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Stem cell-mediated periodontal regeneration: A mini review

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Abstract:
Restoring periodontal attachment in intrabony defects remains unpredictable with conventional therapy. Mesenchymal stem cells, including PDLSCs, DPSCs and GMSCs, aid repair through differentiation, paracrine signaling and immune regulation. Transcriptomic and single-cell RNA sequencing analyses show osteogenic and angiogenic drivers, including RUNX2, BMP2 and PDGFRA-positive lineages. Extracellular vesicle profiling and multi-omics integration, aided by machine learning, are refining biomarkers and cell-free protocols. Thus, molecular signatures with clinical outcomes through standardized pipelines points toward personalized periodontal regeneration.

Keywords: Periodontal regeneration; mesenchymal stem cells (MSCs); single-cell RNA sequencing

Background:
Periodontal intrabony defects are difficult to regenerate and conventional therapy rarely restores full attachment **[1]**. Mesenchymal stem cells, including PDLSCs, DPSCs and GMSCs, aid regeneration through differentiation, immunomodulation and paracrine signaling **[2]**. Transcriptomic profiling links repair to osteogenic markers such as RUNX2, BMP2 and BGLAP **[3]**. Single-cell RNA sequencing resolves cell populations and identifies PDGFRA-positive progenitors that couple angiogenesis with osteogenesis **[4]**. Bioinformatics analyses repeatedly highlight Wnt/β-catenin, BMP and TGF-β signaling as regulators of regeneration **[5]**. Mesenchymal stem cell-derived extracellular vesicles carry microRNAs that promote regeneration, supporting cell-free strategies **[6, 7]**. Therefore, it is of interest to describe current molecular insights into stem cell-mediated regeneration of periodontal intrabony defects.

Multi-omics integration and machine learning:
Large molecular datasets require computational interpretation to guide treatment. Machine learning helps identify molecular patterns and candidate biomarkers that may predict treatment response **[8]**. Applied to pooled randomized trial data, a random forest model trained on 18 baseline clinical, microbiological and treatment-related features predicted individual response to periodontal therapy, showing how algorithmic prognosis could guide case selection for regenerative procedures **[9]**.

Clinical outcomes of stem cell therapy:
A Systematic review of randomized studies on orally derived stem cell therapy found gains in clinical attachment level and radiographic bone fill, with reduced probing depth, though with considerable heterogeneity across protocols **[10]**. A multicenter randomized trial in 132 patients then showed that non-surgical injection of allogeneic dental pulp stem cells reduced attachment loss, probing depth and bone defect depth at six months, supporting a minimally invasive delivery route **[11]**.

Biomaterials and cell-free delivery:
Scaffold design increasingly determines whether molecular signals translate into organized tissue. Three-dimensional bioprinting enables the creation of patient-specific constructs that combine hydrogels, growth factors and mesenchymal stem cells to reproduce the gingiva, bone and periodontal ligament interface **[12]**. Cell-free approaches are advancing in parallel, since periodontal ligament stem cell-derived exosomes deliver microRNA cargo that promotes osteogenic differentiation and angiogenesis while dampening inflammation **[13]**.

Endogenous progenitors and developmental insights:
Recent reviews integrating *in vivo* lineage-tracing and single-cell analyses show that periodontal regeneration also draws on endogenous progenitors. Heterogeneous dental follicle, apical papilla and periodontal ligament populations, governed by Hedgehog, Wnt/β-catenin and BMP/TGF-β signaling, differentiate into cementum, periodontal ligament and alveolar bone, supporting endogenous stem cell-based strategies **[14, 15]**.

Clinical translation and limitations:
Clinical translation nonetheless remains constrained by the absence of standardized protocols, limited scalability, regulatory hurdles and a narrow range of compatible biomaterials.

Conclusion:
Molecular profiling moves periodontal regeneration towards precision and mechanism-based therapy. Single-cell and multi-omics analyses are clarifying the cells, pathways and vesicle

mediators of regeneration. Predictable and personalized treatment will require standardized pipelines, validated biomarkers and integrated clinical data.

Declaration:
This manuscript reports original work, has not been published, is not posted as a preprint and is not under consideration elsewhere. The authors declare no conflicts of interest.

Advancement to knowledge:
This review shows how single-cell and multi-omics analyses, together with extracellular vesicle and machine-learning approaches, are converging to enable predictive, personalized stem cell-mediated periodontal regeneration.

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