EDITORIAL

Dental Pulp Stem Cells in Bone Tissue Engineering: A Decade of Progress and Future Perspectives

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INTRODUCTION

Bone tissue engineering (BTE) offers a therapeutic alternative to conventional bone grafting, which is often limited by scarce autograft supply, donor-site morbidity, and prolonged hospitalization. These constraints, together with risks such as variable graft integration and suboptimal vascularization, continue to drive innovation in BTE. Central to the progress are postnatal mesenchymal stem/stromal cells (MSCs), whose multipotency, self-renewal capacity, and immunomodulatory effects among others play a key role in bone tissue regeneration.

Dentistry is uniquely placed to accelerate this progress. Routine procedures, such as third-molar and orthodontic extractions, pulp therapy, and periodontal surgery, provide reliable, low-morbidity access to postnatal MSC sources originated from the cranial neural crest [1], including dental pulp stem cells (DPSCs), periodontal ligament stem cells (PDLSCs), and stem cells from apical papillae (SCAPs) [2]. In particular, DPSCs merit emphasis for BTE application due to their strong osteogenic capacity, a pro-angiogenic secretome, and immunomodulation in bony environment [3]. Additionally, their neural-crest origin suits craniofacial contexts, and a decade of studies now supports their translational promise [4].

PROGRESS OVER THE LAST DECADE

DPSCs were first reported in 2000, as a highly proliferative, clonogenic, multipotent source of MSCs obtained from adult dental pulp tissue [5]. With their ability to form densely calcified nodules, DPSCs have been explored for BTE, often in combination with osteoconductive/osteoinductive biomaterials [6].

Noteworthy progresses are:

1. Differentiation into the osteogenic lineage *in vitro*

DPSCs consistently acquire osteoblast-like phenotypes under osteoinductive environments, with upregulation of osteogenic markers such as alkaline phosphatase (ALP), osteocalcin, and runt-related transcription factor 2 (RUNX2), and robust matrix mineralization. Notably, DPSCs often exhibit a distinct mineralization phenotype, producing a denser, more compact mineral matrix than that formed by bone-marrow MSCs or other dental stem-cell sources [5, 7]. Recent studies also indicate that DPSC osteogenesis can be induced or enhanced mechanically using perfusion or cyclic-loading bioreactors and tuned substrate stiffness/topography, which activate mechanotransduction pathways (e.g., integrin–FAK and YAP/TAZ) regulating osteogenesis [8].

2. Scaffold-Based DPSC Applications in BTE

Integration of DPSCs with engineered scaffolds underpins successful BTE. Contemporary designs often aim to emulate bone extracellular matrix by tuning stiffness, nano-micro topography, and interconnected porosity, using both synthetic (e.g., polycaprolactone) and natural polymers (e.g., collagen, chitosan) as well as bioceramics (e.g., hydroxyapatite, tricalcium phosphate) [9]. Recent advances in biofabrication now enable nanostructured scaffolds and high resolution 3D printing, alongside electrospinning and melt electrowriting, to produce tightly controlled architectures and topographies that recapitulate features of both cortical and trabecular compartments.

3. DPSC secretome and pro-angiogenic ability

DPSCs release a trophic secretome that supports bone regeneration and neovascularization, including angiogenic factors such VEGF, FGF-2, angiopoietins, PDGF, SDF1, and MMPs [3] as well as extracellular

vesicles (EVs) enriched in proangiogenic and pro-osteogenic microRNAs [10]. Conditioned media and exosomes stimulate endothelial migration and tube formation and enhance vascular ingrowth in scaffolds, coupling osteogenesis with angiogenesis [11, 12]

4. DPSC-driven immunomodulation

DPSCs are low-immunogenic and actively reprogram immune responses through soluble mediators and cell–cell interactions. DPSCs secrete TGF-β, IL-10, and PGE_2, and express IDO, CD39, and CD73, creating an anti-inflammatory milieu that suppresses T-cell proliferation, shifts the Treg/Th17 balance toward regulation, and polarizes macrophages to an M2 phenotype; they also dampen dendritic-cell activation [13]. DPSC-derived extracellular vesicles recapitulate many of these effects, carrying pro-resolving cargo and attenuating NF-κB signaling; their activity often increases after inflammatory priming. Functionally, DPSC secretomes and EVs reduce inflammatory readouts *in vitro* and improve healing in preclinical oral-tissue models, supporting their potential as cell-free immunomodulatory adjuncts for craniofacial regeneration [14].

5. Clinical translation of DPSC-guided BTE

Engineered constructs that combine DPSCs with biomaterials are regulated in most countries as Advanced Therapy Medicinal Products (ATMPs), specifically tissue-engineered medicinal products (TEMPs), with stringent requirements for GMP manufacture and clinical protocols [15]. Despite this high bar, a few case reports and early clinical trials, including randomized clinical trials, have been reported for various conditions including craniofacial and orthopedic bone regeneration with encouraging feasibility and safety [1].

LIMITATIONS AND CHALLENGES

Despite the substantial progress, clinical translation remains constrained. Cell heterogeneity across donors as well as varied expansion protocols hampers standardization and meaningful comparison across studies. Manufacturing at scale is difficult, as prolonged culture risks senescence and phenotype drift, demanding xeno-free, closed, GMP-compliant workflows. Furthermore, most of available evidence base still leans on in-vitro and small-animal studies, with few rigorous, long-term trials. Biomaterials are another bottleneck in BTE. While numerous scaffolding biomaterials show promise, most neither have been clinically exploited nor approved for clinical use. Likewise, innovative BTE technologies such as high-resolution 3D printing remains largely preclinical and not clinically validated. Finally, achieving vascularized, innervated, load-bearing bone with durable remodeling remains challenging, underscoring the need for multidisciplinary strategies that merge stem cell biology, biomaterials science, advanced biofabrication, clinical translation, and regulatory science.

FUTURE PERSPECTIVES

Translating DPSC-guided BTE into durable clinical benefit will require an integrated, data-driven roadmap. Priorities include GMP-ready, xeno-free manufacturing with validated potency assays, in-process controls, and batch-release criteria, alongside donor selection and biobanking standards that preserve function. AI and machine-learning models should fuse single-cell multi-omics, imaging, and manufacturing metadata to predict potency, stratify donors, detect drift, and guide real-time process adjustments. Equally important is a biology-first ethos for regenerative dentistry, moving beyond incremental, materials-only fixes toward therapies grounded in developmental and tissue biology. Insights from lineage tracing and single-cell analyses argue against "one-size-fits-all stem cells in a dish," and instead support niche-aware, indication-matched DPSC products validated *in vivo* [16]. 3D printing/bioprinting paired with smart biomaterials that recapitulate the bone niche, provide controlled factor release, and deliver mechanobiological cues will facilitate achieving the patient-centered goal, while cell-free DPSC secretome and extracellular-vesicle products advance as scalable adjuncts. It is a pivotal moment to galvanize a coordinated multidisciplinary effort, so that DPSCs can move from a decade of research progress to predictable, patient-centered solutions for bone regeneration.

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