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Small extracellular vesicles from dental follicle stem cells provide biochemical cues for periodontal tissue regeneration

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Abstract

Background: Treatments based on stem cell-derived small extracellular vesicles (sEVs) have been explored as an alternative to stem cell transplantation-based therapies in periodontal regeneration. Dental follicle stem cells (DFSCs) have shown great potential for regenerative medicine applications. However, it is unclear whether sEVs derived from DFSCs (DFSCs-sEVs) could be used in periodontal regeneration. This study investigates whether DFSCs-sEVs could regenerate damaged periodontal tissue and the potential underlying mechanism.

Methods: DFSCs-sEVs were isolated and identified, and periodontal ligament stem cells (PDLSCs) were cocultured with the isolated sEVs. The effect of DFSCs-sEVs on the biological behaviour of PDLSCs was examined using EdU assay, CCK-8 assay, cell cycle analysis, wound healing, alizarin red staining, qRT-PCR, and western blot analysis. RNA sequencing and functional enrichment analysis were used to detect the signal pathway involved in the effect of DFSCs-sEVs on PDLSCs. PDLSCs were pretreated with ERK1/2 or p38 MAPK inhibitors to investigate the possible involvement of the ERK1/2 and p38 MAPK pathways. Additionally, DFSCs-sEVs were combined with collagen sponges and transplanted into the periodontal defects in SD rats, and then, pathological changes in periodontal tissue were examined using haematoxylin and eosin (HE) staining and micro-CT.

Results: PDLSCs could internalize DFSCs-sEVs, thereby enhancing the proliferation assessed using EdU assay, CCK-8 assay and cell cycle analysis. DFSCs-sEVs significantly enhanced the migration of PDLSCs. DFSCs-sEVs promoted osteogenic differentiation of PDLSCs, showing deep Alizarin red staining, upregulated osteogenic genes (*RUNX2*, *BSP*, *COL1*), and upregulated protein expression (RUNX2, BSP, COL1, ALP). We found that p38 MAPK signalling was activated via phosphorylation. Inhibition of this signalling pathway with a specific inhibitor (SB202190) partially weakened the enhanced proliferation. After DFSCs-sEVs transplantation, new periodontal ligament-like structures and bone formation were observed in the damaged periodontal area in rats. Labelled DFSCs-sEVs were observed in the newly formed periodontal ligament and soft tissue of the defect area.

Conclusions: Our study demonstrated that DFSCs-sEVs promoted periodontal tissue regeneration by promoting the proliferation, migration, and osteogenic differentiation of PDLSCs. The effect of DFSCs-sEVs in promoting PDLSCs

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