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Analysis of Serum Exosomal LncRNA Expression Profile in Type 1 Diabetes Mellitus

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Abstract

Objective: The study was to compare the expression profile of LncRNA in exosomes between type 1 diabetes mellitus (T1DM) patients and healthy controls, and analyze the potential role of LncRNA in the occurrence and development of T1DM. Methods: A total of 60 patients (30 T1DM and 30 healthy controls) were included in this study. Samples from three patients from each of the two groups were selected for extraction of serum exosomes. Exosomes were identified by particle size analysis and flow cytometry detection of surface markers. The high-throughput sequencing techniques of GO and KEGG pathway were used to detect and evaluate differential expressions of LncRNAs in serum from treated exosomes of the two groups. Result: Compared to the normal group, 261 lncRNAs were up-regulated and 478 three down-regulated in the type 1 diabetic group. 76 differentially expressed LncRNAs as candidate LncRNAs were then screened and predict their target genes. We found a number of genes that had been reported to be present in TIDM, including STAT3, JAK3, SMAD, POU5F1, FZD4, FGFR1, CDK4, SYK, IFNAR1, IL6R, AKT2, MDM, LAMP2, SOCS and Crkl. Functional analysis of all target genes was performed. GO functional analysis results show that LncRNAs may be involved in the metabolic process through protein binding function in the nucleus. KEGG analysis results show that the highest concentrations of exosomal LncRNA target genes were present in metabolic pathways, followed by the PI3K-AKT, Jak-STAT, mTOR, lysosomal and FoxO signaling pathways. Conclusion: The expression profile of serum exosomal LncRNA in patients with type 1 diabetes was constructed, providing new and important information regarding the biological pathways involved in the LncRNA candidate, but also serve as the foundation for the development of new therapeutic targets.

Keywords

Serum Exosome; Lncrna; Type 1 Diabetes Mellitus; Therapeutic Targets.

1. Introduction

T1DM is an autoimmune disease resulting from immune-mediated destruction of pancreatic cells, thus restricting or completely abolishing insulin production and secretion. In patients with type 1 diabetes, the onset of complications is early, which seriously threatens the health of adolescents with type 1 diabetes. Therefore, an early diagnosis of T1DM, along with accurate monitoring of disease

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progression and prevention of related complications would significantly help reduce the incidence and mortality of this disease [1,2].

Exosomes are 30 150-nm membranous vesicles that deliver various types of signaling molecules, including lipids, proteins, and nucleic acids [3,4]. Exosomes are released by numerous cell types, including lymphocytes, pancreatic islets and kidney cells, and are present in the blood and other body fluids [5,6]. Exosomes can deliver signaling molecules to other cells through a variety of mechanisms. For example, exosome surface molecules can bind to target cells and induce signal transduction through receptor-ligand interactions or endocytosis [7], alternatively, exosomes can also fuse with membranes of target cells to deliver their contents to these targets [8]. Findings from recent in-depth studies have indicated that an important relationship exists between exosomes and T1DM. In specific, it has been reported that lymphocyte-derived exosomal microRNAs promote pancreatic β cell death and may contribute to T1DM development [9].

LncRNAs are a class of non-protein-coding RNA molecules comprised of > 200 bp that were initially considered as a by-product of RNA polymerase II transcription with no biological function [10]. However, recent findings [11] have indicated that lncRNA can interact with protein,DNA and RNA, and participate in the regulation of a variety of biological processes, such as chromatin modified transcriptional activation and post-transcriptional regulation inhibition, and can also function as an inducible molecular interference gene expression factor of miRNA. LncRNAs, as one of the biological markers of epigenetics, have been shown to be associated with various diseases. In specific, a wealth of evidence has highlighted the role of LncRNAs in many autoimmune and inflammatory diseases, including Diabetes [12], SLE [13] and Tumors [14].

Recent evidence has indicated that exosomes and their lncRNAs may not only serve as promising new biomarkers, but also as agents for the treatment of diabetes and diabetic complications. There are three characteristics of serum exosomal LncRNAs that enable them to function as ideal biomarkers for non-invasive diagnosis and prevention of this disease [15]. Given this background information on the significance of exosomal LncRNAs as related to diabetes, in this report we analyzed the expression profile of serum exosomal LncRNA in patients with T1DM and performed bioinformatics analysis to study the potential biological pathways of LncRNA regulation as related to T1DM.

2. Materials and methods

2.1 Clinical specimens

Thirty patients with type 1 diabetes mellitus (T1DM) as diagnosed at the First Affiliated Hospital of Henan University of Science and Technology over the period from 2017 to 2019 and 30 healthy controls were selected for this study. The inclusion criteria for T1DM were based upon the 2019ADA diabetes guidelines. The control group consisted of healthy patients who underwent physical examinations at our hospital. Patients excluded from the T1DM group included those patients with: 1) Type 2 diabetes, 2) Tumor-related diseases, 3) Acute complications (such as Diabetic Ketoacidosis, Nonketotic Hyperglycemia - Hyperosmotic Coma), 4) Stress due to acute cerebrovascular disease, infection, fever, surgeries or a life-threatening metabolic disorder, 5) Severe hypertension and cardiovascular disease as confirmed by their physical or auxiliary examination history (6) Severe diseases involving lungs, liver, kidneys and other systems and 7) Pregnant and lactating women.

Fasting venous blood samples were collected to assess the clinical status of these patients and perform the statistical analysis on this clinical data. Subsequently, 3 samples from each of the two groups were used for the experiments of exosomal lncRNA.

2.2 Main reagents and instruments

The following reagents/instruments were used as part of this experiment: RiboTM exosome Isolation reagent kit (Ribo company); ZETASIZER Nano series-Nano-ZS (Malvern company); Accuri C6 flow

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cytomenter (BD company); CD63-Antibody-FITC (BD company) and CD81-Antibody-PE (BD company)

3. Isolation and identification of serum exosomes

Exosomes were extracted with use of the RiboTM Exosome Isolation Reagent Kit according to the instructions provided. According to the Stokes Einstein principle, the Zetasizer instrument (Malvern company) was used to detect particle size, while surface markers were detected with use of CD63 and CD81 antibodies combined with flow cytometry (Accuri C6 flow cytometer, BD company).

3.1 RNA extraction and Transcriptome high throughput sequencing

Total exosomal RNA was extracted according to directions of the Magen HiPure Exosome RNA Kit. Exosomal RNA was then qualified by purity and concentration detection. Transcriptome high throughput sequencing was performed by the Guangzhou Ruibo Biology Co. LTD. The LncRNA transcripts identified were then analyzed. P-value < 0.05 and |log2 (fold change)| > 1 established as the threshold for indicating significantly differential expression by default. In order to facilitate further study, among all obtained differentially expressed lncrnas, the top 76 were selected as candidate genes for subsequent study as based upon two indicators, the RPKM value and the differentially expressed multiple. Cluster R language and other software programs were used to analyze exosomal lncRNA and mRNA from these sequences and the generation of cluster analysis heat and volcano maps.

3.2 Predicting target genes of differentially expressed LncRNA

LncRNA regulates target genes through Cis and Trans mechanisms. Cis regulation refers to LncRNA's capacity to exert its biological function by regulating adjacent genes on the seat of genes. Potential cis-regulated target genes of LncRNA were obtained with use of Ruibo organisms by integrating the difference in mRNA data between different LncRNAs and their neighbors (10kb). Trans regulation usually refers to the manner in which LncRNA regulates mRNAs located on other chromosomes or the distal end of the same chromosome. Some of these LncRNA target genes can then be predicted by using the complementary pairing relationship of RNA nucleic acid bases. For predictions as based upon trans regulation, the sequences of LncRNA and mRNA with different expressions are first extracted using blast software (e<1E-5) for initial screening followed by use of RNAplex software for additional screening to identify the possible target genes of LncRNAs.

3.3 Gene ontology (GO) and KEGG pathway analysis

Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were used to estimate the quantities of the differentially expressed genes and identify signaling pathways. Differential genes were grouped into hierarchical categories as based on molecular function, biological processes and cellular components as determined with use of the Gene Ontology database (http://www.geneontology.org/). In addition, pathway analysis was performed to assess potential pathways of the differentially expressed genes according to KEGG (http://www. genome. jp/kegg/). By using hypergeometric distribution to test the hypothesis, the P values of the enrichment results were obtained. P values were corrected using DESeq for multiple testing then get the Q value. The lower the Q value, the more significant the difference in gene expression.

3.4 Statistical analysis

Data conforming to a normal distribution were analyzed with use of parametric statistics and results shown as the means $\pm$SEM. Data not conforming to a normal distribution were analyzed with use of the non-parametric rank sum test and results shown as quartiles. Data that were tallied were analyzed with use of the chi-square test. Statistical analyses were performed using the SPSS 22.0 software program and differences with a p-value < 0.05 were considered statistically significant.

3.5 Results

Patient characteristics

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Statistical analysis on the clinical data of the 60 patients (30 T1DM and 30 healthy controls) included in this study are summarized in Table 1. As compared with that of the control group, T1DM patients were significantly younger, had a lower body mass index and higher fasting blood glucose levels ($p<0.05$).

Table 1. The clinical characteristics of T1DM patients and controls

Clinical index	Clinical samples		p-valure
	T1DM (n=30)	normol (n=30)	
Sex (male)	53.3%	63.3%	0.601
Age (years)	22.0±0.5	39.0±1	0.000
BMI (kg/m^2)	19.2±0.8	22.2±0.5	0.002
Course (years)	1.3	-	-
SBP (mmHg)	114(97.5,120.5)	112(108.5,117.7)	0.839
DBP (mmHg)	74(64.5,80.5)	71(68.8,76.0)	0.866
GLU (mmol/l)	8.1(5.7,12.7)	4.8(4.6,4.9)	0.000
HbA1c (%)	11.0	-	-
TG (mmol/l)	1.0(0.6,1.4)	1.1(0.7,1.9)	0.288
TC (mmol/l)	4.4±0.1	4.5±0.1	0.574

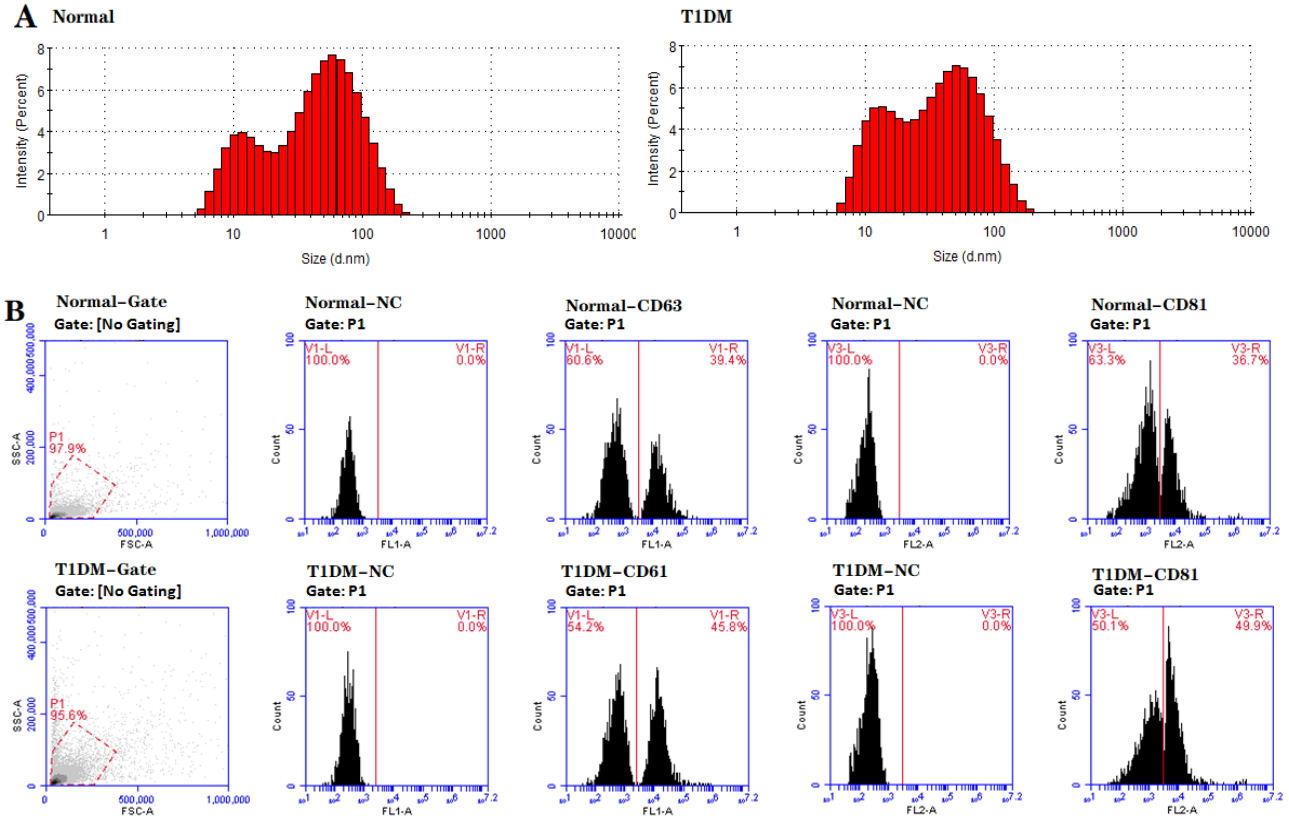

Figure 1. Identification of exosomes. A: The abscissa represents the range of particle size. The ordinate represents the percentage in the particle size range distribution coefficient (PDI), the distribution coefficient obtained by the cumulative distance method is a dimensionless value, which represents the distribution of particle length. B: Surface markers were detected with use of CD63 and CD81 antibodies combined with flow cytometry.

4. Identification of exosomes

We found that the average size of this vesicle and the major peak of particle sizes were within the range of sizes for exosomes. The detected particle distribution coefficient (PDI) was between 0.08

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and 0.7. These findings indicate that the dispersion degree of the system was moderate and the test results suggest a high degree of confidence. In these samples we found that particle sizes in the range of 20-200 nm accounted for 70.8% of the particles present in the TIDM group and 79.2% in the healthy control group (Fig. 1A), which is consistent with particle size distributions of exosomes. Surface markers were detected with use of CD63 and CD81 antibodies (BD company) combined with flow cytometry (Accuri C6 flow cytomenter, BD company). Both proteins were present in the two groups with positive signals and rates of CD63 and CD81 in the T1DM group being 45.8% and 49.9% (Fig. 1 B), while those within the healthy control group being 39.4% and 36.7, respectively.

4.1 Transcriptome sequencing

According to the fold change (|log2 (FoldChange)|>1) and significance level (p-value<0.05), we found significant differences in the expression of 739 lncrnas (261 significantly up-regulated and 478 significantly down-regulated) and 2340 differentially expressed mRNAs (818 significantly up-regulated and 1522 significantly down-regulated). With use of R language, we illustrated these screened lncRNAs and mRNAs into a volcanic map, with down-regulated genes presented in green and up-regulated genes in red (Fig. 2). Among these differentially expressed lncrnas, 162 were LincRNAs (46 significantly up-regulated and 113 significantly down-regulated), 138 were antisense LncRNAs (59 significantly up-regulated and 79 significantly down-regulated) and 203 were reported as long-chain non-coding RNAs (54 significantly up-regulated and 149 significantly down-regulated). According to the fold change (|log2(FoldChange)|>4), RPKM>1 and significance level (p-value <0.05), 76 differentially expressed LncRNAs were screened as candidate genes (30 down-regulated and 46 up-regulated), among which 30 of these LncRNAs had been verified in previous reports. A superheat diagram was used to represent the overall distribution of candidate LncRNAs. Clustering of the same group of samples indicated that gene expression trends of these samples were consistent from green to red, with the intensity of darkness indicating the degree of significance (Fig. 3).

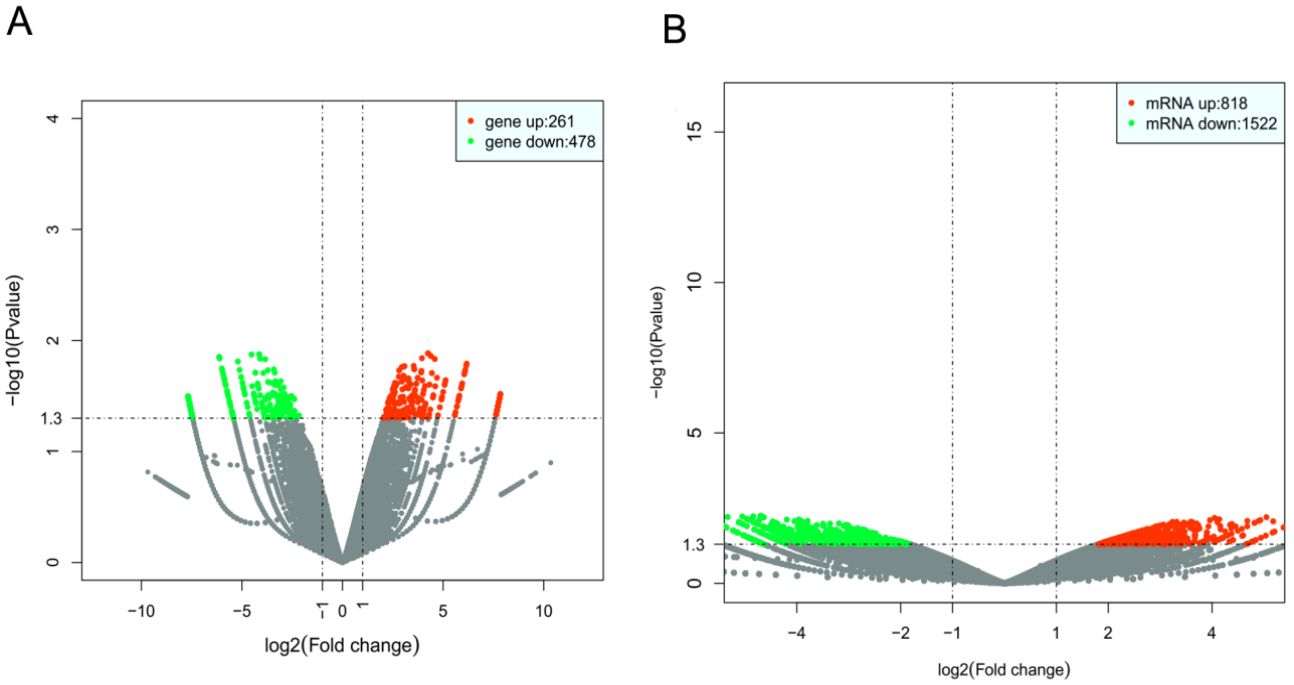

Figure 2. Analysis of mRNA and lncRNA expression differences between normal control group and T1DM group (R language). A: volcano map of differentially expressed LncRNA; B: volcano map of differentially expressed mRNA.

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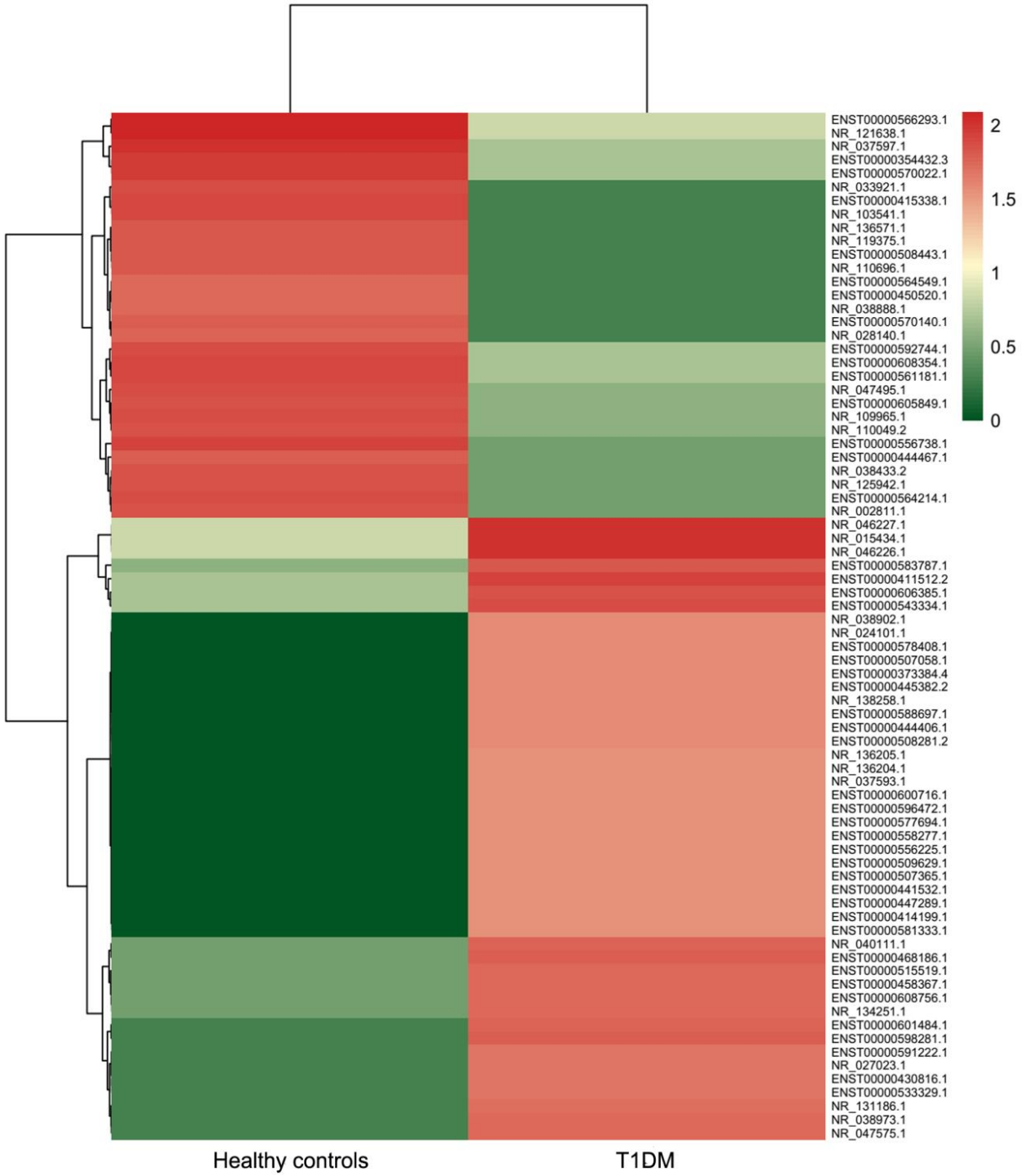

Figure 3. Hierarchical clustering of 76 exosomal lncRNAs. The Heat map shows the relationships among the expression levels of samples. Red indicates high relative expression, and green indicates low relative expression.

4.2 Prediction of LncRNA target genes

We identified 76 differentially expressed LncRNAs and the prediction results showed that among these 76 LncRNAs, 2917 target genes may be affected. We also found a number of genes which had been previously reported as being associated with TIDM, including STAT3, JAK3, SMAD, POU5F1, FZD4, FGFR1, CDK4, SYK, IFNAR1, IL6R, AKT2, MDM, LAMP2, SOCS and Crkl (Table 2).

Functional enrichment analysis of LncRNAs target genes

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Table 2. The network of genes and lncRNAs

Genes	LncRNAs	Genes	LncRNAs
STAT3	ENST00000445382.2	SYK	NR_047575.1
	NR_047575.1	IFNAR1	NR_038888.1
JAK3	ENST00000556225.1		NR_125942.1
	NR_038433.2	IL6R	NR_103541.1
	ENST00000556738.1	AKT2	ENST00000458367.1
POU5F1	NR_110696.1		
	NR_119375.1	LAMP2	NR_110049.2
FZD4	NR_046226.1	SOCS	NR_038433.2
	NR_038433.2		NR_038888.1
	NR_046227.1	Crkl	ENST00000588697.1
FGFR1	ENST00000570140.1	CDK4	ENST00000508443.1
	ENST00000591222.1	SMAD	ENST00000556738.1
MDM	ENST00000570140.1		NR_038433.2
	NR_046226.1		
	NR_046227.1		
	NR_110049.2		
	NR_110696.1		
	NR_119375.1		

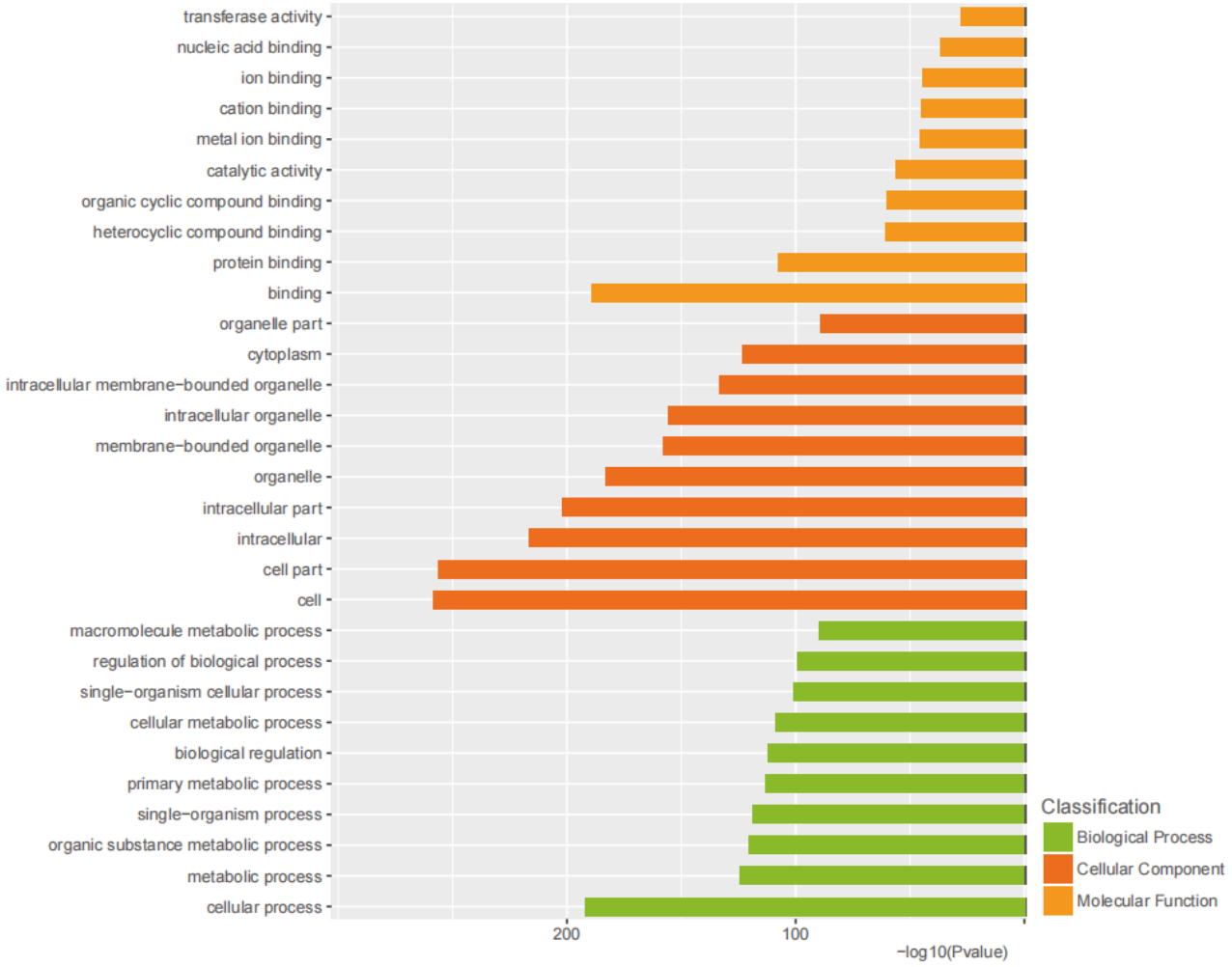

Figure 4. GO database enrichment degree ranked top 30.Functional enrichment analysis of lncRNA target genes differentially expressed between normal control group and T1DM group.

To investigate the functional role of the differential LncRNAs in T1DM, target genes, which were significantly different, were selected to conduct GO and KEGG pathway analyses. GO analysis was performed as based upon three functional domains: biological processes, cellular components and

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molecular function. In terms of molecular function, 1036 target genes were enriched by binding function (q-value=5.41E-187), of which protein binding function was the highest (q-value=8.68E-106), followed by heterocyclic compounds binding organic compounds and binding functions of nucleic acids (q-value<0.05). In terms of cellular components, 1068 target genes were enriched in intracellular components (q-value=3.49E-256), with the highest concentration of target genes located in organelles which have cell membranes (q-value =1.10E-156), and in particular, within the nucleus (q-value =2.23E-66). In terms of biological function, the highest concentration of target genes was found in cell processes (q-value = 1.04E-188), primarily metabolic and cell regulation processes, followed by metabolic (q-value =1.35E-121) and biological (q-value =1.41E-109) regulation processes (Fig.4). Results from KEGG pathway analyses showed that exosomal LncRNA target genes were involved in many pathways associated with type 1 diabetes, including metabolic pathways (q-value =3.84E-8), the signaling pathways of PI3K-Akt (q-value=0.002), Jak-STAT (q-value=0.002), mTOR (q-value=0.002), lysosomal (q-value=0.000), FoxO (q-value=0.01) as well as signaling pathways regulating pluripotency of stem cells (q-value=0.000),. These findings revealed that exosomal LncRNAs regulated the formation and development of T1DM by targeting specific genes and signaling pathways (Fig.5). [16-23]

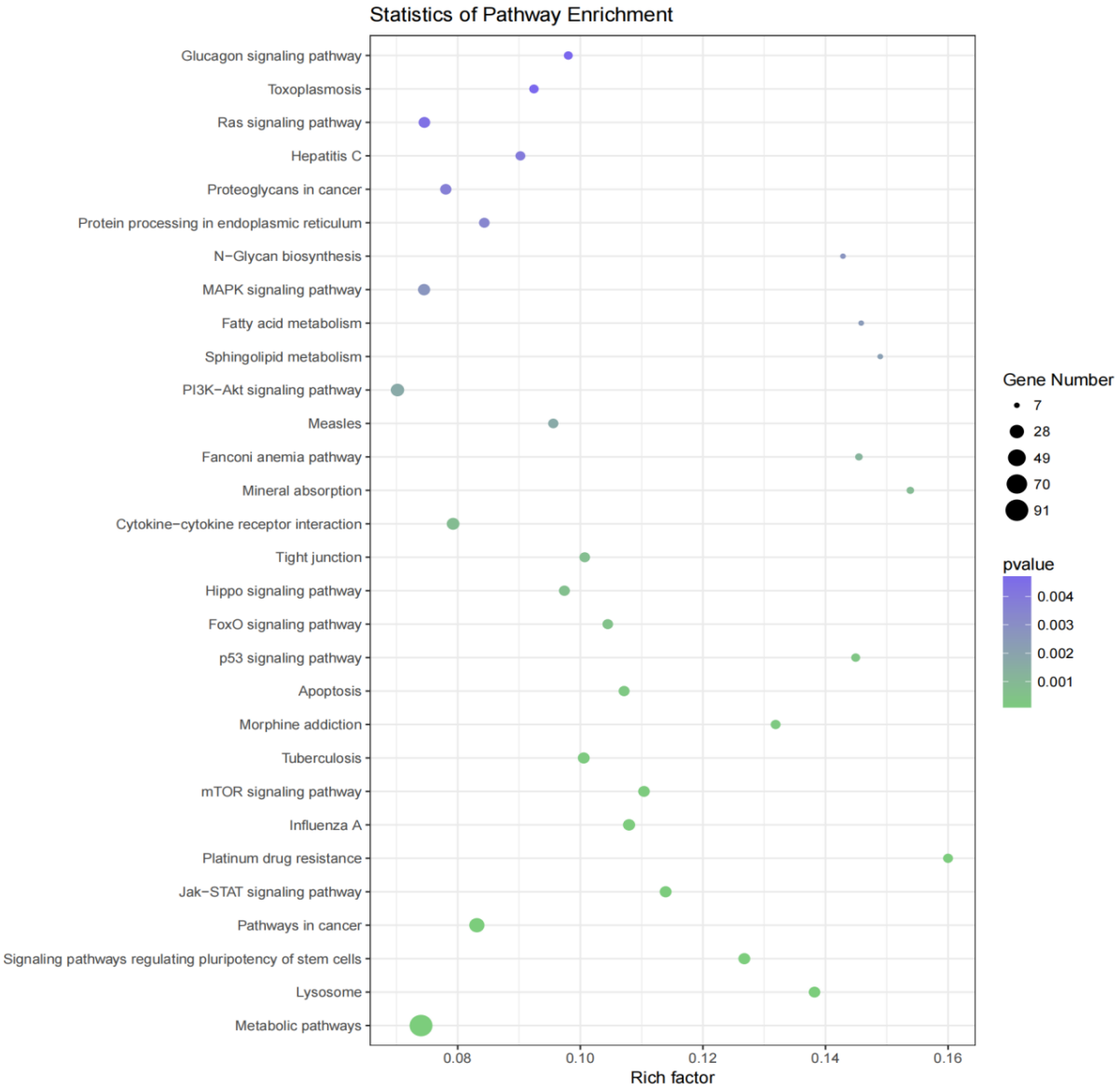

Figure 5. KEGG database enrichment degree ranked top 30. Bubble diagram of KEGG pathway analysis of target genes differentially expressed lncRNAs between T1DM group and Normal group

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5. Discussion

Exosomes and their LncRNAs have been shown to be promising prospects that can serve as biomarkers and have therefore attracted considerable attention in recent years. In this study, we selected LncRNAs that may be closely related to T1DM as revealed with use of high-throughput sequencing technology and conducted functional enrichment analysis of these exosomal LncRNAs. With this technique, it was possible to arrive at a preliminarily determination of possible functions and an analysis of potential functions and pathways. Such information provides a framework for future studies on the functions of exosomal LncRNAs in T1DM as well as a foundation for further studies on exosomal LncRNAs in serum samples from T1DM patients.

In this study, exosomes were isolated and identified from the serum of T1DM patients. Exosomes are important carriers of information which allow communication between cells. To achieve this function, exosomes can act directly on, or release, internal signal molecules of targeted cell membrane receptors through membrane surface signal molecules. They can then release their contents into the target cell through membrane fusion to change the gene expression network of receptor cells and affect the biological function of these target cells. A role for exosomes in type 1 diabetes has been suggested from results of previous reports. For example, Guay Claudiane et al. found that lymphocytes in T1DM patients can secrete miRNA-carrying exosomes that function as intercellular signals between immune and islet cells which induce apoptosis of islet cells, thus leading to the occurrence of T1DM. It has also been reported that the exosomes secreted by pancreatic islet cells and their non-coding RNA constituted a new intercellular communication mechanism that can regulate the activity of pancreatic islet cells. These studies suggest that exosomes may be potential biomarkers for early diagnosis of disease progression and autoimmunity in T1DM.

Recently, LncRNAs have been recognized as agents which can serve as ideal biomarkers due to their high tissue specificity. However, at present, the functions of most LncRNAs remain unclear. To investigate the functional role of differential LncRNAs in T1DM, here, we chose significantly different target genes to conduct GO and KEGG pathway analyses. The GO analysis revealed that the differential expression of exosomal LncRNA was mainly involved in various biological regulatory processes. This function was accomplished by binding with proteins and other compounds in cytoplasmic organelles, particularly the nucleus, which can then affect various cell and metabolic processes. In this study, we found that the differentially expressed exosomal LncRNAs in peripheral blood of T1DM patients were mainly associated with several important signaling pathways, such as the metabolic, PI3K-Akt, JAK-STAT, mTOR, lysosomal and FOXO pathways. LncRNAs have been found that are involved in related metabolic pathways, among which the most prominent is that of the metabolic pathway including glucose and lipid metabolism. In addition, other pathways with high LncRNA target gene enrichment, which can play an important role, have also been identified in this experiment. Rachdi Latif et al. have demonstrated that activation of PI3K/Akt /mTOR signaling pathways can participate in improving insulin secretion and lowering blood glucose levels by increasing the number of β cells. Moreover, Yuting Ruan et al. found that LncRNA-p3134 was detected in the serum of diabetic patients, and the content of LncRNA-p3134 in exosomes was 4 times that in serum, and its overexpression positively regulates PI3K/AKT2/mTOR signaling pathways, which can then protect the ability for insulin secretion. Results from Mark A. Russell et al. indicated that IL-3 secretion by immune cells can protect islet β cells and improve the survival ability of islet β cells by activating JAK kinase and inducing STAT phosphorylation to play an anti-inflammatory role. Support for these findings have come from a number of studies which have shown that LncRNA is expected to become a new therapeutic target by regulating the Jak-STAT signal, as well as from the findings of our current study demonstrating that exosomal LncRNAs were involved in this pathway as found in the serum of T1DM patients. In addition, as based upon the results of Kenneth maiese et al. that the FOXO protein, as a nuclear transcription factor, can regulate the insulin signal, gluconeogenesis, insulin resistance, immune cell migration and cell aging. Therefore, it seems clear that that the FOXO gene also plays an important role in diabetes and cell metabolism. Taken

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together, these findings demonstrate the vital role played by these pathways in the occurrence and development of diabetes mellitus and diabetes related complications, which then indirectly implicates the differential expression of exosomal LncRNA as being involved in the regulation of these pathways and thus participate in the regulation of T1DM pathological processes.

This study serves as an important source not only as a reference frame, but also a foundation for future follow-up cell experiments. A limitation of this study is that 30 samples of the 78 candidate LncRNAs were verified by other researchers in previous studies. Therefore, the large number of unverified screened samples and overall small sample size will require further verification and sample size expansion. The main asset of this study involved the selection of stable and highly specific exosomal LncRNAs as the research object and use of high-throughput sequencing technology to analyze their expression profile. In addition, we provide the first demonstration of exosomal LncRNA determinations within a clinical practice, which illustrates the scientific validity and capacity to study this combination of exosomal LncRNAs as related to T1DM within a clinical setting.

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