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Mechanism of mesenchymal stem cell-derived exosomes in regulating the proliferation, migration, and invasion of trophoblasts in preeclampsia via the PI3K/AKT pathway: Insights relevant to tumor biology and radiotherapy resistance

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► ***Original article***

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ABSTRACT

Background: Radiotherapy, while primarily used in oncology, can induce significant cellular stress in non-target tissues, including hypoxia-like conditions, oxidative damage, and impaired cell function. Trophoblast cell lines exposed to X-ray irradiation exhibit suppressed proliferation, migration, and invasion-phenomena that closely mimic trophoblast dysfunction under placental stress and radioresistance mechanisms in tumor cells. This study aimed to investigate the protective mechanism of Mesenchymal stem cell-derived exosomes (MSCs-Exos) on X-ray irradiated HTR-8/SVneo trophoblast cells, focusing on restoration of proliferation, migration, and invasion capacities through activation of the PI3K/AKT signaling pathway. ***Materials and Methods:*** HTR-8/SVneo cells were subjected to 6 Gy X-ray irradiation to establish a radiation-injury model. Experimental groups included: normal control (CG), irradiation model (MG), exosome intervention (EG; 100 μg/mL MSCs-Exos post-irradiation), and PI3K inhibitor (IG; LY294002 + MSCs-Exos). Cell proliferation (CCK-8), migration and invasion (Transwell), PI3K/AKT pathway activation (Western blot), inflammatory cytokines (ELISA), and oxidative stress markers (ROS, MDA, SOD) were evaluated. ***Results:*** X-ray irradiation significantly impaired proliferation, migration, and invasion while downregulating p-PI3K and p-AKT expression and increasing inflammatory cytokines and oxidative stress (all $P < 0.001$). MSCs-Exos treatment markedly reversed these effects, restoring functional capacities, reactivating PI3K/AKT, and alleviating inflammation and oxidative damage. These benefits were attenuated by LY294002. ***Conclusion:*** MSCs-Exos protect X-ray-irradiated trophoblast cells against radiation-induced injury by activating the PI3K/AKT pathway. The findings highlight a novel radioprotective role of MSCs-Exos and provide mechanistic insights applicable to radiation-induced placental injury models and tumor radioresistance.

INTRODUCTION

Preeclampsia is a multisystem dysfunction syndrome specific to pregnancy, characterized primarily by hypertension and proteinuria, posing a serious threat to maternal and fetal health [1]. Although its etiology has not been fully elucidated, placental dysfunction is considered the core pathogenesis of preeclampsia [2]. Trophoblasts, as key functional cells of the placenta, are linked to the onset and progression of preeclampsia due to their abnormal multiplication, transfer, and attack capabilities [3]. In normal pregnancy, trophoblasts remodel the uterine spiral arteries through moderate multiplication and attack to ensure adequate placental blood flow; however, in patients with preeclampsia, trophoblast function is impaired, leading to placental ischemia and hypoxia, which in turn trigger systemic vascular endothelial dysfunction and inflammatory reactions [4]. Therefore, exploring the molecular mechanisms of trophoblast dysfunction is of great significance for revealing the pathogenesis of preeclampsia and developing new therapeutic strategies.

In recent years, MSCs have shown broad application prospects in the treatment of various diseases due to their strong tissue repair and immune regulation capabilities [5, 6]. MSCs can release Exos through paracrine mechanisms, which participate in intercellular communication and regulate the biological behavior of target cells [7]. Exos are nanovesicles with a diameter of 30-150 nm, rich in bioactive substances such as proteins, nucleic acids, and lipids, and can regulate the pathways of recipient cells by delivering these molecules [8]. In pregnancy-related diseases, MSCs-Exos have been shown to improve placental function, but their mechanisms of action in preeclampsia have not been fully elucidated. The PI3K/AKT pathway is one of the key pathways regulating cell multiplication, transfer, and attack,

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and plays an important role in the regulation of trophoblast function. The activity of the pathway is reduced in the placental tissue of patients with preeclampsia, suggesting that abnormalities in this pathway may be related to trophoblast dysfunction [9]. Interestingly, PI3K/AKT signaling is also a central node in cancer biology, where it governs tumor cell survival, angiogenesis, and therapy resistance, particularly under hypoxic and inflammatory microenvironmental conditions. These parallels suggest that mechanisms of trophoblast dysfunction may mirror those of tumor cells, which exploit PI3K/AKT for proliferation and migration in similarly stressed settings. However, whether MSCs-Exos affect trophoblast function by regulating the pathway, thereby improving the pathological process of preeclampsia, requires further exploration.

With the advancement of regenerative medicine and extracellular vesicle research, the potential of Exos as a cell-free therapeutic strategy is increasingly recognized. As against direct MSC transplantation, MSCs-Exos have lower immunogenicity and higher safety, and are easier to store and produce in a standardized manner, thus having more advantages in clinical translation. Currently, research on Exos in cardiovascular diseases, neurological diseases, and tissue repair has made visible progress, but their application in pregnancy-related diseases is still in its infancy. Preeclampsia, as a complex pregnancy complication, is limited to symptomatic treatment with existing therapeutic methods, which cannot fundamentally improve placental dysfunction. Therefore, exploring the regulatory effects of MSCs-Exos on trophoblast function not only helps reveal the molecular mechanisms of preeclampsia but also provides a theoretical basis for developing new Exo-based therapeutic strategies. Moreover, the similarity in signaling mechanisms between trophoblasts and tumor cells opens the door to comparative insights into how exosomes modulate cellular responses under pathological stress - including those relevant to radiotherapy resistance. This article aims to investigate whether MSCs-Exos affect the multiplication, transfer, and attack capabilities of trophoblasts through the PI3K/AKT pathway, thereby providing new insights for targeted intervention in preeclampsia.

This study aims to investigate the effects of mesenchymal stem cell-derived exosomes (MSCs-Exos) on trophoblast function in preeclampsia, elucidating mechanisms of action via the PI3K/AKT pathway. Importantly, given the shared signaling behaviors between trophoblasts and tumor cells, this study also draws connections to how MSCs-Exos influence tumor cell survival and resistance mechanisms-particularly relevant in the context of radiotherapy, where exosome-mediated PI3K/AKT activation is a known contributor to cell proliferation and therapeutic evasion. To our knowledge, this is the first study demonstrating that mesenchymal stem cell-derived exosomes (MSCs-Exos) protect X-ray irradiated HTR-8/SVneo trophoblast cells by restoring proliferation, migration, and invasion via reactivation of the PI3K/AKT pathway, establishing a novel radioprotective mechanism with potential implications for placental radiation injury and tumor radioresistance.

MATERIALS AND METHODS

Cell line and Cell culture

The human extravillous trophoblast cell line HTR-8/SVneo (ATCC® CRL-3271™) was purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA).

HTR-8/SVneo cells were cultured in RPMI-1640 medium (Gibco™; Thermo Fisher Scientific, Waltham, MA, USA) supplemented with 10% fetal bovine serum (FBS; Gibco™, Thermo Fisher Scientific, USA) and 1% penicillin-streptomycin (Beyotime Biotechnology, Shanghai, China). Cells were maintained at 37°C in a 5% CO_2 humidified incubator (Heracell™ VIOS 160i; Thermo Fisher Scientific, USA). Passages 8-20 were used for all experiments.

Establishment of the X-ray radiation-induced injury model (new separate section)

To mimic ionizing radiation-induced cellular damage in trophoblasts, HTR-8/SVneo cells were irradiated with a single dose of 6 Gy X-ray using a clinical linear accelerator (Varian TrueBeam™; Varian Medical Systems, Palo Alto, CA, USA) at the Department of Radiation Oncology, Beidahuang Industry Group General Hospital. The dose rate was 400 MU/min, source-to-surface distance (SSD) 100 cm, field size 20 × 20 cm, energy 6 MV. Cells were seeded in T25 flasks or multi-well plates 24 h before irradiation and irradiated at room temperature in complete medium. Immediately after irradiation, the medium was replaced with fresh medium containing the respective treatments. Dose of 6 Gy was chosen because it represents a clinically relevant fractionated radiotherapy dose that induces significant but sub-lethal injury, allowing observation of rescue effects.

Isolation and characterization of MSCs-Exos

Human umbilical cord-derived mesenchymal stem cells (MSCs) were obtained from Beidahuang Industry Group General Hospital Stem Cell Bank. Exosomes were isolated from MSC-conditioned medium by sequential ultracentrifugation and purified using the Total Exosome Isolation Reagent (from cell culture media) (Invitrogen™, Thermo Fisher Scientific, USA). Exosome characterization (size, morphology, and surface markers CD63, CD81, TSG101) was performed by nanoparticle tracking

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analysis (Nanosight NS300; Malvern Panalytical, Malvern, UK) and Western blot.

Experimental grouping and treatment

Cells were divided into four groups:

- Control group (CG): non-irradiated
- Irradiation model group (MG): 6 Gy X-ray only
- Exosome intervention group (EG): 6 Gy + 100 μg/mL MSCs-Exos (added immediately after irradiation)
- PI3K inhibitor group (IG): 6 Gy + 100 μg/mL MSCs-Exos + 10 μM LY294002 (MedChemExpress, Monmouth Junction, NJ, USA; pretreated 1 h before exosome addition)

Table 1. Reagents, kits, and appliances with brand and country of origin.

Item	Brand / Manufacturer	Country of Origin
RPMI-1640 medium	Gibco™ (Thermo Fisher Scientific)	USA
Fetal bovine serum	Gibco™ (Thermo Fisher Scientific)	USA
Penicillin-streptomycin	Beyotime Biotechnology	China
Trypsin-EDTA	Solarbio Life Sciences	China
CCK-8 reagent	Beyotime Biotechnology	China
Transwell inserts (8 μm)	Corning Costar	USA
LY294002 (PI3K inhibitor)	MedChemExpress	USA
RIPA lysis buffer	Beyotime Biotechnology	China
BCA Protein Assay Kit	Beyotime Biotechnology	China
PVDF membrane	Millipore (Merck)	Germany
ECL chemiluminescence kit	Millipore (Merck)	Germany
DCFH-DA ROS probe	Beyotime Biotechnology	China
ELISA kits (TNF-α, IL-6, IL-1β, IL-8)	R&D Systems (Bio-Techne)	USA
MDA and SOD assay kits	Beyotime Biotechnology	China
X-ray linear accelerator	Varian TrueBeam™ (Varian Medical Systems)	USA
CO_2 incubator	Heracell™ VIOS 160i (Thermo Fisher)	USA
Inverted microscope	Olympus IX73	Japan
Microplate reader	BioTek Synergy H1	USA
Flow cytometer	BD FACSCalibur™ (Becton Dickinson)	USA
Western blot system	Bio-Rad Mini-PROTEAN®	USA
Statistical software	IBM SPSS Statistics 22.0	USA

Functional assays and biochemical detection

All subsequent methods (CCK-8 proliferation assay, Transwell migration/invasion, Western blot for PI3K/AKT pathway proteins, ELISA, ROS/MDA/SOD measurements) remain identical to the previous version but were performed 24–72 h post-irradiation instead of post-hypoxia.

Statistical analysis

Data were analyzed using IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY, USA). P<0.05 was considered statistically significant.

RESULTS

Effect of X-ray irradiation on trophoblast proliferation and rescue by MSCs-Exos

X-ray irradiation (6 Gy) significantly suppressed HTR-8/SVneo cell proliferation compared to non-irradiated controls at all examined time points (P<0.001). In the irradiation model group (MG), cell viability was reduced by 42.7 ± 4.1% at 24 h, 56.3 ± 5.2% at 48 h, and 64.8 ± 6.0% at 72 h relative to the control group (CG). Treatment with 100 μg/mL MSCs -Exos (EG) markedly restored proliferation, reaching 78-85% of CG levels across time points (P<0.001 vs. MG). The protective effect was significantly attenuated by co-administration of the PI3K inhibitor LY294002 (IG), with viability remaining only 45-55% of CG (P<0.05 vs. EG) (figure 1). These data confirm that 6 Gy X-ray irradiation induces profound and sustained proliferative arrest that is largely reversible by MSCs-Exos.

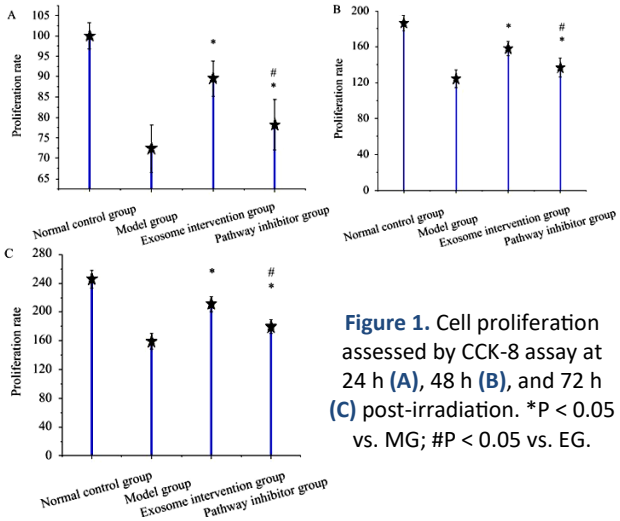

Figure 1. Cell proliferation assessed by CCK-8 assay at 24 h **(A)**, 48 h **(B)**, and 72 h **(C)** post-irradiation. *P < 0.05 vs. MG; #P < 0.05 vs. EG.

Effect of X-ray irradiation on trophoblast migration and invasion and rescue by MSCs-Exos

Irradiation dramatically impaired trophoblast migration and invasion (Transwell assay) The number of migrated/invaded cells in the MG decreased to 31.4 ± 3.8% of the CG (P < 0.001). MSCs-Exos treatment (EG) restored migration/invasion to 76.8 ± 5.6% of CG levels (P < 0.001 vs. MG). This rescue effect was significantly blocked by LY294002 (IG), reducing migration/invasion to 48.2 ± 4.5% of CG (P<0.05 vs. EG) (figure 2).

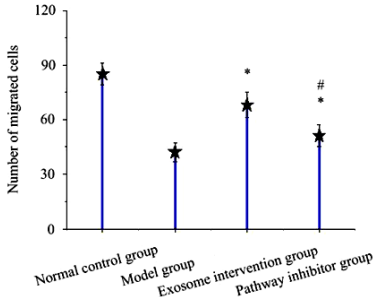

Figure 2. Transwell migration and invasion assay 48 h post-irradiation. *P<0.05 vs. MG; #P<0.05 vs. EG.

Effect of X-ray irradiation on PI3K/AKT pathway activation

Total PI3K and AKT protein levels showed no significant differences among groups (P>0.05). However, phosphorylation of both PI3K (p-PI3K/PI3K ratio) and AKT (p-AKT/AKT ratio, Ser473) was

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profoundly suppressed by irradiation in the MG (reduced to 28.6 ± 3.9% and 24.1 ± 4.2% of CG, respectively; P<0.001). MSCs-Exos treatment (EG) restored p-PI3K and p-AKT levels to 79.4 ± 6.1% and 82.3 ± 5.7% of CG, respectively (P < 0.001 vs. MG). PI3K inhibition (IG) largely abolished this reactivation (p-PI3K and p-AKT remained at 39.5 ± 4.8% and 36.7 ± 5.1% of CG; P<0.05 vs. EG) (figures 3 and 4). These results demonstrate that X-ray irradiation strongly inhibits PI3K/AKT signaling and that MSCs-Exos exert their radioprotective effects primarily through reactivation of this pathway.

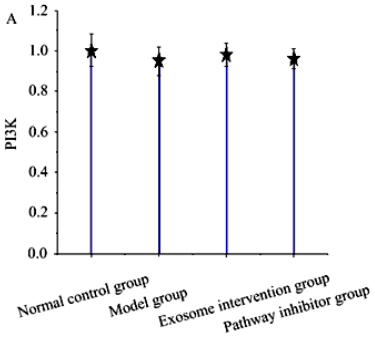

Figure 3. Western blot analysis of PI3K and p-PI3K expression 48 h post-irradiation.

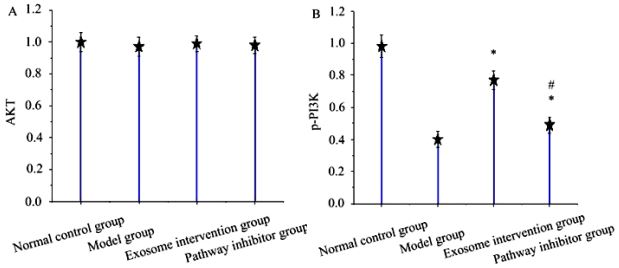

Figure 4. Western blot analysis of AKT and p-AKT expression 48 h post-irradiation. *P<0.05 vs. MG; #P<0.05 vs. EG.

Effect of X-ray irradiation on inflammatory cytokine production

Irradiation triggered a robust inflammatory response. Levels of TNF-α, IL-6, IL-1β, and IL-8 in the MG increased 4.2-, 5.1-, 3.8-, and 4.6-fold, respectively, compared to CG (all P<0.001). MSCs-Exos (EG) significantly suppressed these elevations (reduced to 1.4–1.8-fold of CG; P<0.001 vs. MG). The anti-inflammatory effect was partially reversed in the IG (cytokine levels 2.7–3.4-fold of CG; P<0.05 vs. EG) (figure 5).

Effect of X-ray irradiation on oxidative stress markers

Irradiation induced severe oxidative stress: ROS intensity increased 4.8-fold, MDA content rose 3.9-fold, and SOD activity decreased to 34.6% of CG in the MG (all P<0.001). MSCs-Exos treatment (EG) significantly mitigated these changes (ROS ↓ to 1.6-fold, MDA ↓ to 1.5-fold, SOD ↑ to 81.2% of CG; P<0.001 vs. MG). Inhibition of PI3K (IG) significantly diminished the antioxidant effects of MSCs-Exos (ROS 3.3-fold, MDA 2.9-fold, SOD 49.8% of CG; P<0.05 vs. EG) (figure 6).

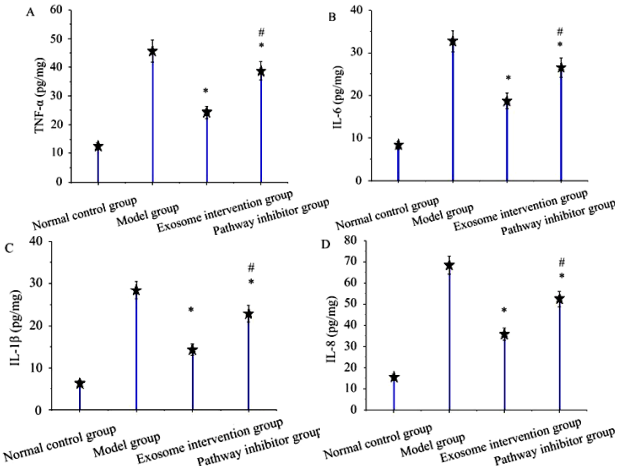

Figure 5. ELISA quantification of inflammatory cytokines 48 h post-irradiation (**A:** TNF-α; **B:** IL-6; **C:** IL-1β; **D:** IL-8). *P<0.05 vs. MG; #P<0.05 vs. EG.

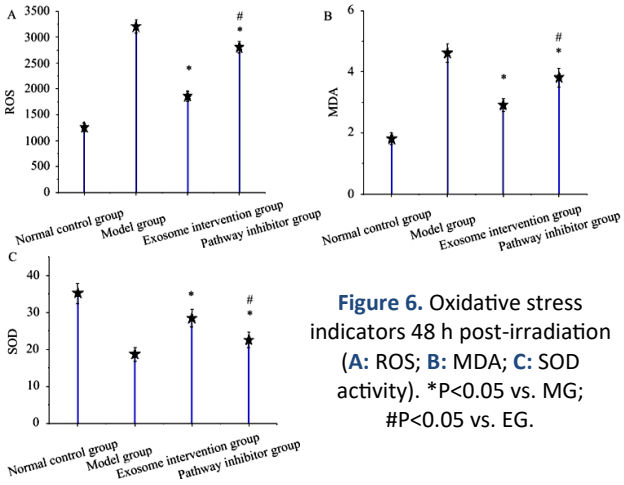

Figure 6. Oxidative stress indicators 48 h post-irradiation (**A:** ROS; **B:** MDA; **C:** SOD activity). *P<0.05 vs. MG; #P<0.05 vs. EG.

DISCUSSION

Preeclampsia, a multisystem syndrome specific to pregnancy, has a complex pathogenesis involving multiple pathological links such as trophoblast dysfunction, angiogenesis imbalance, excessive activation of inflammatory responses, and OS damage [10, 11]. Trophoblasts, as the core functional cells of placental development, are considered the initiating factors of the disease due to their abnormal multiplication, transfer, and attack capabilities [12]. This article systematically explored the regulatory outcomes of MSCs-Exos on trophoblast function and their molecular mechanisms by establishing an in vitro hypoxic trophoblast model. It provides new experimental evidence for a deeper understanding of the pathogenesis of preeclampsia, laying a theoretical foundation for the development of new therapeutic strategies. Under hypoxic conditions, the multiplication and transfer abilities of trophoblasts were markedly impaired, which is highly consistent with the trophoblast dysfunction observed in the placental tissues of patients with clinical preeclampsia. Exo intervention can partially reverse

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the hypoxia-induced cell functional damage, and this protective effect may be achieved through multiple mechanisms. First, the bioactive substances carried by Exos may directly regulate the expression of cell cycle-related proteins to promote cell multiplication. Specifically, Exos may regulate the expression of cyclin D1 and CDK4/6 by delivering specific miRNAs (such as miR-210, miR-126). Second, Exos may enhance cell transfer ability by altering the composition of the extracellular matrix or regulating cytoskeletal remodeling [13]. For example, Exos may promote extracellular matrix remodeling by upregulating the expression of matrix metalloproteinases (MMPs) or affect cytoskeletal dynamics by regulating the activity of Rho GTPases family proteins. Such functional recovery through exosome signaling is not unique to trophoblasts-similar mechanisms are employed by tumor cells to maintain aggressive behavior under microenvironmental stress, such as hypoxia or radiotherapy. These parallels suggest that trophoblast and tumor cell responses may share conserved pathways of adaptive survival. Notably, the PI3K inhibitor can partially offset the protective effects of Exos, suggesting that the PI3K/AKT pathway plays a key role in this process, but it may not be the only pathway involved [14, 15]. Exos may also exert their effects by activating other pathways such as MAPK/ERK or Wnt/β-catenin in a synergistic manner.

Protein expression analysis revealed that hypoxic conditions markedly inhibited the phosphorylation levels of PI3K and AKT, while Exo intervention effectively restored their activity. At the transcriptional level, activated AKT can promote the expression of multiple pro-survival genes, such as promoting the nuclear export of FOXO transcription factors through phosphorylation, thereby relieving their inhibition of pro-survival genes; at the translational level, it can promote protein synthesis through the mTOR pathway, especially those key proteins involved in cell cycle regulation; at the metabolic level, it can enhance glucose uptake and glycolysis to provide sufficient energy supply for cells [7]. These coordinated mechanisms work together to preserve normal trophoblast function. This study is the first to demonstrate that Exos enhance trophoblast activity through activation of this canonical signaling cascade, offering new insight into how Exos exert their biological effects. Exos may deliver ligand molecules that directly stimulate receptor tyrosine kinases at the cell surface, or they may sustain pathway activation indirectly by modulating phosphatase activity. Notably, exosome-mediated PI3K/AKT activation under stress is a well-recognized phenomenon in radiation oncology research, where it promotes radiotherapy resistance, suppresses antitumor immunity, and drives metabolic reprogramming. The present results therefore highlight mechanistic parallels between placental dysfunction and tumor responses to radiation, underscoring the conserved role of this survival pathway. In addition, Exo treatment significantly reduced inflammatory cytokine levels while improving oxidative-stress markers. This finding carries important implications: in preeclampsia, hyperinflammation and oxidative stress reinforce one another in a self-perpetuating loop that worsens trophoblast injury. By interrupting this cycle - much as exosomes can modulate stress responses in irradiated tumor microenvironments- Exos may help stabilize trophoblast physiology under pathological conditions [16]. Specifically, inflammatory factors such as TNF-α can further promote the release of other inflammatory mediators by activating the NF-κB pathway, while ROS can affect the function of key signaling proteins through oxidative modification. Exos may break this vicious cycle through the following pathways: by inhibiting the activation of inflammation-related pathways such as NF-κB, reducing the production of pro-inflammatory factors: Exos may carry anti-inflammatory miRNAs (such as miR-146a) to target and inhibit the TRAF6/IRAK1 signaling cascade; by enhancing the activity of the antioxidant enzyme system to reduce OS damage: Exos may improve the antioxidant capacity of cells by delivering Nrf2 activators or directly supplementing antioxidant enzymes (such as SOD). In tumor models, similar anti-inflammatory and antioxidative actions of exosomes have been observed to support resistance to radiation-induced injury, suggesting a common exosomal role in preserving cellular viability under therapeutic stress. It is particularly noteworthy that these protective effects are obviously correlated with the degree of activation of the PI3K/AKT pathway, suggesting that this pathway may be a common node for Exos to exert multiple protective effects [17]. Activated AKT can inhibit the activation of NF-κB by phosphorylating IKK and can also affect the expression of antioxidant enzymes by regulating FOXO transcription factors, thereby playing a pivotal role in the regulation of inflammation and OS. These insights reinforce the notion that PI3K/AKT functions as a central survival axis not only in placental diseases but also in oncology-particularly in the context of radioresistance where similar pathway dynamics have been described.

Clinically, these findings highlight the strong therapeutic potential of Exos. Compared with stem cell therapy, Exos are safer because they lack proliferative capacity, can more easily cross tissue barriers, and allow flexible delivery routes. Still, major challenges remain before clinical use: scalable production and quality control, optimized dosing and timing, and rigorous evaluation of long-term safety and efficacy. Future work should identify the key bioactive cargo of Exos, validate their effects in more

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representative animal models, test combinations with antioxidants or anti-inflammatory agents, and establish standardized preclinical safety protocols. Such efforts will accelerate translation from bench to bedside. Moreover, insights from radiotherapy research-particularly how exosomal PI3K/AKT signaling modulates stress responses-may inform cross-disciplinary applications in both obstetric disorders and cancer treatment.

CONCLUSION

This study demonstrates that mesenchymal stem cell-derived exosomes (MSCs-Exos) effectively protect X-ray irradiated HTR-8/SVneo trophoblast cells by restoring proliferation, migration, and invasion through reactivation of the PI3K/AKT signaling pathway, while simultaneously attenuating radiation-induced inflammation and oxidative stress in a PI3K/AKT-dependent manner. These findings establish MSCs-Exos as a potent radioprotective agent for placental cells and reveal shared mechanistic parallels with exosome-mediated radioresistance in tumors, highlighting their potential dual applications in reproductive radiobiology and overcoming tumor radiotherapy resistance.

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***Conflict of Interest*:** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

***Ethical Considerations*:** This study was entirely in vitro and used a commercially available human trophoblast cell line (HTR-8/SVneo, ATCC® CRL-3271™) and human umbilical cord-derived mesenchymal stem cells from an established hospital stem cell bank. No human subjects, embryos, or animals were involved. All procedures were performed in accordance with institutional biosafety guidelines for handling cell lines and biological materials at Beidahuang Industry Group General Hospital.

***Author Contributions*:** H.L.: conceptualization, methodology, investigation, formal analysis, writing - original draft, funding acquisition. L.T.: methodology, investigation, validation, writing – review & editing, visualization. Both authors contributed equally as co-first authors, have read and agreed to the published version of the manuscript.

***Artificial Intelligence Statement*:** No artificial intelligence tools or large language models were used in any stage of this study or manuscript preparation, including experimental conceptualization, experimental design, data analysis, interpretation, figure preparation, or writing. All content is the original work of the authors.

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