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Network exploration of gene signatures underlying low birth weight induced metabolic alterations

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Abstract

Background: This study explored underlying gene signatures of low birth weight (LBW) by analyzing differentially expressed genes (DEGs) between LBW and normal birth weight (NBW) subjects.

Methods: Subjects with different birth weight was collected from GEO database. $P < .05$ and $|\log FC| \geq 1.0$ were used for screening DEGs. David (2021 Update) was used to perform GO annotation and KEGG signaling pathway enrichment analysis. The protein-protein interaction network of DEGs was constructed using the STRING database, in which hub genes were mined through Cytoscape software.

Results: A total of 326 DEGs were identified, including 287 up-regulated genes and 39 down-regulated genes. The GO biological processes enriched by DEGs mainly involved epidermal growth, keratinization and intermediate fibrous tissue. The DEGs were significantly enriched in intracellular insoluble membranes, desmosomes and extracellular space. Their molecular functions mainly focused on structural molecular activity, structural components of epidermis and structural components of cytoskeleton. PI3K/AKT signaling pathway and tight junction were highlighted as critical pathways enriched by DEGs. Ten hub genes which included KRT14, EGF, DSP, DSG1, KRT16, KRT6A, EPCAM, SPRR1B, PKP1, and PPL were identified from the constructed protein-protein interaction network.

Conclusion: A total of 326 DEGs and 10 hub genes were identified as candidates for metabolic disorders in LBW individuals. Our results indicated PI3K/AKT signaling pathway as an intrauterine adaptive mechanism for LBW individuals. We observed activated PI3K/AKT pathway in LBW individuals, which would promote growth and development at the early stage of life, but adversely introduce extra metabolic stress and thereby potentially induce metabolic disorders in adulthood.

Abbreviations: BP = biological process, CC = cellular component, DAVID = database for annotation, visualization and integrated discovery, DEGs = differentially expressed genes, GEO = gene expression omnibus, GO = gene ontology, KEGG = kyoto encyclopedia of genes and genomes, LBW = low birth weight, MF = molecular function, PPI = protein-protein interaction.

Keywords: bioinformatics analysis, differentially expressed genes, low birth weight, PI3K/AKT pathway, umbilical cord tissue

1. Introduction

Low birth weight (LBW), defined as birth weight <2500 g, is an objective statistical indicator of fetal development and pregnancy outcome.[1] LBW is considered a significant public health problem as it is estimated that 15% to 20% of all birth worldwide are LBW.[2] Emerging evidence have suggested the birth weight as a crude assessment of the intrauterine circumstances.[3] An adverse intrauterine environment, such as maternal malnutrition, may perturb the growth and development of the fetus during pregnancy and finally induce LBW.[4,5] To adapt to the negative intrauterine environment, structural changes and functional modifications occurred in fetal organs and tissues to ensure the survival of the newborn.[6] Previous studies pointed out that LBW not only was associated with a high risk of infection, morbidity and mortality but also increases the risk of insulin resistance, diabetes, hypertension and metabolic syndrome in adulthood.[7–10] However, the molecular mechanism of LBW-induced metabolic disorders still remains unknown.

The authors have completed the MDAR reporting checklist.HM and LY contributed equally to this work.

The datasets generated during and/or analyzed during the current study are publicly available.

The original data we used in this study were downloaded from the public database - GEO database (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE37100), so the ethical approval was not necessary. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

The authors have no funding and conflicts of interest to disclose.

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Table 1

Differential genes between LBW group and CON group.

LBW vs CON	Gene symbol
Up regulated genes (287)	GSTT1,KRTDAP,KRT1,AADACL2,CHP2,CXCL17,DSC1,CWH43,MMP10,CXCL14,COL4A4,GRTP1,PHACTR3,SBSN,APOBEC3A,ELF5,PHACTR3,-CLIC5,SPINK5,CCDC85A,OR7D2,CLDN1,COBL,CXADR,SPINK5,TMEM45B,MUC22,PRR15L,KREMEN1,CCDC85A,CLIC5,KRT4,TMPRSS1 1E,SPINK5,CT45A1,HOMER2,SERPINB4,SLC15A1,SERPINB3,SSTR1,UPK1A,LY6D,SLC1A6,KRT16,EDN2,MAL,BSPRY,LINGO2,MUC15,L-GR5,SLITRK6,HS3ST4,SGPP2,SLC16A12,EGF,ARAP2,FABP7,CXADR,SPRR3,AGR3,AREG,FREM2,IRX2,ATP10B,TMPRSS11F,CHRM2,A2M-L1,UPK1B,SEMA3D,HLADQA1,IL36RN,ADAMTS5,PPP2R2B,DSG1,CERS3,DMKN,LIPH,MUC22,RNF222,HES5,ZNF750,PPP2R2C,KRT-6B,PAQR5,SLN,SPRR1B,SPP2,KCNK13,TMPRSS11A,KRT23,KRT23,FAM84A,C10orf99,VTCN1,CTSL2,PARD6B,BNIPL,B3GNT4,HOOK1,E-HF,KRT17,GRHL3,MPZL3,CDS1,HAND1,CREG2,KRT77,DMKN,RASEF,ZDHHC23,FBXL16,FAM83B,CST6,MYO5B,KRT6A,CEACAM6,SULT-2B1,LAD1,COL4A6,MFSD4,STON2,OR4F21,DST,PTK6,BNIPL,ANO4,PVRL4,DST,TMEM30B,CSTA,FXYD3,RNF39,KRT14,ERBB3,ELOVL7,GNG4,-FOSB,MTUS2,DACT2,TTC39A,C1orf106,GJB4,EPB41L4B,WNT7B,WNT11,DLX2,SERPINB7,SFTA2,PP14571,TMPRSS7,SERPINB5,BBOX-1,FAM84A,KRT16P2,IRX2,FXYD3,SERPINB2,PPARG,IL22RA1,PRR9,PRSS3,CYP2J2,TRIML1,AIM1L,SPRR1A,C2orf54,LY6G6C,S100P,NTF4,-CAPNS2,RAB25,C4orf7,UNC93A,DLX5,MREG,TMEM63C,MTUS2,FOS,RNF43,CLCA2,DSG3,HLADQA1,KLC3,ENTPD3,KRT75,EPS8L1,LYPD3,S-FN,C17orf109,FAM169A,OVOL2,BNC1,CDH18,MAL2,SGCG,NEBL,GJB3,EPS8L1,DHRS2,EFR3B,RASSF7,AGR2,TNS4,PPL,PTPRZ1,PKP1,FAM-26D,DSP,PKP1,FAM3D,KRT6C,PRRG4,C9orf169,LOC100130899,VILL,CRB3,APP,LOC100128657,FGL1,PPP1R14C,MIAT,PRSS2,GRHL2,FAB-P5,IL28RA,KLF5,C9orf169,GNG4,AIM1L,FAM169A,TJP2,C1orf172,TMEM132B,COL17A1,SH2D3A,CHRM1,CARD14,FAM176A,PKP3,ANK-FN1,CDS1,LYPD3,LRRC1,AJAP1,PRSS8,NELL1,RGNEF,CYP3A7,FABP5,DUOXA1,WFDC5,AQP3,PLA2G5,POF1B,ANK3,C19orf21,SYT1,DFN-B31,LOC728342,LINC00113,PCDH20,CDC42BPG,FABP5,PPARG,PDZK1,AREG,POF1B,LOC391322,DUOX2,ODZ2,VIPR1,DSP,DUOX1,CHRM3,CY-P3A5,OVOL1,STYK1,B3GNT3,ANXA8L2,EPCAM,P2RY2,RHOV,C10orf113,UCN2,ANK3,LRRN4CL,BEX2
Down regulated genes (39)	DEFA3,CAMP,VSTM1,LTF,SAA2,PRSS57,OLFM4,NLRP11,ELANE,OLIG1,MGC34800,CEACAM8,TCL1A,PGLYRP1,CCDC87,LOC441601,SCM-L4,LOC650293,PF4,CLDN10,PRPH,FLJ43390,BTNL9,DCAF12L1,CCR2,BCKDHA,IGSF1,AZU1,SPIB,LOC442421,TBX21,SIRPD,LOC100128946,VN-N3,LOC100509175,PABPN1L,SNX22,TRAF3IP3,FCRLA

CON = control group, LBW= low birth weight.

The umbilical cord plays a key role in the intrauterine growth of fetal, which demonstrates great potential in the research of LBW.[11,12] A pilot study showed that miRNAs in umbilical cord could be novel biomarkers for the early identification of metabolic diseases in infants with LBW.[13] In this context, the present study analyzed microarray data of fetal umbilical cord tissues in LBW and NBW individuals by using bioinformatics methods, which helped to explore critical DEGs underlying the pathogenesis of metabolic disorders caused by LBW and would provide novel insights for the health management of adult life of LBW subjects.

We present the following article in accordance with the MDAR reporting checklist.

2. Materials and methods

2.1. Sources of microarray data

Gene expression data of LBW subjects were collected from the Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo/) database by setting keywords as: "Fetal Nutrition Disorder" or "Nutrition Disorder, Fetal" or "Nutrition Disorders, Fetal" or "Fetal Malnutrition" or "Malnutrition, Fetal" or "Intrauterine malnutrition" or "Low-Birth-Weight" or "Low Birth Weight" or "Birth Weight, Low" or "Birth Weights, Low" or "Low Birth Weights" or "Malnutrition during pregnancy." Totally, 11 LBW samples and 17 control samples in GSE37100 were downloaded to extract the gene expression data. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

2.2. Data processing and DEGs screening

The logFC (log2foldchange) and *P* value of each gene were calculated, *P* value was obtained by *t* test. DEGs were identified according to the cutoff of $P < .05$ and $|logFC| > 1.0$. Based on detected DEGs, volcano plots and heatmaps were drawn using R-related visualization capabilities.

2.3. Functional enrichment analysis of DEGs

In this study, David (2021 Update) was used for Gene Ontology (GO) annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. GO annotation, which consists of biological processes (BP), cellular components (CC) and molecular functions (MF), helps to summarize the main functions of relevant proteins. KEGG signaling pathway enrichment analysis assigns a series of DEGs to specific pathways, thereby building a network of intermolecular interactions, responses and relationships. The DEGs were uploaded to David (2021 Update) for GO annotation and KEGG signaling pathway analysis, and then the corresponding bar and bubble charts were drawn.

2.4. Construction of PPI network between DEGs and HUB gene identification

The protein-protein interaction network of DEGs was constructed with the criterion of "confidence > 0.7" based on the STRING (Search Tool for the Retrieval of Interacting Genes/Proteins, https://string-db.org/) database. The algorithm of the Hubba plugin of Cytoscape v3.9.1 was used for hub gene analysis. The top 10 genes with the highest stress in the constructed network were identified.

3. Results

3.1. Differentially expressed genes (DEGs)

A total of 326 significant DEGs were obtained. Compared with the control group, 287 genes were up-regulated and 39 genes were down-regulated in the LBW group (Table 1). Volcano plots and heatmaps of DEGs were shown in Figure 1.

3.2. Functional analysis of DEGs

GO annotation and KEGG signaling pathway enrichment analysis were performed on the screened DEGs using David (2021 Update) online tool. The GO annotation includes BP, CC and MF, and the corresponding bubble chart was shown in Figure 2. The Top 10 biological processes (BP) enriched by DEGs mainly included epidermal growth, keratinization, intermediate fiber organization, epithelial cell differentiation, intermediate filament cytoskeleton organization, negative regulation of endopeptidase activity, peptide cross-linking, wound

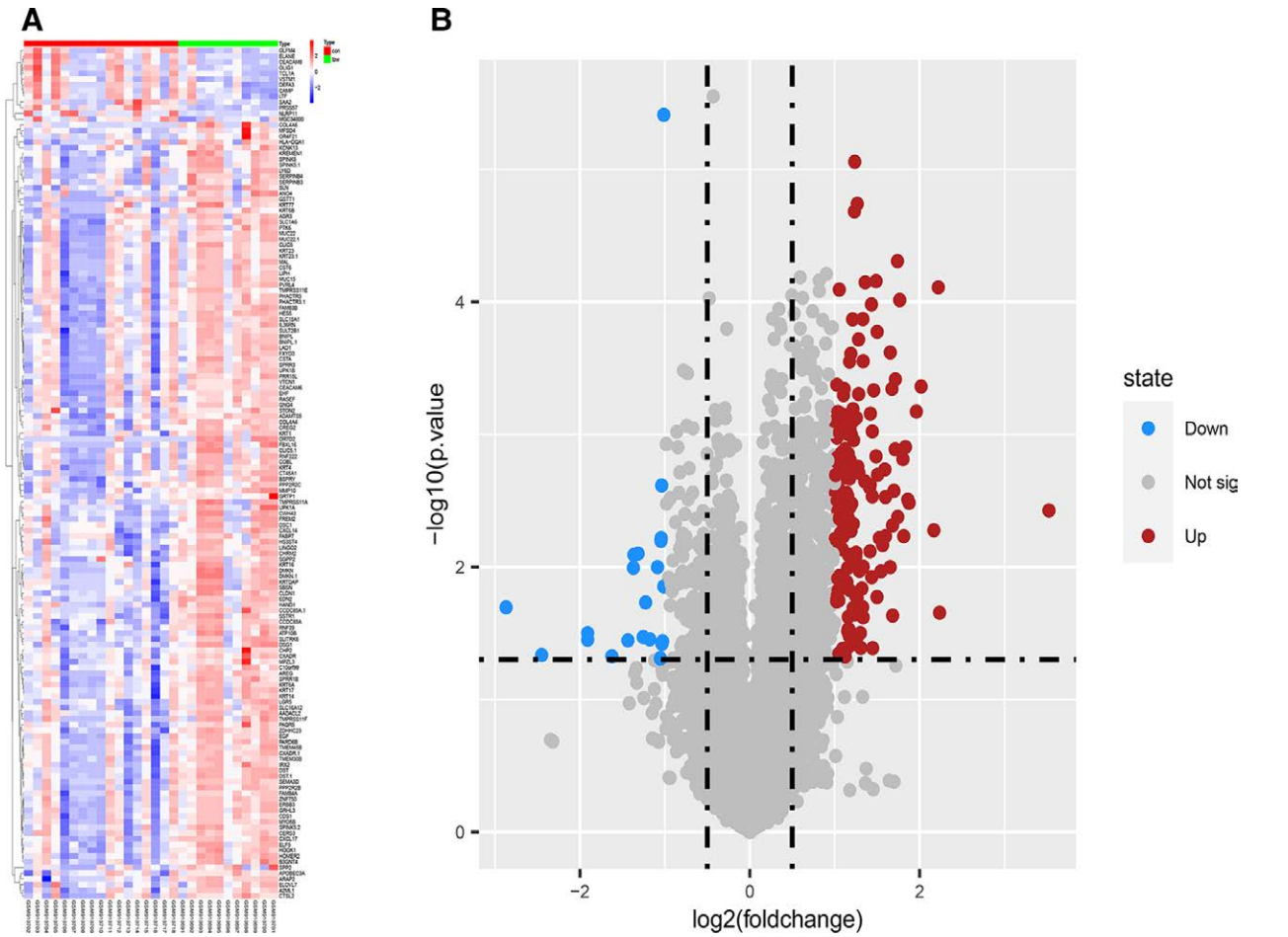

Figure 1. Processing result of data set. (A) The heat map shows the top 150 genes with the most significant differences. Red represents a high expression signal, and blue represents a low expression signal. (B) Volcano map, showing the DEGs in the chip compared with normal umbilical cords; red dots represent LBW highly expressed genes, and blue dots represent LBW low expressed genes. DEGs = differentially expressed genes. LBW = low birth weight.

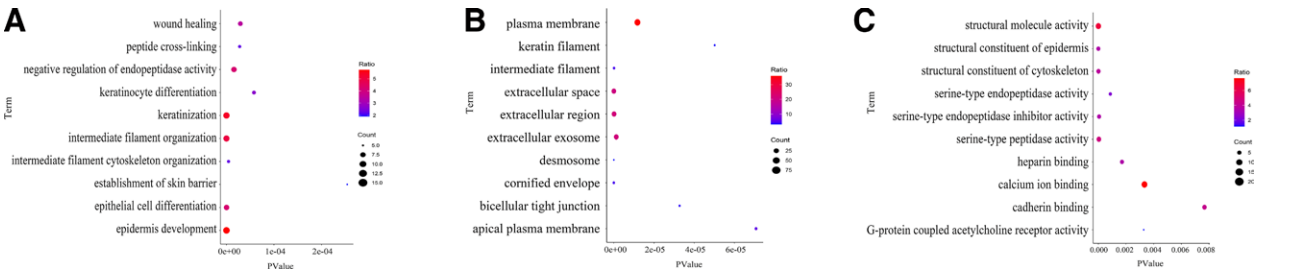

Figure 2. GO enrichment analysis results. The abscissa represents the *P* value, and the ordinate represents different terms. The larger the dots in the figure, the more genes contained in this term; the redder the dot color, the higher the probability of genes rich in this term. (A) Top 10 enrichment analysis results of BP. (B) Top 10 enrichment analysis results of CC. (C) Top 10 enrichment analysis results of MF. BP = biological process, GO = gene ontology, MF = molecular function.

healing, differentiation of keratinocytes and establishment of the skin barrier. Cellular component (CC) results showed that these genes were mainly involved in intracellular insoluble membranes, desmosomes, extracellular space, extracellular domain, intermediate filaments, extracellular exosomes, plasma body membranes, tight junctions of double cells, keratin fibers, and apical plasma membranes. Their molecular functions (MF) mainly focus on structural molecular activity, structural components of epidermis, structural components of cytoskeleton, serine-type endopeptidase activity, serine-type endopeptidase inhibitor activity and serine-type peptidase activity (Table 2).

Totally, 9 KEGG signaling pathways were enriched by our identified DEGs, including PI3K/AKT signaling pathway, tight junctions, protein digestion and absorption, human papillomavirus infection, pancreatic secretion, neuroactive ligand-receptor interaction effect, Hippo signaling pathway, cholinergic synapse and estrogen signaling pathway. Corresponding detailed data were shown in Figure 3 and Table 3. Interestingly, PI3K/AKT pathway is commonly correlated with insulin resistance, a major pathogenic factor for type 2 diabetes mellitus (T2DM) (Fig. 4).

3.3. Core network of LBW

Based on the DEGs between the LBW and the control group, the PPI network of LBW was constructed using the STRING database, which was displayed in Figure 5A. The constructed

Table 2

GO enrichment analysis of DEGs.

Category	Term	Description	Count	*P* value
GOTERM_BP_DIRECT	GO:0008544	epidermis development	15	1.05E-12
GOTERM_BP_DIRECT	GO:0031424	keratinization	14	7.97E-12
GOTERM_BP_DIRECT	GO:0045109	intermediate filament organization	13	1.71E-11
GOTERM_BP_DIRECT	GO:0030855	epithelial cell differentiation	11	1.69E-07
GOTERM_BP_DIRECT	GO:0045104	intermediate filament cytoskeleton organization	6	4.33E-06
GOTERM_BP_DIRECT	GO:0010951	negative regulation of endopeptidase activity	11	1.58E-05
GOTERM_BP_DIRECT	GO:0018149	peptide cross-linking	6	2.78E-05
GOTERM_BP_DIRECT	GO:0042060	wound healing	9	2.93E-05
GOTERM_BP_DIRECT	GO:0030216	keratinocyte differentiation	7	5.79E-05
GOTERM_BP_DIRECT	GO:0061436	establishment of skin barrier	5	2.54E-04
GOTERM_CC_DIRECT	GO:0001533	cornified envelope	13	2.34E-13
GOTERM_CC_DIRECT	GO:0030057	desmosome	8	1.79E-08
GOTERM_CC_DIRECT	GO:0005615	extracellular space	54	2.33E-08
GOTERM_CC_DIRECT	GO:0005576	extracellular region	56	1.17E-07
GOTERM_CC_DIRECT	GO:0005882	intermediate filament	13	1.28E-07
GOTERM_CC_DIRECT	GO:0070062	extracellular exosome	55	1.23E-06
GOTERM_CC_DIRECT	GO:0005886	plasma membrane	94	1.17E-05
GOTERM_CC_DIRECT	GO:0005923	bicellular tight junction	10	3.27E-05
GOTERM_CC_DIRECT	GO:0045095	keratin filament	9	5.02E-05
GOTERM_CC_DIRECT	GO:0016324	apical plasma membrane	16	7.08E-05
GOTERM_MF_DIRECT	GO:0005198	structural molecule activity	17	2.29E-09
GOTERM_MF_DIRECT	GO:0030280	structural constituent of epidermis	9	1.79E-08
GOTERM_MF_DIRECT	GO:0005200	structural constituent of cytoskeleton	10	7.54E-06
GOTERM_MF_DIRECT	GO:0004252	serine-type endopeptidase activity	12	3.65E-05
GOTERM_MF_DIRECT	GO:0004867	serine-type endopeptidase inhibitor activity	9	5.33E-05
GOTERM_MF_DIRECT	GO:0008236	serine-type peptidase activity	6	8.66E-04
GOTERM_MF_DIRECT	GO:0008201	heparin binding	9	.0017072
GOTERM_MF_DIRECT	GO:0016907	G-protein coupled acetylcholine receptor activity	3	.0032791
GOTERM_MF_DIRECT	GO:0005509	calcium ion binding	20	.0033332
GOTERM_MF_DIRECT	GO:0045296	cadherin binding	11	.0076713

DEGs = differentially expressed genes, GO = gene ontology.

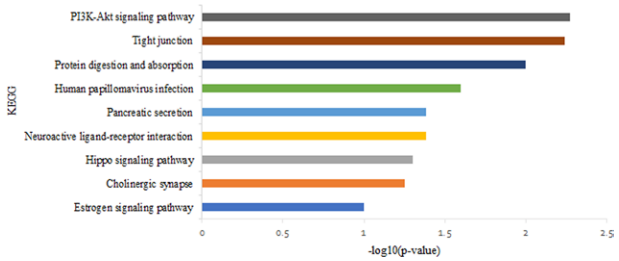

Figure 3. The KEGG pathway enrichment results of DEGs. DEGs = differentially expressed genes, KEGG = Kyoto encyclopedia of genes and genomes.

Table 3

KEGG pathway enrichment analysis of DEGs.

Category	Term	Description	Count
KEGG_PATHWAY	hsa04151	PI3K/AKT signaling pathway	12
KEGG_PATHWAY	hsa04530	Tight junction	8
KEGG_PATHWAY	hsa04974	Protein digestion and absorption	6
KEGG_PATHWAY	hsa05165	Human papillomavirus infection	10
KEGG_PATHWAY	hsa04972	Pancreatic secretion	5
KEGG_PATHWAY	hsa04080	Neuroactive ligand-receptor interaction	10
KEGG_PATHWAY	hsa04390	Hippo signaling pathway	6
KEGG_PATHWAY	hsa04725	Cholinergic synapse	5
KEGG_PATHWAY	hsa04915	Estrogen signaling pathway	5

DEGs = differentially expressed genes, KEGG= Kyoto Encyclopedia of Genes and Genomes.

network of LBW is comprised of 184 nodes and 457 interaction edges. The degree of connectivity of each gene was calculated using the Hubba plug-in of Cytoscape V3.9.1. Accordingly, Top10 genes with the highest degree were obtained (Fig. 5B), which included KRT14, EGF, DSP, DSG1, KRT16, KRT6A, EPCAM, SPRR1B, PKP1 and PPL. To further construct the core network of LBW, these hub genes and their neighbors were extracted and reconnected. Finally, we obtained a core network of LBW comprised of 73 nodes and 271 edges (Fig. 5C).

4. Discussion

The 9 months of gestation constitute the most consequential period of our lives, the life as a fetus makes us the way we are.[14] The conditions we encounter in utero shape our susceptibility to disease, our appetite and metabolism. Previous studies have shown that LBW is closely associated with chronic metabolic diseases such as diabetes, obesity and metabolic syndrome in adult life.[15,16] Our previous meta-analysis also showed that LBW significantly increased the future risk of developing T2DM.[17] However, the exact mechanism of LBW causing metabolic disorders is still not well understood. In this study, we collected the microarray data from human umbilical cord tissue, and a total of 326 DEGs were identified. Through functional analysis, PI3K/AKT signaling pathway was shown as the most enriched pathway, highlighting its importance in LBW subjects. This pathway is not only a key regulator of early embryonic development but also closely connected with the development of insulin resistance.[18–20] Insulin resistance is a disorder of glucose metabolism that plays a crucial role in T2DM.[21] The activation of the PI3K/AKT signaling pathway could improve insulin sensitivity and alleviate T2DM.[19,22] The impaired PI3K/AKT signaling pathway is strongly related to insulin resistance,[18–20] and therefore was suggested as a potential target for treating T2DM.[23–26] Notably, in the core network of LBW, we also observed a key modulator of this pathway, EGF, which showed the highest stress in the PPI network of

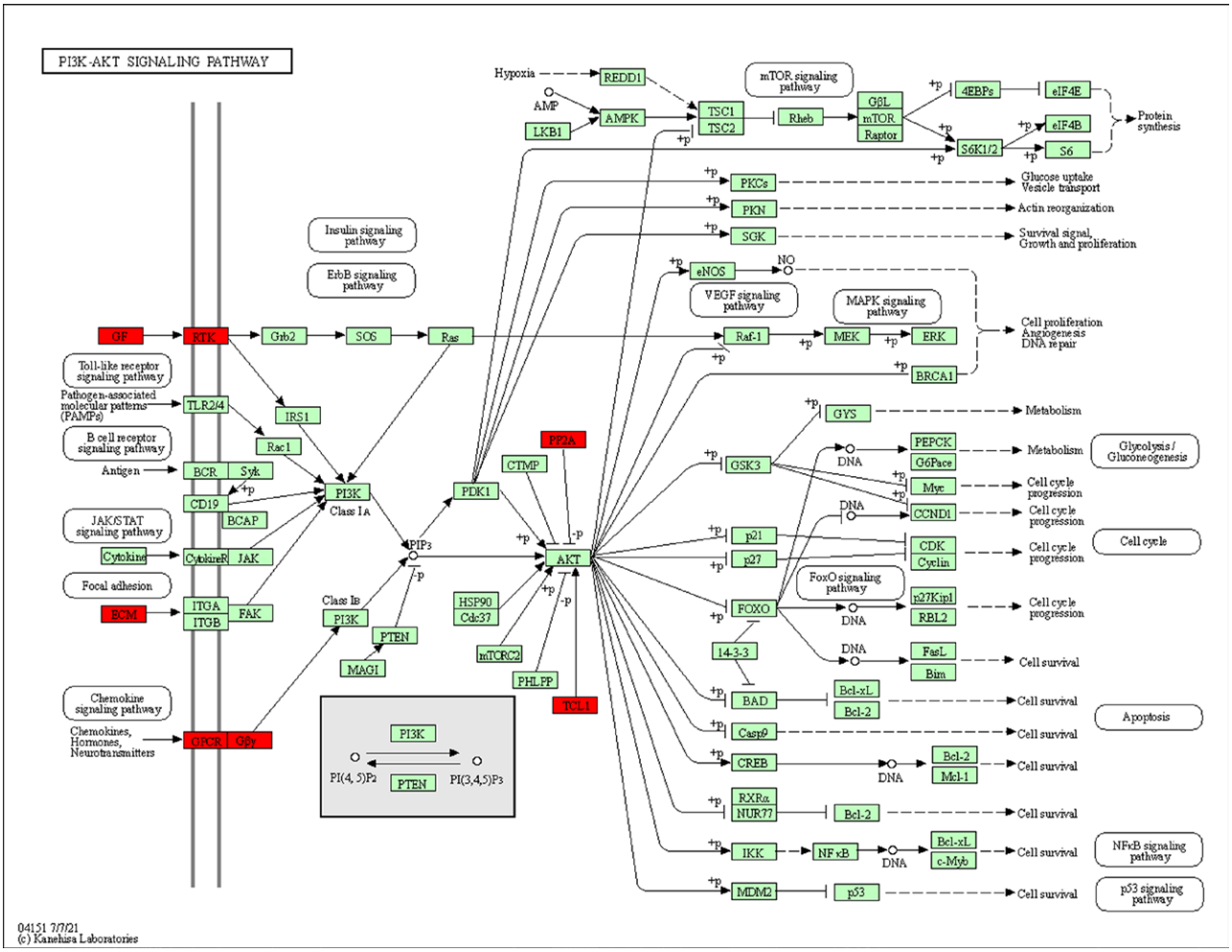

Figure 4. PI3K/AKT signaling pathway.

LBW. Together, the enrichment of the PI3K/AKT signaling pathway and its important regulator existing in the core network of LBW highlighted an underlying role of this pathway in metabolic challenges induced by LBW.

In this study, upstream signaling molecules of the PI3K/AKT signaling pathway including EGF, AREG, ERBB3, CHRM1 and COL4A6, were shown to be significantly increased in the umbilical cord of LBW individuals. ErbB3 can activate the PI3K/AKT pathway through phosphorylation, thereby enhancing insulin sensitivity.[27] EGF, a member of the EGFR-like ligand family, acts by binding to EGF receptors, including ErbB3 (HER3).[28] AREG is an epidermal growth factor receptor (EGFR) ligand, the protein encoded by this gene is a member of the epidermal growth factor family,[29] AREG also induces phosphorylation of ErbB3 to activate the PI3K/AKT pathway,[30] and then improves insulin resistance. COL4A6 can activate fibroblasts to synthesize collagen via PI3K/AKT pathway.[31] CHRM1 is capable of activating PI3K/AKT pathway through methylation.[30] The upregulation of these genes suggested an activated PI3K/AKT signaling pathway in LBW infants, which may help them to adapt to the nutrient-deprived environment and facilitate their growth and development. At birth, LBW infants display increased insulin sensitivity which may promote their short-term development.[32,33] Yet the excessive enhanced insulin sensitivity may adversely increase the risk of chronic diseases and may be detrimental to long-term health.[34,35] Animal studies have revealed that LBW individuals exhibited lower insulin levels and increased insulin sensitivity at birth compared to NBW individuals, but their fasting insulin levels increased with the advanced age and the LBW subjects would finally develop insulin resistance in adult life.[36,37] A clinical study also reported that LBW infants showed a marked transition from increased insulin sensitivity at birth to insulin resistance over the first 3 years of life.[38] Considering the significant role of the PI3K/AKT pathway in the regulation of insulin sensitivity,[22,39] its activation in LBW individuals may be an important mechanism for short-term benefits but adversely cause extra metabolic stress when the nutritional environment improves and thereby potentially induce metabolic disorders in adulthood.

According to the "thrifty phenotype hypothesis" proposed by Barker and Hales, to survive in a nutrient-deprived environment, the fetus would make adaption to grow and develop rapidly with limited energy.[40] Such alterations are beneficial if the undernutrition persists after birth but may predispose the individual to obesity and impaired glucose tolerance if conditions improve.[41] Therefore, long-term monitoring of insulin sensitivity and blood glucose levels in LBW infants is extremely significant. In the meantime, healthy nutritional habits during pregnancy should be strongly emphasized before pregnancy to ensure that the fetus receives proper nutrition from the first moment of the mother's pregnancy. Avoiding the rapid weight gain caused by overnutrition after birth and adopting healthy lifestyle habits early may be an effective way to prevent insulin resistance in individuals with LBW. From this aspect, our observations based on umbilical cord tissues may provide potent targets for the prevention of chronic diseases such as diabetes in LBW infants in the future.

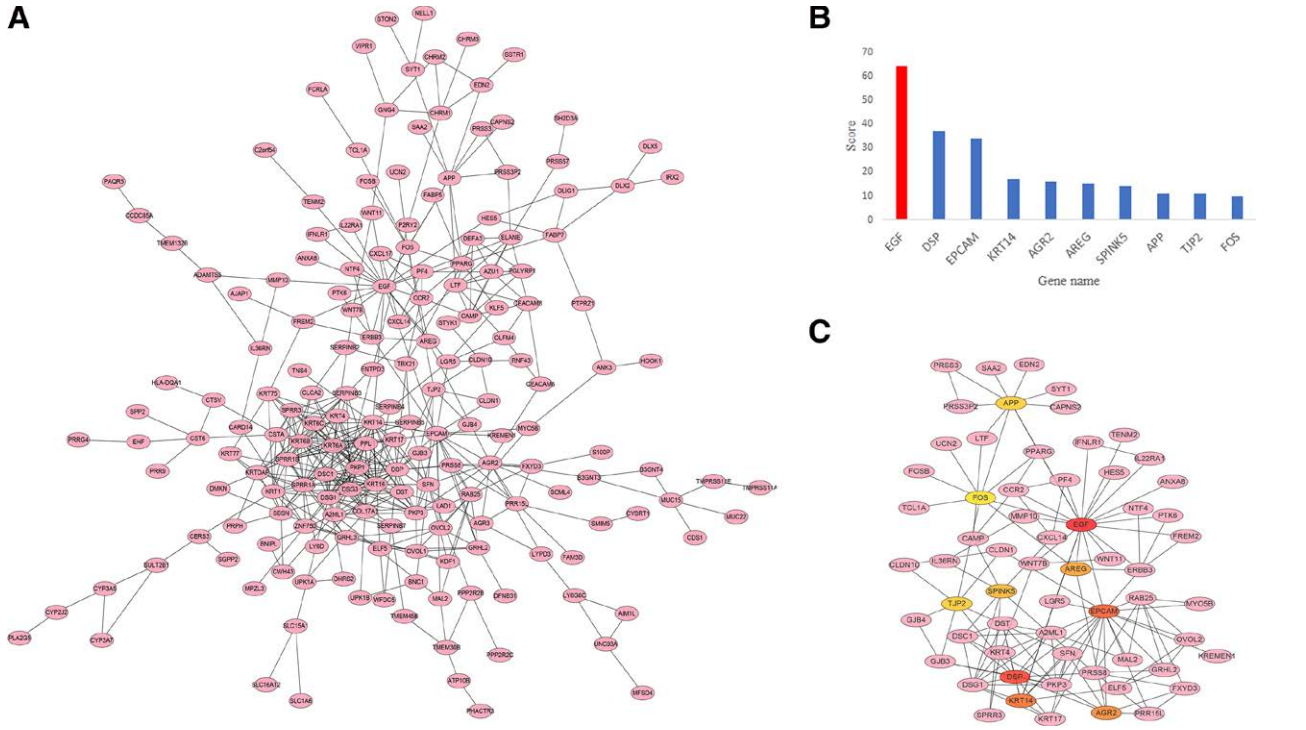

Figure 5. PPI network of DEGs and hub genes. (A) PPI network of DEGs. Pink nodes represent the interaction among DEGs. Only the 184 DEGs that interact with other ones were demonstrated in the network. (B) The score of degree top10 with neighbors and shortest paths. (C) Top 10 hub genes identified from the PPI network. From the red nodes to the yellow ones, the connection degree of each molecule with others gradually decreases. DEGs = differentially expressed genes, PPI = protein-protein interaction.

As umbilical cord tissue is only representative of the state of LBW infants in utero or at birth, long-term monitoring of metabolic changes in LBW individuals is undoubtedly necessary and proper postnatal nutritional interventions in health control of LBW infants are important directions for future following studies.

5. Conclusion

A total of 326 DEGs and 10 hub genes were identified as candidate genes for metabolic disorders in LBW individuals. Our results indicated the changes of the PI3K/AKT signaling pathway as an important intrauterine adaptive mechanism for LBW individuals. We observed activated PI3K/AKT pathway in LBW individuals, which may promote the growth and development at the early stage of life, but may adversely introduce extra metabolic stress and thereby potentially induce metabolic disorders in adulthood. Our study provided a theoretical basis for the molecule mechanism of early prevention in LBW individuals and a new target for the treatment of chronic metabolic diseases such as T2DM.

Author contributions

Fei Zhou performed the data analysis and wrote this manuscript. Tiantian Cheng sorted out the data. Fei Zhou conceived and designed the experiments. Linlin Yang revised the manuscript. Linlin Yang and Huijuan Ma performed project coordination and supervised the project. All authors have seen and approved the final manuscript.
Conceptualization: Linlin Yang, Huijuan Ma.
Data curation: Fei Zhou.
Formal analysis: Tiantian Cheng.
Methodology: Linlin Yang.
Supervision: Yuling Xing.
Validation: Tiantian Cheng.
Visualization: Fei Zhou.
Writing – original draft: Fei Zhou.
Writing – review & editing: Linlin Yang, Huijuan Ma.

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