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

Fei Zhou, MM, Tian Tian Cheng, MM, Yuling Xing, MM, Huijuan Ma, MD, Linlin Yang, MD

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 | logFC | ≥ 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 intraterine 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.[1] An adverse intrauterine environment, such as maternal malnutrition, may perturb the growth and development of the fetus during pregnancy and finally induce LBW.[3,4] 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.

*Correspondence: Huijuan Ma, Hebei Key Laboratory of Metabolic Diseases, Hebei General Hospital, (e-mail: huijuanma76@163.com)

Copyright © 2022 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Zhou F, Cheng T, Xing Y, Ma H, Yang L. Network exploration of gene signatures underlying low birth weight induced metabolic alterations. Medicine 2022;101:43(e31489).

Received: 24 May 2022 / Received in final form: 4 October 2022 / Accepted: 4 October 2022

http://dx.doi.org/10.1097/MD.0000000000031489
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 of fetal, which demonstrates great potential in the research of metabolic disorders caused by LBW and would provide novel help to explore critical DEGs underlying the pathogenesis of diseases in infants with LBW.[13] In this context, the present study could be novel biomarkers for the early identification of metabolic down regulated and Genomes (KEGG) pathway enrichment analysis. GO Ontology (GO) annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) 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), 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. 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 searching 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, Low” 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 log2FC (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 < 0.05 and log2FC > 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.
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
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. 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. Our previous meta-analysis also showed that LBW significantly increased the future risk of developing T2DM. 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. Insulin resistance is a disorder of glucose metabolism that plays a crucial role in T2DM. The activation of the PI3K/AKT signaling pathway could improve insulin sensitivity and alleviate T2DM. 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 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. 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. Our previous meta-analysis also showed that LBW significantly increased the future risk of developing T2DM. 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. Insulin resistance is a disorder of glucose metabolism that plays a crucial role in T2DM. The activation of the PI3K/AKT signaling pathway could improve insulin sensitivity and alleviate T2DM. 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 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. 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. Our previous meta-analysis also showed that LBW significantly increased the future risk of developing T2DM. 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. Insulin resistance is a disorder of glucose metabolism that plays a crucial role in T2DM. The activation of the PI3K/AKT signaling pathway could improve insulin sensitivity and alleviate T2DM. 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 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. 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. Our previous meta-analysis also showed that LBW significantly increased the future risk of developing T2DM. 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. Insulin resistance is a disorder of glucose metabolism that plays a crucial role in T2DM. The activation of the PI3K/AKT signaling pathway could improve insulin sensitivity and alleviate T2DM. 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 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).
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 EGFR 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 adulthood.\(^{[36,37]}\) 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 adaptations 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.
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.

References
[1] Scherb H, Hayashi K. Spatiotemporal association of low birth weight with Cs-137 deposition at the prefecture level in Japan after the Fukushima nuclear power plant accidents: an analytical-ecologic epidemiological study. Environ Health. 2020;19:82.
[2] Anil KC, Basel PL, Singh S. Low birth weight and its associated risk factors: health facility-based case-control study. PLoS One. 2020;15:e0234907.
[3] Salmi I, Hannawi S. Birthweight predicts adult cardiovascular disorders: population based cross sectional survey. Clin Cardiol. 2020;43:1133–41.
[4] Resnik R. Intrauterine growth restriction. Obstet Gynecol. 2002;99:490–6.
[5] Xu XF, Hu QY, Liang LF, et al. Epigenetics of hyper-responsiveness to allergen challenge following intrauterine growth retardation rat. Respir Res. 2014;15:137.
[6] LaBarre JL, Puttabyatappa M, Song PXK, et al. Maternal lipid levels across pregnancy impact the umbilical cord blood lipidome and infant birth weight. Sci Rep. 2020;10:14209.
[7] Ribel-Madsen A, Hellgren LI, Brøns C, et al. Plasma amino acid levels are elevated in young, healthy low birth weight men exposed to short-term high-fat overfeeding. Physiol Rep. 2016;4:e13044.
[8] Tran NT, Alexandre-Gouabau MC, Pagniez A, et al. Neonatal citrulline supplementation and later exposure to a high fructose diet in rats born with a low birth weight: a preliminary report. Nutrients. 2017;9:375.
[9] Felicioni F, Santos TG, Paula T, et al. Intrauterine growth restriction: screening and diagnosis using animal models. Anim Reprod. 2020;16:66–71.
[10] Singh S, Singh VK, Rai G. Identification of differentially expressed hematopoiesis-associated genes in term low birth weight newborns by systems genomics approach. Curr Genomics. 2019;20:469–82.
[11] Goyal U, Sen A, Ta M. Isolation and molecular characterization of progenitor cells from human umbilical cord. Methods Mol Biol. 2019;2029:1–13.
[12] Balkawade NU, Shinde MA. Study of length of umbilical cord and fetal outcome: a study of 1,000 deliveries. J Obstet Gynaecol India. 2012;62:520–5.

[13] Mas-Pares B, Xargay-Torrent S, Bonmati A, et al. Umbilical cord miRNAs in small-for-gestational-age children and association with catch-up growth: a pilot study. J Clin Endocrinol Metab. 2019;104:5258–98.

[14] Paul A. How the first nine months shape the rest of your life. Time Mag. 2010;176:31–5.

[15] Talie A, Tadele M, Alemayehu M. Magnitude of low birth weight and associated factors among newborns delivered in Dangla primary hospital, Amhara Regional State, Northwest Ethiopia, 2017. J Pregnancy. 2019;2019:3587239.

[16] Martin-Calvo N, Goni L, Tur JA, et al. Low birth weight and small for gestational age are associated with complications of childhood and adolescence obesity: systematic review and meta-analysis. Obes Rev. 2022;23(Suppl 1):e13380.

[17] Zhao H, Song A, Zhang Y, et al. The association between birth weight and the risk of type 2 diabetes mellitus: a systematic review and meta-analysis. Endocr J. 2018;65:923–33.

[18] Dai HB, Wang HY, Wang FZ, et al. Adrenomedullin ameliorates palmitic acid-induced insulin resistance through PI3K/Akt pathway in adipocytes. Acta Diabetol. 2022;59:661–73.

[19] Sun R, Li D, Sun M, et al. Bacillus natto ameliorates obesity by regulating PI3K/AKT pathways in rats. Biochem Biophys Res Commun. 2022;603:160–6.

[20] Aierken A, Li B, Liu P, et al. Melatonin treatment improves human umbilical cord mesenchymal stem cell therapy in a mouse model of type II diabetes mellitus via the PI3K/AKT signaling pathway. Stem Cell Res Ther. 2022;13:164.

[21] Kuang JR, Zhang ZH, Leng WL, et al. Dapper1 attenuates hepatic gluconeogenesis and lipogenesis by activating PI3K/Akt signaling. Mol Cell Endocrinol. 2017;447:106–15.

[22] Li Y, Tang Y, Shi S, et al. Tetrahedral framework nucleic acids ameliorate palmitic acid-induced insulin resistance through PI3K/Akt pathway in adipocytes. Acta Diabetol. 2022;59:661–73.

[23] Zheng XD, Huang Y, Li H. Regulatory role of Apelin-13-mediated PI3K/AKT signaling pathway in the glucose and lipid metabolism of mouse with gestational diabetes mellitus. Immunobiology. 2021;226:152135.

[24] Gao C, Fei X, Wang M, Chen Q, Zhao N. Cardamomin protects from diabetes-induced kidney damage through modulating PI3K/AKT and JAK/STAT signaling pathways in rats. Int Immunopharmacol. 2022;107:108610.

[25] Ren BC, Zhang YF, Liu SS, et al. Curcumin alleviates oxidative stress and inhibits apoptosis in diabetic cardiomyopathy via Sirt1-Foxo1 and PI3K-Akt signalling pathways. J Cell Mol Med. 2020;24:12355–67.

[26] Hou N, Mai Y, Qiu X, et al. Carvacrol attenuates diabetic cardiomyopathy by modulating the PI3K/AKT/GLUT4 pathway in diabetic mice. Front Pharmacol. 2019;10:998.

[27] Meng D, Pan H, Chen Y, et al. Roles and mechanisms of NRG1 in modulating the pathogenesis of NAFLD through ErbB3 signaling in hepatocytes (NRG1 modulates NAFLD through ErbB3 signaling). Obes Res Clin Pract. 2021;15:145–51.

[28] Hu Q, Xu S, Ye C, et al. Novel pituitary actions of epidermal growth factor: receptor specificity and signal transduction for UTS1, EGR1, and MMP13 regulation by EGFR. Int J Mol Sci. 2019;20:28.

[29] Wang L, Wang L, Zhang H, et al. AREG mediates the epithelial-mesenchymal transition in pancreatic cancer cells via the EGFR/ERK/NF-κB signalling pathway. Oncol Rep. 2020;43:1558–68.

[30] Tian T, Lai X, Xiang K, et al. Hypermethylilation of PI3K-AKT signalling pathway genes is associated with human neural tube defects. Epigenetics. 2022;17:133–46.

[31] Ryu D, Lee C. Expression quantitative trait loci for PI3K/AKT pathway. Medicine. 2017;96:e5817.

[32] Sena S, Sridhar MG, Bhat V, et al. Insulin sensitivity and insulin secretion at birth in intrauterine growth retarded infants. Pathology. 2006;38:236–8.

[33] Camacho LE, Chen X, Hay WW, Jr, et al. Enhanced insulin secretion and insulin sensitivity in young lambs with placental insufficiency-induced intrauterine growth restriction. Am J Physiol Regul Integr Comp Physiol. 2017;313:R101–9.

[34] Pal A, Barber TM, Van de Bunt M, et al. PTEN mutations as a cause of constitutive insulin sensitivity and obesity. N Engl J Med. 2012;367:1002–11.

[35] Christopher BA, Huang HM, Berthiaume JM, et al. Myocardial insulin resistance induced by high fat feeding in heart failure is associated with preserved contractile function. Am J Physiol Heart Circ Physiol. 2010;299:H1917–27.

[36] Isganaitis E, Jimenez-Chillaron J, Woo M, et al. Accelerated postnatal growth increases lipogenic gene expression and adipocyte size in low birth weight mice. Diabetes. 2009;58:1192–200.

[37] Stutte S, Gohlke B, Peiler A, et al. Impact of early nutrition on body composition in children aged 9.5 years born with extremely low birth weight. Nutrients. 2017;9:124.

[38] Merico V, Ong KK, Bazaes R, et al. Longitudinal changes in insulin sensitivity and secretion from birth to age three years in small- and appropriate-for-gestational-age children. Diabetologia. 2005;48:2609–14.

[39] Merico V, Ong KK, Bazaes R, et al. Longitudinal changes in insulin sensitivity and secretion from birth to age three years in small- and appropriate-for-gestational-age children. Diabetologia. 2005;48:2609–14.

[40] Su X, Gu D, Xu L, et al. PI3K/Akt pathway expression in children with different obesity degrees and its relationship with glucolipid metabolism in insulin resistance. Am J Trans Res. 2021;13:6592–8.

[41] Pal A, Barber TM, Van de Bunt M, et al. PTEN mutations as a cause of constitutive insulin sensitivity and obesity. N Engl J Med. 2012;367:1002–11.

[42] Stutte S, Gohlke B, Peiler A, et al. Impact of early nutrition on body composition in children aged 9.5 years born with extremely low birth weight. Nutrients. 2017;9:124.

[43] Merico V, Ong KK, Bazaes R, et al. Longitudinal changes in insulin sensitivity and secretion from birth to age three years in small- and appropriate-for-gestational-age children. Diabetologia. 2005;48:2609–14.

[44] Hu Q, Xu S, Ye C, et al. Novel pituitary actions of epidermal growth factor: receptor specificity and signal transduction for UTS1, EGR1, and MMP13 regulation by EGFR. Int J Mol Sci. 2019;20:28.

[45] Vaara J, Weimer E, Levy M, et al. The thrifty phenotype hypothesis: the association between ultrasound and Doppler studies in fetal growth restriction and the development of adult disease. 2021;3:100473.