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Exosomes derived from endothelial progenitor cells ameliorate glyoxylate deprivation (OGD)-induced neuronal apoptosis by delivering miR-221-3p

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Summary. This study evaluated the potential of endothelial progenitor cell (EPC)-derived exosomes as a therapeutic factor for neuronal apoptosis. Mouse EPCs were cultured *in vitro*, and exosomes were isolated and identified using transmission electron microscopy (TEM), particle size analysis and by determining the protein expressions of exosome markers (CD9, CD63 and Alix). The apoptotic rate of OGD-treated neurons was detected by Flow cytometry assay. The mRNA and protein expression levels were detected by RT-PCR and Western blot assay, respectively. Luciferase reporter assays determined the interaction between miR-221-3p and Bcl2l11. The results showed that most exosomes are 80-120 nm in diameter. Western blot assay showed that CD9, CD63 and Alix were enriched in exosomes. EPC-derived exosomes ameliorated OGD-induced neuronal apoptosis. Mechanistically, miR-221-3p from EPC-derived exosomes decreased the expression of bcl2l11 in OGD-induced neuronal apoptosis. Moreover, exosomes from miR-221-3p mimics transfected EPCs reduced OGD-induced neuronal apoptosis. In conclusion, miR-221-3p in EPC derived exosomes ameliorates OGD-induced neuronal apoptosis, which establish its potential as a new therapeutic method for patients with cerebrovascular diseases.

Key words: Exosomes, Endothelial progenitor cells, Glyoxylate deprivation, Neuronal apoptosis

Introduction

Cerebrovascular diseases have become one of the main diseases that endanger the health and lives of middle-aged and elderly people in China. Globally, stroke is a major public health problem for all countries, ranking the third most common cause of cardiovascular disease (Sozio et al., 2009). Ischemic stroke, also known as cerebral infarction, accounts for about 80% of strokes. It refers to brain blood supply disorders caused for various reasons, leading to ischemia and hypoxic necrosis of brain tissue (Meschia and Brott, 2018). The neurological dysfunction caused by cerebral infarction is an urgent problem in the field of neurology, which brings a heavy economic burden to families and society. Therefore, searching for practical and effective nerve repair methods has very important social and practical significance.

The key to the treatment of cerebral infarction is to restore and improve the blood oxygen supply in the ischemic penumbra after cerebral infarction quickly, so as to avoid the death of damaged neurons, glial cells and vascular endothelial cells. With the discovery of endothelial progenitor cells (EPCs), this provides a new therapy for the treatment of ischemic cerebrovascular diseases. Under physiological conditions, EPCs mainly exist in the bone marrow. The EPCs in the bone marrow enter the peripheral blood circulation, and under the action of chemokines, they can quickly migrate and aggregate to the damaged area for repair. The damaged endothelial tissue differentiates and forms a new blood vessel network. EPCs secrete G-CSF, VEGF and other angiogenic growth factors to promote angiogenesis through paracrine or autocrine mode, or secrete VEGF, FGF2 and other cell growth factors to promote endogenous nerve generation and function recovery (Esquiva et al., 2018). Devanesan et al. (2009) believe that the recovery effect of EPCs in the treatment of ischemic cerebrovascular disease is not entirely dependent on the number of cell transplantations, but due to the paracrine effect of EPCs that causes the reorganization of damaged brain nerve fibers to enhance neuroplasticity and improve the clinical prognosis of the patient with cerebral infarction.

Besides, exosomes, a vesicle-like structure with a diameter of 40-100 nm and wrapped by a lipid bilayer, are also effective ingredients that play a role in the

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paracrine mechanism of EPCs. Studies have found that exosomes are widely presented in the blood, urine, saliva and milk of humans and animals. They can be transmitted between cells such as protein, mRNA and miRNA, mediate the exchange of information between cells, and regulate the development of target cells, and also affect physiological and pathological functions (Mathieu et al., 2019). In 2015, Burger et al. (2015) injected the exosomes secreted by human umbilical cord blood EPCs into mice with renal ischemia-reperfusion injury through the tail vein, and found that the exosomes can effectively repair the renal injury in mice. The proliferative activity and anti-apoptotic ability of vascular endothelial cells were enhanced, the inflammatory cell infiltration was significantly reduced, and blood urea nitrogen and blood creatinine levels were significantly reduced; However, injection of culture supernatant from EPCs (without exosome) did not produce these effects. It can be concluded that exosomes secreted by EPCs have certain tissue repair functions. Subsequently, increasing evidence has indicated the therapeutic effect of exosomes from EPCs. For example, Zhou et al. (2018) found that injection of exosomes from EPCs into sepsis mice significantly improved the survival rate, inhibited lung and renal vascular leakage, and reduced liver and kidney dysfunction. Further analysis revealed that exosomes from EPCs are rich in miR-126-3p and miR-126-5p, which respectively inhibited the expression of HMGB1 and VACAM1. Importantly, injection of exosomes from EPCs transfected with miR-126-3p/5p inhibitors eliminated the role, indicating that exosomes may improve sepsis by delivering miR-126. Subsequent studies also found that exosomes from EPCs promoted endothelial cell proliferation, migration, and angiogenesis by delivering miR-126, and improved acute lung injury (Wu et al., 2018; Zhou et al., 2019). Cui et al. (2019) found that exosomes from EPCs could promote the differentiation of osteoclasts by transferring lncRNA MALAT1, increase the neovascularization at the fracture site in mice, and promote fracture healing.

In addition, high-throughput sequencing showed that miR-221-3p was highly expressed in EPC-derived exosomes (Xu et al., 2020). Based on these findings, the present study evaluated the mechanism of miR-221-3p in EPC-derived exosomes as a therapeutic factor for neuronal apoptosis, which will provide important insights into the efficacy of EPC-derived exosomes as a new therapeutic method for patients with cerebral infarction and cerebrovascular disease.

Table 1. Primer sequence.

Gene	Primer sequence (5'-3')
MiR-221-3p	F: 5'- ACACTCCAGCTGGGACCTGGCATACAATGT-3' R:5'- TGGTGTCGTGGAGTCG-3'
U6	F:5′- CTCGCTTCGGCAGCACA-3′ R:5′-CGCTTCACGAATTTGCGTGTCAT-3′
Bcl2l11	F: 5'-TAAGTTCTGAGTGTGACCGAGA-3' R: 5'-GCTCTGTCTGTAGGGAGGTAGG-3'
Actin	F:5'-CATGTACGTTGCTATCCAGGC-3' R:5'-CTCCTTAATGTCACGCACGAT-3'

Materials and methods

Isolation and identification of exosomes from EPCs.

The EPCs were obtained from Shanghai Institute Cell Bank (Shanghai, China) and maintained in CO_2 (5%; 37°C) with DMEM (Gibco, Grand Island, NY, USA) containing FBS (10%, without exosomes; Gibco) for 48h. The cell supernatant was centrifuged (3000×g, 10 min) to remove cells and residual cell debris. Exosomes were extracted by a SBI kit as per the instructions. The morphology of the exosomes was observed and photographed under a transmission electron microscopy (TEM). The size of the exosomes was analyzed by particle size instrument. The expressions of CD9, CD63 and Alix were detected by Western blot.

Cell culture and coculture with exosomes

Mouse hippocampal neuronal cell line HT22 was obtained from Shanghai Institute Cell Bank and cultured in DMEM (Gibco), supplemented with FBS (10%, Gibco) and penicillin/streptomycin in a CO_2 (0.1%; 37°C) atmosphere. Cells were grouped: Control, OGD, OGD+PBS, OGD+exosomes (Exo). For OGD induction, the cells were cultured in glucose-free DMEM in an anaerobic chamber (94% N_2 /5% CO_2 and 1% O_2; 4h; 37°C). Afterwards, the cells were cultured in completed medium under normoxic conditions for reoxygenation (24h; 37°C). OGD was added to the cells for 1h. After that, cells in OGD+PBS, OGD+ Exo group were co-cultured with PBS or exosomes (200 μg/mL). The cells were cultured in RPMI-1640 (Gibco) with exosomes-FBS (10%; 37°C; 5% CO_2).

Luciferase Reporter Assay

The binding site between miR-221-3p and 3' UTR of bcl2l11 was predicted by TargetScan and dual luciferase reporter method was used to verify whether bcl2l11 was the direct target gene of miR-221-3p. Artificially synthesized bcl2l11 3'UTR (wild type, WT) and mutant sequence (MUT) were respectively introduced into pGL3 plasmid (Promega, WI, USA). The WT and MUT plasmids were co-transfected with miR-221-3p mimic into HEK-293T cells, and the luciferase activity was measured using the Dual-Luciferase Reporter Assay System kit (Promega).

Flow cytometry

Cell apoptosis assay was performed as the Apoptosis

Kit instructions (Abbkine Scientific, Beijing, China). The neurons were collected, washed, and then suspended in the binding buffer. Annexin V-FITC and PI (Sigma-Aldrich) were then added to the binding buffer and incubated in the dark at room temperature for 15 minutes. Finally, the cell apoptosis rate was analyzed by flow cytometry and cell quest software (BD Biosciences).

RT-qPCR

Total RNA was extracted from cells and exosomes using TRIZOL. The primers (Table 1) were synthesized, and PrimeScript RT Reagent Kit (Takara, Japan) or MiScript Reverse Transcription kit (Qiagen) was used for reverse transcription. SYBR Premix Ex Taq II (TaKaRa, Japan) or MiScript SYBR-Green PCR kit (Qiagen) was used to perform qPCR on 7900HT real-time PCR system to determine the expression level of bcl2l11 and miR-221-3p. The U6 and actin were used as internal references. Data were analyzed using the $2^{-\Delta\Delta Ct}$ method.

Western blot assay

Cells were lysed with RIPA lysis buffer (Beyotime, China). Equal amounts of protein extracts were separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE; 10%). Then proteins were transferred to polyvinylidene fluoride membrane (Bio-Rad, Hercules, CA, USA) and blocked with skim milk (5%), and the membranes were incubated with the following primary rabbit antibodies at 4°C overnight: anti-CD9 (Abcam, Cambridge, UK; cat#ab2215), anti-CD63 (Abcam; 1:500, cat# ab134045), anti-Alix (Abcam; 1:500, cat#ab275377), anti-cleaved caspase-3 (Abcam; 1:200, cat#ab32042), anti-Bax (Abcam; 1:200, cat#ab32503), anti-Bcl-2 (Abcam; 1:1000, cat#ab32124) anti-GAPDH (Abcam; 1:500, cat#ab9485). Subsequently, membranes were incubated with secondary antibody (HRP-conjugated goat anti-rabbit IgG; 1:2000, #ab6721, Abcam). The

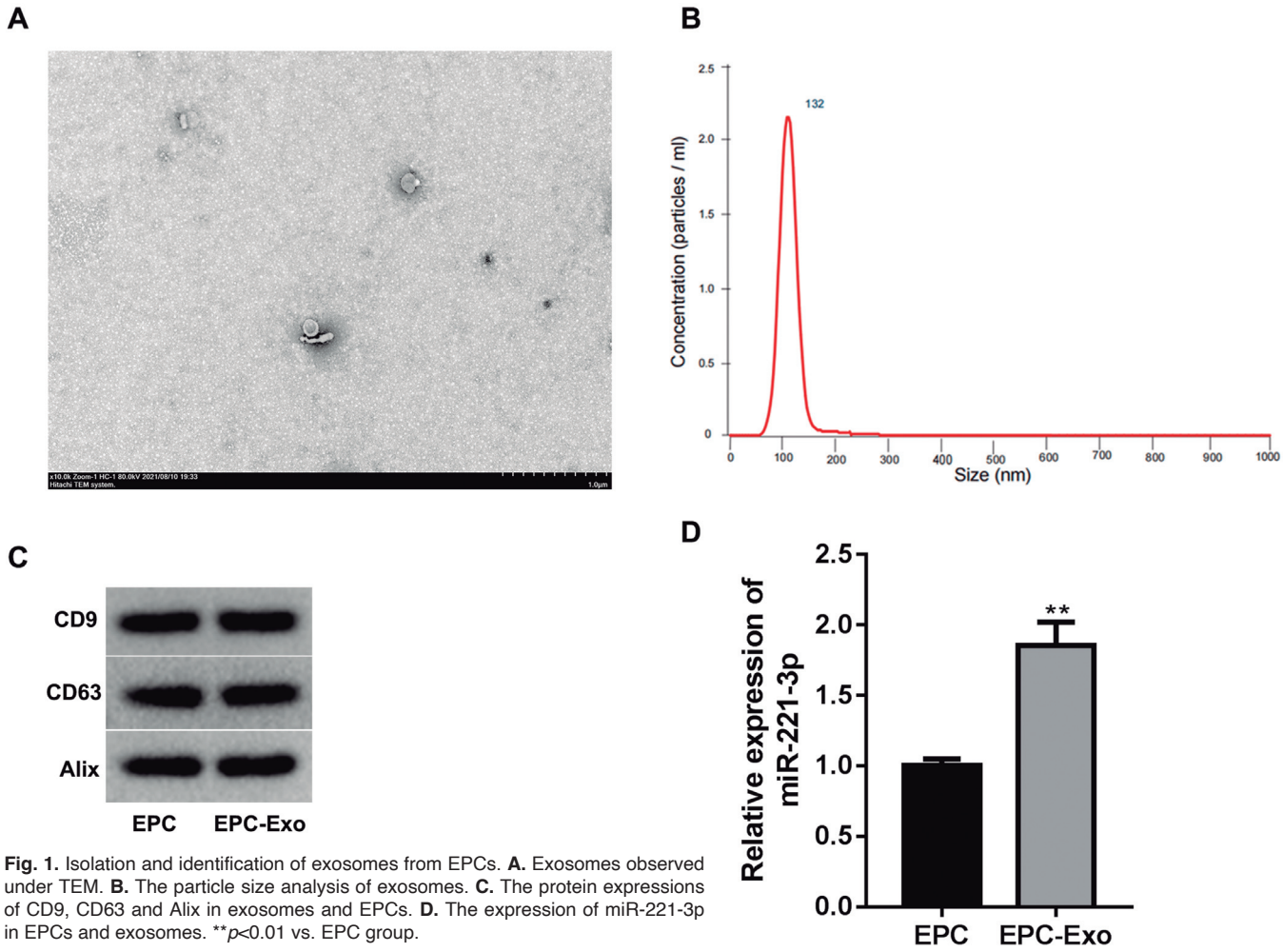

Fig. 1. Isolation and identification of exosomes from EPCs. **A.** Exosomes observed under TEM. **B.** The particle size analysis of exosomes. **C.** The protein expressions of CD9, CD63 and Alix in exosomes and EPCs. **D.** The expression of miR-221-3p in EPCs and exosomes. ***p*<0.01 vs. EPC group.

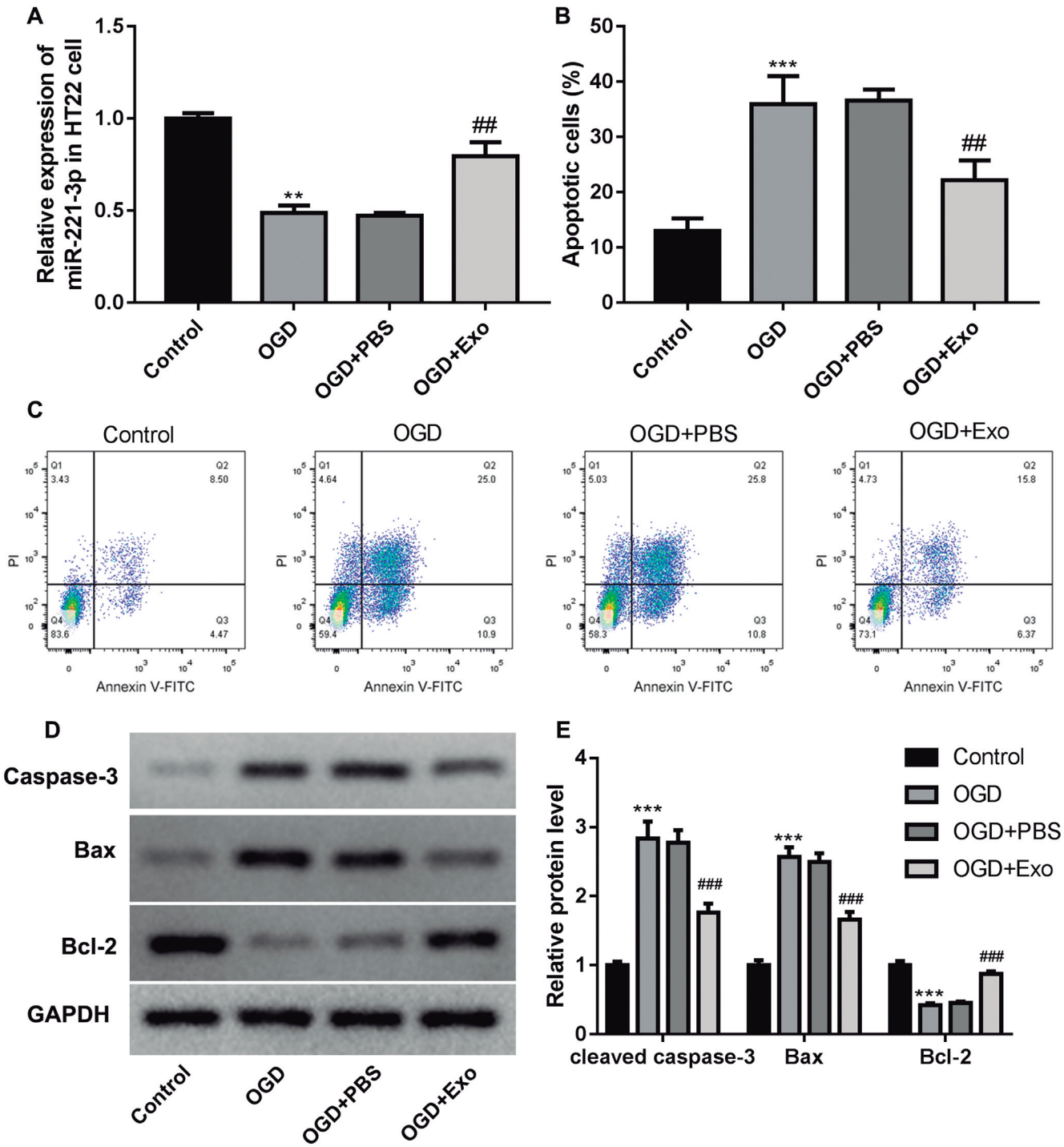

Fig. 2. EPC-derived exosomes ameliorated OGD-induced neuronal apoptosis. **A.** The expression of miR-221-3p in HT22 cells. **B, C.** Apoptosis quantification by flow cytometry. **D, E.** The protein expression levels of cleaved caspase-3, Bax, and Bcl-2 in neurons. ***p<0.001 vs. Control group, ##p<0.01, ###p<0.001 vs. OGD + PBS group.

bands were visualized and protein expression was detected.

Statistical analysis

All results are shown as means ± SD and analyzed by statistical product and service solutions (SPSS, version 20.0) and GraphPad Prism 7.0 The comparisons between two groups or among multi-groups were analyzed using Student's t-test or one-way ANOVA. $p< 0.05$, $p< 0.01$ or $p< 0.001$ were considered as statistically significant.

Results

Isolation and identification of exosomes from EPCs

Mouse EPCs were cultured *in vitro*, and exosomes were isolated and identified. As shown in Figure 1A,B, most exosomes are 80-120 nm in diameter. Western blot assay showed that CD9, CD63 and Alix were enriched in exosomes (Fig. 1C). These results implied that exosomes were successfully extracted.

EPC-derived exosomes reduce OGD-induced neuronal apoptosis

As we knew, miR-221-3p was enriched in EPC-derived exosomes (Fig. 1D). Then, the OGD-induced HT22 cells were co-cultured with EPC-derived exosomes. As shown in Figure 2A, OGD treatment decreased miR-221-3p, while EPC-derived exosomes upregulated miR-221-3p in OGD-induced HT22 cells. Meanwhile, OGD treatment significantly induced neurons apoptosis. However, after incubating with EPCs exosomes, the apoptotic rate of OGD-treated neurons was markedly decreased (Fig. 2B,C). The Western blot results showed that OGD treatment significantly increased the protein expressions of cleaved caspase-3 and Bax, while it decreased the protein expression of Bcl-2 in neurons. Interestingly, administration of EPC-derived exosomes reversed the results (Fig. 2D,E). These data suggested that EPC-derived exosomes could reduce OGD-induced neuronal apoptosis.

MiR-221-3p targets Bcl2l11

The binding site between miR-221-3p and Bcl2l11 was predicted by Targetscan. Before verifying that Bcl2l11 was a target of miR-221-3p, we first detected the expression of Bcl2l11 in the OGD-induced HT22 cells that co-cultured with EPC-derived exosomes. The RT-qPCR and western blot results showed that OGD treatment significantly increased the expressions of Bcl2l11, and incubation with EPC-derived exosomes decreased the expressions of Bcl2l11 (Fig. 3A-C). Then, we performed the luciferase activity assay to confirm the relationship between miR-221-3p and Bcl2l11. As shown in Figure 3D, co-transfection of Bcl2l11-WT and miR-221-3p mimic suppressed the luciferase activity while that of Bcl2l11-MUT and miR-221-3p mimic did not affect luciferase activity. These results indicated that

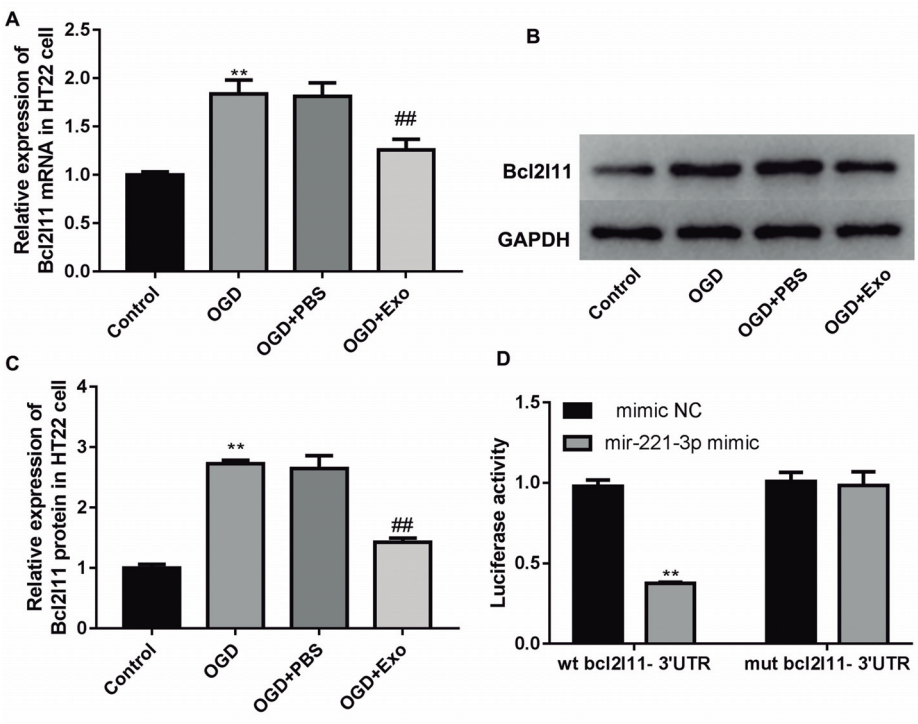

Fig. 3. miR-221-3p targets Bcl2l11. **A-C.** The mRNA and protein expression of Bcl2l11 in HT22 cells. **D.** The regulation of miR-221-3p on Bcl2l11 gene transcription by dual luciferase reporter gene assay. $^{**}p<0.01$ vs. Control group or mimic NC, $^{\#\#}p<0.01$ vs. OGD + PBS group.

Bcl2l11 was a target of miR-221-3p.

EPCs carrying miR-221-3p protect neurons from OGD-induced injury

To investigate the role of miR-221-3p from EPC-derived exosomes on OGD-induced neurons, the EPCs were transfected with miR-221-3p mimic or miR-221-3p inhibitor, and exosomes were isolated. As shown in Fig. 4A, mimic/inhibitor transfection significantly increased/decreased the expression of miR-221-3p in EPC-derived exosomes. EPCs-Exo overexpressing miR-221-3p reduced apoptosis of OGD-treated neurons (Fig. 4B,C). The results of RT-qPCR and western blot indicated that EPCs-Exo carrying miR-221-3p mimic suppressed the expression of apoptosis related proteins (bcl2l11, cleaved caspase-3 and Bax), but increased anti-apoptotic protein (Bcl-2) expression (Fig. 4D-G). These data demonstrated that exosomes derived from EPCs reduces OGD-induced neuronal apoptosis by delivering miR-221-3p.

Discussion

Several clinical studies have shown that, compared to cell transplantation, cardiac progenitor cell-derived exosomes have better therapeutic effects on cardiac repair (Sahoo and Losordo, 2014). In fact, cardiac progenitor cell-derived exosomes containing specific agents have been effectively used to treat cardiovascular diseases. For example, cardiac progenitor cell exosomes

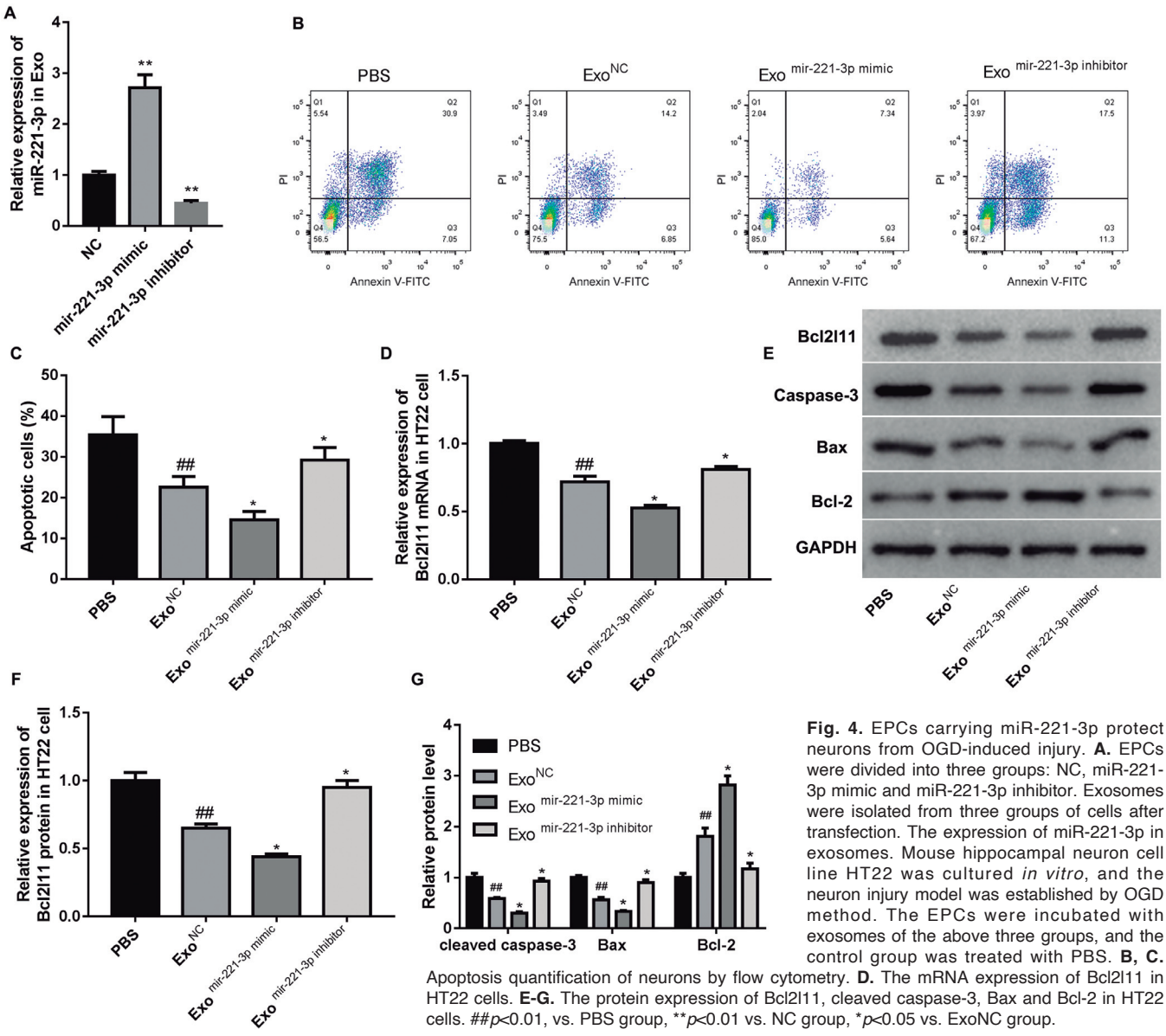

Fig. 4. EPCs carrying miR-221-3p protect neurons from OGD-induced injury. **A.** EPCs were divided into three groups: NC, miR-221-3p mimic and miR-221-3p inhibitor. Exosomes were isolated from three groups of cells after transfection. The expression of miR-221-3p in exosomes. Mouse hippocampal neuron cell line HT22 was cultured *in vitro*, and the neuron injury model was established by OGD method. The EPCs were incubated with exosomes of the above three groups, and the control group was treated with PBS. **B, C.** Apoptosis quantification of neurons by flow cytometry. **D.** The mRNA expression of Bcl2l11 in HT22 cells. **E-G.** The protein expression of Bcl2l11, cleaved caspase-3, Bax and Bcl-2 in HT22 cells. ##p<0.01, vs. PBS group, **p<0.01 vs. NC group, *p<0.05 vs. ExoNC group.

protected H9C2 *in vitro* from oxidative stress by inhibiting the activation of caspase 3/7 (Xiao et al., 2016). In a mouse model of acute myocardial ischaemia/reperfusion, *in vivo* delivery of cardiac progenitor cell exosomes inhibited cardiomyocyte apoptosis by 53%. In the reperfusion model, the inhibition of cardiomyocyte apoptosis was approximately 53% compared to PBS control. It has also been reported that exosomes derived from cardiac progenitor cells could prevent the apoptosis of cardiomyocytes by targeting PDCD4 via exosomal miR-21 (Xiao et al., 2016). Another study indicated that c-kit+ CPCs repaired and recovered the ischemic myocardium by a robust secretion of paracrine factors that can trigger and activate various endogenous cardiac repair mechanisms (Sharma et al., 2016). Some studies have reported the role of exosomes in cerebrovascular diseases. For example, Goetzl et al. showed that in patients with cerebrovascular disease, the levels of platelet-derived exosomes and plasma endothelial cell–derived exosomes cargo proteins related to the pathogenesis of atherosclerosis are significantly higher than that in matched control subjects (Goetzl et al., 2017). Deftu et al. concluded that the cardiovascular system acted like a well-trained orchestra, where exosomes played a role in paracrine and autocrine signaling (Deftu et al., 2020).

However, as far as we know, no studies have reported the potential of EPC-derived exosomes as a therapeutic factor for neuronal apoptosis, which may provide important insights into the efficacy of EPC-derived exosomes as a new therapeutic method for patients with cerebral infarction and cerebrovascular disease. In this study, EPCs were cultured *in vitro*, and endothelial progenitor exosomes were isolated. The results indicated that most exosomes were 80-120 nm in diameter. Western blot assay showed that CD9, CD63 and Alix, well-known as exosomal markers (Xiao et al., 2016; Chen et al., 2017), were enriched in exosomes. Importantly, EPC-derived exosomes ameliorated OGD-induced neuronal apoptosis. Besides, EPC-derived exosomes regulated the expressions of apoptosis-related protein in OGD-treated neurons. Pei et al. suggested that exosomes derived from astrocytes suppressed autophagy and reduced ameliorated neuronal damage in experimental ischemic stroke (Pei et al., 2019). Tsutsumi et al. found that exosomes isolated from culture media of IFN-γ/LPS-treated slices could trigger dopaminergic neurodegeneration (Tsutsumi et al., 2019). Li et al. indicated that bone marrow mesenchymal stem cell-derived exosomes might be a promising therapeutic option for severe spinal cord injury by activation of the Wnt/β-catenin signaling pathway (Li et al., 2019). Our article reveals exosomes derived from EPCs ameliorate OGD-induced neuronal apoptosis by delivering miR-221-3p.

To sum up, this study suggests that miR-221-3p in EPC_derived exosomes ameliorates OGD-induced neuronal apoptosis, which establishes its potential as a new therapeutic method for patients with cerebrovascular diseases.

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Competing interests. The authors declare that they have no competing interests, and all authors can confirm its accuracy.

References

Burger D., Viñas J.L., Akbari S., Dehak H., Knoll W., Gutsol A., Carter A., Touyz R.M., Allan D.S. and Burns K.D. (2015). Human endothelial colony-forming cells protect against acute kidney injury: Role of exosomes. Am. J. Pathol. 185, 2309-2323.

Chen S., Ma P., Zhao Y., Li B., Jiang S., Xiong H., Wang Z., Wang H., Jin X. and Liu C. (2017). Biological function and mechanism of MALAT-1 in renal cell carcinoma proliferation and apoptosis: Role of the MALAT-1-Livin protein interaction. J. Physiol. Sci. 67, 577-585.

Cui Y., Fu S., Sun D., Xing J., Hou T. and Wu X. (2019). EPC-derived exosomes promote osteoclastogenesis through lncRNA-MALAT1. J. Cell. Mol. Med. 23, 3843-3854.

Deftu A.T., Radu B.M., Cretoiu D., Deftu A.F., Cretoiu S.M. and Xiao J. (2020). Exosomes as intercellular communication messengers for cardiovascular and cerebrovascular diseases. In: Exosomes. Chapter 9. Edelstein L., Smythies J, Quesenberry P. and Noble D. (eds). Academic Press. pp 199-238.

Devanesan A.J., Laughlan K.A., Girn H.R. and Homer-Vanniasinkam S. (2009). Endothelial progenitor cells as a therapeutic option in peripheral arterial disease. Eur. J. Vasc. Endovasc. Surg. 38, 475-481.

Esquiva G., Grayston A. and Rosell A. (2018). Revascularization and endothelial progenitor cells in stroke. Am. J. Physiol. Cell Physiol. 315, C664-c674.

Goetzl E.J., Schwartz J.B., Mustapic M., Lobach I.V. Daneman R., Abner E.L. and Jicha G.A. (2017). Altered cargo proteins of human plasma endothelial cell-derived exosomes in atherosclerotic cerebrovascular disease. FASEB J. 31, 3689-3694.

Li C., Jiao G., Wu W., Wang H., Ren S., Zhang L., Zhou H., Liu H. and Chen Y. (2019). Exosomes from bone marrow mesenchymal stem cells inhibit neuronal apoptosis and promote motor function recovery via the wnt/β-catenin signaling pathway. Cell Transplant. 28, 1373-1383.

Mathieu M., Martin-Jaular L., Lavieu G. and Théry C. (2019). Specificities of secretion and uptake of exosomes and other extracellular vesicles for cell-to-cell communication. Nat. Cell. Biol. 21, 9-17.

Meschia J.F. and Brott T. (2018). Ischaemic stroke. Eur. J. Neurol. 25, 35-40.

Pei X., Li Y., Zhu L. and Zhou Z. (2019). Astrocyte-derived exosomes suppress autophagy and ameliorate neuronal damage in experimental ischemic stroke. Exp. Cell Res. 382, 111474.

Sahoo S. and Losordo D.W. (2014). Exosomes and cardiac repair after myocardial infarction. Circ. Res. 114, 333-344.

Sharma S., Mishra R., Bigham G.E., Wehman B., Khan M.M., Xu H.,

Saha P., Goo Y.A., Datla S.R., Chen L., Tulapurkar M.E., Taylor B.S., Yang P., Karathanasis S., Goodlett D.R. and Kaushal S. (2016). A deep proteome analysis identifies the complete secretome as the functional unit of human cardiac progenitor cells. Circ. Res. 120, 816-834.

Sozio S.M., Armstrong P.A., Coresh J., Jaar B.G., Fink N.E., Plantinga L.C., Powe N.R. and Parekh R.S. (2009). Cerebrovascular disease incidence, characteristics, and outcomes in patients initiating dialysis: The choices for healthy outcomes in caring for esrd (choice) study. Am. J. Kidney Dis. 54, 468-477.

Tsutsumi R., Hori Y., Seki T., Kurauchi Y., Sato M., Oshima M., Hisatsune A. and Katsuki H. (2019). Involvement of exosomes in dopaminergic neurodegeneration by microglial activation in midbrain slice cultures. Biochem. Biophys. Res. Commun. 511, 427-433.

Wu X., Liu Z., Hu L., Gu W. and Zhu L. (2018). Exosomes derived from endothelial progenitor cells ameliorate acute lung injury by transferring miR-126. Exp. Cell Res. 370, 13-23.

Xiao J., Pan Y., Li X.H., Yang X.Y., Feng Y.L., Tan H.H., Jiang L., Feng J. and Yu X.Y. (2016). Cardiac progenitor cell-derived exosomes prevent cardiomyocytes apoptosis through exosomal miR-21 by targeting PDCD4. Cell Death Dis. 7, e2277.

Xu J., Bai S., Cao Y., Liu L., Fang Y., Du J., Luo L., Chen M., Shen B. and Zhang Q. (2020). MiRNA-221-3p in endothelial progenitor cell-derived exosomes accelerates skin wound healing in diabetic mice. Diabetes Metab. Syndr. Obes. 13, 1259-1270.

Zhou Y., Li P., Goodwin A.J., Cook J.A., Halushka P.V., Chang E. and Fan H. (2018). Exosomes from endothelial progenitor cells improve the outcome of a murine model of sepsis. Mol. Ther. 26, 1375-1384.

Zhou Y., Li P., Goodwin A.J., Cook J.A., Halushka P.V., Chang E., Zingarelli B. and Fan H. (2019). Exosomes from endothelial progenitor cells improve outcomes of the lipopolysaccharide-induced acute lung injury. Crit. Care 23, 44.

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