UNVEILING THE HIDDEN POTENT: MESENCHYMAL STEM CELLS FROM WISDOM TEETH IN TISSUE REPAIR AND DISEASE THERAPY

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Abstract : Wisdom-tooth (third-molar) tissues harbour multiple populations of mesenchymal stem/stromal cells (DMSCs) principally dental pulp stem cells (DPSCs), periodontal ligament stem cells (PDLSCs), dental follicle stem cells (DFSCs), and stem cells from the apical papilla (SCAPs). These cells are readily accessible from routinely extracted teeth, possess robust proliferative and multilineage differentiation potential, and exert reparative effects through paracrine, immunomodulatory, angiogenic and neurotrophic mechanisms. Preclinical evidence supports their use in pulp–dentin regeneration, periodontal and alveolar bone repair, craniofacial reconstruction and emerging non-dental applications such as neuroprotection. Translation to routine clinical use, however, is limited by donor and population heterogeneity, variable isolation and expansion protocols, safety and tumorigenicity concerns, and the absence of standardized potency assays and GMP workflows. This review synthesizes the current biology of wisdom-tooth MSCs, summarizes mechanisms of action, biomaterial and engineering strategies, preclinical and early clinical data, safety and regulatory considerations, and future directions highlighting pathways to accelerate safe, reproducible therapeutic translation.

Keywords: *Wisdom tooth; Mesenchymal stem/stromal cells; Dental pulp stem cells; Periodontal ligament stem cells; Dental follicle stem cells; Stem cells from apical papilla; Regenerative medicine; Tissue engineering; Immunomodulation; Neuroregeneration; Craniofacial reconstruction.*

INTRODUCTION (Background and rationale)

Mesenchymal stem/stromal cells (MSCs) have been isolated from a broad range of postnatal tissues and are defined by clonogenicity, tri-lineage differentiation (osteogenic, chondrogenic, adipogenic), a characteristic surface marker profile, and immunomodulatory functions. While bone marrow and adipose tissue were early MSC sources, tooth-derived tissues (especially third molars) have emerged as attractive alternatives because of accessibility, low morbidity of harvest, and a neural-crest developmental origin that endows particular functional advantages for craniofacial and neural repair. The landmark isolation of clonogenic dental pulp stem cells (DPSCs) from adult human teeth demonstrated that postnatal teeth contain multipotent mesenchymal progenitors capable of dentinogenesis and in vivo tissue formation [1]. Subsequent studies identified additional discrete stem/progenitor populations in dental compartments — PDLSCs from the periodontal ligament, DFSCs from the dental follicle, and SCAPs from the apical papilla — each with overlapping MSC features but also niche-specific functional biases [2–6]. The third molar is clinically useful as a stem-cell source because extraction is routine in many populations and tissues can be obtained without additional invasive procedures. The combination of convenience, potency, and ethical acceptability drives intensive interest in translating wisdom-tooth MSCs for regenerative medicine.

SOURCES AND CHARACTERIZATION OF WISDOM-TOOTH MSCS

i. Dental pulp stem cells (DPSCs)

DPSCs reside within the dental pulp — a vascularized, innervated connective tissue inside the tooth. They were first isolated and characterised as clonogenic, highly proliferative cells capable of generating dentin-like structures in vivo and expressing MSC markers CD73, CD90 and CD105 while lacking hematopoietic markers [1]. DPSCs show strong odontogenic/osteogenic differentiation in appropriate conditions and also a notable propensity for neurogenic differentiation and secretion of neurotrophic factors. They are frequently used as a model DMSC for dental and non-dental regenerative studies.

ii. Periodontal ligament stem cells (PDLSCs)

PDLSCs were isolated from the periodontal ligament around tooth roots and can give rise to cementum- and ligament-like tissues in vivo, making them logical candidates for periodontal regeneration. PDLSCs share MSC markers but often display unique gene expression linked to extracellular matrix, attachment, and tendon/ligament lineages. They were first reported as multipotent stem cells in the early 2000s and have since been studied extensively for reconstructing the cementum-periodontal ligament complex.

iii. Dental follicle stem cells (DFSCs)

DFSCs are derived from the follicular sac of unerupted teeth and present osteogenic and cementogenic potential suited for alveolar bone and periodontal complex regeneration. They have been isolated from developing third molars and display immunomodulatory and trophic activities that support tissue repair.

iv. Stem cells from the apical papilla (SCAPs)

SCAPs are found in the apical papilla of immature permanent teeth and are characterized by high proliferative capacity and potent dentinogenic/osteogenic differentiation, contributing to root development and regeneration. Their relative immaturity compared with pulp cells often confers higher proliferation and migration potential.

v. Phenotype, markers and heterogeneity

All DMSC populations express standard MSC markers (CD73, CD90, CD105) and typically lack CD34/CD45. However, expression of markers like STRO-1, CD146, and niche-specific transcripts varies between cell types and donors. Donor age, tooth development stage (immature vs mature teeth), systemic health, and processing method (enzymatic digestion vs explant) all influence yield, proliferation and functional potency. Recent transcriptomic comparisons reveal niche-specific expression patterns (neurogenic, angiogenic, extracellular matrix genes) that rationalize selecting a particular DMSC subtype for a given clinical indication.

BIOLOGICAL PROPERTIES AND MECHANISMS OF THERAPEUTIC ACTION

i. Multipotency and lineage differentiation

In vitro, DMSCs differentiate into osteo/odontogenic, chondrogenic, adipogenic and sometimes neurogenic lineages depending on inductive cues. In vivo transplantation models demonstrate dentin-like tissue formation (DPSCs), periodontal ligament/cementum formation (PDLSCs), and alveolar bone repair (DFSCs). Neural-crest derivation is believed to underpin their relatively stronger craniofacial osteogenic and neurotrophic tendencies compared with some mesodermal MSCs.

ii. Paracrine secretome and extracellular vesicles (EVs)

A substantial body of work indicates that much of the reparative capacity of DMSCs is mediated by their secretome: soluble growth factors (VEGF, FGF family), cytokines, matrix-remodeling enzymes, and extracellular vesicles/exosomes containing proteins, mRNAs and regulatory miRNAs. DMSC-derived exosomes have been shown to promote angiogenesis, modulate macrophage polarization toward reparative phenotypes, reduce apoptosis, and recruit endogenous progenitor cells. These findings underpin interest in cell-free therapies using conditioned media or EVs as alternatives to cell transplantation.

iii. Immunomodulation

Like bone-marrow MSCs, DMSCs modulate innate and adaptive immune responses: they suppress T-cell proliferation, alter dendritic cell maturation, and shift macrophages to anti-inflammatory M2 states via secreted factors (IL-10, TGF-β, PGE2) and cell–cell interactions. These immunoregulatory properties help reduce inflammation, facilitate graft integration and permit allogeneic approaches with lower rejection risk.

iv. Angiogenesis and neurotrophic support

DMSCs produce angiogenic mediators (VEGF, Ang-1) and neurotrophins (BDNF, NGF), promoting neovascularization and neural survival/regeneration. Angiogenesis is central to long-term tissue survival and function; in pulp regeneration, coupling angiogenic support with odontogenic differentiation is essential for rebuilding a vital pulp complex. The neurotrophic secretome makes DMSCs attractive for peripheral nerve and certain central nervous system applications in preclinical studies.

BIOMATERIALS AND ENGINEERING STRATEGIES FOR DELIVERY

Successful application of DMSCs typically requires an appropriate delivery matrix that supports cell survival, directs differentiation, and integrates with host tissue. Both natural (collagen, fibrin, decellularized extracellular matrices, gelatin) and synthetic (PLGA, PCL, PEG-based hydrogels, bioactive glass) scaffolds have been used. Key engineering strategies include:
(1) controlled release of growth factors to drive odontogenesis or osteogenesis,
(2) porosity and mechanical tuning to influence cell fate,
(3) incorporation of angiogenic cues or endothelial cells to prevascularize constructs, and
(4) injectable hydrogels for minimally invasive pulp or periodontal defects. 3D bioprinting and gradient scaffolds that mimic native tooth or periodontal architecture are rapidly advancing and allow precise spatial patterning of cells and bioactive cues.

PRECLINICAL EVIDENCE — HIGHLIGHTS ACROSS INDICATIONS

i. Pulp–dentin complex regeneration

Multiple animal studies have shown that DPSCs, often combined with suitable scaffolds or treated canals, can regenerate pulp-like tissue with blood vessels and sensory innervation and deposit dentin-like matrix on root canals or in root fragments. EV-based therapies and growth factor-loaded hydrogels also promote pulp-dentin repair, suggesting both cell-based and cell-free viable routes.

ii. Periodontal regeneration and alveolar bone repair

PDLSCs and DFSCs have been effective in periodontal defect models, producing new cementum, organized periodontal ligament fibers, and alveolar bone when delivered with scaffolds. Combined cell–scaffold–growth factor constructs outperform scaffolds alone in many models, indicating synergistic effects.

iii. Craniofacial bone and implant integration

DMSCs seeded on osteoconductive scaffolds or in combination with platelet concentrates have shown accelerated cranial or alveolar bone repair. Their osteogenic potential, amplified by osteoinductive signals, supports reconstruction in segmental defects and augmentation procedures.

iv. Non-dental applications — neuroprotection, cardiac and musculoskeletal models

Preclinical work demonstrates DMSC benefits in ischemic stroke, spinal cord injury, peripheral nerve repair, and myocardial infarction models, largely via paracrine anti-inflammatory and pro-angiogenic effects rather than durable engraftment. While promising, translational gaps remain regarding dosing, timing, and delivery routes.

CLINICAL TRANSLATION — CURRENT HUMAN STUDIES AND TRIALS

Clinical experience with DMSCs is still early but expanding. Small clinical studies and case reports describe DPSC-based or DPSC-conditioned therapies for pulp regeneration, alveolar bone augmentation, and periodontal repair with favourable short-term safety and functional outcomes. Regulatory-grade, randomized, large-cohort trials are scarce, and many published clinical reports lack

standardized cell manufacturing descriptions, potency assays, or long-term follow-up. The need for harmonized protocols and robust trial design is paramount to move from proof-of-concept to approved therapies.

SAFETY, POTENCY, AND MANUFACTURING CONSIDERATIONS

i. Safety and tumorigenicity

While MSCs (including DMSCs) generally show low tumorigenic potential relative to pluripotent stem cells, long-term safety data are limited. In vitro expansion can introduce senescence, chromosomal abnormalities or epigenetic drift; therefore genomic stability testing and tumorigenicity assays are critical for clinical products.

ii. Donor variability and potency assays

Donor age, dental health, tooth developmental stage, and previous infections affect DMSC phenotype and function. Developing quantitative potency assays (secretome signatures, immunomodulation assays, specific differentiation readouts) correlated with in vivo efficacy is an unmet need for product release testing.

iii. GMP manufacturing and cryopreservation

Transition to clinical use requires GMP-compliant isolation, serum-free/xeno-free expansion media, standardized cryopreservation and validated release criteria. Scale-up should preserve phenotype and potency; closed system bioreactors and defined culture supplements are being explored to address variability and contamination risk.

REGULATORY LANDSCAPE AND ETHICAL CONSIDERATIONS

DMSC therapies fall into advanced therapy medicinal product (ATMP) frameworks in many jurisdictions and are subject to strict manufacturing, characterization, and clinical trial requirements. The ethical advantage of using discarded dental tissue simplifies donor consent relative to embryonic sources, but informed consent, traceability, and biobanking governance remain essential. Allogeneic products raise additional regulatory scrutiny regarding immunogenicity, donor screening and viral safety. Harmonization across regions would accelerate multicentre studies and product development.

EMERGING TRENDS AND FUTURE DIRECTIONS

i. Cell-free therapies and exosome biology

Exosome and conditioned media approaches are attractive for reducing safety risks and simplifying manufacturing and storage. Ongoing research defines optimal isolation methods, dosing regimens and cargo modification (e.g., miRNA loading) to enhance function.

ii. Omics, potency markers and precision cell selection

Single-cell and bulk transcriptomics, proteomics and metabolomics are clarifying DMSC heterogeneity and identifying molecular signatures linked to reparative potency. Such biomarkers could enable donor stratification and selection of the best DMSC subtype for each indication.

iii. Biofabrication and organ-level constructs

3D bioprinting, microfluidic vascularization strategies, and hybrid biomaterials enable fabrication of tooth-like or periodontal structures with spatial patterning of cells and factors. These technologies aim to recreate functional tissue architecture for more complete regeneration.

iv. Immunomodulatory engineering and disease targets

Engineering DMSCs to overexpress specific trophic factors or immune-modulatory molecules can focus therapeutics on persistent inflammatory diseases or ischemic injuries. Combining DMSCs with immunotherapies may broaden their application to autoimmune and degenerative disorders.

CONCLUSIONS

Wisdom-tooth-derived MSCs are a biologically promising, ethically straightforward and clinically accessible source for regenerative medicine. Their neural crest heritage, trophic secretome, angiogenic and neurotrophic outputs, and immunomodulatory capabilities support a broad therapeutic spectrum spanning dental, craniofacial and non-dental indications. To translate DMSC promise into approved therapies, the field must prioritize standardized isolation and potency testing, GMP manufacturing, robust long-term safety assessment, and high-quality clinical trials. Parallel advances in cell-free exosome therapeutics, biofabrication, and omics-guided donor selection will accelerate clinical maturity and broaden therapeutic impact. With coordinated multidisciplinary effort, the regenerative potential stored in routinely extracted wisdom teeth can be responsibly and effectively harnessed to benefit patients.

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