

Umbilical cord mesenchymal stem cells improve PINK1/PARKIN-mediated mitophagy inhibition in preeclampsia

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Abstract

Background

Preeclampsia (PE) is a progressive multisystem disorder that arises after 20 weeks of gestation and poses severe risks to both maternal and fetal health. Umbilical cord mesenchymal stem cells (UC-MSCs) exhibit antioxidant and pro-angiogenic properties, which have been shown to be effective in treating various diseases.

Methods

HTR8/SVneo cells were induced by lipopolysaccharide (LPS) to establish a PE cell model. Western blot (WB) and real-time quantitative PCR (RT-qPCR) were conducted to detect the expression of genes related to mitophagy. Meanwhile, ATP level was detected using an ATP content assay kit and mitochondrial membrane potential (MMP) level was detected under a fluorescence microscope using an MMP detection kit. Next, a PE rat model was induced using N(ω)-nitro-L-arginine methyl ester (L-NAME), followed by UC-MSCs transplantation. Enzyme-linked immunosorbent assay (ELISA) was used to measure serum levels of PE biomarkers, and the expression of mitophagy related genes was assessed via RT-qPCR, WB, and immunohistochemistry.

Results

UC-MSCs modulated the levels of Phosphatase and Tensin Homolog-induced Kinase 1 (PINK1), Parkin RBR E3 ubiquitin protein ligase (PARKIN), reversed the inhibition of mitophagy in the PE model and increased both ATP content and MMP. Importantly, UC-MSCs alleviated hypertension and proteinuria in PE rats, improved pregnancy outcomes, and mitigated the imbalance in angiogenesis.

Conclusion

This study demonstrates that UC-MSCs improve PE trophoblast injury and vascularization imbalance through regulating mitochondrial autophagy. Our results indicate that UC-MSCs may hold significant potential for treating PE.

1. Introduction

Preeclampsia (PE) is a unique multisystem progressive syndrome, characterized mainly by elevated blood pressure, often accompanied by proteinuria and other multiple organ dysfunction, and typically occurs following 20 weeks of gestation (1). In the general population, its prevalence ranges from around 2% to 6% (2). Of note, PE remains one of the leading causes of maternal and perinatal

morbidity/mortality in the world (3). Currently, the only effective measure is the timely termination of pregnancy (4).

With advancing research, the understanding of PE pathogenesis has evolved from the "two-stage theory" to the central pathogenic axis involving impaired spiral artery remodeling, placental ischemia and hypoxia, and maternal systemic endothelial dysfunction (5). Placental dysfunction is widely regarded as the main cause of PE, with mitochondrial dysfunction considered a key contributing factor, although the precise etiology remains incompletely understood (6–8). Meanwhile, hypoperfusion and ischemia-reperfusion injury in the placenta trigger oxidative stress by disrupting the equilibrium between antioxidants and reactive oxygen species (ROS). Under these conditions, the secretion of pro-angiogenic factor, placental growth factor (PLGF), decreases, while the level of anti-angiogenic factor, soluble fms-like tyrosine kinase-1 (sFlt-1), increases (9). Thus, the sFlt-1/PLGF ratio has become an important indicator for the diagnosis and assessment of PE (10–12).

As an important organelle for cellular energy metabolism and ROS production, the functional integrity of mitochondria is crucial for maintaining high-energy-demand placental trophoblasts and vascular endothelial cells (13, 14). Mitophagy, the process of selective autophagy to clear damaged mitochondria, is a central defense mechanism for maintaining mitochondrial quality control and cellular homeostasis. In recent years, increasing evidence has demonstrated significant mitochondrial morphological abnormalities and dysfunction in the placentas of PE patients, which are closely associated with altered expression of key mitophagy regulatory molecules (15–17). Importantly, these findings suggest that the dysregulation of mitophagy may be a key molecular bridge linking placental ischemia/hypoxia, cellular stress, and maternal systemic inflammatory response. Mitophagy driven by Phosphatase and Tensin Homolog-induced Kinase 1 (PINK1) and Parkin RBR E3 ubiquitin protein ligase (PARKIN) is a well-established ubiquitin-dependent mechanism for mitochondrial clearance. In damaged mitochondria, the loss of mitochondrial membrane potential (MMP) leads to the accumulation of PINK1 on the outer mitochondrial membrane, where it recruits and activates PARKIN through phosphorylation, thereby initiating the ubiquitin cascade and triggering mitophagy (18–20). Besides, Translocase of Outer Mitochondrial Membrane 20 (TOMM20) has been shown to play a significant role in mitochondrial autophagy (21), with Yu et al. also reporting that TOMM20 expression is downregulated in preeclampsia (22).

Mesenchymal stem cells (MSCs) possess anti-inflammatory, anti-oxidative, and pro-angiogenic properties (23). Notably, umbilical cord mesenchymal stem cells (UC-MSCs) are considered a highly suitable source of MSCs due to their accessibility, ease of *in vitro* culture, strong proliferative capacity, and low immunogenicity (24). Studies have previously shown that adipose-derived MSCs (AD-MSCs) can enhance mitochondrial autophagy, reduce intracellular ROS, and improve mitochondrial quality (25). Besides, Zhu et al. revealed that MSCs could improve mitochondrial function via PINK1/PARKIN-mediated mitochondrial autophagy (26). Several studies have also demonstrated that UC-MSCs can reduce blood pressure and urinary protein levels in PE rats (27–29). Nevertheless, no research has yet examined how UC-MSCs influence mitophagy in placenta tissues or trophoblast cells in PE. To that end,

the present study investigated whether UC-MSCs could exert a protective effect on PE by evaluating their effect on trophoblast injury and mitophagy modulation.

2. Material and methods

2.1 Cell Culture

UC-MSCs used in the present study were kindly sourced and prepared by the Shanxi Provincial Clinical Cell Pilot Base (Taiyuan, China). The HTR8/SVneo cell line was obtained from the Shanghai Cell Bank of the Chinese Academy of Sciences (Shanghai, China). UC-MSCs and HTR8/SVneo were seeded in T25 flasks (NEST, Wuxi, China) and cultured using DMEM/F12 (Gibco, USA) and RPMI 1640 (Gibco, USA), respectively, supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin (Solarbio, China) at 37°C in a 5% CO₂ humidified incubator.

HTR8/SVneo cells were divided into three groups: the control group, which was cultured in normal culture medium; the PE group, which was treated with 100 ng LPS (30); and the PE + UC-MSCs group, which was treated with LPS and co-cultured with UC-MSCs. UC-MSCs and HTR8/SVneo were co-cultured at a 1:5 ratio.

2.2 WB Assay

The cultured cells or placental tissues were washed with PBS, and total protein was extracted using RIPA lysis buffer (AR0102, Boster) supplemented with protease inhibitors (AR1193, Boster). Total protein concentration was quantified using a bicinchoninic acid assay kit (AR1189, Boster). Samples were then separated by 10% SDS-PAGE (AR0138, Boster), followed by electrophoretic transfer to polyvinylidene difluoride membranes (IPFL85R, Millipore). Next, the membranes were blocked using 10% skimmed milk (RM00014, Abclonal) and incubated overnight at 4°C with the following primary antibodies: anti-PINK1 (1:1000, 23274-1-AP, Proteintech), anti-PARKIN (1:1000, ab77924, Abcam), anti-TOMM20 (1:10000, 11802-1-AP, Proteintech), and anti-β-actin (1:10,000, AC028, Abclonal). After washing, the membranes were incubated with horseradish peroxidase-conjugated secondary antibodies (1:10,000, BA1055/1050, Boster) for 2 hours. Protein bands were visualized using an ECL system and quantified using ImageJ software. Each assay was performed in at least three independent replicates.

2.3 RT-qPCR

TRIzol reagent (MF1048-01, Mei5bio) was used to isolate total RNA from the placental homogenates or cell lines. RNA concentration and purity were first assessed, then reverse-transcribed into cDNA using a cDNA synthesis kit (MF166-plus-01). Next, qPCR was performed using SYBR Green-based master mix (MF787-01), and β-actin was used as the internal reference gene for normalization. The primer sequences used in this study are summarized in Table 1.

Table 1
Primers used for RT-qPCR

Gene	Forward primer sequence	Reverse primer sequence
<i>H-PINK1</i>	GGAGGAGTATCTGATAGGGCAG	AACCCGGTGCTCTTTGTCAC
<i>H-PARKIN</i>	ACACCAAGCATCTTCCAGCTCA	TTTCTCCACGGTCTCTGCAC
<i>H-TOMM20</i>	GGTACTGCATCTACTTCGACCG	TGGTCTACGCCCTTCTCATATTC
<i>H-ACTB</i>	CCTCGCCTTTGCCGATCC	GGATCTTCATAGTCAGTC
<i>R-Pink1</i>	CTGTCAGGAGATCCAGGCAATT	GCATGGTGGCTTCATACACAGC
<i>R-Parkin</i>	GACAAGCAACCCTCACCTTG	CTCTCCACTCATCCGGTTTG
<i>R-Tomm20</i>	CCAACCTTCAAGAACAGGCTTCG	CTGAGCACTGACAATTCTCTGAC
<i>R-Actb</i>	CACCCGCGAGTACAACCTTC	CCCATACCCACCATCACACC

2.4 Mitochondrial membrane potential (MMP) and ATP Content Determination

MMP was assessed using the JC-1 assay kit (Beyotime Biotechnology) and analyzed under a fluorescence microscope. Cellular ATP levels were measured with an ATP assay kit (Nanjing Jiancheng Bioengineering Institute) according to the manufacturer's instructions.

2.5 In vivo Model establishment

Six to eight-week-old, specific pathogen-free grade male and female Sprague–Dawley rats (220–280 g) were obtained from the Experimental Animal Center of Shanxi Medical University. Ethical approval for this study was granted by the Ethics Committee of the First Hospital of Shanxi Medical University (DWLL-AF-001/01). Rats were housed at 18°C–23°C under a 12-h light-dark cycle with ad libitum access to water and food, and co-housed at a 1:1 ratio of females to males. Vaginal smears of female rats were examined every morning, and gestational day 0 (GD0) was designated following the detection of sperm in the smear. Continuous subcutaneous injections of saline (control, n = 8) or N(ω)-nitro-L-arginine methyl ester (L-NAME) (200mg/kg/ day, N5751, Sigma, USA) were administered from day 13 to day 17 of gestation (31). The rats that received L-NAME were then divided into two groups: the preeclampsia model group (L-NAME group, n = 8) and the UC-MSCs treatment group (treated with tail vein injections of 2×10^6 cells in 1 mL PBS per rat on GD15, GD17, and GD19, n = 8). Blood pressure was measured on GD0, GD6, GD12, GD15, GD17, and GD19 using a tail-cuff blood pressure device (BW–NIBP1106, Calvin). Urine was collected in metabolic cages on GD12 and GD19, and 24-hour urinary protein levels were quantified using the Coomassie Brilliant Blue method (A045-2-2, Nanjing Jiancheng). On GD20, rats were anesthetized via inhalation using an isoflurane small animal anesthesia ventilator (MSSN17118, MEDICAL SUPPLIES & SERVICES INT. LTD.), anesthesia was induced with 5% isoflurane in 1 L/min oxygen flow rate, and maintained at 2% isoflurane in 1 L/min oxygen flow rate after confirming that the

rats had lost consciousness. Following anesthesia, blood samples were collected from the abdominal aorta, and the rats were subjected to cesarean section and finally executed using cervical dislocation. Placentas were harvested and weighed, and the body length and weight of the fetuses were measured. Blood samples were centrifuged at 4°C and 3500 × g for 10 min. The resulting serum was then separated and stored at -80°C for subsequent analysis. Placental tissues were either fixed using 4% paraformaldehyde or snap-frozen and stored at -80°C for further use.

2.6 Enzyme-linked immunosorbent assay (ELISA)

Serum concentrations of sFlt-1 and PLGF were measured using ELISA kits (JL48077, JL11559, Jianglai Biotech). Optical density values were quantified and recorded using a microplate spectrophotometer. Each experiment was performed in triplicate to ensure accuracy.

2.7 Immunohistochemistry

Paraffin-embedded tissues were sectioned, dried, deparaffinized, and rehydrated. Antigen retrieval was performed using EDTA (ZLI-9069, Beijing Zhongshan Golden Bridge), followed by inactivation of endogenous peroxidase with 3% H₂O₂ for 10 min. Sections were then washed three times with PBS for five min each, and blocked with 5% BSA (SW3015, Solarbio, Beijing, China) for 20 min. The tissues were subsequently incubated overnight at 4°C with primary antibodies against PINK1 (1:1000), PARKIN (1:50, 14060-1-AP, Proteintech), and TOMM20 (1:500). After rewarming the tissue sections at room temperature for 30 minutes and washing with PBS for three times, the slides were incubated with secondary antibodies (PV-6000, Beijing Zhongshan Golden Bridge) for an additional 30 minutes. Diaminobenzidine was used as the chromogen, and hematoxylin was applied for counterstaining. The stained tissues were then examined under a microscope.

2.8 Statistical Analyses

All analyses were performed using Graphpad Prism 8.0 and/or ImageJ. Quantitative data are presented as means ± standard deviation (SD). Statistical comparisons across multiple groups were conducted using the one-way analysis of variance (ANOVA). All experimental dates were performed in at least three independent replicates. Statistically significant differences are defined as: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.

3. Results

3.1 UC-MSCs Attenuated PINK1/PARKIN-Mediated Mitophagy Inhibition

MSCs have been extensively studied in preeclampsia for several years. Herein, we investigated whether UC-MSCs could modulate PINK1/PARKIN-mediated mitophagy in PE. The protein and mRNA expression levels of PINK1, PARKIN, and TOMM20 were assessed by WB and qPCR. Specifically, WB analysis revealed that the expression levels of PINK1 and TOMM20 were lower in the PE group compared with the

control group, while the expression levels of PINK1, PARKIN, and TOMM20 were significantly increased in the UC-MSC-treated group relative to the PE group. Importantly, these findings were further validated by qPCR analysis (Fig. 1A-D).

3.2 UC-MSCs Mitigated LPS-Mediated Mitochondrial Dysfunction

Next, we assessed mitochondrial function by measuring ATP content and MMP. In contrast to the control group, the PE group exhibited significantly reduced MMP and ATP levels, indicating severe mitochondrial dysfunction under preeclamptic conditions. Conversely, UC-MSCs intervention could reverse these impairments, with both MMP and ATP content being significantly higher in the UC-MSC intervention group than in the PE group, demonstrating an improvement in mitochondrial function (Fig. 1. E and F).

3.3 UC-MSCs Reduced the Levels of Hypertension and Proteinuria in PE Rats

We next examined whether UC-MSC treatment could mitigate the hallmark features of preeclampsia, hypertension and proteinuria, in L-NAME–induced PE rat models. In comparison to the control group, the L-NAME group exhibited significantly elevated diastolic and systolic blood pressure from GD15 onward and remained at a high level at GD18 and GD20. In the UC-MSC-treated group, blood pressure was slightly elevated at GD12 but decreased significantly by GD18 and GD20. At GD12, 24-hour urinary protein levels were comparable between groups. However, by GD19, the L-NAME group exhibited a marked increase in urinary proteins, while the L-NAME+MSCs group had significantly lower levels compared with the L-NAME group alone. Together, these results indicate that UC-MSCs can effectively alleviate hypertension and proteinuria in PE rat models (Fig. 2A-D).

3.4 UC-MSCs Improve the Pregnancy Outcome of PE Rats

We further assessed the effects of UC-MSCs on fetal and placental development in PE rats, we found that L-NAME administration led to significant decreases in pup length, pup weight, and placental weight compared with controls, which were partially rescued by UC-MSC treatment, indicating improved pregnancy outcomes (Fig. 2E-G).

3.5 UC-MSCs Affect the Level of Angiogenic Factors in PE Rats

Subsequently, the expression levels of angiogenic and anti-angiogenic factors were measured and compared across the three rat groups. In contrast to the control group, the L-NAME group exhibited a significant increase in sFlt-1 and a decrease in PLGF, suggesting impaired angiogenesis in PE rats. Following UC-MSCs intervention, sFlt-1 levels were reduced and PLGF levels were increased relative to the L-NAME group, suggesting that UC-MSCs can promote angiogenesis and decrease the production of anti-angiogenic factors in PE rats (Fig. 2H-J).

3.6 UC-MSCs Ameliorated PINK1/PARKIN-Mediated Mitophagy in PE Rats

To investigate the effect of UC-MSCs on mitophagy in PE rats, the mRNA and protein levels of PINK1, PARKIN, and TOMM20 in placentas were assessed. WB analysis revealed that the expression of PINK1, PARKIN, and TOMM20 was downregulated in the L-NAME group, whereas this downregulation was partially reversed in the L-NAME + UC-MSC group. This was further confirmed by qPCR and immunohistochemistry, which yielded results consistent with the Western blot data. Collectively, the above findings indicate that UC-MSCs can enhance PINK1/PARKIN-mediated mitophagy in PE rat models (Fig. 3).

4. Discussion

Although the therapeutic effects of UC-MSCs on PE have been minimally explored, this study is the first to investigate whether UC-MSCs can alleviate PE symptoms and reverse the inhibition of PINK1/PARKIN-mediated mitophagy. Specifically, our *in vitro* experiments demonstrated that PINK1/PARKIN-mediated mitophagy was impaired in PE trophoblast cells, while UC-MSCs intervention enhanced mitophagy and restored mitochondrial function in the affected cells. In the present study, L-NAME was utilized to establish a PE animal model, which exhibited worse pregnancy outcomes and impaired mitophagy compared with control rats. However, UC-MSCs intervention not only alleviated hypertension and proteinuria in PE rats, but also significantly improved offspring length and weight. Moreover, UC-MSCs restored the balance of angiogenic factors in maternal blood and enhanced mitophagy levels in placental tissue. Therefore, our findings show that UC-MSCs can mitigate trophoblast cell injury and PINK1/PARKIN-mediated mitophagy inhibition in PE, suggesting that targeting the PINK1/PARKIN pathway may represent a novel therapeutic approach for UC-MSC-based treatment of PE.

Mitophagy is essential for the selective removal of damaged mitochondria, playing a critical role in maintaining mitochondrial homeostasis. Among the known pathways, PINK1/PARKIN-mediated mitophagy represents the classical, ubiquitin-dependent mechanism responsible for targeting and eliminating impaired mitochondria. In preeclampsia, impaired mitophagy contributes to increased placental oxidative stress, vascular endothelial damage, and cellular dysfunction (17). Of note, Sun et al. uncovered decreased PINK1 and PARKIN levels in PE patients and in cell models of PE (32), while Chen et al. observed downregulation of PINK1 in PE mice (33), consistent with our findings.

The placenta serves as a key communication and regulatory hub between the mother and fetus, crucial for maintaining the well-being and development of both. Consequently, oxidative stress in the placenta can affect the maternal circulation, causing vascular endothelial damage, promoting the release of inflammatory mediators, and increasing the production of anti-angiogenic factors while reducing pro-angiogenic factors (3, 34–36). Pan et al. previously reported that the sFlt-1 /PLGF ratio is a characteristic indicator of the progression from hypertensive disorders of pregnancy (HDP) to PE (11). Meanwhile, Zhao et al. demonstrated that UC-MSCs could improve the pregnancy outcomes and promote placental

angiogenesis in PE rats by regulating the balance of pro-angiogenic and anti-angiogenic factors (37). In our study, we observed that in the L-NAME-induced PE rat model, sFlt-1 levels were elevated, PLGF levels were reduced, and the sFlt-1/PLGF ratio was disrupted. Following UC-MSC intervention, sFlt-1 levels decreased, PLGF levels increased, and the sFlt-1/PLGF ratio was restored, leading to improvements in PE symptoms and pregnancy outcomes. These findings demonstrate that UC-MSCs alleviate PE by regulating angiogenesis, consistent with previous research.

Nevertheless, our study has several limitations that warrant further in-depth investigation. For instance, our current experiments focused primarily on changes in trophoblast cells during disease progression and after UC-MSC intervention, while vascular endothelial cells also undergo significant alterations during PE. Future studies should therefore examine the functional responses of endothelial cells to both the disease and UC-MSC treatment. Furthermore, identifying the specific pathways and mechanisms by which UC-MSCs regulate mitochondrial autophagy will provide a more comprehensive understanding of their therapeutic effects, offering stronger experimental evidence for the potential use of UC-MSCs in improving PE outcomes.

5. Conclusions

In conclusion, the present study elucidated, for the first time, that UC-MSCs can alleviate trophoblast injury and restore vascular balance in PE by modulating PINK1/PARKIN-mediated mitochondrial autophagy. Taken together, our findings indicate the therapeutic potential of UC-MSCs in preeclampsia and suggest that targeting mitochondrial autophagy may represent a promising strategy to improve maternal and fetal outcomes, ultimately benefiting millions of PE patients worldwide.

Abbreviations

AD-MSCs, adipose-derived MSCs; ANOVA, one-way analysis of variance; ELISA, enzyme-linked immunosorbent assay; HDP, hypertensive disorders of pregnancy; L-NAME, N(ω)-nitro-L-arginine methyl ester; LPS, lipopolysaccharide; MMP, mitochondrial membrane potential; MSCs, Mesenchymal stem cells; PARKIN, Parkin RBR E3 ubiquitin protein ligase; PE, Preeclampsia; PINK1, Phosphatase and Tensin Homolog-induced Kinase 1; PLGF, placental growth factor; ROS, reactive oxygen species; RT-qPCR, real-time quantitative PCR; SD, standard deviation; sFlt-1, serum levels of soluble fms-like tyrosine kinase-1; TOMM20, Translocase of Outer Mitochondrial Membrane 20; UC-MSCs, umbilical cord mesenchymal stem cells; WB, Western blot

Declarations

Ethics approval and consent to participate

Ethical approval for this study was granted by the Ethics Committee of the First Hospital of Shanxi Medical University (DWLL-AF-001/01) and the Institutional Animal Care and Use Committee of Shanxi

Medical University Experimental Animal Center (licenses: Animal License: SYXK (Jin) 2019–0008, Animal Production License: SCXK (Jin) 2019–004).

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests

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Author Contribution

Nan Zhang: Writing – original draft, Visualization. Shuqi Liu: Investigation, Software. Mengnan Li: Methodology, Funding acquisition. Huijing Ma: Formal analysis. Hong Yu: Project administration. Jing Ji: Supervision. Miao Xu: Validation. Lijun Yang: Formal analysis. Ruidan Zhang: Methodology. Hailan Yang: Writing – review & editing, Funding acquisition.

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Not applicable

Data Availability

All data supporting the findings of this study are available within the paper and its Supplementary Information.

Clinical trial number

Not applicable

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Figures

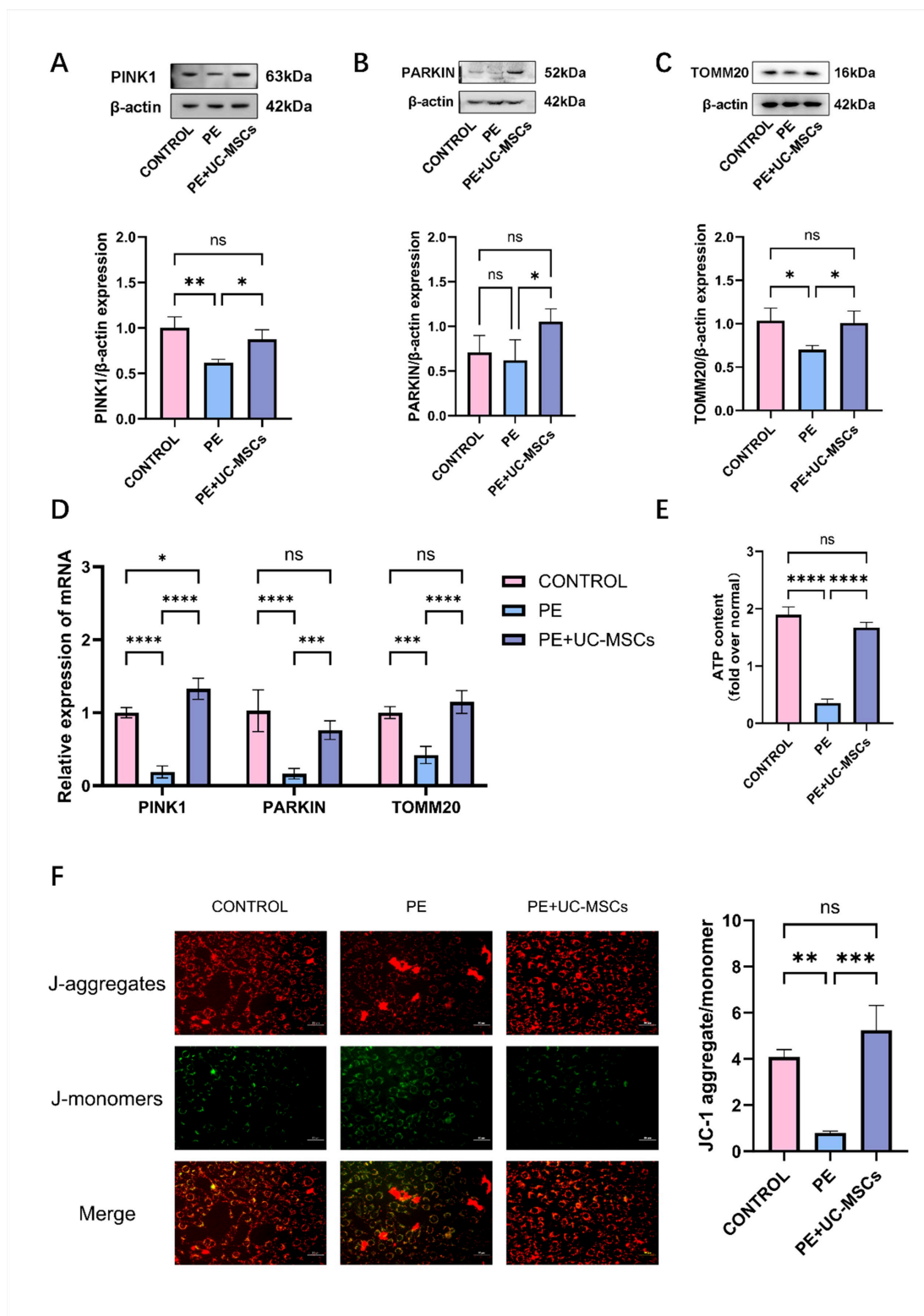


Figure 1

Effects of UC-MSCs on LPS-induced mitochondrial autophagy in trophoblast cells. (A-C) Western blot analysis of PINK1, PARKIN, and TOMM20 protein expression in HTR8/SVeno cells. (D) qPCR analysis of PINK1, PARKIN, and TOMM20 mRNA expression in HTR8/SVeno cells. (E) ATP levels were quantified in HTR8/SVeno cells. (F) Mitochondrial membrane potential was quantified in HTR8/SVeno cells. Data are presented as mean $\pm$ SD. Statistical significance: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.

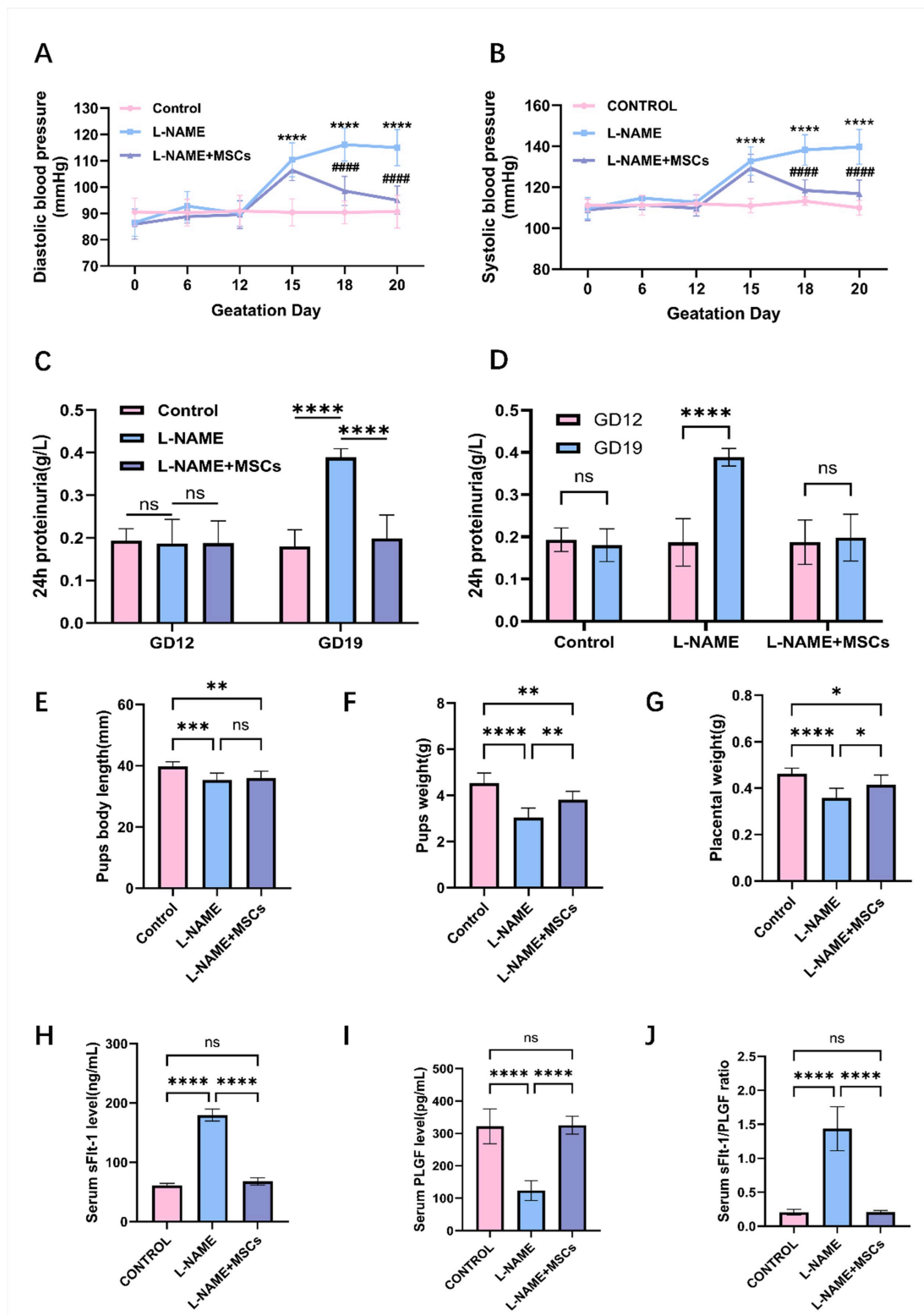


Figure 2

Effects of UC-MSCs on symptoms, pregnancy outcomes, and vascular imbalance-related factors in PE rat models. (A, B) Diastolic and systolic blood pressure were measured using the tail-cuff method (**** $P < 0.0001$ vs. Control; #### $P < 0.0001$ vs. L-NAME). (C, D) 24-hour urinary protein levels measured on GD12 and GD19. (E-G) Comparison of the pup body length, pup weight, and placental weight. (H) Serum sFlt-1

levels. (I) Serum PLGF levels. (J) Serum sFlt-1/PLGF ratio. Data are presented as mean $\pm$ SD. Statistical significance: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.

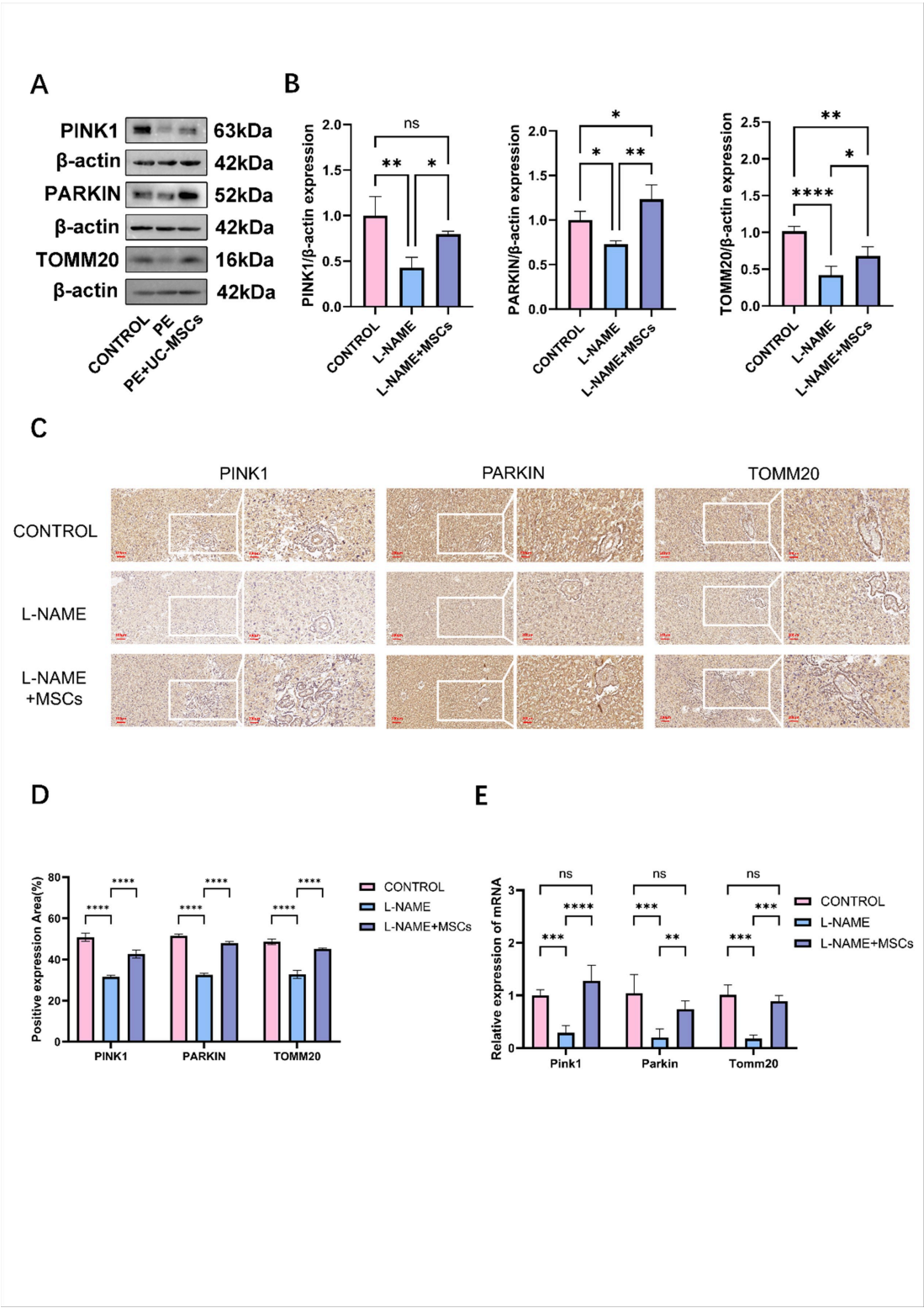


Figure 3

The effect of UC-MSCs on mitochondrial autophagy in PE rat models. (A, B) Western blot analysis of PINK1, PARKIN, and TOMM20 protein expression in rat placental tissues. (C, D) Representative

immunohistochemical staining and quantitative analysis of PINK1, PARKIN, and TOMM20 in rat placental tissues. (E) qPCR analysis of Pink1, PARKIN, and TOMM20 expression in placental tissues. Data are presented as mean $\pm$ SD. Statistical significance: $**P < 0.05$, $**P < 0.01$, $***P < 0.001$, $****P < 0.0001$.

Supplementary Files

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- [Westernblot.pdf](#)