 and miR-145. Overexpression of E33 in RAW 264.7 macrophages upregulates the expression of several proinflammatory and proatherogenic genes under basal conditions and enhances cellular responses to proinflammatory signals such as LPS. E33 overexpession also increases the uptake of Dil-Ac-LDL. Meanwhile, E33 knockdown reduces the induction of inflammatory gene expression in macrophages by high glucose and palmitic acid treatment. These findings suggest that lncRNA E33 could serve as a novel therapeutic target to attenuate deleterious inflammation in diabetes.

Genetic variations of lncRNAs and diabetes

It has been reported that most SNPs associated with T2D lie in noncoding regions. Global genomic and transcriptomic analysis of human pancreatic islets reveals that genetic variants can cause metabolic phenotypes by influencing the expression of lncRNAs [64]. Of the 493 identified RefSeq lincRNAs, 54 are influenced by SNPs or related to HbA1c levels. Notably, 17 lincRNAs are significantly associated with HbA1c levels, of which two - LOC283177 and SNHG5 - also regulate gene expression. This study provides a comprehensive catalog of novel genetic variants influencing gene expression, including that of lincRNAs, in human pancreatic islets and metabolic phenotypes to facilitate diabetes research.

Liu et al. scanned the genome for inflammation-associated lincRNAs in search of potential candidates to account for cardiometabolic diseases characterized by dysregulation of innate immunity [65]. They found substantial tissue-specific changes in the expression of blood and adipose tissue lincRNAs in human subjects before and after low-dose lipopolysaccharide treatment. In particular, the expression of two lincRNAs - DMRT2 and TP53I13 - was reduced in adipose tissues of obese subjects. The authors also investigated established SNPs associated with inflammatory and cardiometabolic traits for their overlap with lipopolysaccharide-regulated lincRNAs. They identified an overlap between lincRNA-CEP110-13 and SNP rs10115586 that is associated with N-glycosylation of immunoglobulin G as well as one between lincRNA-VWF and SNP rs1558324 that is associated with mean platelet volume. Both lincRNAs are induced by lipopolysaccharide in adipose tissues. Whether these lincRNAs regulate glucose homeostasis and diabetes remains unknown.

Future challenges and opportunities

Next generation sequencing has revolutionized genomic research and revealed the complexity of both the human and mouse transcriptomes. Many lncRNAs are expressed, and their expression patterns change in response to different stimuli. Studies have identified a growing number of lncRNAs involved in the regulation of human disease, but the functions of most lncRNAs remain relatively uncharacterized. Challenges going forward include the following: 1) LncRNA annotation: A wide breadth of information about lncRNA annotations is available through databases including NONCODE, GENCODE, lncRNAdb, and LNCipedia, but current annotations of lncRNAs are far from comprehensive [66]. It continues to be challenging to accurately annotate a lncRNA; 2) Structure-function relationship: It has been difficult to elucidate the molecular and biological roles of lncRNAs. In particular, it is challenging to predict lncRNA secondary and tertiary structures - factors that likely influence their function; 3) Conservation and function: Many lncRNAs are species-specific. For example, there is low conservation and sequence homology between lncRNAs found in mice and humans. This raises the question of whether scientists should attempt to identify lncRNAs that are highly conserved among different species or to only study human-specific lncRNAs. In addition, the question of whether it is reasonable to investigate the function of human-specific lncRNAs in mice arises. Nevertheless, it may be less important to assess for primary sequence conservation when considering lncRNAs as opposed to mRNAs. Scientists have proposed to assess lncRNA conservation on the basis of synteny of their gene loci and on the basis of their structure rather than on primary sequence homology [11, 67].

Using lncRNAs as potential therapeutic targets creates additional challenges and opportunities. Inactivating the function of a disease-causing lncRNA beyond an affected tissue or organ can be problematic. The development of

various technologies to facilitate tissue-specific delivery is important to address this problem. It is equally important to identify and target lncRNAs that display tissue- or cell-specific expression.

Biomarkers are often measured and evaluated to examine normal biological processes, pathogenic processes, and pharmacological responses to therapeutic interventions. Possible candidate biomarkers include non-coding RNAs such as lncRNAs. Novel biomarkers are demanded, for example: 1) to identify individuals who are at risk of gestational insulin resistance and diabetes; and 2) to identify new lncRNA expression patterns that may help predict which patients with obesity will develop T2D. The combination of RNA-Seq and genetic variation data (e.g. GWAS results) has enabled the identification of genetic loci correlated with gene expression variation - also known as expression quantitative trait loci; these may contribute to variations in phenotype and complex disease susceptibility across individuals [68].

Concluding remarks

The burden of diabetes is increasing worldwide. Diabetes can lead to serious medical problems such as blindness, kidney malfunction, nerve damage, and vascular complications. Accumulating animal and human studies highlight that lncRNAs regulate these diabetic pathologies. It is important to improve our understanding of how lncRNAs determine each individual's set-point to defend against diabetes. By regulating complex signaling nodes or networks, rather than individual gene targets, lncRNAs provide a therapeutic opportunity to more broadly modify glucose metabolism. A better understanding of lncRNAs and other non-coding RNAs in the regulation of glucose metabolism and diabetic complications by cross-disciplinary teams of basic and clinical investigators will enable the effective translation of new findings from bench to bedside in the management of diabetes and cardiometabolic diseases.

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Disclosure of conflict of interest

None.

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References

[1] Bonnefond A and Froguel P. Rare and common genetic events in type 2 diabetes: what should biologists know? Cell Metab 2015; 21: 357-368.

[2] Ezkurdia I, Juan D, Rodriguez JM, Frankish A, Diekhans M, Harrow J, Vazquez J, Valencia A and Tress ML. Multiple evidence strands suggest that there may be as few as 19,000 human protein-coding genes. Hum Mol Genet 2014; 23: 5866-5878.

[3] Hangauer MJ, Vaughn IW and McManus MT. Pervasive transcription of the human genome produces thousands of previously unidentified long intergenic noncoding RNAs. PLoS Genet 2013; 9: e1003569.

[4] Kumar V, Westra HJ, Karjalainen J, Zhernakova DV, Esko T, Hrdlickova B, Almeida R, Zhernakova A, Reinmaa E, Vosa U, Hofker MH, Fehrmann RS, Fu J, Withoff S, Metspalu A, Franke L and Wijmenga C. Human disease-associated genetic variation impacts large intergenic noncoding RNA expression. PLoS Genet 2013; 9: e1003201.

[5] Chen G, Qiu C, Zhang Q, Liu B and Cui Q. Genome-wide analysis of human SNPs at long intergenic noncoding RNAs. Hum Mutat 2013; 34: 338-344.

[6] Pennisi E. Shining a light on the genome's 'dark matter'. Science 2010; 330: 1614.

[7] Hindorff LA, Sethupathy P, Junkins HA, Ramos EM, Mehta JP, Collins FS and Manolio TA. Potential etiologic and functional implications of genome-wide association loci for human diseases and traits. Proc Natl Acad Sci U S A 2009; 106: 9362-9367.

[8] Iyer MK, Niknafs YS, Malik R, Singhal U, Sahu A, Hosono Y, Barrette TR, Prensner JR, Evans JR, Zhao S, Poliakov A, Cao X, Dhanasekaran SM, Wu YM, Robinson DR, Beer DG, Feng FY, Iyer HK and Chinnaiyan AM. The landscape of long noncoding RNAs in the human transcriptome. Nat Genet 2015; 47: 199-208.

[9] Rinn JL and Chang HY. Genome regulation by long noncoding RNAs. Annu Rev Biochem 2012; 81: 145-166.
[10] Ulitsky I and Bartel DP. lincRNAs: genomics, evolution, and mechanisms. Cell 2013; 154: 26-46.
[11] Cabili MN, Trapnell C, Goff L, Koziol M, Tazon-Vega B, Regev A and Rinn JL. Integrative annotation of human large intergenic noncoding RNAs reveals global properties and specific subclasses. Genes Dev 2011; 25: 1915-1927.
[12] Pauli A, Valen E, Lin MF, Garber M, Vastenhouw NL, Levin JZ, Fan L, Sandelin A, Rinn JL, Regev A and Schier AF. Systematic identification of long noncoding RNAs expressed during zebrafish embryogenesis. Genome Res 2012; 22: 577-591.
[13] Guttman M, Garber M, Levin JZ, Donaghey J, Robinson J, Adiconis X, Fan L, Koziol MJ, Gnirke A, Nusbaum C, Rinn JL, Lander ES and Regev A. Ab initio reconstruction of cell type-specific transcriptomes in mouse reveals the conserved multi-exonic structure of lincRNAs. Nat Biotechnol 2010; 28: 503-510.
[14] Ulitsky I, Shkumatava A, Jan CH, Sive H and Bartel DP. Conserved function of lincRNAs in vertebrate embryonic development despite rapid sequence evolution. Cell 2011; 147: 1537-1550.
[15] Kelley D and Rinn J. Transposable elements reveal a stem cell-specific class of long noncoding RNAs. Genome Biol 2012; 13: R107.
[16] Batista PJ and Chang HY. Long noncoding RNAs: cellular address codes in development and disease. Cell 2013; 152: 1298-1307.
[17] Johnsson P, Lipovich L, Grander D and Morris KV. Evolutionary conservation of long non-coding RNAs; sequence, structure, function. Biochim Biophys Acta 2014; 1840: 1063-1071.
[18] Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, Guernec G, Martin D, Merkel A, Knowles DG, Lagarde J, Veeravalli L, Ruan X, Ruan Y, Lassmann T, Carninci P, Brown JB, Lipovich L, Gonzalez JM, Thomas M, Davis CA, Shiekhattar R, Gingeras TR, Hubbard TJ, Notredame C, Harrow J and Guigo R. The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. Genome Res 2012; 22: 1775-1789.
[19] Orom UA, Derrien T, Beringer M, Gumireddy K, Gardini A, Bussotti G, Lai F, Zytnicki M, Notredame C, Huang Q, Guigo R and Shiekhattar R. Long noncoding RNAs with enhancer-like function in human cells. Cell 2010; 143: 46-58.
[20] Lai F, Orom UA, Cesaroni M, Beringer M, Taatjes DJ, Blobel GA and Shiekhattar R. Activating RNAs associate with Mediator to enhance chromatin architecture and transcription. Nature 2013; 494: 497-501.
[21] Kim TK, Hemberg M and Gray JM. Enhancer RNAs: a class of long noncoding RNAs synthesized at enhancers. Cold Spring Harb Perspect Biol 2015; 7: a018622.
[22] Guttman M, Amit I, Garber M, French C, Lin MF, Feldser D, Huarte M, Zuk O, Carey BW, Cassady JP, Cabili MN, Jaenisch R, Mikkelsen TS, Jacks T, Hacohen N, Bernstein BE, Kellis M, Regev A, Rinn JL and Lander ES. Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. Nature 2009; 458: 223-227.
[23] Wapinski O and Chang HY. Long noncoding RNAs and human disease. Trends Cell Biol 2011; 21: 354-361.
[24] Guil S, Soler M, Portela A, Carrere J, Fonalleras E, Gomez A, Villanueva A and Esteller M. Intronic RNAs mediate EZH2 regulation of epigenetic targets. Nat Struct Mol Biol 2012; 19: 664-670.
[25] Faghihi MA and Wahlestedt C. Regulatory roles of natural antisense transcripts. Nat Rev Mol Cell Biol 2009; 10: 637-643.
[26] Katayama S, Tomaru Y, Kasukawa T, Waki K, Nakanishi M, Nakamura M, Nishida H, Yap CC, Suzuki M, Kawai J, Suzuki H, Carninci P, Hayashizaki Y, Wells C, Frith M, Ravasi T, Pang KC, Hallinan J, Mattick J, Hume DA, Lipovich L, Batalov S, Engstrom PG, Mizuno Y, Faghihi MA, Sandelin A, Chalk AM, Mottagui-Tabar S, Liang Z, Lenhard B and Wahlestedt C. Antisense transcription in the mammalian transcriptome. Science 2005; 309: 1564-1566.
[27] He Y, Vogelstein B, Velculescu VE, Papadopoulos N and Kinzler KW. The antisense transcriptomes of human cells. Science 2008; 322: 1855-1857.
[28] Rinn JL, Kertesz M, Wang JK, Squazzo SL, Xu X, Brugmann SA, Goodnough LH, Helms JA, Farnham PJ, Segal E and Chang HY. Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. Cell 2007; 129: 1311-1323.
[29] Wang X, Arai S, Song X, Reichart D, Du K, Pascual G, Tempst P, Rosenfeld MG, Glass CK and Kurokawa R. Induced ncRNAs allosterically modify RNA-binding proteins in cis to inhibit transcription. Nature 2008; 454: 126-130.
[30] Zhao XY, Li S, Wang GX, Yu Q and Lin JD. A long noncoding RNA transcriptional regulatory circuit drives thermogenic adipocyte differentiation. Mol Cell 2014; 55: 372-382.
[31] Gong C and Maquat LE. lncRNAs transactivate STAU1-mediated mRNA decay by duplexing with 3' UTRs via Alu elements. Nature 2011; 470: 284-288.

[32] Pachnis V, Belayew A and Tilghman SM. Locus unlinked to alpha-fetoprotein under the control of the murine raf and Rif genes. Proc Natl Acad Sci U S A 1984; 81: 5523-5527.
[33] Brannan CI, Dees EC, Ingram RS and Tilghman SM. The product of the H19 gene may function as an RNA. Mol Cell Biol 1990; 10: 28-36.
[34] Bartolomei MS, Zemel S and Tilghman SM. Parental imprinting of the mouse H19 gene. Nature 1991; 351: 153-155.
[35] Gabory A, Jammes H and Dandolo L. The H19 locus: role of an imprinted non-coding RNA in growth and development. Bioessays 2010; 32: 473-480.
[36] Monnier P, Martinet C, Pontis J, Stancheva I, Ait-Si-Ali S and Dandolo L. H19 lncRNA controls gene expression of the Imprinted Gene Network by recruiting MBD1. Proc Natl Acad Sci U S A 2013; 110: 20693-20698.
[37] Keniry A, Oxley D, Monnier P, Kyba M, Dandolo L, Smits G and Reik W. The H19 lincRNA is a developmental reservoir of miR-675 that suppresses growth and Igf1r. Nat Cell Biol 2012; 14: 659-665.
[38] Luo M, Li Z, Wang W, Zeng Y, Liu Z and Qiu J. Long non-coding RNA H19 increases bladder cancer metastasis by associating with EZH2 and inhibiting E-cadherin expression. Cancer Lett 2013; 333: 213-221.
[39] Gao Y, Wu F, Zhou J, Yan L, Jurczak MJ, Lee HY, Yang L, Mueller M, Zhou XB, Dandolo L, Szendroedi J, Roden M, Flannery C, Taylor H, Carmichael GG, Shulman GI and Huang Y. The H19/let-7 double-negative feedback loop contributes to glucose metabolism in muscle cells. Nucleic Acids Res 2014; 42: 13799-13811.
[40] Zhou J, Yang L, Zhong T, Mueller M, Men Y, Zhang N, Xie J, Giang K, Chung H, Sun X, Lu L, Carmichael GG, Taylor HS and Huang Y. H19 lncRNA alters DNA methylation genome wide by regulating S-adenosylhomocysteine hydrolase. Nat Commun 2015; 6: 10221.
[41] Leighton PA, Ingram RS, Eggenschwiler J, Efstratiadis A and Tilghman SM. Disruption of imprinting caused by deletion of the H19 gene region in mice. Nature 1995; 375: 34-39.
[42] Petry CJ, Evans ML, Wingate DL, Ong KK, Reik W, Constancia M and Dunger DB. Raised late pregnancy glucose concentrations in mice carrying pups with targeted disruption of H19delta13. Diabetes 2010; 59: 282-286.
[43] Petry CJ, Seear RV, Wingate DL, Acerini CL, Ong KK, Hughes IA and Dunger DB. Maternally transmitted foetal H19 variants and associations with birth weight. Hum Genet 2011; 130: 663-670.
[44] Palatianou ME, Simos YV, Andronikou SK and Kiortsis DN. Long-term metabolic effects of high birth weight: a critical review of the literature. Horm Metab Res 2014; 46: 911-920.
[45] Kallen AN, Zhou XB, Xu J, Qiao C, Ma J, Yan L, Lu L, Liu C, Yi JS, Zhang H, Min W, Bennett AM, Gregory RI, Ding Y and Huang Y. The imprinted H19 lncRNA antagonizes let-7 microRNAs. Mol Cell 2013; 52: 101-112.
[46] Hanson RL, Craig DW, Millis MP, Yeatts KA, Kobes S, Pearson JV, Lee AM, Knowler WC, Nelson RG and Wolford JK. Identification of PVT1 as a candidate gene for end-stage renal disease in type 2 diabetes using a pooling-based genome-wide single nucleotide polymorphism association study. Diabetes 2007; 56: 975-983.
[47] Millis MP, Bowen D, Kingsley C, Watanabe RM and Wolford JK. Variants in the plasmacytoma variant translocation gene (PVT1) are associated with end-stage renal disease attributed to type 1 diabetes. Diabetes 2007; 56: 3027-3032.
[48] Alvarez ML and DiStefano JK. Functional characterization of the plasmacytoma variant translocation 1 gene (PVT1) in diabetic nephropathy. PLoS One 2011; 6: e18671.
[49] Alvarez ML, Khosroheidari M, Eddy E and Kiefer J. Role of microRNA 1207-5P and its host gene, the long non-coding RNA Pvt1, as mediators of extracellular matrix accumulation in the kidney: implications for diabetic nephropathy. PLoS One 2013; 8: e77468.
[50] You L, Wang N, Yin D, Wang L, Jin F, Zhu Y, Yuan Q and De W. Downregulation of Long Noncoding RNA Meg3 Affects Insulin Synthesis and Secretion in Mouse Pancreatic Beta Cells. J Cell Physiol 2015; [Epub ahead of print].
[51] Zhu X, Wu YB, Zhou J and Kang DM. Upregulation of lncRNA MEG3 promotes hepatic insulin resistance via increasing FoxO1 expression. Biochem Biophys Res Commun 2016; 469: 319-325.
[52] Wallace C, Smyth DJ, Maisuria-Armer M, Walker NM, Todd JA and Clayton DG. The imprinted DLK1-MEG3 gene region on chromosome 14q32.2 alters susceptibility to type 1 diabetes. Nat Genet 2010; 42: 68-71.
[53] Zhou L, Xu DY, Sha WG, Shen L, Lu GY and Yin X. Long non-coding MIAT mediates high glucose-induced renal tubular epithelial injury. Biochem Biophys Res Commun 2015; 468: 726-732.
[54] Ishii N, Ozaki K, Sato H, Mizuno H, Saito S, Takahashi A, Miyamoto Y, Ikegawa S, Kamatani N, Hori M, Nakamura Y and Tanaka T. Identification of a novel non-coding RNA, MIAT, that confers risk of myocardial infarction. J Hum Genet 2006; 51: 1087-1099.
[55] Yan B, Yao J, Liu JY, Li XM, Wang XQ, Li YJ, Tao ZF, Song YC, Chen Q and Jiang Q. lncRNA-MIAT regulates microvascular dysfunction by functioning as a competing endogenous RNA. Circ Res 2015; 116: 1143-1156.

[56] Awata T, Yamashita H, Kurihara S, Morita-Ohkubo T, Miyashita Y, Katayama S, Mori K, Yoneya S, Kohda M, Okazaki Y, Maruyama T, Shimada A, Yasuda K, Nishida N, Tokunaga K and Koike A. A genome-wide association study for diabetic retinopathy in a Japanese population: potential association with a long intergenic non-coding RNA. PLoS One 2014; 9: e111715.

[57] Liu JY, Yao J, Li XM, Song YC, Wang XQ, Li YJ, Yan B and Jiang Q. Pathogenic role of lncRNA-MALAT1 in endothelial cell dysfunction in diabetes mellitus. Cell Death Dis 2014; 5: e1506.

[58] Puthanveetil P, Chen S, Feng B, Gautam A and Chakrabarti S. Long non-coding RNA MALAT1 regulates hyperglycaemia induced inflammatory process in the endothelial cells. J Cell Mol Med 2015; 19: 1418-1425.

[59] Lanz RB, McKenna NJ, Onate SA, Albrecht U, Wong J, Tsai SY, Tsai MJ and O'Malley BW. A steroid receptor coactivator, SRA, functions as an RNA and is present in an SRC-1 complex. Cell 1999; 97: 17-27.

[60] Lanz RB, Razani B, Goldberg AD and O'Malley BW. Distinct RNA motifs are important for coactivation of steroid hormone receptors by steroid receptor RNA activator (SRA). Proc Natl Acad Sci U S A 2002; 99: 16081-16086.

[61] Xu B, Gerin I, Miao H, Vu-Phan D, Johnson CN, Xu R, Chen XW, Cawthorn WP, MacDougald OA and Koenig RJ. Multiple roles for the non-coding RNA SRA in regulation of adipogenesis and insulin sensitivity. PLoS One 2010; 5: e14199.

[62] Liu S, Xu R, Gerin I, Cawthorn WP, Macdougald OA, Chen XW, Saltiel AR, Koenig RJ and Xu B. SRA regulates adipogenesis by modulating p38/JNK phosphorylation and stimulating insulin receptor gene expression and downstream signaling. PLoS One 2014; 9: e95416.

[63] Liu S, Sheng L, Miao H, Saunders TL, MacDougald OA, Koenig RJ and Xu B. SRA gene knockout protects against diet-induced obesity and improves glucose tolerance. J Biol Chem 2014; 289: 13000-13009.

[64] Fadista J, Vikman P, Laakso EO, Mollet IG, Esguerra JL, Taneera J, Storm P, Osmark P, Ladenvall C, Prasad RB, Hansson KB, Finotello F, Uvebrant K, Ofori JK, Di Camillo B, Krus U, Cilio CM, Hansson O, Eliasson L, Rosengren AH, Renstrom E, Wollheim CB and Groop L. Global genomic and transcriptomic analysis of human pancreatic islets reveals novel genes influencing glucose metabolism. Proc Natl Acad Sci U S A 2014; 111: 13924-13929.

[65] Liu Y, Ferguson JF, Xue C, Ballantyne RL, Silverman IM, Gosai SJ, Serfecz J, Morley MP, Gregory BD, Li M and Reilly MP. Tissue-specific RNA-Seq in human evoked inflammation identifies blood and adipose LincRNA signatures of cardiometabolic diseases. Arterioscler Thromb Vasc Biol 2014; 34: 902-912.

[66] Mattick JS and Rinn JL. Discovery and annotation of long noncoding RNAs. Nat Struct Mol Biol 2015; 22: 5-7.

[67] Diederichs S. The four dimensions of noncoding RNA conservation. Trends Genet 2014; 30: 121-123.

[68] Majewski J and Pastinen T. The study of eQTL variations by RNA-seq: from SNPs to phenotypes. Trends Genet 2011; 27: 72-79.