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# Screening of Biomarkers for Hypertension Susceptibility in Pregnancy

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**[Abstract]** ***Objective:*** To study the differential lncRNA / mRNA expression profiles of placental tissues in patients with gestational hypertension, analyze their possible mechanisms of action, and explore their target genes and small molecule drug-related lncRNAs. ***Methods:*** Three patients with gestational hypertension who were treated in our hospital from May 2018 to May 2019 were selected as the research subjects and three healthy pregnant women who underwent a prenatal examination in the same hospital were selected as the control group. The placental tissues were taken from the patients. RNA-sequencing was performed to construct lncRNA/mRNA differential expression profiles; screening differentially expressed lncRNAs were used to predict target genes, and GO and KEGG enrichment analysis predicted the biological functions of target genes and the enriched signal pathways, respectively. Protein-protein interaction network, lncRNA-miRNA-mRNA network, and differentially expressed gene-small molecule drug association networks were constructed. ***Results:*** RNA-seq analysis revealed 19 differentially expressed lncRNA (4 up-regulated; 15 down-regulated) ($P<0.05$). Moreover, 423 differentially expressed genes (DEGs) (84 up-regulated; 339 down-regulated)($P<0.05$). GO and KEGG enrichment analysis found that gestational hypertension is mainly related to endothelial cell damage, inflammatory response, abnormal immune regulation, and abnormal trophoblast invasion. The PPI network and lncRNA-miRNA-mRNA network were constructed. Differentially expressed gene-drug small molecule prediction results found 19 pairs of differentially gene-small drug relationship pairs, mainly including antibody, inhibitor et al. Conclusion: Differently expressed lncRNAs in the placenta of patients with gestational hypertension can participate in the regulation of multiple biological functional level-related signal pathways through targeted regulation of their target genes, and play an important role in the occurrence and development of gestational hypertension. The predicted small molecule drug can be used as a reference for clinical treatment.

**Keywords:** Gestational hypertension; LncRNA; Competitive endogenous RNA; Small molecule drug prediction

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Gestational hypertension is a common clinical condition during pregnancy, usually appearing after 20 weeks of gestation, characterized by increased blood pressure and proteinuria. Gestational hypertension is an important cause of maternal and perinatal morbidity and even mortality[1]. At present, the pathogenesis of gestational hypertension has not been clarified, and there is a lack of effective diagnosis and treatment, so termination of pregnancy is the fundamental solution[2]. Recent studies have found significant differences in gene expression and epigenetic mechanisms between the placenta of patients with gestational hypertension and the placenta of normal pregnancies, suggesting that

the gene expression differences between gestational placentas and normal placentas can be studied to investigate the mechanism of gestational hypertension[3].

Long noncoding RNA is a widespread class of noncoding protein genes in the human genome, which plays an important role in biological functions such as epigenetics and transcriptional levels[4]. Recent studies have found that certain lncRNAs can affect the expression blockade of the mRNAs of target genes and their protein expression levels by competitively adsorbing miRNAs[5]. This regulatory pattern(lncRNA-miRNA-mRNA) is known as the ceRNA (competitive endogenous RNA) network. Under normal physiological conditions, the members of the ceRNA network are in a state of equilibrium, but when this competitive balance is disrupted, it can lead to disease[6]. Therefore, it is biologically important to study the ceRNA network during the development of gestation.

In this paper, the lncRNA and mRNA expression profiles of placenta tissues in gestational hyperemia patients and normal maternal were sequenced to screen for gestational hyperemia-associated differential lncRNAs and mRNAs, and functional studies of differential mRNAs were performed by enrichment analysis. By constructing a ceRNA network, lncRNA-miRNA-mRNA regulatory relationships that may be associated with the occurrence of gestational hypertension were screened, and small molecule drug prediction of the differential mRNAs was performed finally. The findings have implications for the pathogenesis of gestational hypertension and the screening of therapeutic agents.

## 1 Objects and methods

### 1.1 Materials

Three patients with gestational hypertension treated at our hospital from May 2018 to May 2019 were selected as the study subjects, and three healthy pregnant women who underwent a prenatal examination in the same hospital were selected as the control group. Both groups were aged 25-35 years and delivered at full term. Within 5 min after delivery of the placenta, 1 cm × 1 cm of placental tissue was cut from different areas of the placenta and frozen in liquid nitrogen after PBS rinsing. This study was approved and agreed upon by the ethics committee of this institution.

### 1.2 Inclusion and exclusion criteria

Inclusion criteria: (1) compliance with the Obstetrics and Gynecology criteria for the diagnosis of gestational hypertension[5]; (2) singleton; (3) informed and signed consent of the subjects.

Exclusion criteria: (1) combination of heart, liver, and other organ diseases; (2) combination of mental illness; (3) combination of pregnancy-related complications such as gestational hypertension and gestational diabetes; (4) combination of immune system diseases; (5) combination of coagulopathy.

### 1.3 Materials and reagents

TRIzol kit (Invitrogen, USA); Nanodrop microspectrophotometer, Qubit fluorescence quantifier (Thermo Fisher, USA); Agilent 2100 biochip analysis system (Thermo Fisher, USA); ribs-zero kit. Illumina Sequencer (Illumina, USA); RNA Fragmentation Reagents (ABI, USA); Agencourt RNA Clean XP Kit (Beckman, USA); Agilent 2100 Bioanalyzer (US) (Agilent); cDNA synthesis was entrusted to Shanghai Ouyi Biomedical Technology Co.

### 1.4 RNA extraction and RNA sequencing of tissue samples

The total RNA in the different tissues was extracted by the TRIzol method; RNA integrity, degradation, and contamination were measured by agarose gel electrophoresis; RNA purity was measured by microspectrophotometry; the concentration was determined by fluorescence quantification, and the purity and integrity of RNA were measured by the biochip analysis system. The lncRNA and mRNA gene chip expression profiles were amplified by PCR after completion of quality control, and sequenced after quality control was passed[7]. The raw signals were log2 transformed using a fractional algorithm. The screening conditions for differential expression of lncRNA and mRNA were: multiplicative change in gene expression value ($|\log2\ FC(\text{fold change})| > 0.585$ and $P < 0.05$.

### 1.5 GO functional enrichment analysis and KEGG signaling pathway analysis

The differentially expressed lncRNA target genes were enriched and mapped using Gene Ontology and Kyoto Encyclo dia of Genes and Genomes pathway. GO functionally annotated the differentially expressed lncRNA target genes in tissue samples to screen the biological functions of differentially expressed genes; KEGG signaling pathway was used to annotate the biological pathways of differentially expressed lncRNA target genes to screen the signaling regulatory networks associated with gestational hyperacusis. $P < 0.05$ indicates statistically significant signaling pathway

entries[8].

### 1.6 Target gene PPI network construction and module analysis

Target gene PPI networks were constructed using STRING database analysis and Cytosca gestalt software. After the list of protein names of target genes was entered into the STRING database (https://string-db.org/cgi/input.pl), the species was selected as human gestosis and the protein interaction score was >0.7, and these genes were selected for PPI network analysis. PPI networks were mapped using Cytosca Gestalt 3.6.1 software, and protein-coding genes with node degree≥10 were set as core genes in PPI. The most significantly clustered modules in the PPI network were analyzed using the Cytoscape gestalt plugin MCODE (Version 1.4.2, http://apps.cytosca.org/apps/MCODE) method, with a threshold selection score≥10[9].

### 1.7 LncRNA-miRNA-mRNA ceRNA network construction analysis

Using data from differentially expressed lncRNAs and mRNAs, the gestational correlation coefficient was calculated for each differentially expressed mRNA and lncRNA, and correlation tests were performed to further screen|r|> 0.9 and P < 0.05 for lncRNA-mRNA co-expression relationships.

Top50 lncRNA-mRNA with positive lncRNA-mRNA relationship pairs were screened and miRNAs interacting with lncRNAs were predicted by LncBase Predicted v.2. DIANA-micro web server v5.0 was used to organize the miRNA-target regulatory data, screen the mRNAs belonging to the lncRNA-mRNA positive correlation pairs in their target genes, and organize the miRNA-mRNA regulatory relationship pairs obtained. Construction of lncRNA-miRNA-mRNA complex networks using Cytoscape gestosis.

### 1.8 Small molecule prediction of differentially expressed genes corresponding to drugs

We used DGIdb2.0 (http://www.dgidb.org/) to predict the genes in the network. Parameter settings were selected to default all, all small-molecule drug-gene relationship pairs were predicted, and small molecule drug-gene network maps were constructed using Cytoscape gestosis[10].

### 1.9 Statistical analysis

The data were analyzed using SPSS 19.0 software. Data are presented as mean ± standard deviation (x ± s),

**Table 1.** CDifferential expression of lncRNA results

| lncRNA | LogFC | AveExpr | t | P |
|---|---|---|---|---|
| FAM157C | 1.600172 | 2.550985 | 6.318292 | 0.001456 |
| LINC00456 | 1.104517 | 1.87919 | 3.541389 | 0.016501 |
| LUCAT1 | 0.805575 | 1.076365 | 3.886149 | 0.011539 |
| SNHG9 | 0.750271 | 1.29222 | 4.246097 | 0.008098 |
| LINC00330 | -0.58877 | 0.672528 | -4.95819 | 0.004239 |
| MBNL1-AS1 | -0.60822 | 0.711577 | -6.8825 | 0.000986 |
| LINC00636 | -0.61111 | 0.975464 | -2.94279 | 0.0321 |
| LINC01140 | -0.62678 | 1.258545 | -3.39959 | 0.019219 |
| LINC01128 | -0.64 | 2.305968 | -2.9653 | 0.031274 |
| LINC01192 | -0.65661 | 1.750965 | -2.84022 | 0.036181 |
| LINC00698 | -0.69443 | 0.980105 | -2.73328 | 0.04106 |
| MIR2052HG | -0.69447 | 0.67808 | -5.26448 | 0.003274 |
| LINC01036 | -0.73062 | 1.658452 | -3.45124 | 0.018174 |
| TSPOAP1-AS1 | -0.74248 | 1.773524 | -5.72767 | 0.00226 |
| TRG-AS1 | -0.76327 | 0.903662 | -4.08928 | 0.009427 |
| FAM87B | -0.90674 | 0.545416 | -9.65009 | 0.000201 |
| PTCHD1-AS | -0.91074 | 4.13314 | -3.87263 | 0.011698 |
| MIR325HG | -0.95023 | 0.575451 | -4.72485 | 0.005202 |
| LINC01320 | -1.65409 | 1.728522 | -2.92259 | 0.032861 |

Table 2. Differentially expressed mRNA expression results (partial).

| Symbol | LogFC | AveExpr | *t* | *P* |
|---|---|---|---|---|
| CGB3 | 5.523845 | 5.692345 | 5.343965 | 0.002595 |
| CGB8 | 3.760718 | 5.588646 | 3.104613 | 0.024784 |
| LEP | 3.684564 | 3.957328 | 3.569609 | 0.014591 |
| IL1RL1 | 3.112503 | 5.588131 | 10.40725 | 0.000101 |
| DERL3 | 2.646095 | 2.127056 | 3.45751 | 0.016527 |
| ARMS2 | 2.548396 | 2.049296 | 3.20463 | 0.022051 |
| CPXM2 | 2.171579 | 3.079242 | 4.828824 | 0.004099 |
| OR2T10 | 2.111463 | 1.079378 | 4.03245 | 0.008905 |
| COL8A1 | -2.06833 | 2.823396 | -4.47092 | 0.005745 |
| CNN1 | -2.06877 | 2.567256 | -7.05776 | 0.000698 |
| SULF1 | -2.1027 | 2.830619 | -4.26242 | 0.007052 |
| CD74 | -2.11289 | 6.982375 | -6.69603 | 0.0009 |
| GNLY | -2.15642 | 3.37024 | -2.98927 | 0.028413 |
| CXCL10 | -2.1713 | 1.733418 | -7.63938 | 0.000474 |
| CCL14 | -2.17205 | 1.906973 | -5.93778 | 0.001593 |
| CXCL9 | -2.17466 | 1.406116 | -3.3683 | 0.018276 |
| CYP4B1 | -2.17599 | 2.236887 | -4.70966 | 0.004578 |
| HLA-DRB1 | -2.36595 | 5.054898 | -4.789 | 0.004252 |
| DEFB1 | -2.47778 | 2.451533 | -3.17793 | 0.022746 |
| PAEP | -3.69272 | 5.572724 | -2.90058 | 0.031605 |
| CCL21 | -4.86204 | 2.485521 | -9.50786 | 0.00016 |

and differences between groups were analyzed by one-way ANOVA, with $P < 0.05$ indicating a statistically significant difference.

## 2 Results

### 2.1 LncRNA and mRNA expression analysis

Differences in lncRNA and mRNA expression heat maps and volcano maps between gestational and normal maternal placental tissues are shown in Figure 1. A total of 19 differentially expressed lncRNAs, including 4 up-regulated lncRNAs and 15 down-regulated lncRNAs, were screened in gestational placentas compared to normal placentas (see Table 1). 423 differentially expressed mRNAs ($|\log2\ FC| > 0.585$ and $P < 0.05$), including 84 up-regulated mRNAs and 339 down-regulated mRNAs, were screened (Table 2).

### 2.2 GO enrichment analysis

GO enrichment analysis of differential lncRNA/mRNA expression showed that Biological Process was predominantly enriched in entries for the inflammatory response, regulation of cytokine secretion, interferon γ secretion and regulation, regulation of T helper immune response, regulation of leukocyte migration adhesion, and regulation of T cell activation migration (Figure 2A to Figure 2B). Cellular Component is mainly enriched in the extracellular matrix, transfer vesicles, endoplasmic reticulum-Golgi, and other entries (Figure 2C to Figure 2D). The molecular Function process was enriched in the entries for receptor-ligand activation, growth factor binding, hormone activation, cytokine receptor binding, and transaminase activation (Figure 2E to Figure 2F).

### 2.3 KEGG metabolic pathway analysis

KEGG pathway metabolic pathway enrichment analysis revealed the following: differentially expressed up-regulated mRNAs were mainly enriched in signaling pathways such as cytokine-cytokine receptor interaction, MAPK signaling pathway, Ras signaling pathway, lysosomes, 2-monocarboxylic acid metabolism, amino

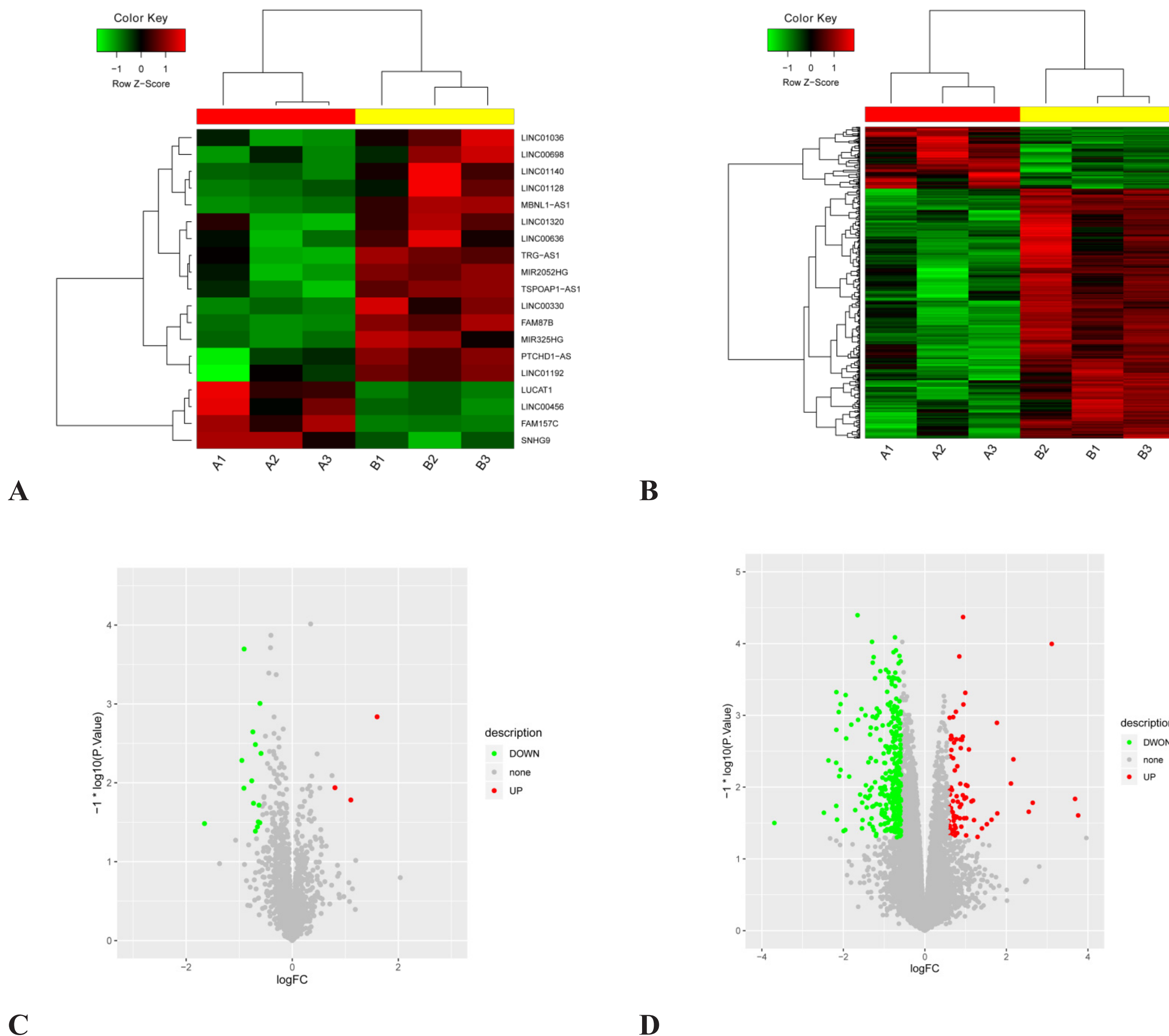



**Figure 1.** Differential lncRNA and mRNA expression profiles and volcano maps of the gestational placenta. (A: differentially expressed lncRNA heat map; B: differentially expressed mRNA heat map; C differential lncRNA volcano map; D: differential mRNA volcano map).

acid biosynthesis, and EGFR tyrosine kinase inhibitor resistance (Figure 3A). Differentially expressed down-regulated mRNAs were mainly enriched in Th1 and Th2 cell differentiation, cell adhesion molecules, chemokine signaling pathways, and interactions of the viral protein with cytokines and cytokine receptors (Figure 3B).

## 2.4 PPI network and sub-network modules

The PPI network of differential mRNAs is shown in Figure 4. The network has 219 nodes and 639 interacting relationship pairs. Two subnetwork modules of the PPI network were obtained using Cytosca gestalt plugin MCODE (score ≥ 10) aggregation: module-A (score=15) with 15 nodes and 105 interacting pairs; module-B (score=10) with 17 nodes and 117 interacting pairs. Module-a module core genes include the chemokine superfamily (CXCL9, CXCL10, CXCL11, CXCL12) and its receptor (CXCR3), the chemokine superfamily ligand family (CCL13, CCL21), the G protein coupling factor superfamily (CCR5) and its receptor (GPR17, GPR183), complement component 3a receptor 1 (C3AR1), the formyl peptide receptor 3 antigen (FPR3), the growth suppressor gene (SST), the neuropeptide Y1 receptor (NPY1R), and the purinergic receptor (P2RY14). Module-b module core genes include vascular cell adhesion molecule 1 (VCAM1), the human leukocyte DR antigen family (HLA-DRB1, HLA-DRB5, HLA-DPA1), CD molecules (CD2, CD247, CD8A), the Fc fragment of IgG receptor Ia (FCGR1A), the guanosine binding protein family (GBP1. GBP2, GBP3, GBP5) triple protein matrix sequence 22 (TRIM22), type II histocompatibility

A B

C D

E F

**Figure 2**. Differentially expressed mRNAs significantly enriched in GO entries (A, B: top ten up-regulated and down-regulated BP entries; C, D: top ten up-regulated and down-regulated CC entries; E, F: top ten up-regulated and down-regulated MF entries)

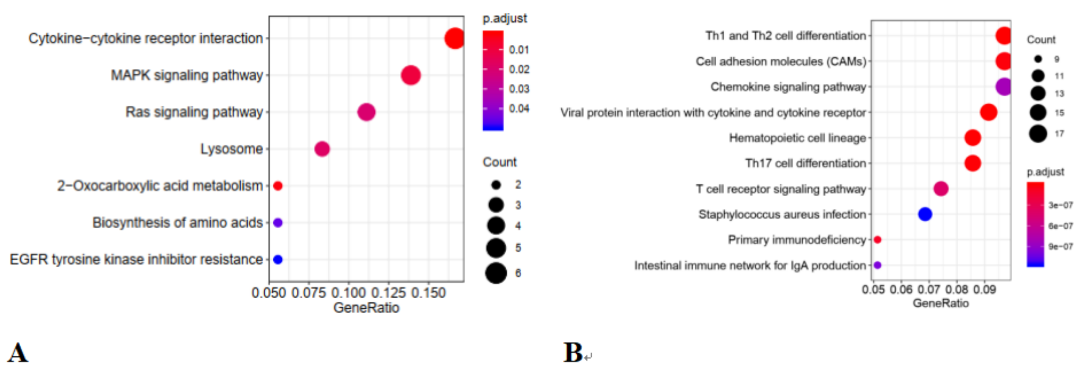
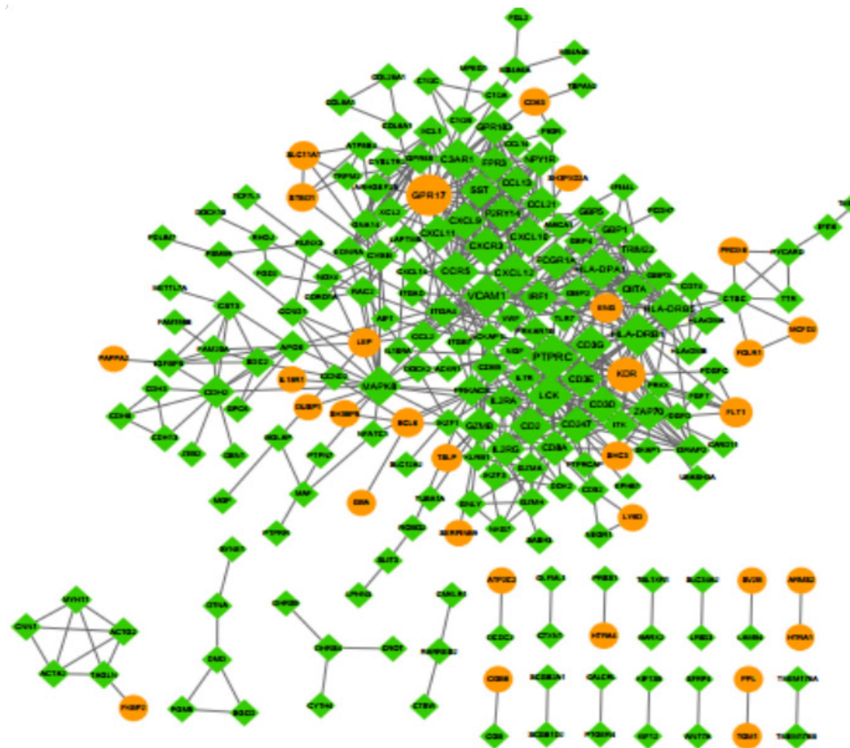
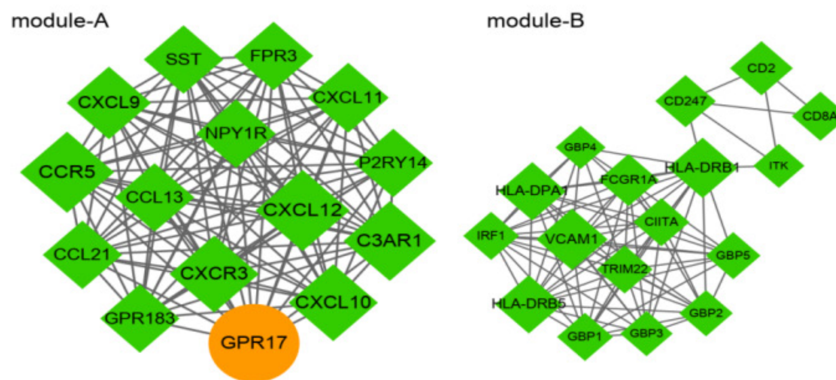



**Figure 3.** Results of KEGG pathway enrichment analysis (A: top ten up-regulated expressed pathway genes; B top ten down-regulated expressed pathway genes).



A




B

**Figure 4.** PPI network diagram and module diagram. (A: PPI network; B: PPI network module analysis). The yellow circle means up, the green prism means down, node size was in accordance with the degree value, the higher the degree value, the bigger the node.

complex trans-activator (CIITA), and interferon regulatory factor 1 (IRF1) (Table 3).

## 2.5 lncRNA-miRNA-mRNA ceRNA network construction

A total of 78 lncRNA-miRNA-mRNA relationship pairs were obtained, including 26 lncRNA-mRNA positive correlation co-expression pairs, 34 miRNA-mRNA regulatory relationship pairs, and 18 miRNA-lncRNA regulatory relationship pairs. A lncRNA-miRNA-mRNA network was constructed using Cytoscape gestalt. The network contained 18 miRNAs, 30 mRNAs, and 4 lncRNAs (Figure 5). Among them, LINC01128 regulates the most miRNAs and mRNAs in the network and has a central role in the network. Multiple ce-RNA relationships can be found in the network, e.g. LINC01128 regulates SAMD12 expression through competitive adsorption to hsa-miR-3148: LINC01128 can regulate PARPBP expression by competitive adsorption to hsa-miR-580-3p.

Red triangles are miRNAs, green prisms are down-gene; blue hexagons are down-regulated lncRNAs, red lines are positively correlated co-expression relationships,

**Table 3.** Module - Genotype list

| module-A | | | module-B | | |
|---|---|---|---|---|---|
| nodes | Gene expression direction | degree (of intensity) | nodes | Gene expression direction | degree (of intensity) |
| CXCL12 | DOWN | 23 | VCAM1 | DOWN | 26 |
| CCR5 | DOWN | 23 | HLA-DRB1 | DOWN | 25 |
| C3AR1 | DOWN | 22 | HLA-DRB5 | DOWN | 23 |
| GPR17 | UP | 21 | HLA-DPA1 | DOWN | 23 |
| CXCL10 | DOWN | 20 | CD2 | DOWN | 19 |
| CXCR3 | DOWN | 20 | FCGR1A | DOWN | 17 |
| CXCL9 | DOWN | 17 | CD247 | DOWN | 17 |
| CXCL11 | DOWN | 15 | CD8A | DOWN | 14 |
| FPR3 | DOWN | 14 | GBP1 | DOWN | 13 |
| CCL21 | DOWN | 14 | TRIM22 | DOWN | 13 |
| SST | DOWN | 14 | CIITA | DOWN | 13 |
| NPY1R | DOWN | 14 | IRF1 | DOWN | 13 |
| P2RY14 | DOWN | 14 | GBP5 | DOWN | 12 |
| GPR183 | DOWN | 14 | GBP2 | DOWN | 11 |
| CCL13 | DOWN | 14 | GBP3 | DOWN | 10 |

**Figure 5.** lncRNA-miRNA-mRNA network diagram

**Figure 6.** Prediction of small molecule drug-gene relationships

yellow lines are miRNA-lncRNA regulatory relationships, blue lines are miRNA-mRNA regulatory relationships, node size is based on the degree value, the higher the degree value, the bigger the node

## 2.6 Small molecule prediction of differentially expressed genes corresponding to drugs

Based on the DGIdb predictions of network genes, we obtained 19 small molecule drug-gene

interaction pairs, including 9 down genes and 19 drugs (Figure 6). Among them, PAEP was paired with CHEMBL1231458, PALMITIC ACID, and GLYCERIN, but the interaction type was unknown; KCND2 was paired with DALFAMPRIDINE and the interaction type was antagonist|blocker. IL2RA was paired with DENILEUKIN DIFTITOX and the interaction type was a binder, IL2RA was paired with HUMAN INTERLEUKIN-2 and the interaction type was agonist|modulator, IL2RA was paired with BASILIXIMAB and the interaction type was antibody|inhibitor, IL2RA was paired with DACLIZUMAB and the interaction type was antibody|inhibitor. HNMT was paired with AMODIAQUINE and the interaction type was inhibitor, HNMT was paired with S-ADENOSYLHOMOCYSTEINE, CHEMBL1230270, METOPRINE, but the interaction type was unknown. LAP3 was paired with LEUCINE PHOSPHONIC ACID and ZOFENOPRILAT, but the type of interaction was unknown. ACE2 paired with LISINOPRIL, and the interaction type was inhibitor; PLA2G2D paired with DODECANOATE and the interaction type was unknown. CD247 was paired with MUROMONAB-CD3 and the type of interaction was unknown. ONLY was paired with MYELO gestational ROXIDASE, but the type of interaction was unknown (Table 4).

## 3 Discussion

RNAs in organisms can be divided into mRNAs with protein-coding functions and ncRNAs (non-coding RNA, ncRNA), where protein-coding genes account for only 1% to 2% of human genes and ncRNAs account for up to 98% of human genes[11]. In recent years, an increasing number of studies have shown that ncRNAs also have important biological functions in living organisms. Unlike other ncRNAs such as miRNAs, lncRNAs have longer molecular chains (more than 200 nucleotides), more complex structures, can regulate gene expression at the transcriptional, post-transcriptional, and epigenetic levels, which are widely involved in the physiopathological processes of the body, playing an important role in the development of tumors, cardiovascular diseases, and psychiatric disorders[12-13]. Since the process of placental implantation during pregnancy is similar to that of tumor metastasis, the study of lncRNAs in pregnancy-related diseases is gaining importance[14].

Recent studies have shown that lncRNA is strongly

**Table 4.** Drug small molecule - gene prediction results

| genetic | medicines | Type of interaction |
|---|---|---|
| PAEP | CHEMBL1231458 | / |
| PAEP | PALMITIC ACID | / |
| PAEP | GLYCERIN | / |
| KCND2 | DALFAMPRIDINE | antagonist\|blocker |
| IL2RA | DENILEUKIN DIFTITOX | binder |
| IL2RA | HUMAN INTERLEUKIN-2 | agonist\|modulator |
| IL2RA | BASILIXIMAB | antibody\|inhibitor |
| IL2RA | DACLIZUMAB | antibody\|inhibitor |
| HNMT | AMODIAQUINE | inhibitor |
| HNMT | S-ADENOSYLHOMOCYSTEINE/ | / |
| HNMT | CHEMBL1230270 | / |
| HNMT | METOPRINE | / |
| LAP3 | LEUCINE PHOSPHONIC ACID | / |
| LAP3 | ZOFENOPRILAT | / |
| ACE2 | LISINOPRIL | inhibitor |
| PLA2G2D | DODECANOATE | / |
| PLA2G2D | STEARIC ACID | / |
| CD247 | MUROMONAB-CD3 | / |
| GNLY | MYELO ROXIDASE | / |

associated with the occurrence of several adverse pregnancy outcomes, but less research has been done on lncRNA in gestational hypertension[15]. In this paper, 19 differentially expressed lncRNAs and 423 differentially expressed mRNAs (P<0.05) were sequenced from the placenta of patients with gestational hypertension and normal maternal placenta samples, and the differential expression profile of gestational hypertensive placenta-associated lncRNAs was successfully established. GO functional enrichment analysis of target genes that significantly differentially expressed lncRNAs revealed the following: differentially expressed mRNAs are mainly enriched in entries for the inflammatory response, regulation of cytokine secretion, interferon-gamma secretion and regulation, and regulation of T-assisted immune response; Metabolic pathway enrichment analysis revealed the following: differentially expressed lncRNAs are enriched mainly in cytokine-cytokine receptor interactions, MAPK signaling pathway, Ras signaling pathway, and lysosomes. The above findings suggest that gestational hypertension is associated with endothelial cell injury, inflammatory response, abnormal immune regulation, and abnormal trophoblast invasion, which is generally consistent with the etiology of gestational hypertension reported in the literature[16].

The PPI network construction of the target gene was carried out to obtain a target gene containing 219 nodes. The genes with high modality are the chemokine superfamily (CXCL9, CXCL10, CXCL11, CXCL12) and its receptor (CXCR3), and the chemokine superfamily ligand family (CCL13, CCL21). The link between CXC chemokine expression and trophoblast invasion has also been studied more frequently because trophoblast cells have similar invasive properties to malignant tumor cells[17]. As CXCL10 is expressed in the vascular endothelium and vascular smooth muscle cells of the placenta, vascular extracellular trophoblast-induced CXCL10 expression contributes to the remodeling of spiral arteries by altering the motility and differentiation status of vascular smooth muscle cells in the vasculature[18-19]. This is consistent with our conclusion. Therefore, CXC chemokines are involved in the pathogenesis of gestational hyperemia and play an important role in gestational hyperemia-mediated neovascularization, embryonic development, and inflammatory response. The most typical immunological finding in gestational hypertension is the activation of the innate and adaptive immune systems[20]. It has been suggested that the lack of maternal tolerance to invasive trophoblasts may be a possible immunological trigger for the invasion of undesirable trophoblasts and the subsequent development of aura gestational. Tersigni et al[21] found that type II HLA-DR was detected in the gestational placenta but not in normal controls.

The pathogenesis of gestational hypertension is unclear and there are no ideal early clinical biomarkers to predict gestational hypertension. A ceRNA hypothesis is a new approach to uncovering the molecular pathology of gestational hypertension. In the text, a ceRNA network was constructed that contained ceRNA relationships between 18 miRNAs, 30 mRNAs, and 4 lncRNAs. Cheng et al[22] found that lncRNA Linc00261 is upregulated in gestational hypertension and affects trophoblast invasion and migration by regulating the miR-558 / TIMP4 signaling pathway. Xu et al[23] found that the lncRNA AGAP2-AS1 is downregulated in gestational hypertension and acts as a JDP2 ceRNA to disrupt the trophoblast phenotype. Four lncRNA (LINC01128, LINC01320, LINC01140, and FAM87B) related ceRNA networks were constructed in this study. Although these lncRNAs have been somewhat studied in tumors, their mechanism of action in gestational hypertension has not been investigated. Therefore, more experiments are still needed to validate the mechanism of action of this lncRNA-associated ceRNAs in gestational hypertension.

Through differentially expressed gene-drug small molecule predictions, we screened 19 differentially expressed gene-drug small molecule drug relationship pairs. The interaction types of small molecule drugs with differential genes were antagonist|blocker, antibody|inhibitor, inhibitor, such as davapyridine, barycizumab, dalizumab, amodiaquine, and lenopril, which may have the potential for the treatment of gestational hyperplasia.

In summary. The differentially expressed lncRNAs in the placenta of patients with gestational hypertension can play an important role in the development of gestational hypertension by targeting and regulating their target genes involved in the regulation of a variety of biological function-level related signaling pathways. Predicted small molecules can be used as a reference for the clinical treatment of gestational hypertension.

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