Magna Scientia Advanced Research and Reviews

eISSN: 2582-9394

Cross Ref DOI: 10.30574/msarr

Journal homepage: https://magnascientiapub.com/journals/msarr/

(RESEARCH ARTICLE)

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Meta-Analysis: Harnessing dental pulp mesenchymal stem cells for inducing reparative dentin: A synthesis of mechanisms and therapeutic strategies

Tjing Yung Loo *, Mary Ngan Bing Cheung and Preston Corliss Loo

P&P Dental and Medical Sciences Ltd and Essence Medical Laboratory, Hong Kong.

Magna Scientia Advanced Research and Reviews, 2026, 16(01), 072-076

Publication history: Received on 14 December 2025; revised on 22 January 2026; accepted on 24 January 2026

Article DOI: https://doi.org/10.30574/msarr.2026.16.1.0014

Abstract

Aim: To systematically review and quantitatively synthesize in vivo evidence on the efficacy of dental pulp mesenchymal stem cells (DP-MSCs) and their derived secretome/extracellular vesicles (EVs) in inducing reparative dentin formation, and to analyze the key molecular mechanisms involved.

Materials and Methods: A systematic search of PubMed, Embase, Web of Science, and Scopus was conducted for studies published from inception to January 2024. Controlled animal studies and human clinical trials that evaluated the application of DP-MSCs (or their derivatives) for dentin regeneration and reported histomorphometric outcomes (e.g., dentin bridge thickness, area) were included. Pooled mean differences (MD) with 95% confidence intervals (CI) were calculated using a random-effects model. Subgroup analyses were performed based on cell source (allogeneic vs. autologous), carrier scaffold, and use of conditioned media (CM) or EVs.

Results: Twenty-eight studies (26 animal, 2 human) met the inclusion criteria. Pooled analysis revealed that DP-MSC-based therapies significantly increased reparative dentin formation compared to control groups (MD = 245.51 μm, 95% CI: 189.21 to 301.81, $p < 0.001$). Subgroup analysis showed high efficacy for allogeneic cells (MD = 228.34 μm, $p < 0.001$) and scaffold-based delivery (MD = 267.90 μm, $p < 0.001$). Notably, the use of cell-free derivatives, specifically CM/EVs, also yielded a significant effect (MD = 195.63 μm, $p < 0.001$), suggesting potent paracrine mechanisms. Key associated mechanisms included upregulation of dentinogenic markers (DSPP, DMP-1, BMP-2), angiogenesis (VEGF), and downregulation of inflammatory cytokines.

Conclusion: DP-MSCs and their secretome are highly effective in promoting reparative dentinogenesis in vivo. This effect is mediated through a multifaceted paracrine signaling network that orchestrates cell recruitment, differentiation, and angiogenesis. The proven efficacy of cell-free strategies represents a paradigm shift towards more clinically translatable, off-the-shelf therapies for vital pulp therapy and regenerative endodontics.

Keywords: Dental Pulp Stem Cells; DPSCs; Reparative Dentin; Dentinogenesis; Regenerative Endodontics; Pulp Capping; Mesenchymal Stem Cells; Secretome; Extracellular Vesicles; Exosomes; Meta-Analysis

1. Introduction

The dental pulp possesses a remarkable innate capacity for repair, primarily through the formation of reparative dentin by newly differentiated odontoblast-like cells in response to injury or caries [1,2]. This process is orchestrated by a niche of mesenchymal stem cells (MSCs) residing within the pulp tissue, most notably dental pulp stem cells (DPSCs) and stem cells from human exfoliated deciduous teeth (SHED) [3,4]. While mild stimuli can activate this endogenous response, larger defects often overwhelm the innate healing potential, leading to pulpitis and necrosis [5,6].

* Corresponding author: Tjing Yung Loo

Regenerative endodontic procedures aim to predictably regenerate the dentin-pulp complex [7,8]. The transplantation of ex vivo expanded DP-MSCs represents a promising cell-based strategy to amplify the body's natural repair mechanisms [9,10]. However, significant challenges related to cell sourcing, storage, safety, and regulatory approval have hindered clinical translation [11,12]. This has catalyzed a shift in focus towards the therapeutic use of the *secretome*—the bioactive factors, extracellular vesicles (EVs), and exosomes secreted by these cells—which mediates their regenerative effects through paracrine signaling [13,14].

This meta-analysis quantitatively synthesizes the in vivo evidence for DP-MSCs and their secretome in inducing reparative dentin formation. Furthermore, it systematically reviews the underlying molecular mechanisms, providing a comprehensive overview of current therapeutic strategies and illuminating the path toward clinical application.

2. Materials and Methods

This study was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The protocol was registered on PROSPERO (CRD42024498765).

2.1. Eligibility Criteria

- **Population:** Animal models or human patients with dentin defects.
- **Intervention:** Application of DP-MSCs (any source: DPSCs, SHED) or their derivatives (conditioned media/CM, extracellular vesicles/EVs, exosomes).
- **Comparator:** Control groups receiving vehicle, scaffold alone, or no treatment.
- **Outcome:** Primary: quantitative histomorphometric measurement of reparative dentin thickness or area (in μm or μm^2). Secondary: molecular analysis of dentinogenic markers (e.g., DSPP, DMP-1, BMP-2).
- **Study Design:** Controlled animal studies and human clinical trials.

2.2. Search Strategy

A systematic search was performed in PubMed, Embase, Web of Science, and Scopus from inception to January 15, 2024. Search terms included: ("dental pulp stem cell" OR DPSC OR SHED) AND ("reparative dentin" OR "dentin regeneration" OR "dentinogenesis" OR "pulp capping") AND (in vivo OR "animal model" OR "clinical trial").

2.3. Study Selection and Data Extraction

Two independent reviewers screened records. Data were extracted onto a standardized form, including study characteristics, sample size, intervention details, control type, outcome data, and key mechanistic findings.

2.4. Risk of Bias and Quality Assessment

The risk of bias for animal studies was assessed using the SYRCLE's tool. For the two human studies, the Joanna Briggs Institute (JBI) critical appraisal checklist was used.

2.5. Statistical Analysis

Meta-analysis was performed using RevMan v5.4. The pooled effect size for continuous outcomes (dentin thickness/area) was calculated as the Mean Difference (MD) with 95% CI using a random-effects model due to expected heterogeneity. Statistical heterogeneity was assessed using the I^2 statistic. Subgroup analyses were conducted for cell type (allogeneic vs. autologous), delivery method (scaffold vs. injection), and intervention type (cells vs. secretome/EVs).

3. Results

3.1. Study Selection

The search yielded 2,158 records. After duplicate removal and screening, 28 studies (26 rodent models, 2 human pilot trials) met the inclusion criteria for the systematic review, and 22 provided sufficient data for meta-analysis.

3.2. Study Characteristics

The included studies encompassed 786 treated defects. Interventions included transplantation of DPSCs/SHED (n=18 studies), application of conditioned media (CM) (n=6), and application of extracellular vesicles (EVs) (n=4). Common scaffolds included collagen, hydrogel (e.g., Puramatrix™), and PLA/PGA.

3.3. Meta-Analysis of Reparative Dentin Formation

Pooled data from 22 studies (458 defects) demonstrated a highly significant increase in reparative dentin thickness in the DP-MSC intervention groups compared to controls (MD = 245.51 μm, 95% CI: 189.21 to 301.81, $p < 0.001$; $I^2 = 78\%$).

- **Subgroup - Cell-Based vs. Cell-Free:** Both cell transplantation (MD = 261.44 μm, $p < 0.001$) and cell-free secretome/EV application (MD = 195.63 μm, $p < 0.001$) were significantly effective.
- **Subgroup - Cell Source:** Allogeneic DP-MSCs were highly effective (MD = 228.34 μm, $p < 0.001$), supporting their use as an off-the-shelf product.
- **Subgroup - Scaffold Use:** Scaffold-based delivery yielded a greater effect (MD = 267.90 μm, $p < 0.001$) than cell injection alone.

3.4. Analysis of Mechanisms

A qualitative synthesis of included studies identified consistent mechanistic themes:

- **Odontoblastic Differentiation:** Upregulation of key dentinogenic markers (DSPP, DMP-1, ALP) in resident cells via DP-MSC-secreted BMP-2, TGF-β1, and IGF-1 [15,16].
- **Angiogenesis:** Secretion of pro-angiogenic factors (VEGF, FGF-2, PDGF) promoting neovascularization, which is critical for sustaining the regenerative process [17,18].
- **Immunomodulation:** Polarization of macrophages towards an anti-inflammatory (M2) phenotype and suppression of pro-inflammatory cytokines (TNF-α, IL-1β) via EV-carried miRNAs (e.g., miR-1246, miR-21-5p) [19,20].
- **Stem Cell Recruitment:** Activation of endogenous pulp stem cells via SDF-1/CXCR4 signaling and EV-mediated transfer of pro-proliferative signals [21,22].

4. Discussion

This meta-analysis provides robust quantitative evidence that DP-MSCs and their secretome are powerful inducers of reparative dentinogenesis. The large pooled mean difference of 245.51 μm represents a clinically significant amount of new dentin, capable of sealing pulp exposures and reinforcing dentin walls.

The most transformative finding is the significant efficacy of cell-free approaches, namely conditioned media and extracellular vesicles. This confirms that the therapeutic effect is primarily paracrine-mediated, driven by a cocktail of growth factors, cytokines, and nucleic acids packaged within EVs [23,24]. This bypasses the major hurdles of cell-based therapy, such as tumorigenicity risk, immune rejection, and complex manufacturing, paving the way for off-the-shelf, acellular biologic products [25,26].

The molecular synthesis reveals a coordinated mechanism: DP-MSC secretions first modulate the inflammatory environment, then recruit and activate host progenitor cells, direct their differentiation into odontoblast-like cells, and simultaneously stimulate angiogenesis to support the new tissue [27,28]. This recapitulates the natural sequence of pulp healing but in an amplified manner.

4.1. Clinical Implications and Future Directions

The evidence supports the progression of acellular DP-MSC secretome products toward clinical trials for direct pulp capping and regenerative endodontic procedures. Future research should focus on:

- **Standardization:** Isolating the most potent EV subpopulations and defining standardized, GMP-compliant production protocols for secretome-based products [29,30].
- **Biomaterial Engineering:** Developing advanced scaffolds that provide controlled spatiotemporal release of EVs and growth factors [31,32].
- **Mechanistic Depth:** Utilizing single-cell RNA sequencing to identify specific host cell populations targeted by DP-MSC paracrine signals [33,34].

5. Conclusion

DP-MSCs represent a potent biological tool for dentin regeneration. Their mechanism of action is predominantly paracrine, orchestrating a complex regenerative program through secreted factors and extracellular vesicles. This meta-analysis strongly supports the strategic shift from cell-based to cell-free therapeutics, leveraging the DP-MSC secretome to develop effective, safe, and commercially viable products for the next generation of regenerative dental treatments.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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