Narrative Review Article

Dental Stem Cells: Advances in Isolation, Characterization, and Therapeutic Applications in Tooth Development, Maintenance, and Regeneration

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ABSTRACT

Dental Stem Cells (DSCs) represent an emerging biological platform with significant potential to advance regenerative dentistry and repair damaged dental tissues. The major contributions of stem cell populations from pulp-associated tissues (including DPSCs, SHEDs & SCAP) are to promote dentin–pulp regeneration and root development, while PDLSCs have a primary contribution to periodontal tissue repair. The potential of these cells has been well established in preclinical studies, demonstrating their ability to differentiate into multiple cell types and thereby contribute to dentin-pulp regeneration, periodontal repair, and root development. Complex epithelial-mesenchymal interactions and molecular signaling pathways regulate odontogenesis, controlling cellular proliferation, differentiation, and tissue morphogenesis. Molecular technological advances, including lineage tracing, single-cell and spatial transcriptomics, and multi-omics analysis, have dramatically increased our understanding of DSC heterogeneity and the organization of the DSC niche. Furthermore, tissue-engineering approaches combining stem cells with biomaterial scaffolds and bioactive molecules have shown significant promise for dental regeneration. In addition to demonstrating feasibility, biomimetic scaffold-based delivery systems capable of delivering both angiogenic and odontogenic growth factors have shown efficacy in promoting dentin-pulp regeneration during endodontic therapy. Three-dimensional culture systems and dental organoid models also provide physiologic relevance for studying stem cell behavior and evaluating regenerative therapies. This review summarizes recent advances in the isolation, characterization, and therapeutic potential of DSCs. Preclinical and clinical evidence support the translational potential of DSCs, although further standardization and long-term validation are required for clinical applications. However, despite the advancements listed above, many barriers remain before this technology is available for everyday clinical practice. Such barriers include limited availability of DSCs, DSC heterogeneity, and limitations of current experimental models.

Keywords: Dental stem cells; regenerative dentistry; odontogenesis; dental pulp stem cells; periodontal ligament stem cells; regenerative endodontics; tissue engineering; dental organoids

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Accepted July 6, 2026
https://doi.org/10.70251/HYJR2348.44154168

INTRODUCTION

Oral diseases are among the most common health issues and place considerable burden upon the public health system because they affect quality of life and systemic health. Oral diseases (dental caries, pulp pathology, periodontal disease, and tooth loss) will

continue to progressively destroy dental tissues. While conventional dental treatments, such as restorative procedures, endodontic therapy, and implants, improve mechanical function, they cannot recreate the living, vascularized, and innervated architecture of natural dental tissues (1). Interest in developing biologically based methods for the regeneration of dental tissues has increased with advances in stem cell biology, tissue engineering, and biomaterials (2, 3). The primary mechanism by which these new biology-based approaches can be developed is through the identification of dental stem/progenitor cell populations within dental tissues capable of both self-renewal and multilineage differentiation (4), which contribute to all aspects of tooth development, maintenance, and repair following injury or disease.

Dental Pulp Stem Cells (DPSCs) were among the first stem cell types found to be multipotent through the formation of a pulp complex in-vitro and in vivo (4). Subsequent investigations have revealed additional stem cell populations residing in different dental tissues, including stem cells from human exfoliated deciduous teeth (SHED), periodontal ligament stem cells (PDLSCs), and stem cells from the apical papilla (SCAP) (5–7) (Figure 1). Odontogenesis is an intricate biological process that involves a series of reciprocal interactions between epithelial and mesenchymal tissues. Odontogenic mesenchyme originates primarily from neural crest cells (8). These epithelial–mesenchymal interactions control the sequential developmental stages of the tooth germ, including the bud, cap, and bell stages (9), and are characterized by ameloblasts and odontoblasts, which differentiate into enamel and dentin, respectively (10). Recent advances in multi-omics analyses have further demonstrated that dental epithelium plays a critical role in orchestrating gene expression programs controlling cellular differentiation and tooth morphogenesis (11). Wnt, bone morphogenetic protein (BMP), Hedgehog, and Notch pathways control stem cell proliferation, differentiation, and tissue patterning during odontogenesis (1). For instance, recent studies have identified CXCL12-expressing progenitor cells in the apical papilla, regulated by Wnt signaling, that contribute to root development and dentin formation (12). These discoveries highlight the importance of stem cell niches and signaling networks to promote dental tissue regeneration (12). Recent technological advancements, such as lineage tracing, scRNA-Seq, and multi-omics analysis, have greatly improved our understanding of how different types of dental stem cells are regulated.

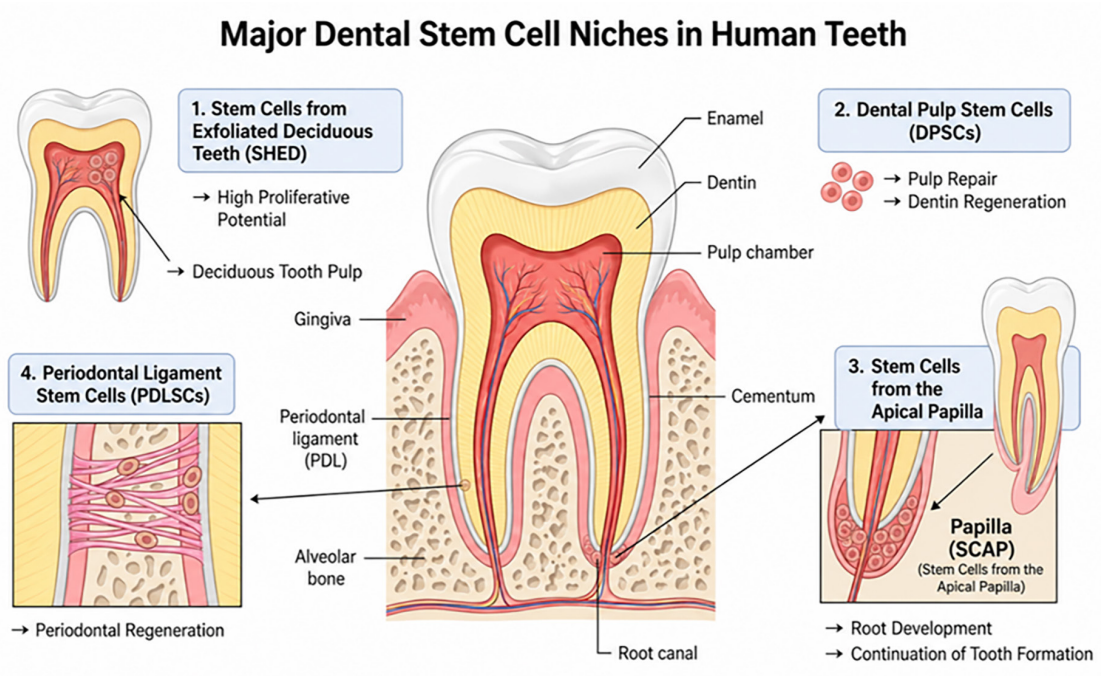

Figure 1. ***Dental stem cell niches and cellular organization.*** *Schematic representation of stem cell niches within dental tissues, including dental pulp, apical papilla, and periodontal ligament, illustrating spatial organization and functional roles in tissue homeostasis and regeneration.*

The use of techniques such as Fluorescence-Activated Cell Sorting (FACS) enables the specific isolation of stem cells. Immunohistochemical staining can confirm protein expression in isolated cells and reveal specific cellular characteristics. Combining all three approaches allows researchers to better characterize the heterogeneity and functional properties of dental stem cells, as well as their spatial arrangement (13–16). Collectively, this review summarizes cell-specific markers and experimental methods for isolating and characterizing dental stem cells, and explores their roles in tooth development, repair, and regeneration, as well as emerging translational applications in regenerative dentistry.

DENTAL CELL TYPES

Dental tissues are composed of highly specialized cell populations that work together to control tooth development, mineralization, and tissue maintenance throughout life (1). The cells that make up dental tissues originate from interactions between epithelial and neural crest-derived mesenchymal tissues during embryonic development and differentiate into distinct structures, including enamel, dentin, pulp, and periodontal tissues (8, 9). Dental tissues harbor distinct stem cell populations, including DPSCs, SCAPs, PDLSCs, and SHEDs (4–7) (Figure 1). Ameloblasts, odontoblasts, dental pulp cells, and periodontal ligament cells collectively maintain tooth integrity by regulating mineralization, immune responses, and localized tissue repair (1, 17). Ameloblasts are epithelial-derived cells that secrete enamel matrix proteins to promote mineralization (10). Odontoblasts originate from dental papilla mesenchyme, synthesize dentin matrix, and maintain the dentin–pulp complex (1). These cells extend cytoplasmic processes into dentinal tubules, enabling their participation in sensory signaling and defensive responses to bacterial invasion or mechanical injury (17). In addition to dentin formation, odontoblasts contribute to reparative dentinogenesis in response to tissue injury, helping preserve pulp vitality (17). Dental pulp is made up of a variety of cell types. These include fibroblasts, endothelial cells, immune cells, and stem/progenitor cells, which are responsible for maintaining homeostasis and repair in the pulp. DPSCs can proliferate and differentiate into multiple cell lineages (4). In addition, stem cells found in the apical papilla are important in root development and dentin formation, especially during the early stages of root development of an immature permanent tooth (7). Finally, periodontal ligament cells form another important cellular component of the tooth support system, maintaining the attachment between the tooth root and alveolar bone while producing extracellular matrix proteins that regulate ligament remodeling and tissue repair. These cells harbor progenitor populations that can differentiate into osteoblasts and cementoblasts, thereby contributing to periodontal tissue regeneration during healing (6).

Early Tooth Development

Odontogenesis occurs through a sequence of morphologically distinct bud, cap, and bell stages (8) (Figure 2). During the bud stage, cells divide rapidly to lay the foundation for tooth development. Cells then

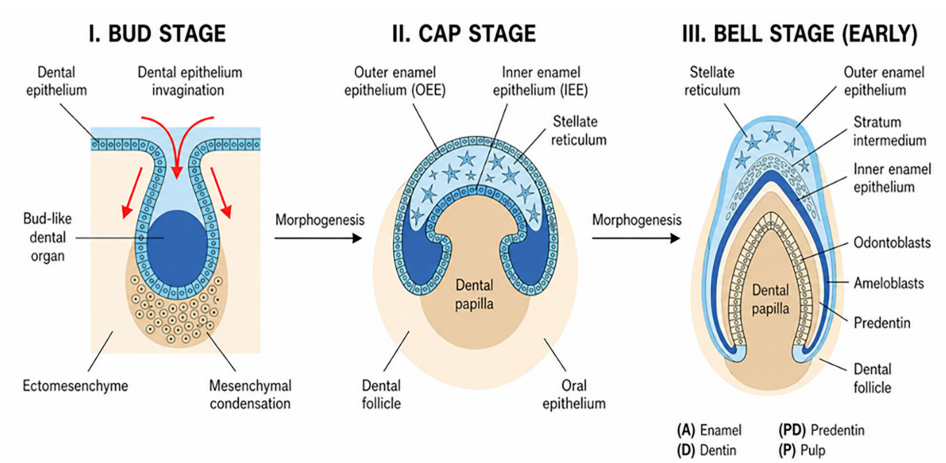

Figure 2. ***Stages of tooth development (odontogenesis).*** *Schematic illustration of tooth development showing the bud, cap, and bell stages, highlighting epithelial–mesenchymal interactions and differentiation of ameloblasts and odontoblasts responsible for enamel and dentin formation.*

enter the cap stage, where the epithelium develops into an enamel organ, which will eventually form the surface layer of the tooth, and cells in the surrounding mesenchyme differentiate into the dental papilla, which forms the dentin and the dental follicle, the connective tissue that surrounds and supports the root (9). In the bell stage, inner enamel epithelial cells differentiate into ameloblasts, which form enamel, while mesenchymal cells of the dental papilla differentiate into dentin-producing odontoblasts (10). Recent multi-omics studies have revealed that human dental epithelium plays a critical regulatory role during tooth development by orchestrating transcriptional programs that control epithelial differentiation and enamel formation.

Cell Type-Specific Disease or Damage

Dental tissues respond to injury and disease through complex cellular mechanisms that restore tissue integrity and maintain tooth function (1). Dental caries result from bacterial metabolism that produces acids capable of demineralizing enamel and dentin, ultimately leading to pulp inflammation if untreated. In response, odontoblasts form tertiary or reparative dentin, creating a protective barrier against further microbial invasion (17). However, severe infection may result in pulp necrosis and the loss of odontoblasts, requiring therapeutic interventions to restore tissue vitality (1). Regenerative endodontic therapies have therefore been developed to stimulate dental stem cells within the pulp tissue to regenerate the dentin–pulp complex and restore tooth vitality (18). Similarly, periodontal disease involves the inflammatory destruction of the periodontal ligament and alveolar bone, leading to progressive tooth mobility and, if untreated, tooth loss. Clinical studies investigating stem cell-based therapies for periodontal regeneration have demonstrated promising outcomes. The studies have demonstrated that transplantation of stem cells derived from dental pulp into areas of damaged or diseased periodontium is effective for improving periodontal healing and restoring lost or damaged periodontal tissues (19). Together, these findings highlight the critical roles of resident dental cells in mediating tissue repair.

INNOVATIONS IN STEM CELL ISOLATION AND CHARACTERIZATION

Modern experimental methods for studying complex tissue and their subpopulations (in this case, stem cells), combined with rapid advancements in both molecular biology and regenerative medicine, are now allowing researchers to identify, isolate, and characterize stem cells located in many types of complex dental tissues (11) (Figure 3). These approaches have transformed the understanding of dental stem cell niches and facilitated

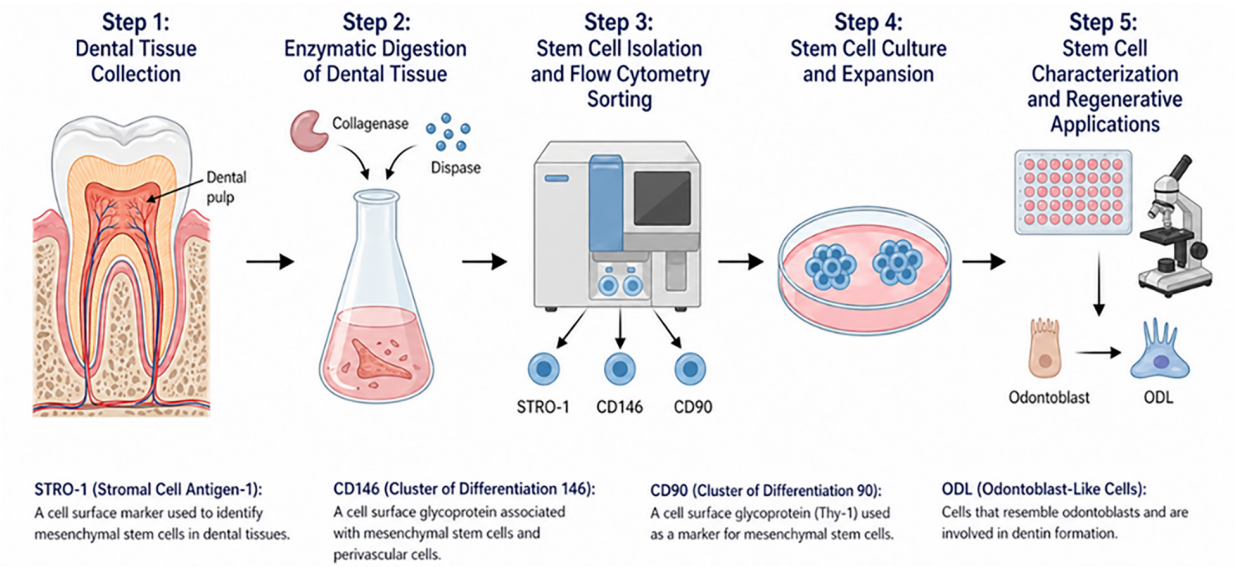

Figure 3. ***Overview of commonly used approaches for dental stem cell identification and characterization.*** *Schematic diagram outlining experimental approaches, including marker-based identification, lineage tracing, scRNA-seq, and validation through immunohistochemistry and functional assays, for the application of reproducible regenerative dental therapies. This integrated workflow improves reproducibility and enables the selection of functionally relevant stem cell populations for translational regenerative applications.*

the discovery of new progenitor cell populations involved in dentin formation, root development, and tissue repair (12). Several complementary experimental approaches are commonly used to identify and characterize dental stem cell populations. Commonly employed approaches include using specific markers for each cell type, lineage tracing to trace the stem cell's origin, scRNA-seq, and immunohistochemical validation (11–13, 20–23).

Dental pulp contains heterogeneous populations of mesenchymal stem cells derived primarily from neural crest cells, which contribute to tooth development, homeostasis, and repair. Evidence from mouse genetic models indicates the presence of distinct stem cell niches, including perivascular and perineural regions, each contributing differently to tissue maintenance and regeneration. These stem cell populations, including DPSCs, SHED, and SCAP, exhibit multilineage differentiation potential and play essential roles in dentin formation and immune modulation within the pulp microenvironment (24).

Cellular Lineage Tracing

Lineage tracing techniques employing inducible genetic labeling systems and fluorescence-based reporters have enabled high-resolution tracking of stem cell fate and spatial distribution during tooth development and regeneration (20, 21). Teeth contain spatially organized stem cell niches that regulate tooth morphogenesis and tissue maintenance (1). Progenitor cells located within the apical papilla give rise to tooth root development and dentin (7). For example, CXCL12-expressing apical progenitors drive tooth root elongation through the regulation of Wnt signaling (12). These findings illustrate how lineage tracing is a critical tool to identify stem cells and their descendants throughout development and disease.

Single Cell And Spatial Transcriptomics

In addition to advances in stem cell biology and molecular profiling, it has been demonstrated that dental tissues comprise diverse populations of stem cells with distinct marker profiles that reflect their developmental lineage and regenerative potential. As an effective tool for studying cellular complexity, single-cell transcriptomics has become a major method for analyzing cellular diversity across many biological systems. Single-cell transcriptomics can effectively reveal cell clustering and the expression and differential regulation of specific marker genes. UMAP (unsupervised clustering), as shown in Figure 4(a), is used to identify distinct populations of dental cells, including DPSCs, PDLSCs, SCAP, and epithelial-derived lineages, based on transcriptional similarities, thereby demonstrating that transcriptional heterogeneity exists within dental tissue. UMAP visualizes transcriptionally similar cells as clustered populations, enabling inference of distinct dental cell subtypes based on shared gene expression profiles. Unlike traditional bulk RNA-sequencing methods, scRNA-seq enables examination of gene expression levels on a per-cell basis, allowing researchers to identify unique cellular populations through molecular signatures (11). Drop-seq, a high-throughput method that enables genome-wide gene expression profiling of thousands of cells simultaneously, is a cost-effective and scalable approach to uncover cellular heterogeneity by capturing and sequencing mRNA from single cells with high resolution (25). The application of single-cell transcriptomics to dental studies has revealed substantial heterogeneity among both epithelial and mesenchymal cells in developing teeth. Multi-omics analysis integrating transcriptomics, epigenomics, and proteomics has further indicated that the dental epithelia play an important role in coordinating signals that regulate tooth development (morphogenesis) and cell differentiation (11). Feature expression analysis (Figure 4b) shows the distribution of canonical mesenchymal stem cell markers, including CD73, CD90, CD105, STRO-1, and CD146, confirming the identity and multipotent nature of these stem cell populations, as well as the niche-associated marker CXCL12. Integration of scRNA-seq with multi-omics platforms has facilitated the identification of rare progenitor populations, thereby refining our understanding of stem cell heterogeneity and lineage specification within dental tissues (11, 13, 23). Fluorescence-Activated Cell Sorting (FACS) is a significant technique that allows researchers to separate or purify a population of dental stem cells based on specific surface protein characteristics. Researchers can also isolate functionally relevant stem cell subpopulations using markers such as STRO-1 and CD146. After isolating these specific stem cell subpopulations through FACS, researchers can conduct further experimentation, including molecular characterization, in vitro differentiation studies, and regenerative research (Figure 4b). In addition, evidence indicates that the use of FACS enhances the accuracy and reliability of any model developed utilizing stem cells (15, 16). Pseudo-time trajectory analysis reveals a continuous differentiation axis from early stem/progenitor populations toward lineage-committed odontoblast and ameloblast cells,

with intermediate progenitor states representing key transitional stages of odontogenesis (Figure 4c).

While single-cell transcriptomics provide detailed information about gene expression patterns in individual cells, spatial transcriptomics allow researchers to map gene expression changes within the anatomical context of tissues. Spatial transcriptomic studies have shown that epithelial and mesenchymal cell populations occupy distinct microenvironments within the tooth germ and interact through localized signaling networks that regulate tissue patterning and differentiation (11) (Figure 4d). Spatial transcriptomic approaches preserve tissue architecture and enable correlation of gene expression with histological localization, thereby identifying microenvironment-specific signaling gradients that regulate stem cell behavior (14, 22). The integration of these approaches provides a comprehensive multi-modal framework linking molecular heterogeneity to spatial organization and regenerative outcomes in dental stem cell biology (Figure 4e-k). Together, the integration

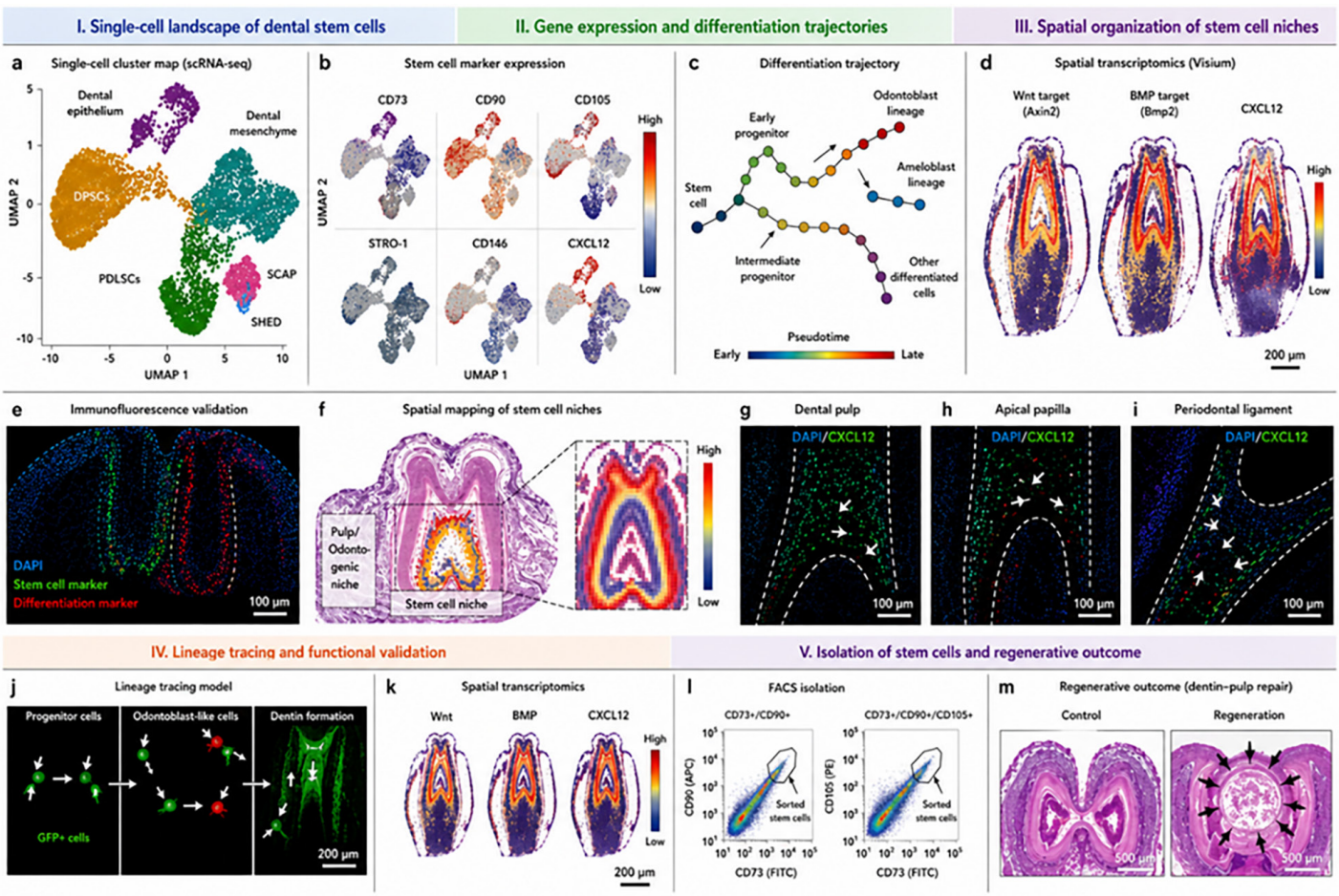

Figure 4. Integrated multi-modal analysis of dental stem cells in tooth development and regeneration (11–14, 20, 21, 23, 24). *(a) UMAP plot of scRNA-seq data showing major dental cell populations, including DPSCs, PDLSCs, SCAP, and epithelial-derived lineages. (b) Feature plots illustrating expression of canonical mesenchymal stem cell markers (CD73, CD90, CD105, STRO-1, CD146) and niche-associated marker CXCL12. (c) Pseudotime trajectory analysis depicting differentiation from stem cells to progenitor and terminally differentiated odontoblast and ameloblast lineages. (d) Spatial transcriptomic mapping of signaling pathways (Wnt, BMP, CXCL12) within developing tooth tissues. (e–i) Immunofluorescence and spatial localization of stem cell niches in dental pulp, apical papilla, and periodontal ligament. (j) Lineage tracing model demonstrating differentiation of progenitor cells into odontoblast-like cells and dentin formation. (k) Spatial gene expression mapping of signaling pathways. (l) Fluorescence-activated cell sorting (FACS) plots showing isolation of stem cell populations based on marker expression. (m) Representative histological sections demonstrating dentin–pulp regeneration compared to control tissues.*

of UMAP clustering, spatial transcriptomics, lineage tracing, FACS isolation, and histological validation strengthens confidence in identifying functionally distinct dental stem cell niches and improves the translational reliability of regenerative models. These integrated technologies are particularly important for regenerative dentistry because they improve identification of functionally relevant stem cell populations and support the design of more targeted scaffold-based regenerative therapies.

Epithelial and Mesenchymal Cell Surface Markers Define Dental Cell Types

Dental mesenchymal stem cells can be identified by the presence of cell-surface antigens such as STRO-1, CD146, CD73, CD90, and CD105. These markers indicate their ability to differentiate into multiple cell types, reflecting a multipotent nature. The most studied type of dental stem cell is the DPSC, which exhibits high expression of the surface antigens listed above and has been shown to produce odontoblast-like cells. In both in-vitro and in-vivo studies, DPSCs have produced dentin-like structures (4). Similarly, SHED and PDLSCs exhibit similar levels of expression of mesenchymal stem cell markers but have different functional characteristics, which are determined by the tissue type from which they originate (5, 6). Moreover, apical papilla stem cells play an important role in root formation, whereas bone marrow mesenchymal stem cells are involved in osteogenesis (4–7).

A specific subpopulation of mesenchymal stem cells in the developing mouse incisor can be identified by their expression of CD90/Thy1; this cell type appears to contribute to cellular differentiation primarily during periods of active tooth development. During these times of active growth, CD90+ cells increase. However, during homeostasis, there are fewer CD90+ cells. Notably, CD90+ cells have been reported to repopulate following injury and are associated with increased growth and regenerative activity (26). In addition to those classical mesenchymal markers, additional molecular markers exist for distinct subpopulations of DSCs. Specifically, researchers have demonstrated that the Axin2 gene regulates the activity of the Wnt signaling pathway, which plays an important role in activating and maintaining stem cells and in regenerating damaged tissues. Studies suggest that Axin2 expression is associated with enhanced proliferation and migration of DPSCs, indicating Axin2 may also regulate the local environment (microenvironment) where pulp repair occurs as well as the formation of reparative dentin (27).

Dental Organoids and Three-Dimensional Culture Systems

Three-dimensional (3D) culture systems and organoid models represent recent advances in the study of dental stem cell biology and regenerative dentistry. Unlike two-dimensional cultures, organoid systems more closely recapitulate epithelial–mesenchymal interactions, extracellular matrix signaling, and scaffold responses observed in native dental tissues. Organoids are self-organizing structures formed by collections of cells derived from stem or progenitor cells, mimicking those found in natural tissues. The use of organoids allows researchers to investigate how individual cells interact with one another, with their surrounding extracellular matrices, and with various signaling mechanisms that influence the differentiation of dental stem cells. Three-dimensional dental pulp models have been used to study pulp biology and evaluate regenerative endodontic therapies designed to restore the dentin-pulp complex (28). The integration of organoid systems with single-cell and spatial transcriptomic technologies further enhances their applicability by enabling high-resolution analysis of cellular interactions and molecular signaling within physiologically relevant three-dimensional microenvironments (13, 14, 28). Organoid systems, therefore, serve as an important bridge between fundamental stem cell research and translational regenerative dentistry by enabling the testing of new therapeutic strategies in controlled laboratory settings. Three-dimensional culture systems and dental organoids mimic the complex structure and function of natural dental tissues by enabling epithelial–mesenchymal interactions, mechanotransduction, self-organization, and scaffold responses in vitro. Biomaterial-based hydrogels help recreate extracellular matrix conditions, guiding organoid development and providing physiologically relevant models to study tooth biology and regeneration. (29, 30) Unlike conventional two-dimensional cultures, organoid systems more accurately reproduce epithelial–mesenchymal interactions and scaffold responses, making them valuable intermediate platforms between laboratory studies and translational regenerative applications.

Although organoid systems can model physiological conditions to study dental stem cell behaviour, it is necessary to test these models in animal models and/or human clinical trials to assess their potential for clinical translation.

Comparison With Human Studies and Clinical Translation

While preclinical models are important for understanding the function and mechanisms of dental stem cells, clinical studies (i.e., randomized controlled trials and translational studies) are crucial for validating findings in a human context. The clinical applications of allogeneic DPSCs have demonstrated a significant improvement in periodontal healing, clinical attachment gain, and decreased inflammatory marker levels in patients diagnosed with periodontitis; therefore, they demonstrate both regenerative and immunomodulatory functions (19).

Important biological differences exist between animal models and human dental tissues, particularly in stem cell niche organization and regenerative capacity (31). Animal models have active stem cell niches that continue to grow over time; for example, an animal's incisors will continually grow throughout its lifetime. On the other hand, human dental tissues have limited capacity to regenerate, and their stem cell niches are more heterogeneous (31). For instance, rodent incisors have continuous mesenchymal stem cell niches (stem cell niches) that continually activate to provide for the lifetime of tooth growth as well as continuous regeneration and repair of their own tissues; however, like many other species, human dentition lacks a similar long-term regenerative ability. Therefore, although some forms of regeneration can be observed in rodent incisor models, they do not fully recapitulate the types of stem cells or the level of repair potential found in mature adult dental tissues (31). Moreover, the controlled in vitro experimental environment cannot accurately simulate or capture all aspects of inflammation, vasculature, and mechanical properties present in human tissue. Therefore, the results obtained from laboratory studies may differ from those achieved clinically.

Recent advances in single-cell RNA sequencing (scRNA-Seq) are providing an improved approach to evaluating human dental tissues with higher resolution than previously possible. Spatial transcriptomics allows investigators to evaluate the similarities/differences of cellular heterogeneity, lineage trajectories, and signaling pathways that exist within the same type of experimental model as compared to similar human samples, which will ultimately improve the ability to translate preclinical data into clinical applications (11, 13, 14, 22). Despite these promising clinical outcomes, challenges remain in standardizing stem cell-based therapies for routine dental practice. Variability in stem cell source, isolation techniques, scaffold materials, long-term safety, and delivery protocols can significantly influence treatment outcomes. Therefore, a translational framework that integrates preclinical evidence with human clinical data is essential for optimizing therapeutic strategies and ensuring the successful clinical implementation of dental stem cell-based regenerative therapies. Among current regenerative applications, dentin–pulp regeneration and periodontal tissue repair demonstrate the strongest translational potential due to encouraging early clinical outcomes.

Although many clinical trials show that DSCs can regenerate tissues, we need to better understand, at the molecular level, what regulates these behaviors so we can use them therapeutically. In large part, this information has come from laboratory experiments using the mouse incisor as a model, which have given us significant insight into how stem cells regulate their own growth (homeostasis) and the pathways by which they signal regeneration.

SIGNALLING PATHWAYS REGULATING STEM CELL BEHAVIOUR IN DIVERSE DENTAL TISSUES

The continuously growing murine incisor serves as an established model for studying dental stem cell populations.

Rodent models have provided important insight into the regulation of dental stem cell niches and their role in tissue regeneration. Rodent incisors grow continuously throughout life and contain persistent stem cell populations (31, 32). Because murine incisors undergo continuous growth throughout life, their stem cell dynamics and regenerative responses may not fully reflect the regenerative capacity observed in mature human teeth (31, 32). These stem cell niches are identified by the expression of specific epithelial and mesenchymal stem cell markers (20, 21). Stem cells located at the incisor cervical loop maintain the ameloblast-generating epithelial stem cells and enamel production. In mice, molars do not grow continuously and therefore rely primarily on limited stem cell populations that support tissue maintenance and repair (31). Thus, the mouse incisor contains a resident stem cell population that supports tooth development, maintenance, and regeneration. (15, 16). Overall, this supports the diversity of cell types in mineralized tissues and indicates that additional studies are required to identify resident stem cell populations across various mineralized tissue

systems.

Transcriptomic and epigenomic analyses of the continuously growing mouse incisors demonstrate that MSCs generate rapidly proliferating transit-amplifying cells (TACs), which are essential for maintaining tissue homeostasis and continuous tooth growth. The polycomb repressive complex 1 (PRC1) regulates TAC proliferation by repressing cell-cycle inhibitors such as Cdkn2a and activating G1–S-phase genes, while also modulating Wnt/β-catenin signaling activity. Importantly, loss of TAC proliferation results in apoptosis of MSCs, revealing a positive feedback mechanism between TACs and stem cells that is critical for maintaining the stem cell niche (33).

Studies utilizing murine incisors as a model have been critical for elucidating the molecular communication pathways that control the processes of maintaining and regulating the number of cells within the stem cell pool, their proliferation, and their differentiation into specific cell types. These studies have identified multiple highly conservative systems that coordinate mesenchyme-epithelium interactions during tooth development and subsequent tissue regeneration.

Dental stem cell activity is tightly regulated by complex molecular signaling pathways that coordinate cell proliferation, differentiation, and tissue morphogenesis during tooth development and regeneration (1). These signaling networks facilitate communication between epithelial and mesenchymal tissues and maintain the balance between stem cell self-renewal and differentiation within dental stem cell niches (8). Several signaling pathways have been identified as key regulators of odontogenesis and stem cell activity, including the Wnt, bone morphogenetic protein (BMP), Notch, and Hedgehog pathways (1) (Figure 5). The functional activity of these signaling pathways is closely linked to stem cell marker expression and lineage specification and is increasingly being investigated using integrated approaches combining lineage tracing, scRNA-seq, and spatial transcriptomics to elucidate pathway-specific effects on stem cell behavior within defined microenvironments (11–13, 20–23).

Wnt Signaling

The Wnt signaling pathway plays a critical role in regulating stem cell proliferation and differentiation during tooth development (34, 35). Wnt signaling is involved in epithelial–mesenchymal interactions that guide the early stages of odontogenesis and regulates progenitor cells in the apical papilla. For example, CXCL12-expressing progenitor cells drive root elongation and dentin formation during tooth maturation by directly regulating Wnt signaling (12). These findings highlight the importance of Wnt-mediated signaling in maintaining stem cell niches responsible for dental tissue regeneration (34, 35).

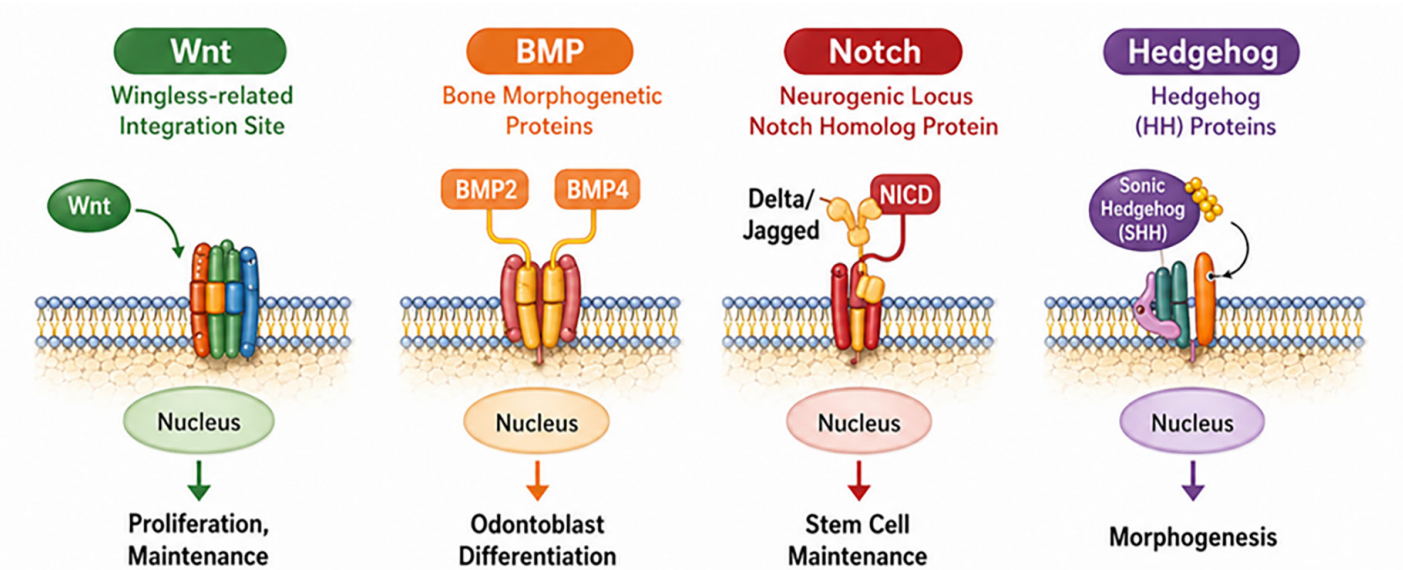

Figure 5. Signaling pathways regulating dental stem cell behavior. *Overview of key molecular pathways, including Wnt, BMP, Notch, and Hedgehog, illustrating their roles in stem cell proliferation, differentiation, and epithelial–mesenchymal interactions during tooth development and regeneration.*

Bmp Signaling

Bone morphogenetic proteins (BMPs) are members of the transforming growth factor-β (TGF-β) superfamily and are essential regulators of cell differentiation and tissue development. BMP signaling controls odontoblast differentiation and dentin formation by regulating transcription factors that guide odontogenic lineage commitment (8, 34–36). Growth factors in the BMP family have also been widely used in regenerative dentistry due to their ability to stimulate stem cell differentiation and tissue regeneration (18). For example, biomaterial scaffolds incorporating BMP2-mimetic peptides enhance odontogenic differentiation of dental stem cells and promote dentin–pulp regeneration in regenerative endodontics (37). Thus, BMP-mediated signaling drives odontogenic differentiation and dental regenerative outcomes (15, 16).

Notch Signaling

Notch signaling regulates epithelial–mesenchymal interactions, stem cell maintenance, and lineage commitment during odontogenesis and reparative dentinogenesis. Following injury, reactivation of the pathway promotes differentiation of dental pulp stem cells into odontoblast-like cells (38–40) while maintaining progenitor cell pools through context-dependent signaling gradients identified by scRNA-seq studies. Notch signaling also contributes to odontoblast and ameloblast differentiation, dentin and enamel matrix formation, cusp patterning, and root development (38). Following an injury to adult dental tissues, Notch signaling is activated again to direct dental pulp stem cell differentiation towards an odontoblastic lineage. As a result, this will support repair dentin formation, as well as promote tissue regeneration (38). Earlier studies on developmental growth demonstrated a direct relationship between Delta-Notch signaling and the cytodifferentiation of odontoblasts and ameloblasts during odontogenesis. These findings also highlighted the role of Notch signaling in epithelial-mesenchymal communication within degenerating dental tissues (41). Furthermore, RBP-Jκ-dependent Notch signaling has been shown to mediate cellular differentiation pathways specific to contextual embryogenic development supporting the concept that controlled levels of Notch activity are necessary for maintaining stem cell fate decisions and tissue homeostasis (42). scRNA-seq studies have revealed that Notch signaling exhibits context-dependent activation across different stem cell subpopulations, thereby contributing to the maintenance of stem cell pools and regulation of differentiation gradients within dental tissues (11, 13, 23).

Hedgehog Signaling

Hedgehog signaling is vital to the regulation of tooth development. The pathway controls how epithelium and mesenchyme interact; regulates the growth and proliferation of progenitor cells; and controls the patterning of tissues involved in odontogenesis. Therefore, it is essential for the normal morphogenesis of teeth. If hedgehog signaling fails to develop properly, there is a risk of developmental defects and improper formation of dental tissues (8). The initial transient expression of Hedgehog proteins maintains the progenitors that form roots at an early stage of development. However, the continuous expression of hedgehog proteins hinders differentiation into osteoblasts and PDL cells, thereby preventing normal alveolar bone development. The effects are partly due to a Hedgehog – Foxf regulatory axis in the progenitor cells of the dental follicle, as well as those expressing PTHrP and have high sensitivity to the Hedgehog signal. It has been shown experimentally that prolonged activation of the Hedgehog signaling pathway will prevent or hinder the final stages of the determination process, and that it needs to be down regulated to allow normal differentiation. Therefore, there appears to exist a tightly regulated on-off system that determines the fate of the stem cells. Interestingly, the pro-osteogenic effect of Hedgehog signaling in other skeletal systems highlights the specific regulatory functions Hedgehog plays in the development of the periodontium (43). Together, these findings underscore the importance of precisely regulated Hedgehog activity in coordinating dental stem cell function and regenerative processes.

Lineage tracing studies in mice have shown that the neurovascular bundle is a key stem cell niche for maintaining mesenchymal stem cells (MSCs) via the Hedgehog pathway. The sensory nerve component of this stem cell niche secretes SHH, activating Gli1 gene expression in periarterial MSCs, which provide all mesenchymal lineages. Conversely, NG2+ pericytes serve as a separate stem cell population largely responsible for tissue repair post-injury; thus, it appears that both stem cell phenotype and function are determined by signals derived from the niche rather than simply relying on phenotypic markers (44). Collectively, these signaling pathways regulate distinct aspects of stem cell behavior; however, Wnt and BMP signaling have been widely investigated in regenerative applications and represent promising therapeutic targets (12, 18, 37).

FUNCTIONAL CHANGES IN STEM CELL MARKERS

The dynamics of stem cell markers are found in a variety of tissues within the oral cavity; this includes variations due to age, physiological states and pathological stimuli. These varying levels of expression of stem cell markers are indicative of variability in the proliferation rates, differentiation potentials and regenerative behaviors of dental stem cells. Thus, understanding how stem cell markers vary because of aging, disease or injury will allow for identification of appropriate treatments for regenerative dentistry.

Age-Dependent Changes

DSCs undergo age-related changes that affect their biological properties and regenerative potential. Early in development, DSCs have a high capacity for proliferation and the ability to differentiate, which allows for the rapid formation of teeth and remodeling of tissues. DSCs from young tissues actively participate in odontogenesis through the process of differentiation into odontoblasts and other specialized cell types that contribute to the formation of dentin and pulp (8). The results from scRNA-seq studies indicate that early stage-dental stem cells express higher levels of genes involved with cellular growth and development associated with an enhanced regenerative phenotype for tissue repair during development (11, 13). The stem cell's ability to grow, differentiate, and regenerate diminishes significantly with aging due to lower proliferative capacity, diminished regeneration potential, alterations in signaling pathways and changes in stem cell marker expression. In addition to these factors, the loss of vasculature and the alteration of extracellular matrix (ECM), create additional barriers to the stem cells' regenerative capabilities (17). Consequently, age-related changes in stem cell function may influence the effectiveness of regenerative therapies in older individuals, associated with a decline in stem cell pool size and functional capacity (15, 16).

Disease-Associated Changes

Dental diseases can significantly alter the expression of stem cell markers and disrupt the microenvironment of stem cell niches within dental tissues (1). Inflammatory conditions such as dental caries and periodontitis can limit stem cell proliferation, differentiation, and signaling pathways involved in tissue repair. Chronic inflammation in periodontal tissues leads to the degradation of extracellular matrix components and the destruction of supporting structures surrounding the tooth (19). Inflammatory microenvironments have been shown to modulate stem cell marker expression through cytokine-mediated signaling pathways (11, 14, 22). Despite these pathological changes, dental stem cells retain the capacity to participate in tissue regeneration when appropriately stimulated. Clinical studies have demonstrated that transplantation of dental pulp stem cells can promote regeneration of periodontal tissues and improve clinical outcomes in patients with periodontitis (19). These findings suggest that, even in diseased microenvironments, dental stem cells can be therapeutically harnessed to restore damaged oral tissues.

Traumatic Injury-Related Changes

Traumatic injury to dental tissues can activate stem cell populations and initiate regenerative responses within the dentin–pulp complex. When dentin is damaged by mechanical trauma or bacterial invasion, odontoblasts and pulp stem cells respond by producing tertiary, or reparative, dentin to protect the pulp tissue (17). This sequence of stem cell activation, proliferation, migration, and differentiation into odontoblast-like cells during reparative dentin formation is illustrated in Figure 6. This process represents a natural defense mechanism that maintains tooth vitality and prevents further damage. Injury-induced activation of stem cells is associated with dynamic shifts in marker expression profiles (11, 13). Regenerative endodontic approaches seek to enhance this natural repair response by providing biomaterial scaffolds and bioactive molecules that stimulate stem cell activity (18). Bioengineered scaffolds capable of delivering angiogenic and odontogenic growth factors promote stem cell proliferation and differentiation, facilitating the regeneration of dentin–pulp tissues (37). These therapeutic strategies demonstrate that understanding stem cell marker dynamics during injury guides the development of regenerative treatments to restore dental tissue structure and function. Spatial transcriptomics further reveals that injury-responsive stem cell niches are regulated by localized signaling gradients coordinating angiogenesis, inflammation, and odontogenic differentiation, thereby providing critical insights for optimizing regenerative endodontic therapies (14, 22). These findings highlight how advances in molecular profiling are increasingly being translated into regenerative endodontic strategies aimed at preserving pulp vitality rather than mechanically replacing damaged tissues.

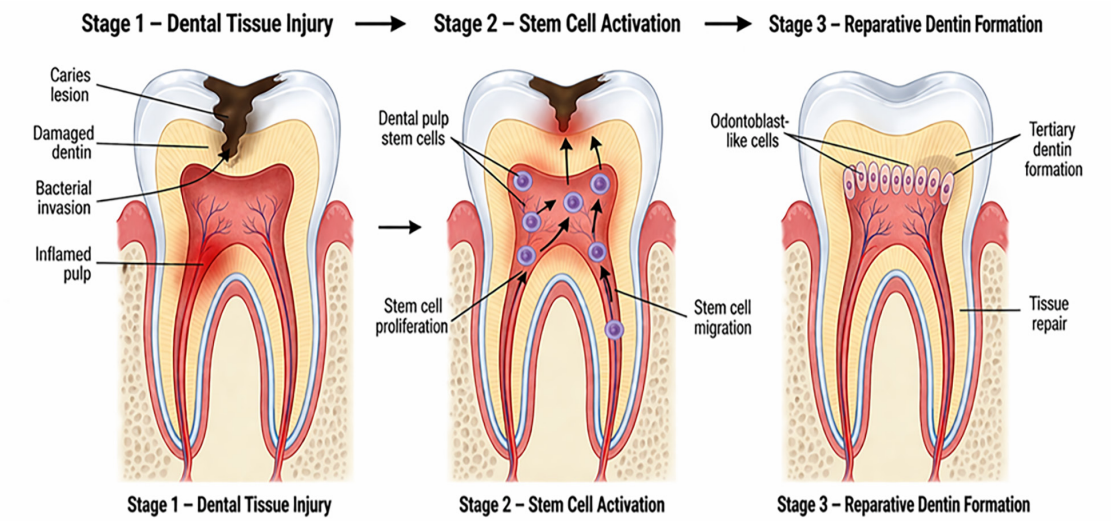

Figure 6. ***Stem cell response to injury in dental tissues.*** *Illustration of activation of dental stem cells following injury, highlighting proliferation, migration, and differentiation into odontoblast-like cells contributing to reparative dentin formation.*

CONCLUSION

Current advances in DSCs research have revolutionized our understanding of dental tissue homeostasis and repair. The identification of diverse populations, DPSCs, SHED, PDLSCs, and SCAP has established a foundation for endogenous regeneration. These multipotent cells are governed by specialized stem cell niches, where the extracellular matrix and signaling pathways (notably Wnt, BMP, Notch, and Hedgehog) coordinate proliferation and differentiation (1, 12). High-resolution methods (e.g., scRNA-Seq, spatial transcriptomics, etc.) are mapping the interactions of epithelial cells with mesenchymal cells. A few groups have developed three-dimensional (3D) cell culture systems and dental organoids that can be used to connect in vitro data to in vivo studies, by creating a model system for testing the efficacy of therapeutic interventions in the dentin-pulp interface. Hydrogels and engineered scaffold materials provide matrices similar to those found naturally and enhance angiogenic and odontogenic processes (29, 30, 37) (Figure 7).

While clinical trials have shown promise for regeneration of periodontium, many challenges exist before they can routinely translate into the clinic. For instance, there has been an ongoing challenge to identify molecular markers for the field. This has led to use of common mesenchymal markers (i.e., CD73, CD90, CD105), which may complicate identification of distinct functional subpopulations. Additionally, most of the research conducted to date utilizes rodents, specifically those animals with continually developing incisors that are unable to accurately model human dental biology. Lastly, the transition to human therapy is hampered by limited access to high-quality donor material; the complexity of conducting large-scale data analyses; and strict regulatory requirements surrounding cell growth, expansion, and delivery. Therefore, numerous technical, biological and logistically related obstacles will require resolution prior to successful clinical application of these technologies.

To progress towards whole tooth regeneration, it is imperative that researchers focus their attention on establishing universal standards and guidelines for reporting stem cell characterization data in a manner that ensures reproducibility across laboratories. Future studies may benefit from integrating lineage tracing and spatial transcriptomic techniques to elucidate niche-specific signaling gradients of signals that direct stem cell fate. Bioactive scaffold and controlled-release technology should also be optimized to appropriately direct stem cells in the clinical setting. In this manner, a paradigmatic shift is taking place in dentistry where instead of replacing damaged teeth artificially, researchers are working towards restoring teeth biologically through the combination of stem cell biology, developmental insights, and biomaterials science. Although significant biological and technical challenges remain, current progress in dentin–pulp regeneration and periodontal tissue engineering suggests that stem cell-based regenerative dentistry is approaching early clinical translation.

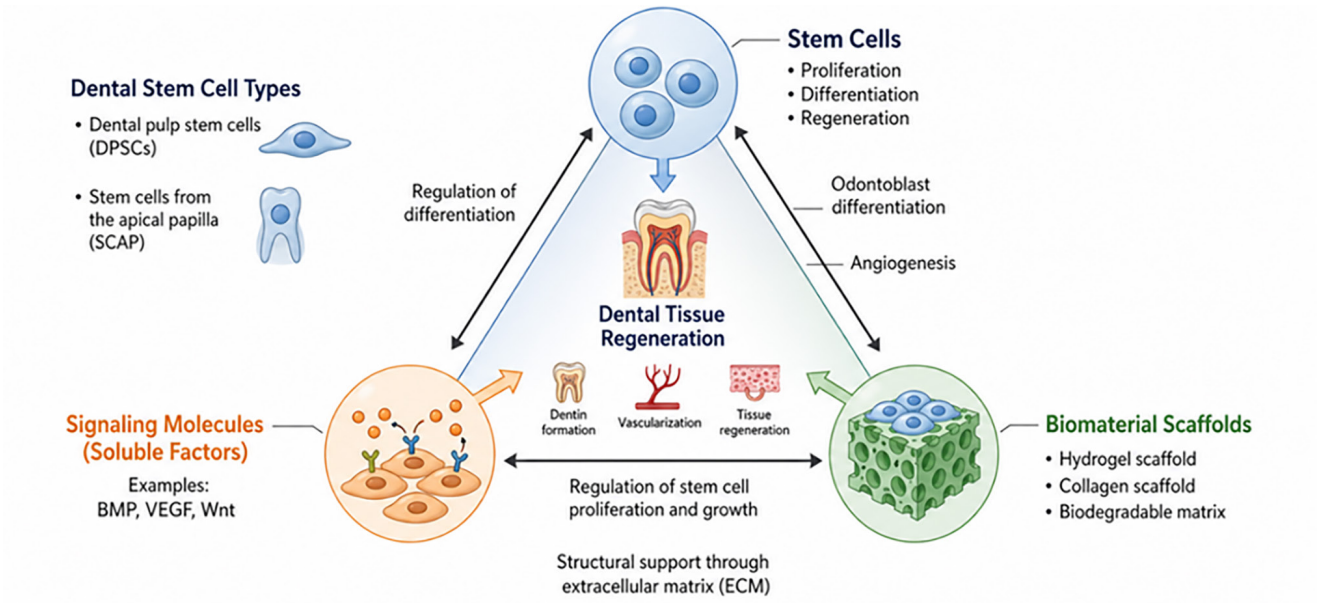

Figure 7. ***Tissue engineering triad in regenerative dentistry.*** *The conceptual framework illustrates the interaction among stem cells, biomaterial scaffolds, and bioactive signaling molecules to promote dental tissue regeneration (3).*

ACKNOWLEDGEMENTS

The author would like to acknowledge Dr. Shawn Hallett for his guidance and Prabhavathy K, Dhvani Thakkar, and Kashif Charania from Inspira Education for their support throughout the conception, writing, and finalization of this manuscript.

FUNDING SOURCES

The present review received no funding to complete.

CONFLICT OF INTEREST

The author declares that there are no conflicts of interest related to this work.

REFERENCES

1. Zhang W, Yelick PC. Tooth Repair and Regeneration: Potential of Dental Stem Cells. *Trends Mol Med*. 2021 May; 27 (5): 501–11. doi:10.1016/j.molmed.2021.02.005 PubMed PMID: 33781688.
2. Mao JJ, Prockop DJ. Stem cells in the face: tooth regeneration and beyond. *Cell Stem Cell*. 2012 Sep 7; 11 (3): 291–301. doi:10.1016/j.stem.2012.08.010 PubMed PMID: 22958928.
3. Langer R, Vacanti JP. Tissue engineering. *Science*. 1993 May 14; 260 (5110): 920–6. doi:10.1126/science.8493529 PubMed PMID: 8493529.
4. Gronthos S, Mankani M, Brahim J, Robey PG, Shi S. Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. *Proc Natl Acad Sci U S A*. 2000 Dec 5; 97 (25): 13625–30. doi:10.1073/pnas.240309797 PubMed PMID: 11087820.
5. Miura M, Gronthos S, Zhao M, Lu B, Fisher LW, Robey PG, *et al*. SHED: stem cells from human exfoliated deciduous teeth. *Proc Natl Acad Sci U S A*. 2003 May 13; 100 (10): 5807–12. doi:10.1073/pnas.0937635100 PubMed PMID: 12716973.
6. Seo BM, Miura M, Gronthos S, Bartold PM, Batouli S, Brahim J, *et al*. Investigation of multipotent postnatal stem cells from human periodontal ligament. *Lancet*. 364 (9429): 149–55. doi:10.1016/S0140-6736(04)16627-0 PubMed PMID: 15246727.
7. Sonoyama W, Liu Y, Yamaza T, Tuan RS, Wang S, Shi S, *et al*. Characterization of the apical papilla and its residing stem cells from human immature permanent teeth: a pilot study. *J Endod*. 2008 Feb; 34 (2): 166–71. doi:10.1016/j.joen.2007.11.021 PubMed PMID: 18215674.
8. Thesleff I. Epithelial-mesenchymal signalling regulating tooth morphogenesis. *J Cell Sci*. 2003 May 1; 116 (Pt 9): 1647–8. doi:10.1242/jcs.00410 PubMed PMID: 12665545.
9. Tucker A, Sharpe P. The cutting-edge of mammalian development; how the embryo makes teeth. *Nat Rev Genet*. 2004 Jul; 5 (7): 499–508. doi:10.1038/nrg1380

PubMed PMID: 15211352.

10. Rakultsev V, Lavicky J, Gonzalez Lopez M, Cigosova K, Adameyko I, Krivanek J. Enamel decussation pattern originates from directional sliding of ameloblasts. *Int J Oral Sci*. 2026 Feb 3; 18 (1): 7. doi:10.1038/s41368-025-00412-5 PubMed PMID: 41629282.
11. Zhang R, Shen Z, Zhao Z, Gu X, Yan T, Wei W, *et al*. Integrated multi-omics profiling characterizes the crucial role of human dental epithelium during tooth development. *Cell Rep*. 2025 Apr 22; 44 (4): 115437. doi:10.1016/j.celrep.2025.115437 PubMed PMID: 40120109.
12. Nagata M, Gadhvi GT, Komori T, Arai Y, Manabe H, Chu AKY, *et al*. Wnt-directed CXCL12-expressing apical papilla progenitor cells drive tooth root formation. *Nat Commun*. 2025 Jul 1; 16 (1): 5510. doi:10.1038/s41467-025-61048-x PubMed PMID: 40595672.
13. Lv Z, Jiang S, Kong S, Zhang X, Yue J, Zhao W, *et al*. Advances in Single-Cell Transcriptome Sequencing and Spatial Transcriptome Sequencing in Plants. *Plants (Basel)*. 2024 Jun 18; 13 (12). doi:10.3390/plants13121679 PubMed PMID: 38931111.
14. Ståhl PL, Salmén F, Vickovic S, Lundmark A, Navarro JF, Magnusson J, *et al*. Visualization and analysis of gene expression in tissue sections by spatial transcriptomics. *Science*. 2016 Jul 1; 353 (6294): 78–82. doi:10.1126/science.aaf2403 PubMed PMID: 27365449.
15. Perfetto SP, Chattopadhyay PK, Roederer M. Seventeen-colour flow cytometry: unravelling the immune system. *Nat Rev Immunol*. 2004 Aug; 4 (8): 648–55. doi:10.1038/nri1416 PubMed PMID: 15286731.
16. Herzenberg LA, Tung J, Moore WA, Herzenberg LA, Parks DR. Interpreting flow cytometry data: a guide for the perplexed. *Nat Immunol*. 2006 Jul; 7 (7): 681–5. doi:10.1038/ni0706-681 PubMed PMID: 16785881.
17. Smith AJ, Scheven BA, Takahashi Y, Ferracane JL, Shelton RM, Cooper PR. Dentine as a bioactive extracellular matrix. *Arch Oral Biol*. 2012 Feb; 57 (2): 109–21. doi:10.1016/j.archoralbio.2011.07.008 PubMed PMID: 21855856.
18. Galler KM, D'Souza RN, Hartgerink JD, Schmalz G. Scaffolds for dental pulp tissue engineering. *Adv Dent Res*. 2011 Jul; 23 (3): 333–9. doi:10.1177/0022034511405326 PubMed PMID: 21677088.
19. Liu Y, Liu Y, Hu J, Han J, Song L, Liu X, *et al*. Impact of allogeneic dental pulp stem cell injection on tissue regeneration in periodontitis: a multicenter randomized clinical trial. *Signal Transduct Target Ther*. 2025 Jul 31; 10 (1): 239. doi:10.1038/s41392-025-02320-w PubMed PMID: 40739139.
20. Krivanek J, Soldatov RA, Kastriti ME, Chontorotzea T, Herdina AN, Petersen J, *et al*. Dental cell type atlas reveals stem and differentiated cell types in mouse and human teeth. *Nat Commun*. 2020 Sep 23; 11 (1): 4816. doi:10.1038/s41467-020-18512-7 PubMed PMID: 32968047.
21. Short S, García-Tejera R, Schumacher LJ, Coutu DL. Next generation lineage tracing and its applications to unravel development. *NPJ Syst Biol Appl*. 2025 Jun 5; 11 (1): 60. doi:10.1038/s41540-025-00542-w PubMed PMID: 40473641.
22. Caetano AJ, Redhead Y, Karim F, Dhami P, Kannambath S, Nuamah R, *et al*. Spatially resolved transcriptomics reveals pro-inflammatory fibroblast involved in lymphocyte recruitment through CXCL8 and CXCL10. *Elife*. 2023 Jan 17; 12. doi:10.7554/eLife.81525 PubMed PMID: 36648332.
23. Inayatullah M, Dwivedi AK, Tiwari VK. Advances in single-cell omics: Transformative applications in basic and clinical research. *Curr Opin Cell Biol*. 2025 Aug; 95: 102548. doi:10.1016/j.ceb.2025.102548 PubMed PMID: 40517461.
24. Nagata M, Ono N, Ono W. Unveiling diversity of stem cells in dental pulp and apical papilla using mouse genetic models: a literature review. *Cell Tissue Res*. 2021 Feb; 383 (2): 603–16. doi:10.1007/s00441-020-03271-0 PubMed PMID: 32803323.
25. Macosko EZ, Basu A, Satija R, Nemesh J, Shekhar K, Goldman M, *et al*. Highly Parallel Genome-wide Expression Profiling of Individual Cells Using Nanoliter Droplets. *Cell*. 2015 May 21; 161 (5): 1202–14. doi:10.1016/j.cell.2015.05.002 PubMed PMID: 26000488.
26. An Z, Sabalic M, Bloomquist RF, Fowler TE, Streelman T, Sharpe PT. A quiescent cell population replenishes mesenchymal stem cells to drive accelerated growth in mouse incisors. *Nat Commun*. 2018 Jan 25; 9 (1): 378. doi:10.1038/s41467-017-02785-6 PubMed PMID: 29371677.
27. Yoshida S, Maruyama EO, Hsu W, Huang GTJ, Maruyama T. Identification of Apically Localized Endogenous Dental Pulp Stem Cells. *J Dent Res*. 2026 May; 105 (5): 668–76. doi:10.1177/00220345251378094 PubMed PMID: 41108143.
28. Smaida R, Hua G, Benkirane-Jessel N, Fioretti F. Three-Dimensional Models of the Dental Pulp: Bridging Fundamental Biology and Regenerative Therapy. *Int J Mol Sci*. 2025 Nov 12; 26 (22). doi:10.3390/ijms262210960 PubMed PMID: 41303443.
29. Zhang X, Contessi Negrini N, Correia R, Sharpe PT, Celiz AD, Angelova Volponi A. Generating Tooth Organoids Using Defined Bioorthogonally Cross-Linked Hydrogels. *ACS Macro Lett*. 2024 Dec 17;

13 (12): 1620–6. doi:10.1021/acsmacrolett.4c00520 PubMed PMID: 39532305.

30. Hermans F, Hemeryck L, Bueds C, Torres Pereiro M, Hasevoets S, Kobayashi H, *et al*. Organoids from mouse molar and incisor as new tools to study tooth-specific biology and development. *Stem Cell Reports.* 2023 May 9; 18 (5): 1166–81. doi:10.1016/j.stemcr.2023.03.011 PubMed PMID: 37084723.
31. Sharpe PT. Dental mesenchymal stem cells. *Development*. 2016 Jul 1; 143 (13): 2273–80. doi:10.1242/dev.134189 PubMed PMID: 27381225.
32. Jing J, Zhang M, Guo T, Pei F, Yang Y, Chai Y. Rodent incisor as a model to study mesenchymal stem cells in tissue homeostasis and repair. *Frontiers in Dental Medicine*. 2022 Nov 30; 3. doi:10.3389/fdmed.2022.1068494
33. An Z, Akily B, Sabalic M, Zong G, Chai Y, Sharpe PT. Regulation of Mesenchymal Stem to Transit-Amplifying Cell Transition in the Continuously Growing Mouse Incisor. *Cell Rep*. 2018 Jun 5; 23 (10): 3102–11. doi:10.1016/j.celrep.2018.05.001 PubMed PMID: 29874594.
34. Zhang F, Song J, Zhang H, Huang E, Song D, Tollemar V, *et al*. Wnt and BMP Signaling Crosstalk in Regulating Dental Stem Cells: Implications in Dental Tissue Engineering. *Genes Dis*. 2016 Dec; 3 (4): 263–76. doi:10.1016/j.gendis.2016.09.004 PubMed PMID: 28491933.
35. Zhou L, Zhao S, Xing X. Effects of different signaling pathways on odontogenic differentiation of dental pulp stem cells: a review. *Front Physiol*. 2023; 14: 1272764. doi:10.3389/fphys.2023.1272764 PubMed PMID: 37929208.
36. Liang C, Liang Q, Xu X, Liu X, Gao X, Li M, *et al*. Bone morphogenetic protein 7 mediates stem cells migration and angiogenesis: therapeutic potential for endogenous pulp regeneration. *Int J Oral Sci*. 2022 Jul 20; 14 (1): 38. doi:10.1038/s41368-022-00188-y PubMed PMID: 35858911.
37. Han Y, Chopra H, Thalakiriyawa DS, Wang H, Dissanayaka WL. Bioengineered Gelatin Hydrogels Functionalized with VEGF/BMP2 Mimetic Peptides for Advancing Regenerative Endodontics. *J Endod*. 2026 Jan 22. doi:10.1016/j.joen.2026.01.015 PubMed PMID: 41580122.
38. Cai X, Gong P, Huang Y, Lin Y. Notch signalling pathway in tooth development and adult dental cells. *Cell Prolif*. 2011 Dec; 44 (6): 495–507. doi:10.1111/j.1365-2184.2011.00780.x PubMed PMID: 21973022.
39. Mitsiadis TA, Feki A, Papaccio G, Catón J. Dental pulp stem cells, niches, and notch signaling in tooth injury. *Adv Dent Res.* 2011 Jul; 23 (3): 275–9. doi:10.1177/0022034511405386 PubMed PMID: 21677078.
40. Mitsiadis TA, Catón J, Pagella P, Orsini G, Jimenez-Rojo L. Monitoring Notch Signaling-Associated Activation of Stem Cell Niches within Injured Dental Pulp. *Front Physiol*. 2017; 8: 372. doi:10.3389/fphys.2017.00372 PubMed PMID: 28611689.
41. Mitsiadis TA, Hirsinger E, Lendahl U, Goridis C. Delta-notch signaling in odontogenesis: correlation with cytodifferentiation and evidence for feedback regulation. *Dev Biol*. 1998 Dec 15; 204 (2): 420–31. doi:10.1006/dbio.1998.9092 PubMed PMID: 9882480.
42. Souilhol C, Cormier S, Tanigaki K, Babinet C, Cohen-Tannoudji M. RBP-Jkappa-dependent notch signaling is dispensable for mouse early embryonic development. *Mol Cell Biol*. 2006 Jul; 26 (13): 4769–74. doi:10.1128/MCB.00319-06 PubMed PMID: 16782866.
43. Nagata M, Gadhvi GT, Komori T, Arai Y, Tsutsumi-Arai C, Chu AKY, *et al*. A Hedgehog-Foxf axis coordinates dental follicle-derived alveolar bone formation. *Nat Commun*. 2025 Jul 2; 16 (1): 6061. doi:10.1038/s41467-025-61050-3 PubMed PMID: 40593802.
44. Zhao H, Feng J, Seidel K, Shi S, Klein O, Sharpe P, *et al*. Secretion of shh by a neurovascular bundle niche supports mesenchymal stem cell homeostasis in the adult mouse incisor. *Cell Stem Cell*. 2014 Feb 6; 14 (2): 160–73. doi:10.1016/j.stem.2013.12.013 PubMed PMID: 24506883.