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ORIGINAL

Impact of Combined Hdpsc-Derived Exosomes and Sdf-1 Application on Pulp Regeneration and Inflammation: Insights into Fitness, Mental Health, and Systemic Well-Being

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ABSTRACT

Objective: To explore the synergistic effects of exosomes secreted by human dental pulp stem cells (hDPSCs) and stromal cell-derived factor-1 (SDF-1) on dental pulp regeneration under inflammatory conditions, with a focus on implications for fitness, mental health, and overall systemic well-being. **Methods:** hDPSCs were isolated, cultured, and exposed to lipopolysaccharide (LPS) to mimic an inflammatory periodontal environment. Exosomes from these inflamed hDPSCs (I-EXO) were then isolated using ultracentrifugation with 30% sucrose density gradients. The exosomes' morphology was examined via transmission electron microscopy (TEM), and the presence of the exosomal marker CD63 was confirmed through Western blot analysis. Dental scaffolds, derived from isolated premolar teeth, facilitated semi-in-situ pulp regeneration in a subcutaneous model with nude mice. The mice were divided into three groups: a blank control (no implant), an S group (SDF-1 alone), and an I+S group (SDF-1 + I-EXO). Regenerated pulp tissue was assessed using Hematoxylin and Eosin (H&E) and Masson's trichrome staining, while immunohistochemistry was employed to evaluate the expression of CD31, a marker for neovascularization. **Results:** H&E staining revealed new dental pulp tissue formation in both treatment groups, with the I+S group displaying significantly more new tissue and cellular organization. Masson's trichrome staining identified blue-stained collagen fibrils across all

groups, with the I+S group showing well-structured dentin and pulp-like tissue formation. Immunohistochemical analysis demonstrated a statistically significant increase in CD31-positive microvessel counts in all treated groups ($p < 0.05$), with the highest counts observed in the I+S group, indicating enhanced vascularization. **Conclusion:** The combined application of hDPSC-derived exosomes and SDF-1 under inflammatory conditions significantly enhances pulp regeneration, tissue vascularization, and the structural organization of collagen fibers and mineralized tissue. These findings suggest potential benefits for dental health, which could indirectly influence fitness levels, mental health, and systemic well-being through the reduction of chronic inflammation and improvement of oral health.

KEYWORDS: Inflammatory environment, dental pulp stem cells, exosomes, stromal cell-derived factor-1, dental pulp regeneration

1. INTRODUCTION

The intricate interplay between oral health and systemic well-being is a burgeoning field of investigation that underscores the profound impact dental conditions can have on overall physical fitness, mental health, and systemic health. Chronic oral inflammatory conditions, such as periodontitis, have been linked to a host of systemic diseases, including cardiovascular disease, diabetes, and rheumatoid arthritis, highlighting the critical need for innovative therapeutic strategies to combat these issues. Among these strategies, the regeneration of dental pulp damaged by inflammation presents a promising avenue for not only restoring oral health but also mitigating the broader impacts on systemic well-being(Nakashima et al., 2017).

Human dental pulp stem cells (hDPSCs) and stromal cell-derived factor-1 (SDF-1) have emerged as pivotal components in the field of regenerative dentistry. hDPSCs are known for their profound regenerative capabilities, including the differentiation into various cell types and the secretion of reparative exosomes. Exosomes are extracellular vesicles that play key roles in cell communication and tissue repair processes. On the other hand, SDF-1 acts as a potent chemoattractant, promoting the migration and homing of stem cells to sites of injury, thereby enhancing tissue regeneration and healing (S. G. Kim, 2021; Nie, Kim, Fu, & Mao, 2011).

The combined application of exosomes secreted by hDPSCs and SDF-1 under inflammatory conditions presents a novel therapeutic modality that could significantly enhance pulp regeneration. This approach not only aims to restore the structural and functional integrity of the dental pulp but also holds the potential to reduce systemic inflammation, thereby contributing to improved systemic health outcomes. Furthermore, the alleviation of chronic oral inflammation through such regenerative therapies could have positive

implications for physical fitness and mental health. Physical fitness benefits from reduced systemic inflammation and improved oral health, leading to enhanced performance and endurance. Similarly, mental health can significantly benefit from the reduction of pain and discomfort associated with dental conditions, alongside the psychological uplift associated with improved health and well-being(D. Wang et al., 2022). This study aims to explore the synergistic effects of hDPSC-derived exosomes and SDF-1 on dental pulp regeneration under inflammatory conditions, with a focus on the broader implications for fitness, mental health, and systemic well-being. Through this investigation, we seek to contribute to the growing body of evidence that supports the critical link between oral health and overall systemic health, highlighting the potential of regenerative dentistry to not only transform dental therapeutic strategies but also to offer insights into holistic health improvement (Swanson et al., 2020).

2. Materials and methods

2.1 Experimental animals and materials

24 Four-week-old male BALB/c nude Mice (nude mice) weighing about 18-20 g were purchased from Hunan Sleek Jingda Laboratory Animal Co. The animal husbandry and animal experiments involved in the experiments were approved by the Experimental Animal Ethics Committee of Xinjiang Medical University.

2.2 Main experimental apparatus and reagents

anti-mouse SDF-1 monoclonal antibody (R&D system, USA), anti-mouse CXCR4 monoclonal antibody (abcam, USA), sodium pentobarbital (Merck, Germany), peptide hydrogel (Corning, USA), anti-rabbit polyclonal antibodies CD34 and CD63 (eBioscience, USA) Calnexin (Signalway Antibody, USA), mineral trioxide aggregate (MTA) (Dentsply, USA), mouse/rabbit ultra-sensitive immunohistochemistry kit (Bioworld Technology, USA), transmission electron microscopy (JEOL, Japan)

2.3 Experimental methods

2.3.1 Isolation and culture of hDPSC

Patients aged 14-30 years attending the Department of Oral and Maxillofacial Surgery of the Second Affiliated Hospital of Xinjiang Medical University were selected and healthy intact third molars or premolars that needed to be extracted for treatment were collected with the patients' informed consent. All patients signed an informed consent form. The dental pulp was removed under aseptic conditions and cultured in Dulbecco's modified Eagle's medumzDMEM with 20 fetal bovine serum using the tissue

block culture method. The hDPSC from passages 3 to 5 with good growth status were used for subsequent studies.

2.3.2 Extraction of exosomes

(Huang, Narayanan, Alapati, & Ravindran, 2016): Select 3rd-5th generation hDPSC, culture the cells to 80%-90% fusion, add LPS at a final mass concentration of 1 mg/L to the medium for 3 d. After 3 d, replace the medium with one containing 10% exosome-free serum, collect the cell supernatant after 48 h. Centrifuge at 300 x g for 10 min at 4°C to remove cells, centrifuge at 2 000 x g for 10 min to remove dead cells, centrifuge at 10 000 x g for 30 min to remove cell debris, centrifuge at 10 000 x g twice for 70 min, discard the supernatant, and precipitate as I-EXO. The supernatant was discarded, and the precipitate was I-EXO.

2.3.3 Exosome identification

(1) transmission electron microscope (TEM) morphological examination: Samples were prepared by diluting the I-EXO precipitate with PBS and dropped onto a glow-dischargeable 150 mesh formvar copper mesh; glow-discharge was followed by incubation at 4°C for 2 min. The mesh was washed, negatively stained with 2% UO2 acetate solution and dried; observed using transmission electron microscopy at 80kv.

(2) Surface marker detection: Total I-EXO protein was extracted, bicinchoninic acid (BCA) was used to determine protein concentration, protein denaturation, gel preparation, loading, electrophoresis, wet transfer to polyvinylidene difluoride membranes, blocking, incubation at 4°C with primary antibody CD63 (1: 1,000). Tris(hydroxymethyl) aminomethane buffer containing polysorbate-20 was used to rinse, incubate the secondary antibody, develop and photograph.

2.4 Tooth scaffold fabrication (Janjić, Lilaj, Moritz, & Agis, 2018)

The anterior molar collected in step 1 was used to fabricate the dental scaffold for in vivo implantation: ①Carefully scraping the periodontal ligament tissue,using the dental microdynamic system to open the pulp and extract the pulp tissue; ②Using the Protaper root canal preparation machine to clean and prepare the inner wall of the root canal,remove the pulp and preform dentin remaining in the canal junction; ③Using a dental microdynamic system under continuous cooling with circulating water to remove the crown, as well as part of the root, preserving the middle 1/3 of the root with a length of 2 mm; ④ The tooth holder was immersed in deionised water and shaken in an ultrasonic cleaning machine for 5 minutes every hour and the deionised water was replaced for 5 hours of continuous treatment; ⑤ 17% EDTA soaking, decalcification treatment for 5 minutes; deionised water rinse for 10 minutes;

⑥ 10% EDTA soaking, decalcification treatment for 5 minutes; deionised water rinse for 10 minutes; ⑦ 5% EDTA soaking, decalcification treatment for 10 minutes; deionised water rinse for 10 minutes; ⑧ Denn tablets were treated with ethylene O and soaked in PBS for 24 hours.

2.5 Construction of subcutaneous semi-in situ animal models

① 4-week-old nude mice were taken and anesthetized with isoflurane by inhalation; ②Iodine voltammetry was used to disinfect the back and four 1cm long incisions were made on the left and right, and symmetrically on the top and bottom of the back to separate the subcutaneous tissues with blunt instruments; ③Each incision was made to implant a dental bracket and the implant material was injected into the root canal of the dental bracket using a 23G syringe at the same time; ④Sutures were made to close the skin incisions;

2.6 Animal grouping intervention

Nude mice were divided into blank group (no implantation of any substance), S group (SDF- 1 alone) and I+S group (SDF-1+I-EXO) according to the implantation material, with 8 animals in each group. The specific implantation materials for each group were as follows ①Blank group: no implantation of any substance in the root canal.

② Group S: 1 mg/L SDF-1 stock solution was prepared for implantation according to the instructions for use of recombinant human SDF-1αlyophilized powder. ③Group I+S (SDF-1+I-EXO): Add 100 ug/L of SDF-1 and 200 mg/L of exosomes to the peptide hydrogel to obtain an exosome-compounded SDF-1 peptide hydrogel. All implant materials were stored at 4°C and ready for use.

2.7 Sample collection and processing

Three months later, nude mice were euthanized by CO_2.The samples were fixed in 4% paraformaldehyde solution for 24 h; rinsed in running water for 24 h, then immersed in 14% EDTA solution and decalcified for 2 months; after complete decalcification, the samples were dehydrated, paraffin-embedded, sectioned, baked and stored.

2.8 Histological analysis

The sections were stained with hematoxylin-eosin (HE) and Masson, observe the tissue neoplasia in the root canals under the pathology microscope. The sections were immunohistochemically stained, and the area of positive expression of CD31, a marker protein of vascular neovascularization, was observed under a pathological microscope, and the

IOD value of positive expression of CD31 was analyzed semi-quantitatively.

2.9 Statistical analyze

Each group of trials was repeated three times and the experimental data were subjected to statistical one-way ANOVA using the SPSS 22.0 software package, with a t-test for comparison between the two groups at a two-sided α=0.05.

3. Results

3.1 Results of exosome identification

The pellets extracted by centrifugation from the LPS supernatant were identified by TEM, the pellets were all around 100 nm in diameter and showed a teatro-like or concave hemisphere-like structure (Fig. 1). The results of western blot showed that the extracts were highly expressed in the exosomal surface marker protein CD63 (Fig. 2). These suggest that I-EXO has been successfully extracted in this experiment.

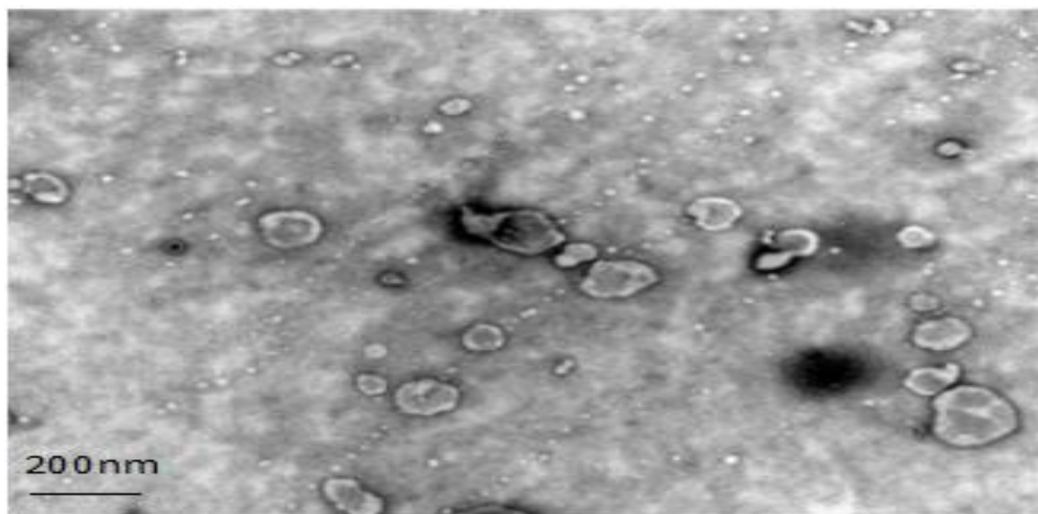

Figure 1: Observe the morphological appearance of exosomes by TEM

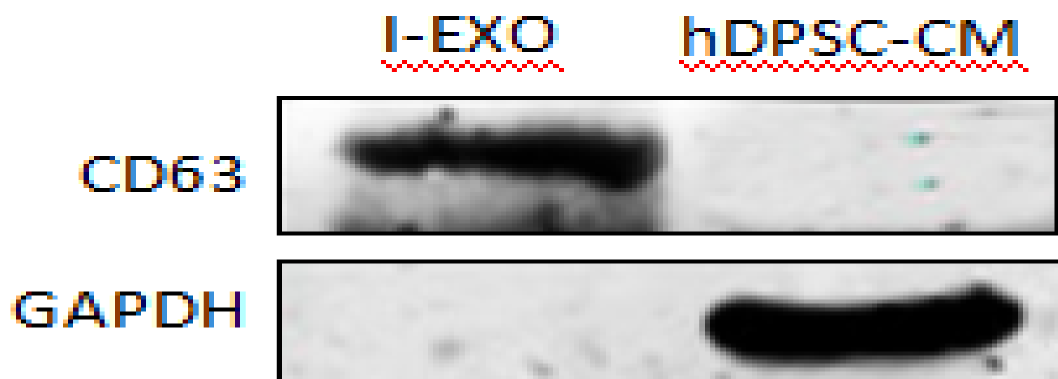

Figure 2: Identify the surface markers CD63 of I-Exo by Western Bbt

3.2 Histological staining results

The results of H&E staining experiment are shown in Fig.3. After 3 months of subcutaneous implantation in nude mice, the formations of new dentin in the root canal were visible in both the I+S group and the S group. Regenerated tissues in the I+S group had the following characteristics: (i) The regenerated pulp tissues were continuous, structurally intact and tightly connected to the dentin. (ii) The presence of thick blood vessels as well as smallest vessels (red arrows) were visible in the new tissue. (iii) A large amount of new dentin formation could be seen, and a clear line of new dentin deposition was seen on top of the original dentin (blue dashed line). (iv) The structures of the dentin tubules in the newly formed dentin were clear and regularly arranged along the original dentin.

The new pulp tissues in the S group were separated and fractured. Although a small amount of new dentin formations was visible, the new dentins were disorganized and did not form clear and regular dentin tubules compared to the I+S group. In the blank group, the pulp regenerations were poor and the tissues in the root canal were sparse, with only a small amount of soft tissue regeneration visible and no significant new dentin formations.

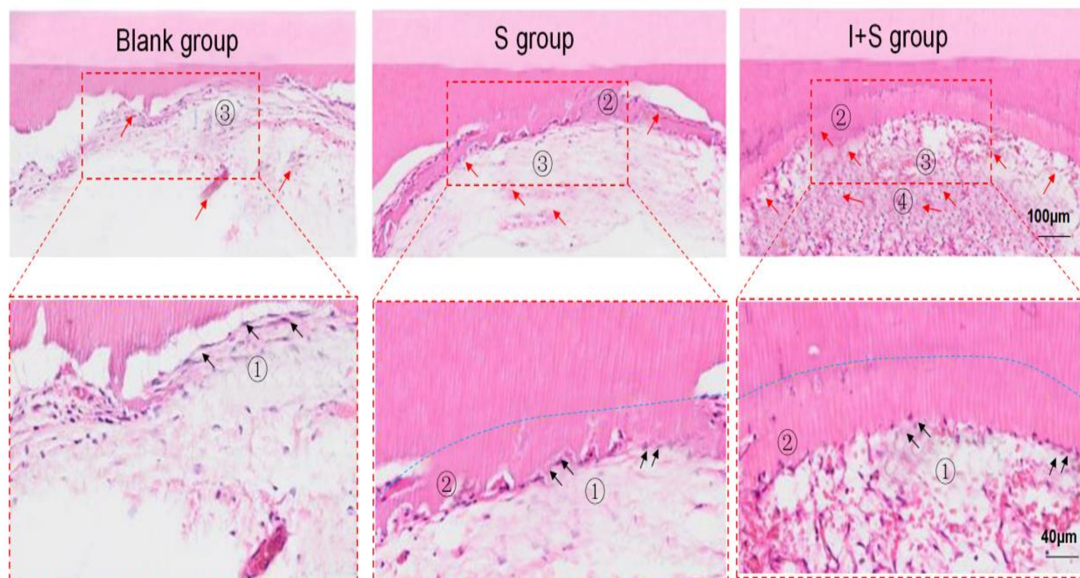

Figure 3: H&E staining results of regenerated pulp tissue. The red arrow indicates blood vessels; the black arrows indicate odontoblasts; ①odontoblast ②new dentin; ③blood vessel; ④dental pulp

Masson staining: As shown in Fig.4, the Masson staining results also showed the formation of well-defined neodontic dentin and pulp-like tissue in the I+S group. Collagen fibers showed blue color in Masson staining, and blue-stained collagen fiber formations could be seen in all three groups of neoplastic tissues. In conclusion, the analysis of the H&E and Masson

staining results showed that the regeneration of semi-in situ pulp tissue was good to bad in the following order: group I+S, group S and blank group.

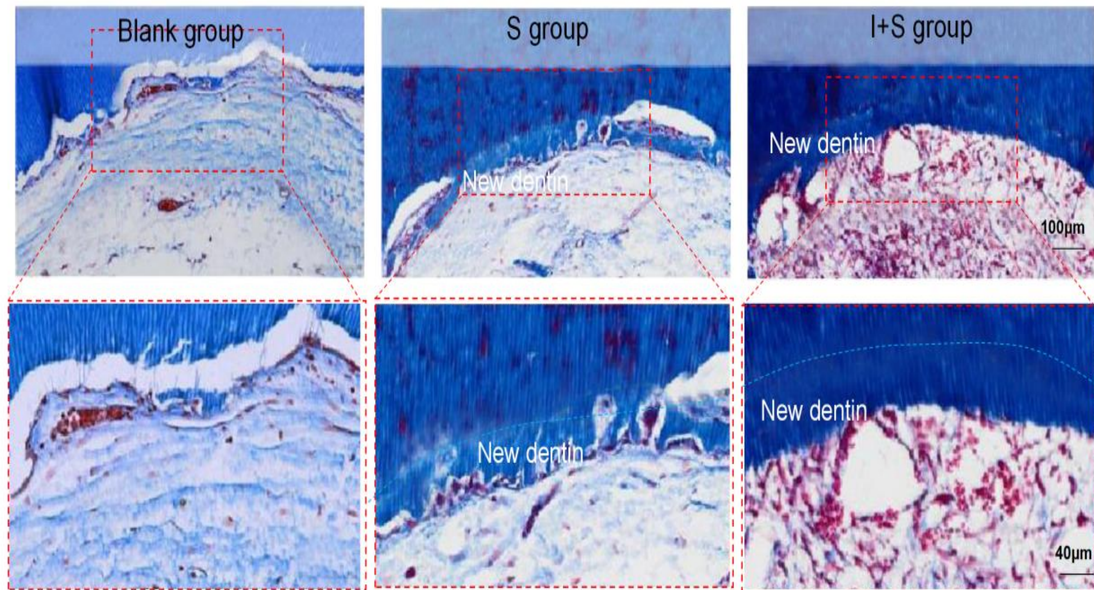

Figure 4: Masson staining results of regenerated pulp tissue

The CD31 immunohistochemistry results showed that more neovascularization was visible in the I+S group that was stained brownish yellow (Fig.5, red arrows), and the luminal structures of the formed vessels were obvious and some of them were thick. Also visible in the S group were more obvious neovascularization than in the blank group.

Further semi-quantitative analysis of the CD31 immuno histochemical staining results was performed, and the experimental results showed that the number of neovascularization in the I+S group was significantly more than that in the S and blank groups ($P < 0.05$, Fig.6). In conclusion, according to the analysis of H & E and Masson staining results, the regeneration effect of semi-in situ dental pulp tissue was changed from good to poor in order: I + S group, S group and blank group.

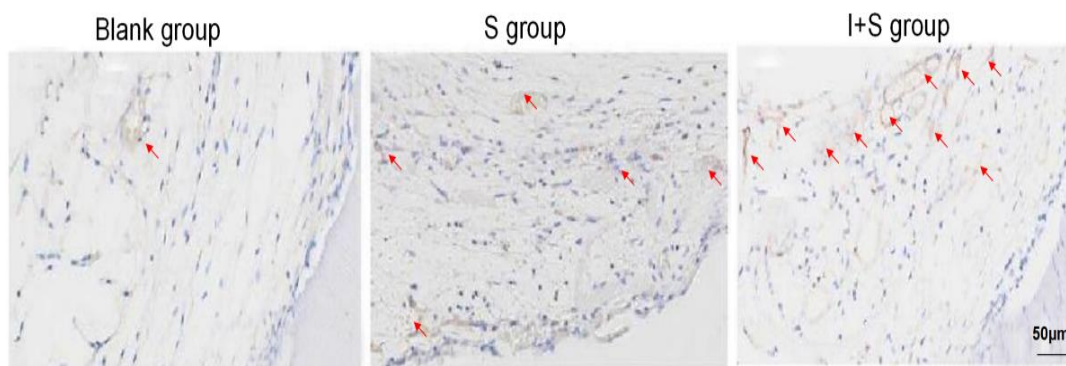

Figure 5: CD31 immuno histochemical staining results of regenerated pulp tissue

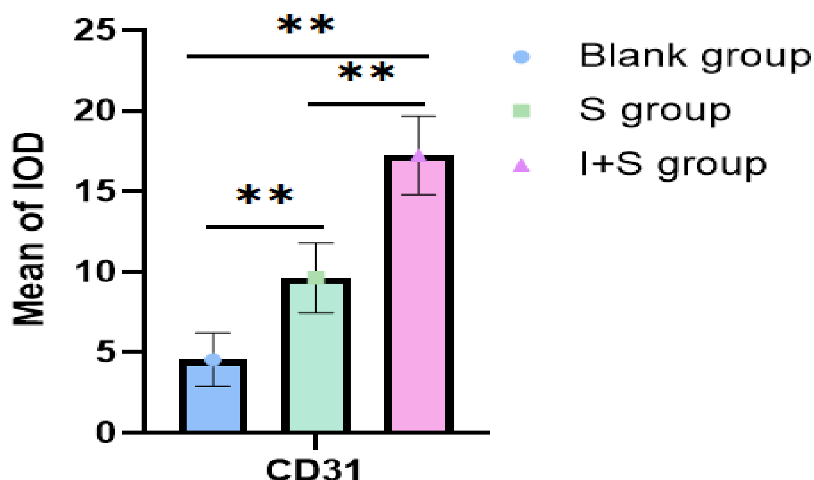

Figure 6: Quantitative analysis of CD31 expression

4. Discussion

Functional regeneration of the whole pulp is the ideal goal in the treatment of endodontic and periapical diseases. The ideal pulp regeneration should be achieved at the histological level by regenerating cells, blood vessels, nerves and extracellular matrix (Ducret et al., 2021; Zaky, Shehabeldin, Ray, & Sfeir, 2021). Although the cell homing way of pulp tissue regeneration treatment also has the three elements of tissue engineering, namely the seed cells, scaffold and cytokines (Saharkhiz, Ayadilord, Emadian Razavi, & Naseri, 2021), due to the uncertainty of homing cell species and the influence of local microenvironment, the results of the previous study on pulp tissue regeneration in this way showed that most of the new tissues in the root canal were disordered cementoid, osteoid and periodontal membrane tissue, with incomplete regeneration (Ayadilord et al., 2021; Kim et al., 2015). In this study, a bioactive scaffold loaded with exosomes and SDF-1α was injected into the pulpless root canal to induce migration and homing, proliferation and differentiation of endogenous stem cells through the chemokine SDF-1 to participate in pulp regeneration, and an attempt was made to replace hDPSC by hDPSC-secreted exosomes to improve the histological structure of the new tissue and bring it closer to the deal target.

SDF-1 is an important chemokine in humans, which was discovered by Nagasawa et al in a cytokine secreted by the mouse bone marrow stromal cell line pA6, and is known as a pre-B cell growth factor because of its important role in the growth and differentiation of B cells (De Falco et al., 2004; Nagasawa et al., 1996). SDF-1 is a chemokine for CD34 hematopoietic stem cells (Kollet et al., 2003), which can promote the growth, survival and osteogenic differentiation of bone marrow mesenchymal stem cells (MSCs). In the case of tissue and organ damage, SDF-1 can promote the recruitment of MSCs and inflammatory cells to the site of injury. It is a key cytokine regulating the repair of tissue and organ damage, and an important

chemokine regulating local inflammation (Wang, Wei, Rong, Wang, & Li, 2022).

Exosomes are tiny vesicles that are secreted by cells and can be taken up by surrounding cells. They not only transport proteins, specifically target recipient cells, exchange proteins and lipids and trigger downstream signaling pathways (Lu et al., 2021), but also transport a variety of nucleic acids, including micro ribonucleic acid (miRNA), and are involved in various vital activities of the body (Valadi et al., 2007). Studies have shown that exosomes can promote the regeneration of tissues such as blood vessels, nerves and many organs (He, Zheng, Luo, & Wang, 2018). Exosomes secreted by the same cells in different environments have different effects. Exosomes secreted by human pulp stem cells under inflammation and those secreted under normal conditions both promote proliferation, migration, angiogenesis and differentiation of BMMSCs, but the effect of exosomes secreted by human pulp stem cells under inflammation is significantly stronger than that of exosomes secreted under normal conditions, and the structures of root canal regeneration tissue in vivo are closer to that of normal pulp (Codispoti, Marrelli, Paduano, & Tatullo, 2018).

The histological results of this study showed that the amount of new tissue, the number of cells in the tissue and the density of blood vessels in the root canal increased significantly in the I+S group compared with the S group and the blank group, indicating that the combination of exosomes and SDF-1 could better promote the proliferation, dentinogenic differentiation and angiogenic ability of homing cells under inflammatory conditions. It was found that exosomes produced after MSC stimulation by LPS can regulate macrophages toward anti-inflammatory phenotype polarization via minute RNA let-7b and promote tissue repair (Ti et al., 2015).This study showed that the exosomes produced by hDPSC in the mild inflammatory state can promote the normal tissue regeneration and make the structure of the nascent tissue more orderly, but the molecular biological regulation mechanism needs to be further investigated. In addition, the immuno histochemical results of this study showed that the CD31 expression was lower in the S group and the blank group compared to the I+S group, which might be due to the fact that I-EXO provided a more suitable microenvironment for stem cell differentiation and the CD31 expression was higher in differentiated cells.

5. Conclusion

The study conclusively demonstrates that the synergistic application of exosomes derived from human dental pulp stem cells (hDPSCs) and stromal cell-derived factor-1 (SDF-1) under conditions of inflammation significantly enhances dental pulp regeneration. This approach not only improves the quantity of newly formed tissue within the root canal but also increases

vascular density and promotes a more organized and regular arrangement of collagen fibers and mineralized tissue. The findings underscore the potential of combining hDPSC-derived exosomes with SDF-1 to advance dental regenerative therapies, offering a promising strategy for restoring dental pulp damaged by inflammation. Furthermore, the implications of improved dental health through such regenerative strategies could extend beyond oral well-being, potentially influencing overall fitness, mental health, and systemic health by mitigating the impacts of chronic oral inflammation.

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REFERENCES

Ayadilord, M., Nasseri, S., Emadian Razavi, F., Saharkhiz, M., Rostami, Z., & Naseri, M. (2021). Immunomodulatory effects of phytosomal curcumin on related-micro RNAs, CD200 expression and inflammatory pathways in dental pulp stem cells. *Cell Biochemistry and Function, 39*(7), 886-895.

Codispoti, B., Marrelli, M., Paduano, F., & Tatullo, M. (2018). Nanometric bio-banked MSC-derived exosome (nanobiome) as a novel approach to regenerative medicine. *Journal of clinical medicine, 7*(10), 357.

De Falco, E., Porcelli, D., Torella, A. R., Straino, S., Iachininoto, M. G., Orlandi, A., . . . Capogrossi, M. C. (2004). SDF-1 involvement in endothelial phenotype and ischemia-induced recruitment of bone marrow progenitor cells. *Blood, 104*(12), 3472-3482.

Ducret, M., Costantini, A., Gobert, S., Farges, J., Bekhouche, M., & Kocourek, T. (2021). Fibrin-based scaffolds for dental pulp regeneration: From biology to nanotherapeutics. *Eur. Cell Mater, 41*, 1-14.

He, C., Zheng, S., Luo, Y., & Wang, B. (2018). Exosome theranostics: biology and translational medicine. *Theranostics, 8*(1), 237.

Huang, C.-C., Narayanan, R., Alapati, S., & Ravindran, S. (2016). Exosomes as biomimetic tools for stem cell differentiation: applications in dental pulp tissue regeneration. *Biomaterials, 111*, 103-115.

Janjić, K., Lilaj, B., Moritz, A., & Agis, H. (2018). Formation of spheroids by dental pulp cells in the presence of hypoxia and hypoxia mimetic agents. *International endodontic journal, 51*, e146-e156.

Kim, D. S., Shin, M. R., Kim, Y. S., Bae, W. J., Roh, D. H., Hwang, Y. S., & Kim, E. C. (2015). Anti-inflammatory effects of glutamine on LPS-stimulated human dental pulp cells correlate with activation of MKP-1 and attenuation of the MAPK and NF-κB pathways. *International endodontic journal, 48*(3), 220-228.

Kollet, O., Shivtiel, S., Chen, Y.-Q., Suriawinata, J., Thung, S. N., Dabeva, M. D., . . . Samira, S. (2003). HGF, SDF-1, and MMP-9 are involved in stress-induced human CD34+ stem cell recruitment to the liver. *The Journal of clinical investigation, 112*(2), 160-169.

Lu, H., Zhang, Y., Xiong, S., Zhou, Y., Xiao, L., Ma, Y., . . . Wang, X. (2021). Modulatory Role of Silver Nanoparticles and Mesenchymal Stem Cell–Derived Exosome-Modified Barrier Membrane on Macrophages and Osteogenesis. *Frontiers in Chemistry, 9*, 699802.

Nagasawa, T., Hirota, S., Tachibana, K., Takakura, N., Nishikawa, S.-i., Kitamura, Y., . . . Kishimoto, T. (1996). Defects of B-cell lymphopoiesis and bone-marrow myelopoiesis in mice lacking the CXC chemokine PBSF/SDF-1. *nature, 382*, 635-638.

Nakashima, M., Iohara, K., Murakami, M., Nakamura, H., Sato, Y., Ariji, Y., & Matsushita, K. (2017). Pulp regeneration by transplantation of dental pulp stem cells in pulpitis: a pilot clinical study. *Stem Cell Research & Therapy, 8*, 1-13.

Saharkhiz, M., Ayadilord, M., Emadian Razavi, F., & Naseri, M. (2021). Effects of phytosomal curcumin treatment on modulation of immunomodulatory and pulp regeneration genes in dental pulp mesenchymal stem cells. *Odontology*, 1-9.

Swanson, W. B., Gong, T., Zhang, Z., Eberle, M., Niemann, D., Dong, R., . . . Ma, P. X. (2020). Controlled release of odontogenic exosomes from a biodegradable vehicle mediates dentinogenesis as a novel biomimetic pulp capping therapy. *Journal of Controlled Release, 324*, 679-694.

Ti, D., Hao, H., Tong, C., Liu, J., Dong, L., Zheng, J., . . . Han, W. (2015). LPS-preconditioned mesenchymal stromal cells modify macrophage polarization for resolution of chronic inflammation via exosome-shuttled let-7b. *Journal of translational medicine, 13*, 1-14.

Valadi, H., Ekström, K., Bossios, A., Sjöstrand, M., Lee, J. J., & Lötvall, J. O. (2007). Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nature cell biology, 9*(6), 654-659.

Wang, D., Lyu, Y., Yang, Y., Zhang, S., Chen, G., Pan, J., & Tian, W. (2022). Schwann cell-derived EVs facilitate dental pulp regeneration through endogenous stem cell recruitment via SDF-1/CXCR4 axis. *Acta biomaterialia, 140*, 610-624.

Wang, R., Wei, W., Rong, S., Wang, T., & Li, B. (2022). Intravenous Injection of SDF-1α-overexpressing Bone Marrow Mesenchymal Stem Cells has a Potential Protective Effect on Myocardial Ischemia in Mice. *Current Stem Cell Research & Therapy, 17*(4), 348-360.

Zaky, S., Shehabeldin, M., Ray, H., & Sfeir, C. (2021). The role of inflammation modulation in dental pulp regeneration. *Eur Cells Mater, 41*, 184-193.