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Exploring differentially expressed genes related to metabolism by RNA-Seq in porcine embryonic fibroblast after insulin treatment

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ABSTRACT

Background: Insulin regulates glucose homeostasis and has important effects on metabolism, cell growth, and differentiation. Depending on the cell type and physiological context, insulin signal has specific pathways and biological outcomes in different tissues and cells. For studying the signal pathway of insulin on glycolipid metabolism in porcine embryonic fibroblast (PEF), we used high-throughput sequencing to monitor gene expression patterns regulated by insulin.
Objectives: The goal of our research was to see how insulin affected glucose and lipid metabolism in PEFs.
Methods: We cultured the PEFs with the addition of insulin and sampled them at 0, 48, and 72 h for RNA-Seq analysis in triplicate for each time point.
Results: At 48 and 72 h, 801 and 1,176 genes were differentially expressed, respectively. Of these, 272 up-regulated genes and 264 down-regulated genes were common to both time points. Gene Ontology analysis was used to annotate the functions of the differentially expressed genes (DEGs), the biological processes related to lipid metabolism and cell cycle were dominant. And the DEGs were significantly enriched in interleukin-17 signaling pathway, phosphatidylinositol-3-kinase-protein kinase B signaling pathway, pyruvate metabolism, and others pathways related to lipid metabolism by Kyoto Encyclopedia of Genes and Genomes enrichment analysis.
Conclusions: These results elucidate the transcriptomic response to insulin in PEF. The genes and pathways involved in the transcriptome mechanisms provide useful information for further research into the complicated molecular processes of insulin in PEF.

Keywords: Insulin; fibroblasts; pigs; lipid metabolism; RNA-Seq

INTRODUCTION

Insulin is an important metabolism regulating hormone secreted by pancreatic β cells. Insulin binds to its homologous cell surface-bound receptor, which results in a conformational change that triggers a cascade of signaling processes [1]. Insulin maintains glucose homeostasis in mammals and is involved in adipogenesis, glycogen and protein

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Conflict of Interest
The authors declare no conflicts of interest.

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production, lipolysis, glycogenolysis, and protein breakdown, as well as cell development and differentiation. Insulin regulates blood glucose levels by boosting glucose absorption while limiting glucose synthesis in muscle and fat tissue [2]. Insulin also increases substrate storage by promoting lipid, glycogen, and protein production while blocking their breakdown in fat, liver, and muscle [3].

Insulin resistance or insufficiency causes substantial dysregulation of these processes, resulting in elevated glucose and fat levels in the fasting and postprandial periods [3]. Defects in this signaling pathway can cause type 2 diabetes, atherosclerosis, hypertension, polycystic ovarian disease, and hyperlipidemia, among other metabolic illnesses [4]. In type 1 diabetic patients, intraperitoneal insulin injection moderately increases plasma triglycerides, reduces cholesterol content of high-density lipoprotein [5].

Pigs are more physiologically, metabolically, and inflammatorily comparable to humans, suggesting that they might serve as a link between experimental therapies and clinical trials [6]. In addition, recent reports have demonstrated that the glucose and lipid metabolism of pigs is similar to that of humans [7]. In pigs with streptozotocin-induced diabetes, the same metabolic alterations occur as in human diabetic patients, and the metabolic changes can be reversed with insulin therapy [8,9]. Fibroblast cells are the most abundant intrinsic cell in the connective tissue and they play a role in regulating fibrosis, organ development, self-tolerance, inflammation, and wound healing [10]. Importantly, the studies showed that fibroblast cells were involved in glucose and lipid metabolism. Fibroblast cells cultured in high glucose Dulbecco's modified Eagle's medium synthesized large amounts of glycosaminoglycans (GAGs). The majority were secreted into the culture media, while the remainder remained attached to the cell layer. GAGs are composed of uronic acids and aminohexoses. These substances are the products of glucose metabolism [11]. Lipid metabolism genes are also highly expressed in fibroblasts cells [12]. The elucidation of insulin signaling pathway in fibroblasts is important to evaluate its role in lipid metabolism.

The RNA-Seq technology is a platform for high-throughput sequencing, it can be used for discovering differentially expressed mRNAs among samples. Here, the effects of insulin on glucose and lipid metabolism of fibroblasts were studied using RNA-Seq technology in pigs. We are primarily interested in the cellular mechanisms of insulin signaling as well as novel insights into pathways that are important for insulin's metabolic effects.

MATERIALS AND METHODS

Porcine embryonic fibroblast (PEF) culture and sample collection

The PEF lines were derived from the Key Laboratory of Animal Cellular and Genetic Engineering of Heilongjiang Province, and the PEF culture method has been published [13]. In short, prior to add human insulin (0.5 ug), PEF lines were thawed and cultured, and the cells were collected at 48 h and 72 h after the addition of insulin. Three biological duplicates were collected at each time point, with the control samples taken at 0 h. **Fig. 1** depicts the sample collection process.

RNA isolation and library preparation

Total RNA was isolated from the cells at 0, 48, and 72 h post-insulin treated. The method of RNA isolation and library preparation has been published [14].

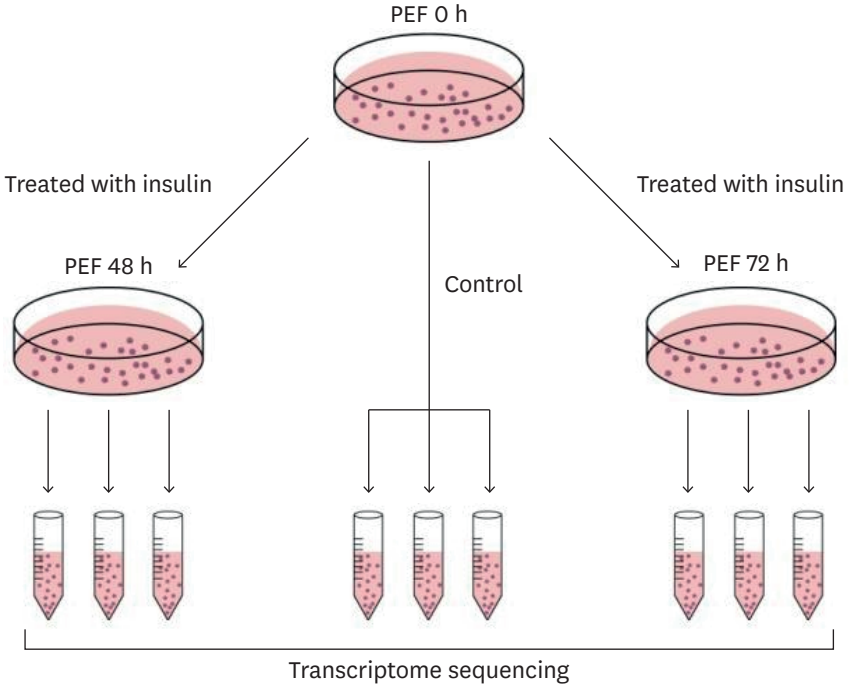

Fig. 1. Schematic representation of sample collection at 0 h, 48 h and 72 h.
PEF, porcine embryonic fibroblast.

Sequencing

Sequencing was carried out using Illumina HiSeqTM 2000 platform by the Genomics Facility at Cornell Biotechnology Resource Center. The RNA-seq data was uploaded as Gene Expression Omnibus GSE193831.

Data analysis

The analysis of each set of experimental data in our study represents the average of three levels of repeated experiments. The significance level is represented by the *p* value. GraphPad Prism 8.0.2 (GraphPad Software, USA) was used to create the figures.

The pipeline of mRNA data analysis has been published [15]. For different, Hisat2 2.2.1 (Johns Hopkins University, USA) was used to align paired-end clean reads to the Sus scrofa reference genome (Ensemble_Sscrofa11.1). The read numbers matched to each gene were counted using Featurecounts 2.0.1(The University of Melbourne, Australia).

Quantitative real-time (qRT)-polymerase chain reaction (PCR) analysis

Twelve differentially expressed genes (DEGs) were chosen for further validation using qRT-PCR. Three RNA samples were used for qRT-PCR for each condition according to the sequencing analyses. And the method of qRT-PCR has been published [16].

RESULTS

Raw sequencing data and quality statistics

To identify DEGs in the PEF stimulated by insulin, we constructed nine cDNA libraries and sequenced by the Illumina Hiseq 2000 sequencing platform (Illumina, USA). A total of

439,950,662 clean reads were filtered from 458,016,778 paired-end raw reads. The Q30 (%) of clean reads varied from 94.14% to 94.42%. And for the nine samples, the total read length was 65.98 GB, 94.89%–97.20% was successfully aligned with the Sus scrofa of these sequence reads (**Supplementary Table 1**). For gene expression analysis, the read counts mapped to all genes were normalized and computed as fragments per kilobase of transcripts per million mapped reads (FPKM). The expression levels of all genes were distributed similarly among libraries. In each library, approximately 35% of all genes were expressed (FPKM > 1), with over 1,200 genes having a high expression level (FPKM > 60). Systematic cluster analysis showed that the nine samples were categorized into two clusters according to whether insulin was added or not and categorized into three clusters according to different time points (**Fig. 2**).

Analysis and enrichment of DEGs

In pair-wise analyses (48 h vs. 0 h, and 72 h vs. 0h, log2[fold change] > 1, P.adjust < 0.05), a total of 1,977 genes were identified as DEGs. Among all of the DEGs, 801 were identified after 48 h of the addition of insulin, and 1,176 were identified after 72 h of the addition of insulin (**Fig. 3**). A Venn diagram illustrates the DEGs in 2 comparisons (**Fig. 4**), DEGs that are present in both time points are shown in **Supplementary Tables 2** and **3**, the gene expression level was also listed in tables. A large number of genes were upregulated by insulin stimulation, such as chemokine (C-C motif) ligand 2 (*CCL2*), alveolar macrophage-derived chemotactic factor-II (*AMCF-II*), and C-X-C motif chemokine ligand 8 (*CXCL8*).

After insulin treatment for 48 h and 72 h, genes that were up-regulated were enriched in 16 Gene Ontology (GO) terms (P.adjust < 0.05). Of these terms, sterol metabolic process (GO:0016125), lipid biosynthetic process (GO:0008610), lipid metabolic process (GO:0006629), steroid metabolic process (GO:0008202), and steroid biosynthetic process (GO:0006694) were significantly enriched (**Fig. 5A**). The pathways defined or influenced by the up-regulated genes were identified using a Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. KEGG pathways enriched included steroid biosynthesis, interleukin (IL)-17 signaling pathway, fat digestion and absorption, pyruvate metabolism, cholesterol metabolism, fatty acid metabolism, biosynthesis of unsaturated fatty acids, and phosphatidylinositol-3-kinase (PI3K)-protein kinase B (Akt) signaling pathway (**Fig. 5B**).

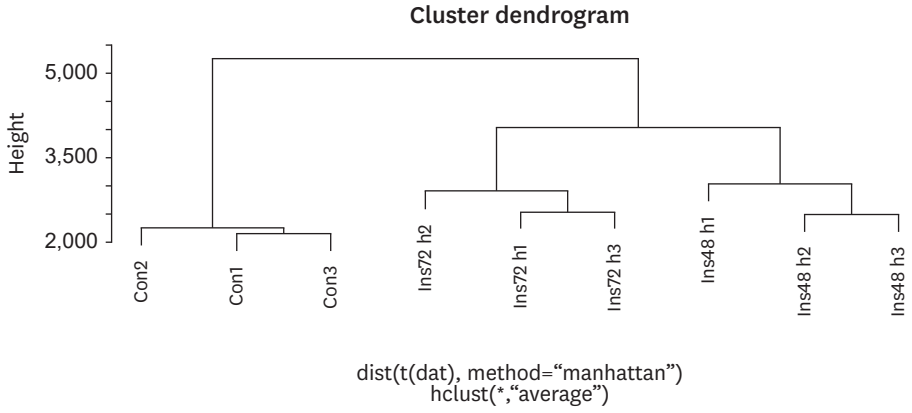

Fig. 2. Systematic cluster analysis of all samples at different time points.

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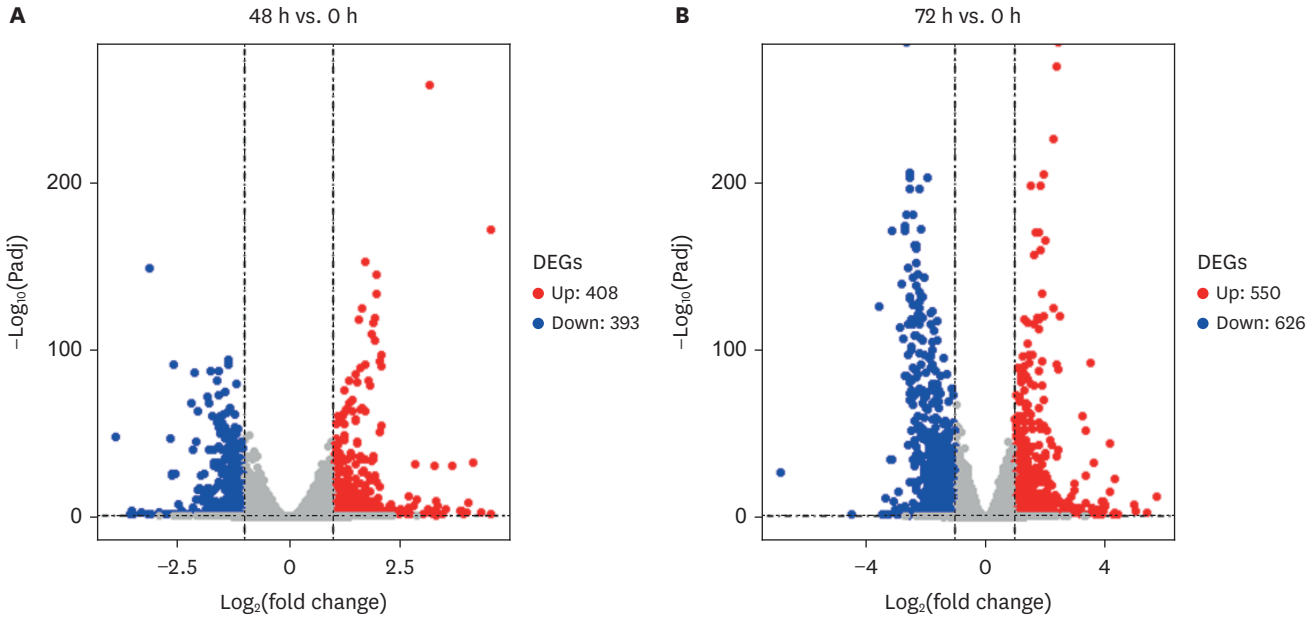

Fig. 3. Differential expression of insulin stimulation in porcine embryonic fibroblast for 48 h and 72 h vs. 0 h: (A) 48 h vs. 0 h; (B) 72 h vs. 0 h. The significantly up-regulated genes are in red, and the genes significantly down-regulated are in blue.
DEG, differentially expressed gene.

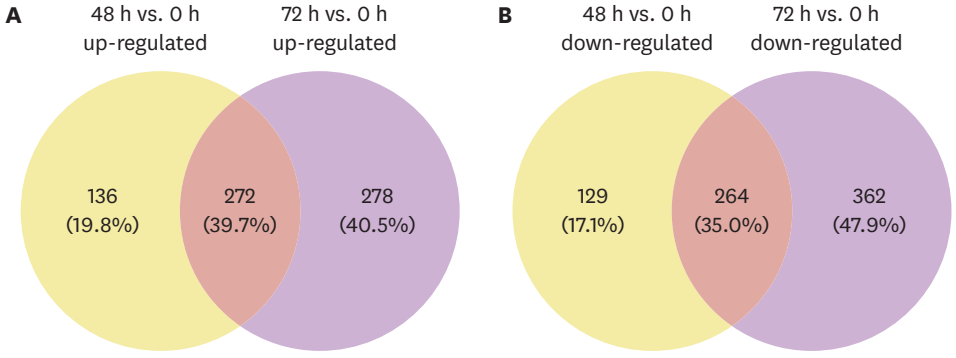

Fig. 4. Two pair-wise treatment group comparisons in a Venn diagram. (A) Venn diagram of up-regulated genes at different time points. (B) Venn diagram of down-regulated genes at different time points.

Down-regulated genes were enriched in 3 KEGG terms and 169 GO terms after treatment with insulin for 48 h and 72 h (P.adjust < 0.05). Of these KEGG terms, cell cycle was significantly enriched (**Fig. 6A**). And almost all 169 GO terms are related to the cell cycle, **Fig. 6B** shows only the most significant of 169.

DEGs validation by qRT-PCR

A total of twelve genes were chosen for qRT-PCR validation. Premier Primer 5 (Sigma-Aldrich, USA) was used to design specialized primers for qRT-PCR (**Supplementary Table 4**). Fold changes from qRT-PCR were compared to the results of RNA-Seq expression analysis, and the qRT-PCR results were shown to be highly correlated with the RNA-Seq results (correlation coefficients = 0.979–0.986, p value < 0.001) (**Fig. 7**). In general, the RNA-Seq results were supported by the qRT-PCR results, demonstrating that the RNA-Seq expression analysis was accurate and reliable.

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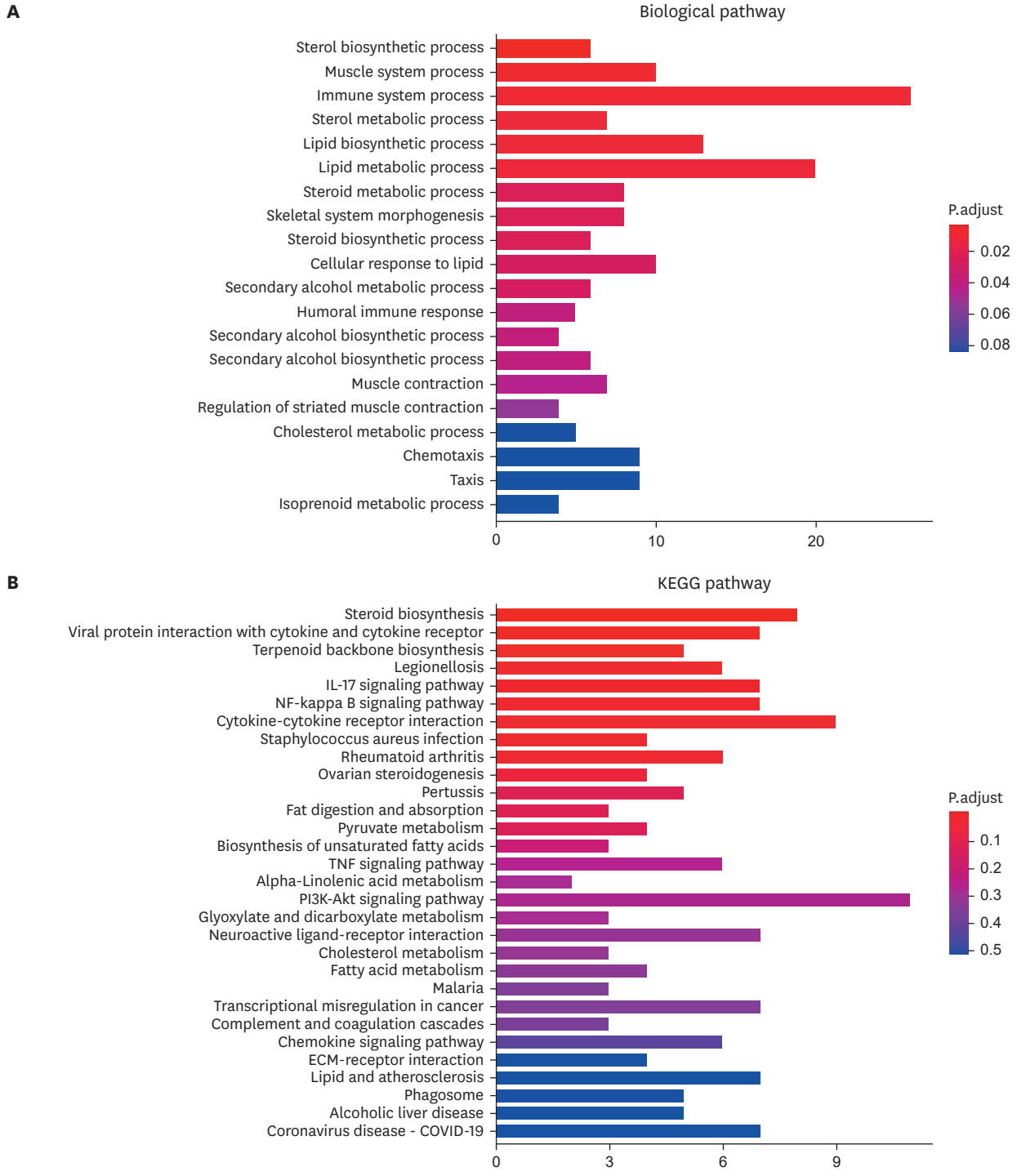

Fig. 5. Pathway analysis of the common up-regulated genes after treated with insulin for 48 h and 72 h. (A) The most enriched Gene Ontology term analysis. (B) KEGG pathway analysis.
KEGG, Kyoto Encyclopedia of Genes and Genomes; IL, interleukin; NF, nuclear factor; TNF, tumor necrosis factor; PI3K-Akt, phosphatidylinositol-3-kinase-protein kinase B; ECM, extracellular matrix; COVID-19, coronavirus disease 2019.

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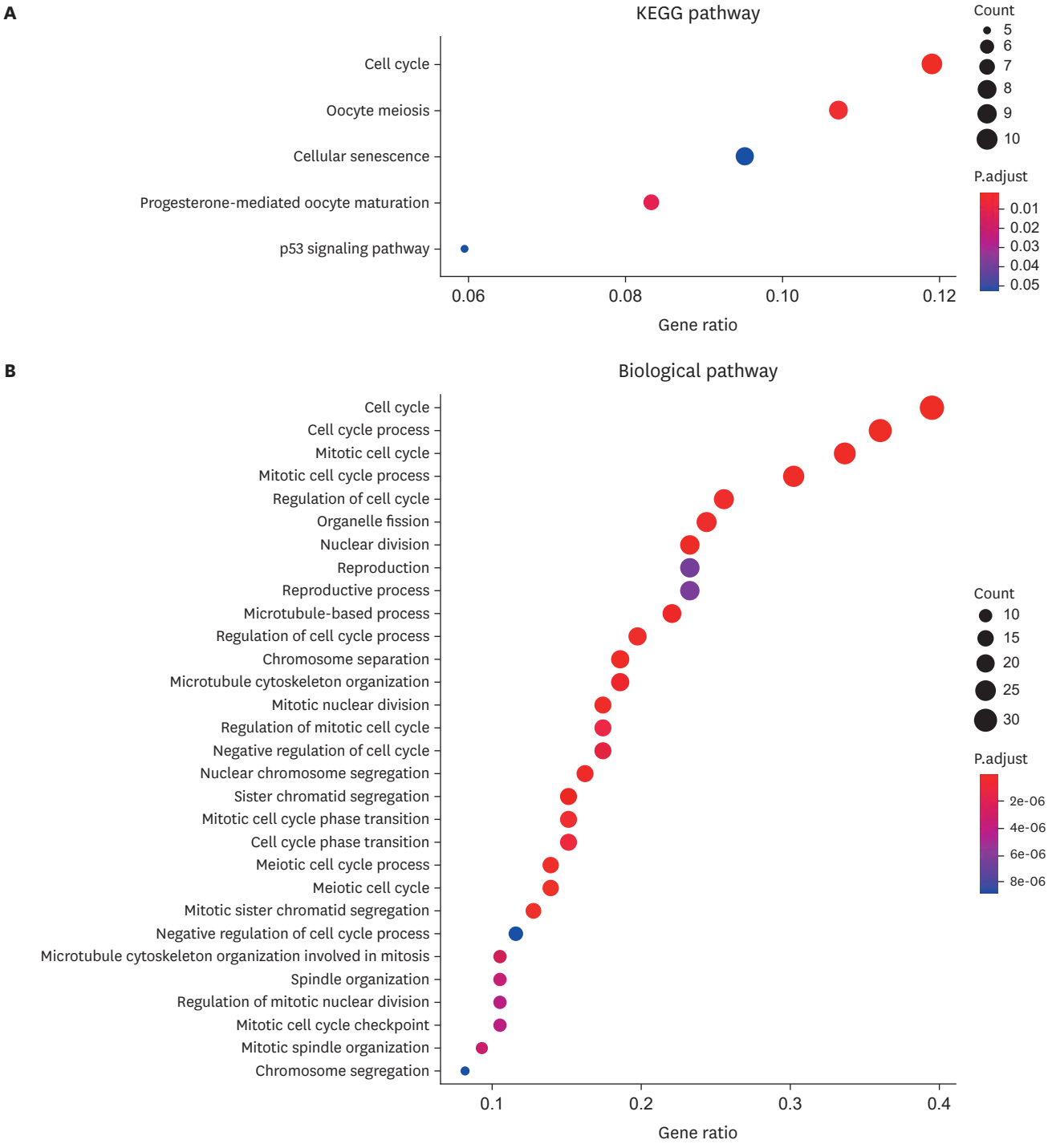

Fig. 6. Pathway analysis of the common down-regulated genes after treated with insulin for 48 h and 72 h. (A) KEGG pathway analysis. (B) The most enriched Gene Ontology term analysis.
KEGG, Kyoto Encyclopedia of Genes and Genomes.

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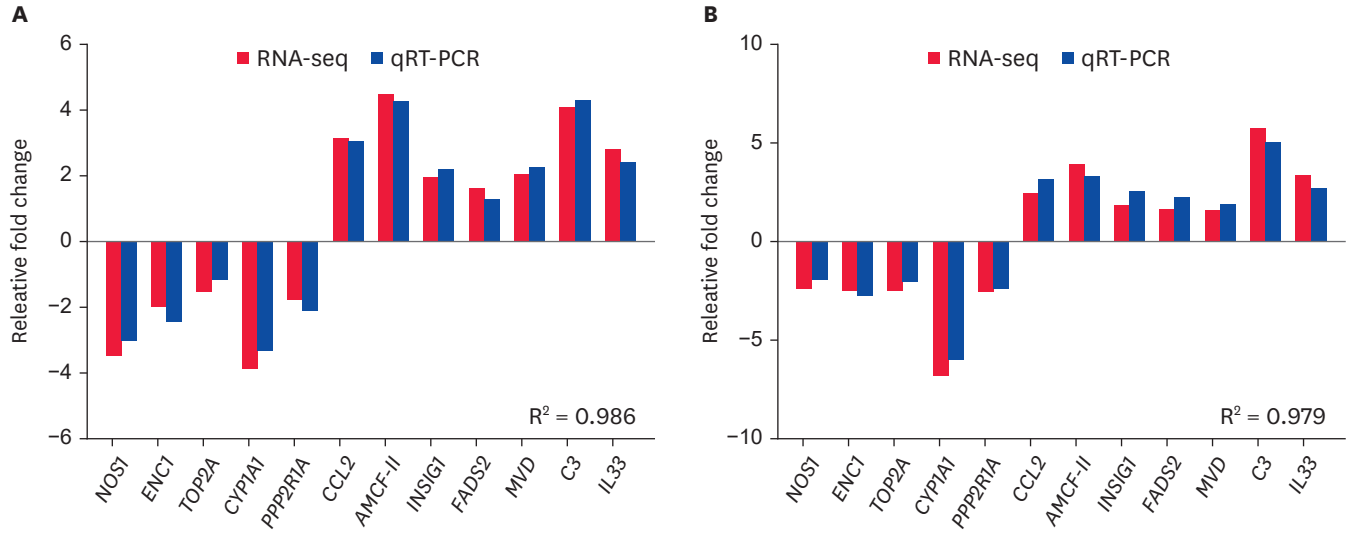

Fig. 7. Validation of RNA-Seq results using qRT-PCR: (A) 48 h after insulin treated; (B) 72 h after insulin treated. Fold changes represent gene expression changes in each group relative to control.
qRT-PCR, quantitative real-time polymerase chain reaction; *NOS1*, nitric oxide synthase 1; *ENC1*, ectodermal-neural cortex 1; *TOP2A*, DNA topoisomerase II alpha; *CYP1A1*, cytochrome P450 family 1 subfamily A member 1; *PPP2R1A*, protein phosphatase 2 scaffold subunit A alpha; *CCL2*, chemokine (C-C motif) ligand 2; *AMCF-II*, alveolar macrophage-derived chemotactic factor-II; *INSIG1*, insulin induced gene 1; *FADS2*, fatty acid desaturase 2; *MVD*, mevalonate diphosphate decarboxylase; *C3*, complement C3; *IL33*, interleukin 33.

DISCUSSION

In order to construct PEF sequencing libraries, nine PEF samples were obtained in this work. The quality and base composition study revealed that the guanine-cytosine content varied from 52.5% to 54%, and Q30 ratio (i.e., quality of bases ≥ 30) was 94.14% (**Supplementary Table 1**), indicating the libraries were constructed successfully and in good sequencing quality.

A GO analysis was used to annotate the functions of the DEGs. The terms related to lipid metabolism, including lipid biosynthetic process, lipid metabolic process, steroid metabolic process, steroid biosynthetic process, sterol metabolic process and sterol biosynthetic process, were dominant in biological processes for up-regulated genes (**Fig. 5A**). And six genes were enriched in each of these six biological processes, namely insulin induced gene 1 (*INSIG1*), methylsterol monooxygenase 1 (*MSMO1*), *FDFT1*, *SQLE*, *HMGCR* and *HSD17B7*. In adipocyte differentiation and fat metabolism, the INSIG1 plays a regulatory function [17]. Insulin, glucose, free fatty acids, and other nutrients have been found to affect the expression of the *INSIG1* gene in recent research [18]. MSMO1 operates function in the regulation of adipogenesis and energy metabolism, MSMO1 was identified as a good candidate to adjust blood glucose levels after an integrated analysis of differential gene expression and biological functions [19]. At the same time, MSMO, FDFT1, SQLE, HMGCR and HSD17B7 are five enzymes in the cholesterol synthesis pathway [20]. MSMO, FDFT1, SQLE and HSD17B7 were key enzymes in steroid biosynthesis pathway (**Supplementary Fig. 1**). Here, Insulin stimulation changed the levels of mRNA expression of these five genes considerably. It is speculated that insulin regulates lipid metabolism mainly by controlling enzymes which are responsible for steroid biosynthesis and cholesterol synthesis in PEF.

Besides steroid biosynthesis pathway, KEGG enrichment analysis also showed that the up-regulated genes were mainly associated with IL-17 signaling pathway, PI3K-Akt signaling

pathway, pyruvate metabolism, and others pathway related to lipid metabolism (**Fig. 5B**). IL-17 signaling pathway may play a key role in the progression of type 1 diabetes and has significant effects in the early stage of insulin therapy, and IL-17 may further accelerate or limit disease progression and affect diabetes complications [21]. The activation of two important downstream signaling pathways, the mitogen-activated protein kinase pathway and the PI3K pathway, occurs after IRS1/2 is recruited to IR [4]. The activation of Akt2 inhibits gluconeogenesis and glucose production and promotes glycogen synthesis [4]. Furthermore, PI(3)K plays an important role in the metabolic and mitogenic effected by insulin [22]. Insulin plays the function of regulating blood glucose mainly by PI3K-Akt signaling pathway [23]. The class-1 PI3K-Akt pathway connects insulin receptor activation to glucose metabolism [2]. Most metabolic activities of insulin are blocked by inhibitors of class Ia PI(3)K or transfections with dominant negative constructs of the enzyme, including glucose transport, lipid and glycogen formation [3]. In type 2 diabetes mellitus rats, PI3K-Akt insulin signaling pathway contributes to the improvement of glucose disposal [24]. In mice, Akt2 deletion results in hepatic insulin resistance [25]. Pyruvate is a key intermediate in various metabolic processes and can be used as a substrate in the synthesis of hepatic glucose [26]. The pyruvate dehydrogenase enzyme complex, which is found in the inner mitochondrial membrane, may convert pyruvate to acetyl coenzyme A [27]. In the tricarboxylic acid (TCA) cycle, acetyl coenzyme A is one of the most important fuels for energy generation. Pyruvate can be converted to oxaloacetate instead of entering the TCA cycle, due to the enzyme pyruvate carboxylase. Oxaloacetate can exit the TCA cycle via phosphoenolpyruvate carboxykinase to generate phosphoenolpyruvate and then glucose [28]. In PEF, insulin regulation of glucose metabolism may be related to PI3K-Akt signaling pathway and pyruvate metabolism, and the glycolipid metabolism of insulin-treated PEF may provide valuable reference for the treatment of diabetes mellitus. Interestingly, in coronavirus disease 2019 (COVID-19), up-regulated genes were also enriched. and diabetes has been linked to severity and mortality of COVID-19 [29], our results may support this view.

Furthermore, the function of down-regulated genes is linked to the cell cycle (**Fig. 6A and B**), there are numerous indications that insulin may have mitogenic effects in β cells, as it works the same way in other cell types. Inactivation of the insulin receptor gene in β cells, for example, results in a partial decrease in postnatal β cell proliferation in mice [30]. Surprisingly, mice with homozygous germline mutations in the two non-allelic mouse insulin genes exhibit an increase in islet cell proliferation rather than a reduction [31]. De Vas and Ferrer [30] also indicate that physiological insulin production can suppress β cell proliferation, counter to the well-known mitogenic actions of insulin in many cell types. In our study, the cell cycle-related genes are down-regulated by insulin, this may suppress proliferation, arrests cell cycle progression in PEF. And we can speculate that the biological outcomes following the effect of insulin on cell cycle are greatly influenced by the cell type and physiological environment.

In addition, KEGG enrichment analysis also showed that 11 genes down-regulated significantly by insulin, namely *PLK1*, *CCNB3*, *CDK1*, *CCNB1*, *CCNB2*, *KIF22*, *BUB1*, *AURKA*, *MAD2L1*, *CDC23*, and *PKMYT*1, were mainly associated with progesterone-mediated oocyte maturation pathway (**Fig. 6A**). All of these genes are involved in meiosis, mitosis, or oocyte maturation [32]. Progesterone is considered as the physiological steroid hormone that triggers meiosis reinitiation in amphibian oocytes. Nevertheless, isolated oocytes can be induced to undergo germinal vesicle breakdown (GVBD) in a saline medium by means of treatment with various hormones or inducing agents such as insulin in Bufo arenarum oocytes. Insulin was able to induce GVBD in oocytes incompetent to mature spontaneously and to enhance

spontaneous and progesterone-induced maturation [33]. A dose-dependent potentiating effect of the action of progesterone was observed with insulin, since in the presence of insulin, the optimally effective concentration of progesterone was much reduced (as an example from 1 μmol/L to 50 nmol/L) in Xenopus laevis oocytes [34]. Our study shows that insulin negatively regulates progesterone-mediated oocyte maturation pathway genes in PEF. This suggests that the effect of insulin on progesterone-mediated oocyte maturation is influenced by cell types. And this may provide some reference for the study of oocyte maturation.

Overall, our data support a role of the insulin on lipid and glucose metabolism, show an association among insulin, glycolipid metabolism and cell cycle in PEF. It also provides new insights into the effect of insulin on progesterone-mediated oocyte maturation. Our research revealed a number of essential genes linked to metabolism, and these genes may be utilised to better understand the mechanism of insulin's ability to alleviate metabolic disturbances. The disorders of glucose and lipid metabolism result in severe diseases including cardiovascular disease, diabetes and fatty liver. The majority of diabetics do not have an insulin deficiency, but rather had elevated insulin levels [35]. Additionally, despite the fact that mice are small and hence helpful for multivariable studies, their metabolism and physiology differ significantly from those of humans [36]. Pigs have significant physical and physiological similarities with humans, as well as a high degree of sequence and chromosomal structural similarity [37]. The structure of animal insulin has minor differences from human insulin. For example, pig insulin differs by one amino acid (alanine instead of threonine at the carboxy-terminal of the B-chain, i.e., position B30). There is nearly a complete homology between human insulin and pig insulin in the amino acid sequence, and studies have also shown that the biological effect of human insulin is comparable to that of pig insulin [38]. Therefore, using human insulin-treated PEFs as a cell model to simulate the glucolipid metabolic response of cells under high insulin level can provide valuable biological basis for studying the treatment of glucolipid metabolic disorders (such as gestational diabetes [GD]) under high insulin level. GD is a relatively common complication of pregnancy. At the current time, insulin remains the first-line treatment for GD, and insulin could act on the fetus through the transplacental passage [39]. However, there is still a lack of the data in the effect of insulin on fetal development [39]. In this study, the cell was PEFs, through this cell model, we can provide valuable reference for the effect of insulin on fetal gene expression or related signal pathways when treating GD with insulin. And insulin regulates lipid metabolism mainly by controlling enzymes responsible for steroid biosynthesis and cholesterol synthesis in PEF, and the genes encoding these enzymes can be used as potential genes to study diabetic glucolipid metabolism or diagnostic biomarkers for diabetes.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Basic read characteristics in nine libraries used for reference genome sequencing read mapping

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Supplementary Table 2

The common significant up-regulated genes in the transcriptional expression of porcine embryonic fibroblast in response to insulin treated for 48 h and 72 h (P.adjust < 0.05)

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Supplementary Table 3

The common significant down-regulated genes in the transcriptional expression of porcine embryonic fibroblast in response to insulin treated for 48 h and 72 h (P.adjust < 0.05)

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Supplementary Table 4

Sequences of primers used for quantitative polymerase chain reaction in pig

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Supplementary Fig. 1

Steroid biosynthesis pathway. MSMO, FDFT1, SQLE and HSD17B7 are marked with red asterisk. Other up-regulated genes riched in this pathway are marked with blue asterisk. Corresponding relationship between enzyme number and enzyme in international enzyme committee: [EC:1.3.1.72], DHCR24; [EC:1.14.18.9], MSMO1; [EC:2.5.1.21], FDFT1; [EC:1.14.14.17], SQLE; [EC:1.14.19.20], SC5D; [EC:1.1.1.62 1.1.1.270], HSD17B7; [EC:1.3.1.70], TM7SF2; [EC:3.1.1.13 3.1.1.3], CEL.

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