Archives of Oral Biology 189 (2026) 106661

Contents lists available at ScienceDirect

Archives of Oral Biology

journal homepage: www.elsevier.com/locate/archoralbio

A historical perspective on the discovery of human dental follicle cells for regenerative dentistry

Christian Morsczeck *, Anja Reck, Torsten E. Reichert

Department of Oral and Maxillofacial Surgery, University Hospital Regensburg, Franz-Josef-Strauss-Allee 11, Regensburg 93053, Germany

ARTICLE INFO

Keywords:
Tissue Engineering
Immunotherapy
Extracellular Vesicle
Biomaterials
Differentiation
Stem Cells

ABSTRACT

Objectives: This narrative review aims to summarize and contextualize more than two decades of research on human dental follicle cells (DFCs), focusing on their biological characteristics, regenerative capacity, and potential applications in dentistry and immunotherapy.

Design: Articles were selected based on the literature of non-human propedeutics since the 1990s and human DFC research since its inception in 2005. The focus was set on the isolation, characterization, cultivation, and therapeutic prospects of DFCs as progenitor cells derived from the mesodermal tooth germ.

Results: DFCs exhibit multipotent differentiation potential and pronounced immunomodulatory properties. Their developmental origin not only provides specific insights into the cellular processes underlying tooth formation and the regeneration of dental tissue, but also opens up perspectives for novel therapies in dentistry, such as the formation of a biological tooth root.

Conclusions: The findings highlight the potential of DFCs for regenerative dentistry and immunotherapies in general, and provide a solid basis for future work in these research areas.

1. Introduction

The biology of tooth germ tissue cells is not only one of the most exciting research areas in modern dental research, but also a prerequisite for regenerative dentistry. Tooth development is a complex interplay between cells of the dental epithelial and dental mesodermal tooth germ tissue, with the dental mesoderm originating from neural crest cells (Bastos et al., 2022; Diekwisch, 2001). A special type of tooth germ tissue, the dental follicle, plays a crucial role in tooth eruption, inducing bone resorption (Wise, 2009). However, this tissue also provides the precursor cells of the periodontal ligament, thus directly involving these cells in the formation of mineralizing tissue (Diekwisch, 2001). During periodontal formation, non-mineralizing periodontal fibroblasts also develop from these tooth germ cells, forming flexible connective tissue between the cementum and the alveolar bone. After tooth eruption and with the formation of the periodontium, the dental follicle disappears (Zhou et al., 2019). However, due to the late development of wisdom teeth, it is possible to obtain the dental follicle from impacted wisdom teeth. Although this may have been obvious for some time, the first work on the isolation and differentiation of human dental follicle cells from impacted wisdom teeth was not published until 2005 (Morsczeck et al., 2005).

Abbreviations: 2D-GE, 2D-gel-electrophoresis; AKT, Protein kinase B signaling pathway; ALP, Alkaline phosphatase; BDFCs, Bovine dental follicle cells; BMP, Bone morphogenetic protein; BMPR, Bone morphogenetic protein receptor; BSP, Bone sialoprotein; β-TCP, Beta-tricalcium phosphate; CGF, Concentrated growth factor; CSF-1, Colony-stimulating factor-1; CX43, Connexin-43; DF, Dental follicle; DFCs, Dental follicle stem cells; DLX3/5, Distal-less homeobox 3/5; EMD, Enamel matrix derivative; EVs, Extracellular vesicles; HDFCs, Human dental follicle cells; IGF2, Insulin-like growth factor 2; IGFBP5, Insulin-like growth factor-binding protein 5; IL-1α, Interleukin-1 alpha; LPS, Lipopolysaccharide; MALDI-TOF-MS, Matrix-assisted laser desorption/ionization-time of flight mass spectrometry; MAPK, Mitogen-activated protein kinase; MCP-1, Monocyte chemoattractant protein-1; MSC, Mesenchymal stem cells; MSX2, Msh homeobox 2; NAC, Stem cell markers, N-acetylcysteineNotch-1 / Nestin / STRO-1; Olig2, Oligodendrocyte lineage transcription factor 2; OPG, Osteoprotegerin; PCL, Polycaprolactone; PDL, Periodontal ligament; PKC, Protein kinase C; PLGA, Polylactic-co-glycolic acid; PLC, Phospholipase C; PRF, Platelet-rich fibrin; PRGF, Plasma-rich growth factors; PTHrP, Parathyroid hormone-related protein; RANKL, Receptor activator of nuclear factor kappa-B ligand; ROS, Reactive oxygen species; RT-PCR, Reverse transcription polymerase chain reaction; Runx2, Runt-related transcription factor 2; VEGF, Vascular endothelial growth factor; WNT, Wingless-related integration site; ZBTB16, Zinc finger and BTB domain-containing protein 16.

* Corresponding author.
E-mail address: christian.morsczeck@ukr.de (C. Morsczeck).

https://doi.org/10.1016/j.archoralbio.2026.106661
Received 9 April 2026; Received in revised form 8 June 2026; Accepted 10 June 2026
Available online 12 June 2026
0003-9969/© 2026 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Over the past 20 years, numerous studies have been published on human dental follicle cells also designated as dental follicle stem cells (DFCs), some of which are summarized in this article. Since it is not possible to discuss all research areas in detail, one focus, for example, is on a chronological overview of works that were essential for considering the isolation of human DFCs. For example, cells had already been isolated for example from the dental follicle of bovine tooth germs before (Handa et al., 2002; Handa et al., 2002). This work was significant, but the cells isolated from bovine dental follicles did not possess the stem cell properties that human dental follicle cells have. The first chapter addressing the scientific background, i.e., which scientific studies were down before research with non-human dental follicle cells have started. It examines the questions that were answered, for example, in the 1990s and early 2000s using cells from murine dental follicles. The aim of this work is to demonstrate that, following the isolation of human DFCs, research into cell therapy for the periodontal tissues, such as the formation of a biologic tooth root with a single stem cell type, is possible; although the principle of a biologic tooth root is also possible with a combination of different types of stem cells (Sonoyama et al., 2006). Unlike a systematic review, this article takes a narrative approach. We have deliberately selected several key studies to serve as exemplary benchmarks for the research period. This methodology was chosen—as is common for such analyses—to evaluate these pioneering works within their specific scientific context. This review examines the potential of DFCs and biomaterials in regenerative dentistry over the past few decades. Because many research groups have contributed only sporadically to this field, the available evidence is highly complex and heterogeneous. Since this heterogeneity often limits the ability to draw generalizable conclusions, parts of this review are intentionally descriptive. The aim is to present the past and present state of research rather than to provide a definitive synthesis of the data.

2. First isolation and cultivation of non-human dental follicle cells

DFCs from rat molars were first successfully isolated and cultured in vitro in 1992 by Wise et al. (1992). This study described the method for extracting the dental follicles and adjacent enamel organs from the first and second mandibular molars of 6- to 7-day-old rats and subsequently cultivating them in a medium that promotes fibroblast growth. The aim of this early study was to determine whether the cells of the follicle could be cultured in vitro, and used the dental follicle cells for studies about tooth eruption. They characterized the cultured cells morphologically and immunologically as fibroblasts that could be stably cultured over many passages (Yao et al., 2004). Wise and colleagues also conducted anatomical studies that helped to show that the dental follicle is essential for tooth eruption, as tooth eruption cannot occur without it (Marks et al., 1983; Marks & Cahill, 1984; Wise et al., 1985). These studies suggested that the dental follicle coordinates osteoclastogenesis, the formation of bone-resorbing cells (osteoclasts) in the upper (coronal) part of the follicle, to create a breakthrough canal in the alveolar bone. This is achieved through the infiltration of monoytes and their maturation into osteoclasts. Therefore, it was necessary to isolate cells from the dental follicle to elucidate the molecular processes involved. They identified with DFCs cytokines such as CSF−1 (colony-stimulating factor−1) and monocyte chemoattractant protein (MCP)−1, which attract precursor cells for bone resorption into the follicle (Grier et al., 1998; Wise et al., 1999, 2002). Further investigations with DFCs showed that genes for pro-inflammatory marker proteins such as interleukin (IL)−1α and NFκB were spatially and temporally precisely activated within the follicle (Que et al., 1999). Additionally, neighboring tissues, such as the stellate reticulum, communicate with the dental follicle via proteins like PTHrP (parathyroid hormone-related protein) to trigger the expression of MCP−1 and CSF−1 for tooth eruption. These are regulated by the cells of the dental follicle via protein kinase A (Wise et al., 2000; Yao & Wise, 2003a). Protein kinase C also appears to be involved in the molecular processes in the dental follicle that are responsible for triggering tooth eruption, such as the expression of TNF-α (Yao & Wise, 2003b). Additionally, a study using conditioned medium of dental follicle cells from another group showed that this medium contains factors for the maturation of osteoclasts (Kawakami, 2000). Overall, these investigations reinforced initial assumptions that the dental follicle is involved in tooth eruption and identified some factors that might play an important role, but a definitive model could not yet be established.

Dental follicle cells from mice were successfully isolated and characterized somewhat later by Martha Somerman's group (D'Errico et al., 1995; Zhao et al., 2004). For many years prior, this research group had focused in particular on the function of matrix proteins such as bone sialoprotein (BSP) and adhesion molecules such as integrins in relation to their role in the development of periodontal tissue (MacNeil, Berry, D'Errico, Strayhorn, Piotrowski, et al., 1995; MacNeil, Berry, D'Errico, Strayhorn, & Somerman, 1995). And even today, the focus remains on questions about the importance of matrix proteins for periodontal development; for example, a recent study with Martha Somerman showed that while BSP is involved in the development of periodontal tissue, its function can probably be replaced by other proteins. (Nagasaki et al., 2022). As part of dental development, questions of regenerative medicine were addressed very early on, including the interaction of dental follicle cells with products already available in the clinic. They used DFCs to investigate the influence of matrix proteins such as the enamel matrix derivative (EMD), which are also used in clinical practice, on cell migration and biomineralization (Hakki et al., 2001). However, the cells that Somerman's group eventually used for cell culture studies were either immortalized or were used after a short cell culture expansion. (Hakki et al., 2001; Zhao et al., 2002, 2004). Later, other researchers took a further step in cell isolation by isolating primary dental follicle cells from mice (Bsoul et al., 2003). An initial study using murine DFCs for tissue engineering of periodontal tissues were not particularly successful (Zhao et al., 2004). In contrast, cells of the dental follicle impaired periodontal regeneration compared to the untreated control. However, prior to this study, the group was able to show that using bone morphogenetic protein (BMP) 2, murine DFCs can be differentiated into osteoblasts and/or cementoblasts (Hakki et al., 2001; Zhao et al., 2002). Interestingly, Wise's research group demonstrated in 2006 that BMP2 is more strongly expressed in the basal part of the follicle, while RANKL, the receptor for NFκB, is more strongly expressed in the coronal part (Wise & Yao, 2006). This suggests that cells of this tissue are heterogeneous and can express different genes depending on whether they are involved in tooth eruption or periodontal formation.

In 2002, Handa et al. published that bovine DFCs (BDFCs) contain precursor cells (progenitor cells) for cementoblasts capable of forming cement-like matrix in vivo (Handa, Saito, Tsunoda, et al., 2002; Handa, Saito, Yamauchi, et al., 2002). Their most important contribution in this area is the identification of differentiation capacity. To this end, they isolated dental follicle cells from bovine tooth germs and investigated their differentiation potential by transplantation into immunodeficient mice. The transplanted cells formed cement-like tissue, proving that they contain precursor cells for cementoblasts (Handa, Saito, Yamauchi, et al., 2002). BDFCs differed phenotypically from bovine alveolar osteoblasts and bovine periodontal ligament cells, making them a useful model for investigating the molecular mechanisms of cementogenesis. This research laid the foundation for the use of DFCs in tissue engineering, even though it could not demonstrate in vitro differentiation, which Hakki et al. had already shown using immortalized mouse DFCs (Hakki et al., 2001). The focus was on the regeneration of periodontal tissue and bone, as these cells exhibit a high potential for differentiation into various cell lineages (multipotent potential). In summary, Handa and his team provided crucial evidence that DFCs represent an accessible source of stem cells suitable for regenerative therapies in dentistry.

3. Isolation of human dental follicle cells and establishment of a cell culture

In the early 2000s, the first research group isolated undifferentiated cells from the human dental follicle (Morsczeck, Gotz, et al., 2005). Human DFCs were characterized as multipotent progenitor cells and demonstrated the expression of typical stem cell markers such as Notch−1 and Nestin (Morsczeck, Gotz, et al., 2005; Morsczeck, Moehl, et al., 2005; Morsczeck, 2006). DFCs differentiated into tooth-specific cells (osteoblasts, cementoblasts) under laboratory conditions (Morsczeck, Moehl, et al., 2005). The work of Philippe Kémoun and colleagues on human DFCs was published shortly thereafter (Kemoun et al., 2007). They identified these undifferentiated cells using the stem cell marker STRO−1 and demonstrated the expression of bone morphogenetic protein receptors (BMPRs). A significant part of this work addresses how DFCs can be stimulated to produce cementum. They showed that stimulation with BMP−2, BMP−7, or EMD leads to DFCs acquiring characteristics of cementoblasts. During this period, it was also demonstrated that DFCs can be cultured under serum-free conditions and differentiate into cells that possess nerve cell-like properties (Völlner et al., 2009). These results demonstrate the multipotential nature of these cells.

Following isolation, an osteogenic in vitro model was established. An initial study demonstrated the ability of DFCs to differentiate into osteoblast-like cells after stimulation with dexamethasone (100 nM) and insulin (5 μg/ml) (Morsczeck, Moehl, et al., 2005). The cells showed a significant increase in alkaline phosphatase (ALP) activity and strong gene expression of BMP2 and osteocalcin, accompanied by calcium deposits (alizarin red S staining). A subsequent study (Morsczeck, 2006) analyzed the expression of transcription factors during differentiation with dexamethasone and insulin using quantitative RT-PCR and showed the expression of osteogenic transcription factors, with genes for the transcription factors Runx2, DLX5, and MSX2 being constitutively expressed. On the other hand, the gene for the transcription factor DLX3 was induced. This expression dynamic did not reflect the known phases of osteoblastogenesis and positioned DFCs as a distinct preosteoblastic cell population (Morsczeck, 2006). Due to their origin, they are also capable of forming periodontal ligament, and therefore, for therapeutic purposes, a better understanding of the mechanisms of differentiation into osteogenic cells is of utmost importance. Analyses of the transcriptome and proteome were therefore performed to provide deeper insights into differentiation mechanisms. Morsczeck et al. (Morsczeck, Petersen, et al., 2009) characterized the proteome using 2D-gel-electrophoresis and MALDI-TOF-MS. After osteogenic differentiation, 115 differentially expressed proteins were identified. Proteins associated with cell cycle progression and protein metabolism were downregulated, while proteins involved in catabolism, cell motility, and defense against oxidative stress were upregulated (Morsczeck et al., 2009). In parallel, an additional study characterized gene expression profiles using Affymetrix microarray analysis (Morsczeck, Schmalz, et al., 2009). Osteogenic differentiation induced the upregulation of 98 genes, including insulin-like growth factor (IGF)2 and IGF-binding protein (IGFBP)5, known osteogenic differentiation markers, while an activator of the WNT signaling pathway, such as WNT2, was downregulated. Saugspier et al. (2010) extended this study by performing gene expression analysis at an earlier time point (day 7). Pathway analyses showed the induction of ZBTB16 and the BMP-signaling pathway by a dexamethasone-containing differentiation medium. More interestingly, it was shown that neither the differentiation nor the expression of ZBTB16 is dependent on activation of the BMP signaling pathway. On the other hand, it was shown that induction of BMP2 induced the differentiation, but not the expression, of ZBTB16. These data suggested the possibility of a BMP-dependent and ZBTB16-independent mechanism.

This established model for investigating osteogenic differentiation under in vitro conditions has been used since its inception and has yielded new insights into the molecular mechanisms. These findings have been summarized extensively in recent years (Morsczeck, 2022; Morsczeck et al., 2023). Therefore, the focus of this article will be on the evaluation of DFCs for regenerative dentistry (medicine).

4. First experiments for tissue engineering with non-human DFCs

Following the initial isolation of human DFCs, the field attracted growing interest, prompting numerous research groups to establish parallel models using non-human organisms. Animal studies conducted—particularly after 2005—were crucial for future translational research; they provided essential concepts in tissue engineering and regenerative dentistry, thereby directly driving progress toward the subsequent application of human DFCs. For example, one study conducted experiments to examine cell-cell interactions, using co-cultures of rat papilla cells and rat DFCs (Bai et al., 2010). Osteogenic differentiation of the DFCs was observed only in the presence of dental papilla cells; without this contact, only connective tissue was retained. DFCs therefore appear to have a strong tendency towards fibroblastoid differentiation. Therefore, most research on DFCs focuses on protocols aimed at optimizing osteogenic processes. This involves the use of de-mineralized dentin, or extracellular matrix proteins, or soluble factors like vitamin D metabolites. However, advanced studies in this field have also been conducted with DFCs that were not derived from human dental follicles. This included the work of Wu et al., who used collagen-free proteins from dentin to support the differentiation of rat DFCs into mineralizing cells (Wu et al., 2008). This result suggests a mechanistic relationship between dentin-derived matrix proteins and cementogenesis, which could be used therapeutically for targeted regeneration of root cementum. Furthermore, Xu et al. (Xu et al., 2009) analyzed the combined effect of BMP−2 and dexamethasone on the osteogenic differentiation of rat dental follicle precursor cells embedded in a three-dimensional β-tricalcium phosphate (β-TCP) scaffold. The results showed that BMP−2 and dexamethasone, both individually and synergistically, enhance the osteogenic differentiation of dental follicle cells on β-TCP, with the combination in particular leading to pronounced expression of osteoblast-specific markers and dense mineralization within the three-dimensional scaffold (Xu et al., 2009). This confirmed β-TCP as a promising scaffold material. Tsuchiya et al. (2008) conducted initial experiments investigating how a collagen I matrix influences the behavior of purified porcine dental follicle cells at the molecular and cellular levels. The results showed that collagen I could play an active role in regulating the DFC phenotype, inducing the expression of osteogenic markers such as bone sialoprotein. Interestingly, the search for a suitable carrier material continues to this day. Vitamin D-loaded chitosan nanostructures and human-derived decalcified tissues have also been tested as carrier materials (Muresan et al., 2025; X.-H. Zhang et al., 2025).

These works show that DFCs exhibit a high tendency towards fibroblastoid differentiation and require external stimuli from specific growth factors or extracellular matrices for osteogenic or cementogenic regeneration. The use of carrier materials such as β-TCP in combination with factors such as BMP−2 promotes differentiation and mineralization, thus giving DFCs great potential for the targeted regeneration of periodontal.

5. Tissue engineering with human DFCs

Tissue engineering is an important part of human dental stem cell research (Zhou et al., 2019) and optimizing osteogenic differentiation is an important area of research. Khanna-Jain et al. investigated, for example, whether vitamin D_3 metabolites can induce osteogenic differentiation in human DFCs (Khanna-Jain et al., 2010). DFCs were cultured with 1α,25-dihydroxyvitamin D_3 and 25-hydroxycholecalciferol in osteogenic medium. The study showed that vitamin D_3 metabolites

significantly increased the expression of osteoblast-specific genes and matrix mineralization. This study was one of the first to attempt to optimize osteogenic differentiation of human DFCs. In another study, human DFCs were considered for dentin regeneration, and experiments were conducted with a demineralized matrix derived from dentin for optimization and tissue engineering (Guo et al., 2009). DFCs were seeded onto this matrix, ad subsequently, differentiation was investigated in vitro, while the ability to form dentin-like structures was examined in vivo (e.g., subcutaneously in an animal model). The study showed that DFCs on the dentin matrix scaffold exhibit pronounced differentiation into cells expressing odontoblast markers (Guo et al., 2009). These results represent a first step towards using DFCs for tissue engineering of non-periodontal tissue and demonstrate the multipotent potential of human DFCs.

Suitable carrier materials are needed for stem cells to create tissue-like structures, which is why studies often focus on the interactions between cells and biomaterial. Initial studies on tissue engineering with human DFCs showed the successful attachment, proliferation and differentiation on already available bone substitute materials such as tricalcium phosphate (Viale-Bouroncle, Bey, et al., 2011; Viale-Bouroncle et al., 2013). However, tricalcium phosphate induced apoptosis in human DFCs, but simultaneously induced the expression of osteogenic differentiation markers, making this combination very special (Viale-Bouroncle et al., 2013). A subsequent study also showed that allogeneic bone substitute materials could be suitable as carrier materials, although apoptosis was induced here as well (Gosau et al., 2015). Although DFCs appear to have more robust antioxidant protection compared to related stem cells (J. Li et al., 2016), this does not allow for the definitive conclusion that the induction of apoptosis has no inhibitory effect on osteogenic differentiation. The selection of material for DFCs for bone formation is further complicated by the fact that higher stiffness inhibits osteogenic differentiation (Viale-Bouroncle, Völlner, et al., 2011). This is related to their potential to also be precursor cells for periodontal fibroblasts. Overall, DFCs are, as expected, probably more suitable as precursor cells for the formation of the periodontal apparatus, a combination of mineralized tissue and connective tissue. However, in another study with human DFCs, the influence of titanium implants with hydroxyapatite was investigated. This modification of the implant led to significantly better adhesion than untreated implants. The authors described this as natural osteogenic differentiation (Lucaciu et al., 2015). Interestingly, graphene oxide also appears to be suitable as a support material for DFCs, as it generates very little oxidative stress in the cells (Olteanu et al., 2015). However, a recent study showed that graphene composite dental materials exhibit good systemic and local biocompatibility in experimental mandibular bone defects (Dreanca et al., 2020). Non-mineralized materials such as lyophilized platelet-rich fibrin (PRF) (Q. Li et al., 2014), collagen I (Viale-Bouroncle et al., 2014) and electrospun cotton cellulose scaffolds (He et al., 2015) with DFCs have also been successfully tested as scaffold materials for differentiation into osteoblasts or bone formation.

Overall, these studies showed that there is a wider selection of different biomaterials suitable for tissue engineering with DFCs. Following these studies on finding a suitable carrier material for DFCs, initial studies have also been conducted that more specifically attempted to construct a complex of the periodontal apparatus (Nivedhitha Sundaram et al., 2016) or therapeutic strategy for spinal cord defect (X. Li et al., 2015). To replicate the complex architecture of the periodontium, Nivedhitha Sundaram et al. (Nivedhitha Sundaram et al., 2016) developed a two-layered construct consisting of an electrospun poly(caprolactone)-(PCL) multiscale membrane to mimic the formation of the periodontal ligament from DFCs and a chitosan/$CaSO_4$ scaffold to form alveolar bone. The expression of osteoblastic and fibroblastic markers after differentiation of the DFCs showed that the developed two-layered construct could be a promising candidate for periodontal regeneration and that this process can be controlled using biomaterials. Tian and colleagues (X. Li et al., 2015) produced an aligned electrospun PCL/PLGA material (tissue-engineered scaffolds made of polylactic-co-glycolic acid (PLGA), polycaprolactone (PCL)) on which DFCs could proliferate and transplanted this construct into a rat with spinal cord damage to repair the defect. Functional observations were performed, but the results did not show statistical significance. Subsequent histological analyses demonstrated that DFCs were able to express the oligodendrogenesis marker Olig2 in vivo, which may have contributed to remyelination. Although the authors concluded that DFCs may represent a promising resource for neuronal regeneration, applications of DFCs in this field are difficult. However, there are always studies that investigate different biomaterials for the differentiation of DFCs in neuronal cells (Heng et al., 2017).

It therefore appears much more promising to use DFCs for tissue regeneration in dentistry. Li et al. (H. Li et al., 2017) investigated whether a xenogeneic bio-root, consisting of porcine treated dentin matrix combined with DFCs, is capable of functionally forming a tooth root. The used dentin matrix is similar to that used in previous studies (see above (Guo et al., 2009)), derived from porcine dentin, but with a treated matrix that retains a bioactive surface structure (H. Li et al., 2017). This matrix was combined with human DFCs and tested in two transplantation models. In the first model, a rat (subcutaneous insertion) was used to analyze the early immune and remodeling response, with a key aspect being the characterization of macrophage phenotypes over time. The authors interpret a shift in the expression pattern of the infiltrated macrophages to an M2 type at a later time point during transplantation as indicating that the xenogeneic material is not only tolerated but actively remodeled into functional tissue (H. Li et al., 2017). Following intraoral transplantation into the jawbone of a rhesus monkey in the second model of this study, functional tests such as masticatory loading and periodontal ligament (PDL) formation were performed over six months. The authors discovered the formation of periodontal ligament-like collagen fiber bundles running between the Bio-Root surface and the surrounding alveolar bone (H. Li et al., 2017). Blood vessels are found in the formed tissue, indicating metabolically active, vital connective tissue. The reconstructed Bio-Root unit exhibits properties that allow for certain masticatory loads—i.e., it is elastically coupled, similar to a natural tooth root with PDL (H. Li et al., 2017). These findings led the group to further refine the protocol in a more recent study, enabling the long-term testing of a biological tooth root in non-human primates. Human DFCs were grown on dentin matrix, formed into cell sheets, and constructed as functional biological tooth roots. After crown construction, the monkey chewed normally without resorption (up to 2 years) (Yang et al., 2023). Another group used human DFCs to create a composite with a drilled porous, decalcified dentin matrix (Feng et al., 2018). This composite was implanted under the renal capsule of mice, resulting in structured fibrous tissue with mineralization. These studies demonstrate that the strategy of using a dentin matrix is a promising approach for tissue engineering and highlight the potential of tissue engineering with DFCs for clinical dental implants as an alternative to titanium in the future. Table 1 briefly summarize representative contributions to tissue engineering with DFCs that have been discussed in this article.

In summary, the present body of research underscores the significant versatility of DFCs within the field of tissue engineering, particularly for applications in dental and maxillofacial surgery. While initial studies prioritized the optimization of scaffold materials—ranging from tricalcium phosphate and collagen to advanced graphene composites—subsequent investigations have successfully engineered complex tissue constructs that replicate the periodontium and functional bioroot structures. Although the potential for neural regeneration remains a secondary area of interest, the primary clinical promise of DFCs clearly resides in the regeneration of dental tissues. Their demonstrated capacity to form organized, vital connective and mineralized tissues in vivo highlights their therapeutic value. Consequently, the ongoing refinement of scaffold designs and bioactive materials, coupled with a more granular understanding of DFC differentiation pathways, is poised

Table 1
Representative studies on tissue engineering with dental follicle cells (DFCs).

Focus Area	Scaffold / Material	Key Findings	Reference
Bioroot Engineering	Treated Dentin Matrix (TDM)	Formation of a functional "Bio-Root" with PDL-like fibers and masticatory load capacity in primates.	H. Li et al. (2017); Yang et al. (2023)
Periodontal Complex	PCL membrane & Chitosan/ $CaSO_4$	Successful dual-layer construct mimicking both periodontal ligament and alveolar bone.	Nivedhitha Sundaram et al. (2016)
Bone Regeneration	β-TCP + BMP−2/Dex	Synergistic effect leads to dense mineralization and osteoblast-specific marker expression.	Xu et al. (2009)
Dentin Regeneration	Demineralized Dentin Matrix	hDFCs differentiate into odontoblast-like cells forming dentin-like structures in vivo.	Guo et al. (2009)
Bone Substitute	TCP / Allogeneic Bone	Successful differentiation but noted induction of apoptosis in hDFCs.	Viale-Bouroncle et al. (2013); Gosau et al. (2015)
Neural Repair	Electrospun PCL/PLGA	DFCs expressed Olig2 in vivo, potentially contributing to remyelination in spinal cord defects.	X. Li et al. (2015)

to transition these cells into clinical applications for periodontal and tooth root regeneration.

6. Miscellaneous studies on basic research with DFCs for regenerative dentistry

Publications in the field of regenerative dentistry have become highly significant for research with DFCs. Although these studies often focused on various aspects and were not as closely aligned with clinical application as the experiments on a biological periodontal apparatus in the previous chapter (Yang et al., 2023), many studies and findings will help to translate DFCs into clinical practice. Among other things, a study was conducted in which the use of material from human and porcine dentin was compared (H. Li et al., 2021). A key focus of this research was the optimization of DFCs for clinical use. For example, a study by Okada et al. (2016) demonstrated that plasma-rich proliferative growth factors (PRGF) stimulates proliferation, migration, and gene expression associated with bone formation in human DFCs. The authors showed in vitro that PRGF dose-dependently induces the expression of osteogenic markers, leading to increased mineralization and representing a promising approach for regenerative dentistry. This underscores the potential of autologous growth factors to promote alveolar bone healing. However, there are also proteins that inhibit osteogenesis. The effect of parathyroid hormone-associated peptide (PTHrP 1–34) on DFCs during tooth development inhibits osteogenesis by inactivating the Wnt/β-catenin signaling pathway, thus accelerating tooth eruption (J. Zhang et al., 2019). Sclerostin has also been identified as a regulator of osteogenic differentiation, which is induced by protein kinase C (De Pellegrin et al., 2024). Protein kinase C appears to play a significant role in the control of osteogenic differentiation and the induction of senescence in DFCs, and thus represents an interesting target for the targeted induction of differentiation, especially after induction of senescence (Ji et al., 2024; Morsczeck et al., 2026; Pieles et al., 2021).

Another preclinical study using DFCs employed autologous bioscaffold material for bone regeneration – the liquid phase of concentrated growth factor (CGF) loaded with DFCs. In vitro and ex vivo results showed improved cell adhesion, proliferation, and osteoinduction via VEGF and BMP signaling, with significant regeneration of trabecular bone in critical defects (Z. Li et al., 2024). A study using DFCs suggests that dietary silicon may promote bone homeostasis and bone health. They demonstrated the inductive effects of soluble silicon on osteogenic differentiation via Connexin−43 (CX43) gap junction communication in DFCs (Uribe et al., 2020). This may lead to increased communication via gap junctions, which promotes differentiation into osteoblasts. Another publication of Zhang et al. investigated how N-acetylcysteine (NAC) improves the bioroot regeneration of bioroots by protecting DFCs from oxidative stress, which impairs their viability, proliferation, migration and differentiation after transplantation (J. Zhang et al., 2021). In vitro experiments showed that NAC pretreatment reduces H_2O_2-induced damage, while in vivo experiments demonstrated that NAC promotes cell survival and enables better long-term bioroot regeneration with transdifferentiation. Another study investigated the effect of NAC on alveolar bone regeneration with DFCs. NAC protects against oxidative stress caused by reactive oxygen species (ROS) via the AKT signaling pathway (Meng et al., 2022). In vitro experiments showed that NAC pretreatment with 5 mM protected against H_2O_2-induced damage, but a higher concentration did not (Meng et al., 2022). Interestingly, this was the same concentration of NAC as in the previous study (J. Zhang et al., 2021).

There are also studies that aim to optimize the cultivation of DFCs. One publication investigated how an agarose-based spheroid culture improves the stem cell properties of human dental follicle cells (HDFCs) and promotes their odontogenic differentiation potential (M. Li et al., 2021). Another group also investigated how biomimetic nanofiber gelatin microspheres, designed to mimic the natural stem cell niche, affect the stem cell properties of DFCs. Tests showed very good cell adhesion, proliferation, metabolic activity, and differentiation on this material. It is ideally suited as an injectable scaffold for stem cell transplantation because it offers structures similar to the extracellular matrix (Sarviya et al., 2022).

However, studies have also been conducted that did not use DFCs for regeneration through the generation of new dental tissues. Extracellular vesicles for immunomodulation are also obtained for preclinical studies on the treatment of periodontitis and other diseases (Liang et al., 2024; Sun et al., 2024). Last year, new studies were conducted to generate neural tissue cells from DFCs. These studies differentiated DFCs into retinal and corneal cells (Lee et al., 2025; Lin et al., 2025). A similar study was conducted many years ago using murine DFCs (Ernst et al., 2009). It remains exciting to see what therapeutic options will be evaluated with DFCs in the future. Some of the questions surrounding the possibilities of dental stem cells are already being clinically evaluated and summarized elsewhere (Ivanovski et al., 2024; Song et al., 2023).

Before we move to the next stage this chapter will be summarized. Studies across very different research areas showed that DFCs possess the ability for tissue regeneration, which is significantly enhanced by combining them with biocompatible scaffolds or autologous growth factors such as PRGF. A critical lesson is the importance of synergy: substances such as silicon or N-acetylcysteine, alongside advanced 3D cultivation techniques like spheroids, drastically improve the cells' survival rates, stability, and overall efficiency. Furthermore, the research highlights that mastering specific signaling pathways—such as Wnt/β-catenin, Protein Kinase C, and AKT—is essential for precisely controlling cell maturation and stress resistance. Perhaps the most groundbreaking insight is that the potential of DFCs extends far beyond dentistry; their ability to modulate the immune system and differentiate into neural or ocular cells opens new therapeutic horizons for treating complex systemic diseases.

7. Immunotherapies with DFCs

In regenerative dentistry, promising approaches exist for

immunotherapies using DFCs and the extracellular vesicles (EVs) derived from them. Immunotherapies using dental stem cells are being tested, particularly in the treatment of inflammatory diseases such as pulpitis and periodontitis. Immunomodulatory, anti-inflammatory, and regenerative effects of dental stem cells have also been investigated in oral and systemic models. These studies have also yielded insights into therapeutic mechanisms. For example, DFC-EVs can reprogram macrophage metabolism and promote anti-inflammatory M2 polarization in pulpitis (Tian et al., 2025). LPS-pretreated EVs exert antioxidant effects via ROS/MAPK signaling and reduce apoptosis and alveolar bone loss in periodontitis (Y. Huang et al., 2024; Y. L. Huang et al., 2022). EVs also inhibit the pathogenicity of Porphyromonas gingivalis and modulate neutrophil activity (Y. Huang et al., 2023; Kriebel et al., 2018). It therefore seems plausible that EVs could be used for periodontal regeneration. Further studies have shown that they provide biochemical signals for periodontal ligament regeneration and promote osteogenesis via PLC/PKC/MAPK and RANKL/OPG balance (Ma et al., 2022; Yi et al., 2022). Furthermore, DFCs support paracrine regeneration in pulpitis (Hong et al., 2020). Interestingly, EVs derived from other mesenchymal stem cells can be taken up by DFCs and, among other things, protect against oxidative stress (Fu et al., 2023). The addition of EVs could thus enhance cell therapy with DFCs. This also makes DFCs interesting for the immunomodulation of systemic diseases. Further studies have yielded remarkable results with DFCs. They alleviate glandular dysfunction in Sjögren's syndrome, suppress T-cell responses in Crohn's disease, and preserve tissue in sepsis (Genc et al., 2022; Topcu Sarica et al., 2020; Zibandeh et al., 2020). These effects are based on broad immunosuppressive properties. Finally, and exceptionally, EVs from DFCs are also being discussed as cell-free therapeutics for the repair of spinal cord injuries, which should demonstrate their great importance for regenerative medicine (Wen et al., 2024). Table 2 briefly summarize important contributions to immunomodulation with DFCs that have been discussed in this article.

These studies underscore the therapeutic potential of DFCs and their EVs as pivotal agents in immunomodulatory and regenerative medicine. By orchestrating macrophage polarization and regulating the RANKL/OPG axis, DFC-derived EVs facilitate potent anti-inflammatory and osteogenic responses. However, despite these promising results in oral and systemic models, significant barriers to clinical translation remain. Critical challenges include the standardization of EV isolation protocols, the scalability of production, and the precise characterization of cargo heterogeneity. Addressing these pharmacological and regulatory hurdles is essential to move from experimental proof-of-concept to reliable, cell-free therapeutic applications in regenerative medicine.

Table 2
Representative studies on immunomodulation and systemic applications of DFCs and DFC-EVs.

Target Condition	Agent	Mechanism / Outcome	Reference
Pulpitis	DFC-EVs	Reprogramming of macrophage metabolism and promotion of anti-inflammatory M2 polarization.	Tian et al. (2025)
Periodontitis	LPS-pretreated EVs	Antioxidant effects via ROS/MAPK; reduction of apoptosis and alveolar bone loss.	Y. Huang et al. (2024)
Sjögren's Syndrome	DFCs	Alleviation of glandular dysfunction via systemic immunosuppressive properties.	Topcu Sarica et al. (2020)
Crohn's Disease	DFCs	Suppression of T-cell responses and reduction of intestinal inflammation.	Zibandeh et al. (2020)
Spinal Cord Injury	DFC-EVs	Evaluated as cell-free therapeutics for neural tissue repair and functional recovery.	Wen et al. (2024)
Oxidative Stress	NAC / DFC-EVs	Protection against H_2O_2-induced damage via AKT and ROS signaling; improved cell survival.	J. Zhang et al. (2021); Fu et al. (2023)

8. Conclusion

DFCs were first isolated from the follicles of impacted wisdom teeth over 20 years ago. They have gained increasing importance in regenerative medicine due to their multipotent differentiation capacity into osteoblasts, cementoblasts, and periodontal ligament fibroblasts, making them a promising candidate for the regeneration of the periodontal ligament in diseases such as periodontitis or alveolar bone defects, including the cultivation of artificial tooth roots through the targeted induction of cementum and bone formation. They modulate inflammatory microenvironments, reprogram immune cells such as macrophages, and significantly promote the regeneration of bone volume and soft tissue, as demonstrated by preclinical studies in animal models, despite potentially low survival rates after implantation. Tables 1 and 2 briefly summarize important contributions to tissue regeneration and immunomodulation with DFCs that have been discussed in this article. A major advantage of DFCs lies in their uncomplicated autologous harvesting from impacted wisdom teeth and their high proliferation capacity. However, in the future, therapies with non-autologous DFCs may also be possible, as has already been shown for dental pulp stem cells in a clinical study (Liu et al., 2025). Over the next decade, the prospect is for personalized therapies that combine DFCs with biomaterials (e.g., enriched with BMP−2), and 3D bioprinting (rapid prototyping) in periodontal and bone regeneration—including implantable artificial tooth roots. The integration of computer-assisted stem cell banking and treatment planning could po-tentially extend these therapies to a broader range of medical indications (Fig. 1).

Despite extensive global research since the initial isolation of human DFCs in 2005, the field remains almost in the preclinical stage. While the first clinical data—expected soon—are eagerly awaited and will yield important initial insights, they are also likely to highlight the significant translational challenges that lie ahead. A major obstacle is the inherent biological heterogeneity among individual isolates. Because these donor-specific differences persist, achieving true standardization of the manufacturing process is difficult; furthermore, standardized cultivation protocols are unlikely to fully overcome this fundamental biological limitation. Nevertheless, these challenges underscore the fact that robust basic research is more important than ever. Elucidating the fundamental cellular mechanisms and biological properties of DFCs provides the essential mechanistic understanding that will ultimately pave the way for the safe and successful development of future regenerative therapies.

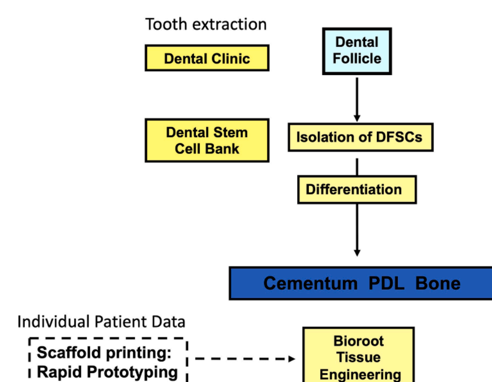

Fig. 1. Vision of a future therapy using isolated DFCs. For tissue engineering of bone replacements or biological roots, individual scaffolds are printed based on patient data, on which DFCs are specifically placed and differentiate into dental tissues for use in patients.

CRediT authorship contribution statement

Anja Reck: Writing – review & editing. **morsczeck christian:** Writing – review & editing, Writing – original draft, Conceptualization. **Torsten E. Reichert:** Writing – review & editing.

Funding

This article received no external funding.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Bai, Y., Bai, Y., Matsuzaka, K., Hashimoto, S., Kokubu, E., Wang, X., & Inoue, T. (2010). Formation of bone-like tissue by dental follicle cells co-cultured with dental papilla cells. *Cell and Tissue Research, 342*(2), 221–231. https://doi.org/10.1007/s00441-010-1046-9

Bastos, V. C., Gomez, R. S., & Gomes, C. C. (2022). Revisiting the human dental follicle: From tooth development to its association with unerupted or impacted teeth and pathological changes. *Dev Dyn, 251*(3), 408–423. https://doi.org/10.1002/dvdy.406

Bsoul, S., Terezhalmy, G., Abboud, H., Woodruff, K., & Abboud, S. L. (2003). PDGF BB and bFGF stimulate DNA synthesis and upregulate CSF-1 and MCP-1 gene expression in dental follicle cells. *Archives of Oral Biology, 48*(6), 459–465. https://doi.org/10.1016/s0003-9969(03)00084-0

De Pellegrin, M., Reck, A., & Morsczeck, C. (2024). Sclerostin inhibits Protein kinase C inhibitor GÖ6976 induced osteogenic differentiation of dental follicle cells. *Tissue & Cell, 90*, Article 102522. https://doi.org/10.1016/j.tice.2024.102522

D'Errico, J. A., MacNeil, R. L., Strayhorn, C. L., Piotrowski, B. T., & Somerman, M. J. (1995). Models for the study of cementogenesis. *Connective Tissue Research, 33*(1–3), 9–17. https://doi.org/10.3109/03008209509016975

Diekwisch, T. G. (2001). The developmental biology of cementum. *The International Journal of Developmental Biology, 45*(5–6), 695–706.

Dreanca, A., Sarosi, C., Parvu, A. E., Blidaru, M., Enacrachi, G., Purdoiu, R., Nagy, A., Sevastre, B., Oros, N. A., Marcus, I., & Moldovan, M. (2020). Systemic and Local Biocompatibility Assessment of Graphene Composite Dental Materials in Experimental Mandibular Bone Defect. *Materials, 13*(11), 2511. https://doi.org/10.3390/ma13112511

Ernst, W., Saugspier, M., Felthaus, O., Driemel, O., & Morsczeck, C. (2009). Comparison of murine dental follicle precursor and retinal progenitor cells after neural differentiation in vitro. *Cell Biology International, 33*(7), 758–764. https://doi.org/10.1016/j.cellbi.2009.04.005

Feng, G., Wu, Y., Yu, Y., Huang, L., An, S., Hu, B., Luo, J., & Song, J. (2018). Periodontal ligament-like tissue regeneration with drilled porous decalcified dentin matrix sheet composite. *Oral Diseases, 24*(3), 429–441. https://doi.org/10.1111/odi.12734

Fu, H., Sen, L., Zhang, F., Liu, S., Wang, M., Mi, H., Liu, M., Li, B., Peng, S., Hu, Z., Sun, J., & Li, R. (2023). Mesenchymal stem cells-derived extracellular vesicles protect against oxidative stress-induced xenogeneic biological root injury via adaptive regulation of the PI3K/Akt/NRF2 pathway. *Journal of Nanobiotechnology, 21*(1), 466. https://doi.org/10.1186/s12951-023-02214-5

Genc, D., Bulut, O., Gunaydin, B., Goksu, M., Duzgun, M., Dere, Y., Sezgin, S., Aladag, A., & Bulbul, A. (2022). Dental follicle mesenchymal stem cells ameliorated glandular dysfunction in Sjogren's syndrome murine model. *PloS One, 17*(5), Article e0266137. https://doi.org/10.1371/journal.pone.0266137

Gosau, M., Viale-Bouroncle, S., Eickhoff, H., Prateeptongkum, E., Reck, A., Götz, W., Klingelhöffer, C., Müller, S., & Morsczeck, C. (2015). Evaluation of implant-materials as cell carriers for dental stem cells under in vitro conditions. *International Journal of Implant Dentistry, 1*(1), 2. https://doi.org/10.1186/s40729-014-0002-y

Grier, R. L., Zhao, L., Adams, C. E., & Wise, G. E. (1998). Secretion of CSF-1 and its inhibition in rat dental follicle cells: Implications for tooth eruption. *European Journal of Oral Sciences, 106*(3), 808–815. https://doi.org/10.1046/j.0909-8836.1998.eos106307.x

Guo, W., He, Y., Zhang, X., Lu, W., Wang, C., Yu, H., Liu, Y., Li, Y., Zhou, Y., Zhou, J., Zhang, M., Deng, Z., & Jin, Y. (2009). The use of dentin matrix scaffold and dental follicle cells for dentin regeneration. *Biomaterials, 30*(35), 6708–6723. https://doi.org/10.1016/j.biomaterials.2009.08.034

Hakki, S. S., Berry, J. E., & Somerman, M. J. (2001). The effect of enamel matrix protein derivative on follicle cells in vitro. *Journal of Periodontology, 72*(5), 679–687. ⟨http://www.ncbi.nlm.nih.gov/pubmed/11394405⟩.

Handa, K., Saito, M., Tsunoda, A., Yamauchi, M., Hattori, S., Sato, S., Toyoda, M., Teranaka, T., & Narayanan, A. S. (2002). Progenitor cells from dental follicle are able to form cementum matrix in vivo. *Connect Tissue Research, 43*(2–3), 406–408.

Handa, K., Saito, M., Yamauchi, M., Kiyono, T., Sato, S., Teranaka, T., & Sampath Narayanan, A. (2002). Cementum matrix formation in vivo by cultured dental follicle cells. *Bone, 31*(5), 606–611.

He, X., Cheng, L., Zhang, X., Xiao, Q., Zhang, W., & Lu, C. (2015). Tissue engineering scaffolds electrospun from cotton cellulose. *Carbohydrate Polymers, 115*, 485–493. https://doi.org/10.1016/j.carbpol.2014.08.114

Heng, B. C., Gong, T., Wang, S., Lim, L. W., Wu, W., & Zhang, C. (2017). Decellularized Matrix Derived from Neural Differentiation of Embryonic Stem Cells Enhances the Neurogenic Potential of Dental Follicle Stem Cells. *Journal of Endodontics, 43*(3), 409–416. https://doi.org/10.1016/j.joen.2016.10.033

Hong, H., Chen, X., Li, K., Wang, N., Li, M., Yang, B., Yu, X., & Wei, X. (2020). Dental follicle stem cells rescue the regenerative capacity of inflamed rat dental pulp through a paracrine pathway. *Stem Cell Res Ther, 11*(1), 333. https://doi.org/10.1186/s13287-020-01841-1

Huang, Y. L., Liu, Q., Liu, L., Huo, F. J., Guo, S. J., & Tian, W. D. (2022). Lipopolysaccharide-Preconditioned Dental Follicle Stem Cells Derived Small Extracellular Vesicles Treating Periodontitis via Reactive Oxygen Species/ Mitogen-Activated Protein Kinase Signaling-Mediated Antioxidant Effect. *International Journal of Nanomedicine, 17*, 799–819. https://doi.org/10.2147/Ijn.S350869

Huang, Y., Li, M., Liu, Q., Song, L., Wang, Q., Ding, P., Tian, W., & Guo, S. (2024). Small extracellular vesicles derived from lipopolysaccharide-preconditioned dental follicle cells inhibit cell apoptosis and alveolar bone loss in periodontitis. *Archives of Oral Bio, 162*, Article 105964. https://doi.org/10.1016/j.archoralbio.2024.105964

Huang, Y., Liu, L., Liu, Q., Huo, F., Hu, X., Guo, S., & Tian, W. (2023). Dental follicle cells-derived small extracellular vesicles inhibit pathogenicity of Porphyromonas gingivalis. *Oral Diseases, 29*(5), 2297–2309. https://doi.org/10.1111/odi.14239

Ivanovski, S., Han, P., Peters, O. A., Sanz, M., & Bartold, P. M. (2024). The Therapeutic Use of Dental Mesenchymal Stem Cells in Human Clinical Trials. *Journal of Dental Research, 103*(12), 1173–1184. https://doi.org/10.1177/00220345241261900

Ji, L., Li, J., Liu, D., Qiao, Y., Zhao, W., Liu, Y., & Zheng, S. (2024). RUNX2 mutation inhibits the cellular senescence of dental follicle cells via ERK signalling pathway. *Oral Diseases, 30*(3), 1337–1349. https://doi.org/10.1111/odi.14607

Kawakami, M. (2000). Dental follicle cell-conditioned medium enhances the formation of osteoclast-like multinucleated cells. *The European Journal of Orthodontics, 22*(6), 675–682. https://doi.org/10.1093/ejo/22.6.675

Kemoun, P., Narayanan, A. S., Brunel, G., Salles, J. P., Laurencin-Dalicieux, S., Rue, J., Farges, J. C., Gennero, I., Conte-Auriol, F., Briand-Mesange, F., Gadelorge, M., & Arzate, H. (2007). Human dental follicle cells acquire cementoblast features under stimulation by BMP-2/-7 and enamel matrix derivatives (EMD) in vitro. *Cell Tissue Research, 329*(2), 283–294.

Khanna-Jain, R., Vuorinen, A., Sándor, G. K. B., Suuronen, R., & Miettinen, S. (2010). Vitamin D(3) metabolites induce osteogenic differentiation in human dental pulp and human dental follicle cells. *The Journal of Steroid Biochemistry and Molecular Biology, 122*(4), 133–141. https://doi.org/10.1016/j.jsbmb.2010.08.001

Kriebel, K., Hieke, C., Engelmann, R., Potempa, J., Müller-Hilke, B., Lang, H., & Kreikemeyer, B. (2018). ***Porphyromonas gingivalis*** Peptidyl Arginine Deiminase Can Modulate Neutrophil Activity via Infection of Human Dental Stem Cells. *Journal of Innate Immunity, 10*(4), 264–278. https://doi.org/10.1159/000489020

Lee, T.-P., Ho, M.-H., Chen, Y.-R., Lin, K.-M., & Li, C.-H. (2025). Induction of retinal progenitors and neurons from dental follicle stem cell under defined conditions. *Journal of Dental Sciences, 20*(3), 1629–1638. https://doi.org/10.1016/j.jds.2025.03.008

Li, H., Ma, B., Yang, H., Qiao, J., Tian, W., & Yu, R. (2021). Xenogeneic dentin matrix as a scaffold for biomineralization and induced odontogenesis. *Biomedical Materials (Bristol, England), 16*(4). https://doi.org/10.1088/1748-605X/abfbbe

Li, H., Sun, J., Li, J., Yang, H., Luo, X., Chen, J., Xie, L., Huo, F., Zhu, T., Guo, W., & Tian, W. (2017). Xenogeneic Bio-Root Prompts the Constructive Process Characterized by Macrophage Phenotype Polarization in Rodents and Nonhuman Primates. *Advanced Healthcare Materials, 6*(5). https://doi.org/10.1002/adhm.201601112

Li, J., Li, H., Tian, Y., Yang, Y., Chen, G., Guo, W., & Tian, W. (2016). Cytoskeletal binding proteins distinguish cultured dental follicle cells and periodontal ligament cells. *Experimental Cell Research, 345*(1), 6–16. https://doi.org/10.1016/j.yexcr.2015.12.011

Li, M., Fu, T., Yang, S., Pan, L., Tang, J., Chen, M., Liang, P., Gao, Z., & Guo, L. (2021). Agarose-based spheroid culture enhanced stemness and promoted odontogenic differentiation potential of human dental follicle cells in vitro. *Vitro Cellular & Developmental Biology Animal, 57*(6), 620–630. https://doi.org/10.1007/s11626-021-00591-5

Li, Q., Reed, D. A., Min, L., Gopinathan, G., Li, S., Dangaria, S. J., Li, L., Geng, Y., Galang, M.-T., Gajendrareddy, P., Zhou, Y., Luan, X., & Diekwisch, T. G. H. (2014). Lyophilized platelet-rich fibrin (PRF) promotes craniofacial bone regeneration through Runx2. *International Journal of Molecular Sciences, 15*(5), 8509–8525. https://doi.org/10.3390/ijms15058509

Li, X., Yang, C., Li, L., Xiong, J., Xie, L., Yang, B., Yu, M., Feng, L., Jiang, Z., Guo, W., & Tian, W. (2015). A therapeutic strategy for spinal cord defect: Human dental follicle cells combined with aligned PCL/PLGA electrospun material. *BioMed Research International, 2015*, Article 197183. https://doi.org/10.1155/2015/197183

Li, Z., Wang, D., Li, J., Liu, H., Nie, L., & Li, C. (2024). Bone Regeneration Facilitated by Autologous Bioscaffold Material: Liquid Phase of Concentrated Growth Factor with Dental Follicle Stem Cell Loading. *ACS Biomaterials Science & Engineering, 10*(5), 3173–3187. https://doi.org/10.1021/acsbiomaterials.3c01981

Liang, L., Wang, L., Liao, Z., Ma, L., Wang, P., Zhao, J., Wu, J., & Yang, H. (2024). High-yield nanovesicles extruded from dental follicle stem cells promote the regeneration of periodontal tissues as an alternative of exosomes. *Journal of Clinical Periodontology, 51*(10), 1395–1407. https://doi.org/10.1111/jcpe.14036

Lin, K.-M., Chen, Y.-R., Ho, M.-H., & Li, C.-H. (2025). The cell-fate decision of dental follicle stem cells (DFSCs) with porcine corneal extracellular matrix (ECM). *Journal of Dental Sciences, 20*(3), 1605–1614. https://doi.org/10.1016/j.jds.2025.02.019

Liu, Y., Liu, Y., Hu, J., Han, J., Song, L., Liu, X., Han, N., Xia, X., He, J., Meng, H., Wan, M., Wang, H., Liu, X., Gao, Z., Wang, X., Wu, C., & Wang, S. (2025). Impact of allogeneic dental pulp stem cell injection on tissue regeneration in periodontitis: A multicenter randomized clinical trial. *Signal Transduction and Targeted Therapy, 10* (1), 239. https://doi.org/10.1038/s41392-025-02320-w

Lucaciu, O., Soriţău, O., Gheban, D., Ciuca, D. R., Virtic, O., Vulpoi, A., Dirzu, N., Câmpian, R., Băciuţ, G., Popa, C., Simon, S., Berce, P., Băciuţ, M., & Crisan, B. (2015). Dental follicle stem cells in bone regeneration on titanium implants. *BMC Biotechnology, 15*, 114. https://doi.org/10.1186/s12896-015-0229-6

Ma, L. Y., Rao, N. Q., Jiang, H., Dai, Y. Z., Yang, S. T., Yang, H. F., & Hu, J. T. (2022). Small extracellular vesicles from dental follicle stem cells provide biochemical cues for periodontal tissue regeneration. *Stem Cell Res Ther, 13*(1). https://doi.org/10.1186/s13287-022-02767-6

MacNeil, R. L., Berry, J., D'Errico, J., Strayhorn, C., Piotrowski, B., & Somerman, M. J. (1995). Role of two mineral-associated adhesion molecules, osteopontin and bone sialoprotein, during cementogenesis. *Connective Tissue Research, 33*(1–3), 1–7. https://doi.org/10.3109/03008209509016974

MacNeil, R. L., Berry, J., D'Errico, J., Strayhorn, C., & Somerman, M. J. (1995). Localization and expression of osteopontin in mineralized and nonmineralized tissues of the periodontium. *Annals of the New York Academy of Sciences, 760*, 166–176. https://doi.org/10.1111/j.1749-6632.1995.tb44628.x

Marks, S. C., Cahill, D. R., & Wise, G. E. (1983). The cytology of the dental follicle and adjacent alveolar bone during tooth eruption in the dog. *The American Journal of Anatomy, 168*(3), 277–289.

Marks, S. C., Jr, & Cahill, D. R. (1984). Experimental study in the dog of the non-active role of the tooth in the eruptive process. *Archives of Oral Biology, 29*(4), 311–322.

Meng, Z., Liu, J., Feng, Z., Guo, S., Wang, M., Wang, Z., Li, Z., Li, H., & Sui, L. (2022). N-acetylcysteine regulates dental follicle stem cell osteogenesis and alveolar bone repair via ROS scavenging. *Stem Cell Research & Therapy, 13*(1), 466. https://doi.org/10.1186/s13287-022-03161-y

Morsczeck, C. (2006). Gene expression of runx2, Osterix, c-fos, DLX-3, DLX-5, and MSX-2 in dental follicle cells during osteogenic differentiation in vitro. *Calcified Tissue International, 78*(2), 98–102. ⟨http://www.ncbi.nlm.nih.gov/pubmed/16467978⟩.

Morsczeck, C. (2022). Mechanisms during Osteogenic Differentiation in Human Dental Follicle Cells. *Int J Mol Sci, 23*(11). https://doi.org/10.3390/ijms23115945

Morsczeck, C., De Pellegrin, M., Reck, A., & Reichert, T. E. (2023). Evaluation of Current Studies to Elucidate Processes in Dental Follicle Cells Driving Osteogenic Differentiation. *Biomedicines, 11*(10), 2787. https://doi.org/10.3390/biomedicines11102787

Morsczeck, C., Gotz, W., Schierholz, J., Zeilhofer, F., Kuhn, U., Mohl, C., Sippel, C., & Hoffmann, K. H. (2005). Isolation of precursor cells (PCs) from human dental follicle of wisdom teeth. *Matrix Biol, 24*(2), 155–165.

Morsczeck, C., Moehl, C., Gotz, W., Heredia, A., Schaffer, T. E., Eckstein, N., Sippel, C., & Hoffmann, K. H. (2005). vitro differentiation of human dental follicle cells with dexamethasone and insulin. *Cell Biology International, 29*(7), 567–575.

Morsczeck, C., Petersen, J., Völlner, F., Driemel, O., Reichert, T., & Beck, H. C. (2009). Proteomic analysis of osteogenic differentiation of dental follicle precursor cells. *Electrophoresis, 30*(7), 1175–1184.

Morsczeck, C., Reck, A., De Pellegrin, M., & Reichert, T. E. (2026). Inhibition of protein kinase C activity enables mineralization of senescent dental follicle cells with almost no osteogenic differentiation potential. *Archives of Oral Biology, 182*, Article 106468. https://doi.org/10.1016/j.archoralbio.2025.106468

Morsczeck, C., Schmalz, G., Reichert, T. E., Völlner, F., Saugspier, M., Viale-Bouroncle, S., & Driemel, O. (2009). Gene expression profiles of dental follicle cells before and after osteogenic differentiation in vitro. *Clinical Oral Investigations, 13*(4), 383–391. https://doi.org/10.1007/s00784-009-0260-x

Muresan, C. G., Mirica, I. C., Forray, A., Petrescu, N., Soritau, O., Gherman, L.-M., Iusan, S. A. L., Vanea, E., Oprita, E., Condor, A., Aluas, M., Mihu, C. M., Boşca, B. A., Mocan, L. P., Onofrei, M. M., Pop, R. M., Andone, B.-A., Barbu-Tudoran, L., Boca, S., … Lucaciu, P. O. (2025). Vitamin D-Loaded Chitosan Nanostructures for Bone Regeneration: A Combined In Vitro and In Vivo Evaluation in an Osteoporotic Rat Model. *Medicina, 62*(1), 73. https://doi.org/10.3390/medicina62010073

Nagasaki, K., Chavez, M. B., Nagasaki, A., Taylor, J. M., Tan, M. H., Ma, M., Ralston, E., Thew, M. E., Kim, D.-G., Somerman, M. J., & Foster, B. L. (2022). The Bone Sialoprotein RGD Domain Modulates and Maintains Periodontal Development. *Journal of Dental Research, 101*(10), 1238–1247. https://doi.org/10.1177/00220345221100794

Nivedhitha Sundaram, M., Sowmya, S., Deepthi, S., Bumgardener, J. D., & Jayakumar, R. (2016). Bilayered construct for simultaneous regeneration of alveolar bone and periodontal ligament. *Journal of Biomedical Materials Research Part B, Applied Biomaterials, 104*(4), 761–770. https://doi.org/10.1002/jbm.b.33480

Okada, H., Takahashi, K., Ogura, N., Tomoki, R., Ito, K., & Kondoh, T. (2016). Plasma rich in growth factors stimulates proliferation, migration, and gene expression associated with bone formation in human dental follicle cells. *Journal of Dental Sciences, 11*(3), 245–252. https://doi.org/10.1016/j.jds.2015.12.001

Olteanu, D., Filip, A., Socaci, C., Biris, A. R., Filip, X., Coros, M., Rosu, M. C., Pogacean, F., Alb, C., Baldea, I., Bolfa, P., & Pruneanu, S. (2015). Cytotoxicity assessment of graphene-based nanomaterials on human dental follicle stem cells. *Colloids and Surfaces B, Biointerfaces, 136*, 791–798. https://doi.org/10.1016/j.colsurfb.2015.10.023

Pieles, O., Reichert, T. E., & Morsczeck, C. (2021). Classical isoforms of protein kinase C (PKC) and Akt regulate the osteogenic differentiation of human dental follicle cells via both β-catenin and NF-κB. *Stem Cell Research & Therapy, 12*(1), 242. https://doi.org/10.1186/s13287-021-02313-w

Que, B. G., Lumpkin, S. J., & Wise, G. E. (1999). Implications for tooth eruption of the effect of interleukin-1alpha on nuclear factor-kappaB gene expression in the rat dental follicle. *Archives of Oral Biology, 44*(11), 961–967. https://doi.org/10.1016/s0003-9969(99)00071-0

Sarviya, N., Basu, S. M., Mani, R., Chauhan, M., Kingshott, P., & Giri, J. (2022). Biomimicking nanofibrous gelatin microspheres recreating the stem cell niche for their ex-vivo expansion and in-vivo like differentiation for injectable stem cell transplantation. *Biomaterials Advances, 139*, Article 212981. https://doi.org/10.1016/j.bioadv.2022.212981

Saugspier, M., Felthaus, O., Viale-Bouroncle, S., Driemel, O., Reichert, T. E., Schmalz, G., & Morsczeck, C. (2010). The differentiation and gene expression profile of human dental follicle cells. *Stem Cells and Development, 19*(5), 707–717. https://doi.org/10.1089/scd.2009.0027

Song, W.-P., Jin, L.-Y., Zhu, M.-D., Wang, H., & Xia, D.-S. (2023). Clinical trials using dental stem cells: 2022 update. *World Journal of Stem Cells, 15*(3), 31–51. https://doi.org/10.4252/wjsc.v15.i3.31

Sonoyama, W., Liu, Y., Fang, D., Yamaza, T., Seo, B. M., Zhang, C., Liu, H., Gronthos, S., Shi, S., Wang, S., & Wang, C. Y. (2006). Mesenchymal stem cell-mediated functional tooth regeneration in swine. *PLoS One, 1*, Article 17183711.

Sun, M., Yu, Y., Zhang, W., Ding, Y., Li, A., & Li, Y. (2024). Extracellular vesicles derived from dental follicle stem cells regulate tooth eruption by inhibiting osteoclast differentiation. *Frontiers in Cell and Developmental Biology, 12*, Article 1503481. https://doi.org/10.3389/fcell.2024.1503481

Tian, J., Lou, Y., Li, M., Duan, Y., Liu, H., Chen, C., Qiu, Y., Chen, W., Pang, C., Xiong, Y., Shen, Y., & Wei, X. (2025). Dental follicle stem cell-derived small extracellular vesicles ameliorate pulpitis by reprogramming macrophage metabolism. *Bioactive Materials, 51*, 179–196. https://doi.org/10.1016/j.bioactmat.2025.04.034

Topcu Sarica, L., Zibandeh, N., Genc, D., Gul, F., Akkoc, T., Kombak, E. F., Cinel, L., Akkoc, T., & Cinel, I. (2020). Immunomodulatory and tissue-preserving effects of human dental follicle stem cells in a rat cecal ligation and perforation sepsis model. *Archives of Medical, 51*(5), 397–405. https://doi.org/10.1016/j.arcmed.2020.04.010

Tsuchiya, S., Honda, M. J., Shinohara, Y., Saito, M., & Ueda, M. (2008). Collagen type I matrix affects molecular and cellular behavior of purified porcine dental follicle cells. *Cell Tissue Research, 331*(2), 447–459.

Uribe, P., Johansson, A., Jugdaohsingh, R., Powell, J. J., Magnusson, C., Davila, M., Westerlund, A., & Ransjö, M. (2020). Soluble silica stimulates osteogenic differentiation and gap junction communication in human dental follicle cells. *Scientific Reports, 10*(1), 9923. https://doi.org/10.1038/s41598-020-66939-1

Viale-Bouroncle, S., Bey, B., Reichert, T. E., Schmalz, G., & Morsczeck, C. (2011). β-tricalcium-phosphate stimulates the differentiation of dental follicle cells. *Journal of Materials Science Materials in Medicine, 22*(7), 1719–1724. https://doi.org/10.1007/s10856-011-4345-0

Viale-Bouroncle, S., Buergers, R., Morsczeck, C., & Gosau, M. (2013). β-Tricalcium Phosphate Induces Apoptosis on Dental Follicle Cells. *Calcified Tissue International, 92*(5), 412–417. https://doi.org/10.1007/s00223-012-9694-2

Viale-Bouroncle, S., Gosau, M., & Morsczeck, C. (2014). Collagen I induces the expression of alkaline phosphatase and osteopontin via independent activations of FAK and ERK signalling pathways. *Archives of Oral Biology, 59*(12), 1249–1255. https://doi.org/10.1016/j.archoralbio.2014.07.013

Viale-Bouroncle, S., Völlner, F., Möhl, C., Küpper, K., Brockhoff, G., Reichert, T. E., Schmalz, G., & Morsczeck, C. (2011). Soft matrix supports osteogenic differentiation of human dental follicle cells. *Biochemical and Biophysical Research Communications, 410*(3), 587–592. https://doi.org/10.1016/j.bbrc.2011.06.031

Völlner, F., Ernst, W., Driemel, O., & Morsczeck, C. (2009). A two-step strategy for neuronal differentiation in vitro of human dental follicle cells. *Differentiation; Research in Biological Diversity, 77*(5), 433–441.

Wen, X., Jiang, W., Li, X., Liu, Q., Kang, Y., & Song, B. (2024). Advancements in Spinal Cord Injury Repair: Insights from Dental-Derived Stem Cells. *Biomedicines, 12*(3), 683. https://doi.org/10.3390/biomedicines12030683

Wise, G. E. (2009). Cellular and molecular basis of tooth eruption. *Orthodontics & Craniofacial Research, 12*(2), 67–73. https://doi.org/10.1111/j.1601-6343.2009.01439.x

Wise, G. E., Frazier-Bowers, S., & D'Souza, R. N. (2002). Cellular, molecular, and genetic determinants of tooth eruption. *Critical Reviews in Oral Biology and Medicine: An Official Publication of the American Association of Oral Biologists, 13*(4), 323–334.

Wise, G. E., Lin, F., & Fan, W. (1992). Culture and characterization of dental follicle cells from rat molars. *Cell and Tissue Research, 267*(3), 483–492.

Wise, G. E., Marks, S. C., & Cahill, D. R. (1985). Ultrastructural features of the dental follicle associated with formation of the tooth eruption pathway in the dog. *Journal of Oral Pathology, 14*(1), 15–26. https://doi.org/10.1111/j.1600-0714.1985.tb00461.x

Wise, G. E., Que, B. G., & Huang, H. (1999). Synthesis and secretion of MCP-1 by dental follicle cells—Implications for tooth eruption. *Journal of Dental Research, 78*(11), 1677–1681.

Wise, G. E., Que, B. G., Huang, H., & Lumpkin, S. J. (2000). Enhancement of gene expression in rat dental follicle cells by parathyroid hormone-related protein. *Archives of Oral Biology, 45*(10), 903–909. https://doi.org/10.1016/s0003-9969(00)00053-4

Wise, G. E., & Yao, S. (2006). Regional differences of expression of bone morphogenetic protein-2 and RANKL in the rat dental follicle. *European Journal of Oral Sciences, 114* (6), 512–516. https://doi.org/10.1111/j.1600-0722.2006.00406.x

Wu, J., Jin, F., Tang, L., Yu, J., Xu, L., Yang, Z., Wu, G., Duan, Y., & Jin, Y. (2008). Dentin non-collagenous proteins (dNCPs) can stimulate dental follicle cells to differentiate into cementoblast lineages. *Biology of the Cell, 100*(5), 291–302. https://doi.org/10.1042/BC20070092

Xu, L.-L., Liu, H.-C., Wang, D.-S., E, L.-L., Xu, L., Jin, Z.-L., & Duan, Y.-Z. (2009). Effects of BMP-2 and dexamethasone on osteogenic differentiation of rat dental follicle

progenitor cells seeded on three-dimensional beta-TCP. *Biomedical Materials (Bristol, England), 4*(6), Article 065010. https://doi.org/10.1088/1748-6041/4/6/065010

Yang, B., Yang, X. T., Luo, X. Y., Chen, G., Chen, J. L., Huo, F. J., Zhu, Z. L., Tian, Y., Guo, W. H., & Tian, W. D. (2023). DFCs/TDM based artificial bio-root to obtain long-term functional root regeneration in non-human primate. *Chemical Engineering Journal, 451*. https://doi.org/10.1016/j.cej.2022.138738

Yao, S., Norton, J., & Wise, G. E. (2004). Stability of cultured dental follicle cells. *Cell Proliferation, 37*(3), 247–254. https://doi.org/10.1111/j.1365-2184.2004.00309.x

Yao, S., & Wise, G. E. (2003a). Protein kinase A expression and its possible roles in regulating tooth eruption genes in the dental follicle. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research, 9*(5), 160–167.

Yao, S., & Wise, G. E. (2003b). Regulation of gene expression of tumour necrosis factor-α by protein kinase C in the rat dental follicle. *Archives of Oral Biology, 48*(9), 643–648. https://doi.org/10.1016/S0003-9969(03)00115-8

Yi, G., Zhang, S., Ma, Y., Yang, X., Huo, F., Chen, Y., Yang, B., & Tian, W. (2022). Matrix vesicles from dental follicle cells improve alveolar bone regeneration via activation of the PLC/PKC/MAPK pathway. *Stem Cell Res Ther, 13*(1), 41. https://doi.org/10.1186/s13287-022-02721-6

Zhang, J., Lan, T., Han, X., Xu, Y., Liao, L., Xie, L., Yang, B., Tian, W., & Guo, W. (2021). Improvement of ECM-based bioroot regeneration via N-acetylcysteine-induced antioxidative effects. *Stem Cell Research & Therapy, 12*(1), 202. https://doi.org/10.1186/s13287-021-02237-5

Zhang, J., Liao, L., Li, Y., Xu, Y., Guo, W., Tian, W., & Zou, S. (2019). Parathyroid hormone-related peptide (1-34) promotes tooth eruption and inhibits osteogenesis of dental follicle cells during tooth development. *Journal of Cellular Physiology, 234*(7), 11900–11911. https://doi.org/10.1002/jcp.27857

Zhang, X.-H., Wang, H., Cao, Y., Liu, L., Zhang, Z.-Q., Liu, J.-N., Mu, S.-H., Yuan, Y., Cai, X.-Y., Sui, B.-D., Zheng, C.-X., Xu, H.-K., Jin, F., & Lei, X. (2025). Optimizing natural human-derived decellularized tissue materials for periodontal bone defect repair. *Biochemical and Biophysical Research Communications, 748*, Article 151297. https://doi.org/10.1016/j.bbrc.2025.151297

Zhao, M., Jin, Q., Berry, J. E., Nociti, F. H., Giannobile, W. V., & Somerman, M. J. (2004). Cementoblast delivery for periodontal tissue engineering. *Journal of Periodontology, 75*(1), 154–161. https://doi.org/10.1902/jop.2004.75.1.154

Zhao, M., Xiao, G., Berry, J. E., Franceschi, R. T., Reddi, A., & Somerman, M. J. (2002). Bone morphogenetic protein 2 induces dental follicle cells to differentiate toward a cementoblast/osteoblast phenotype. *Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research, 17*(8), 1441–1451. https://doi.org/10.1359/jbmr.2002.17.8.1441

Zhou, T., Pan, J. H., Wu, P. Y., Huang, R. J., Du, W., Zhou, Y. C., Wan, M., Fan, Y., Xu, X., Zhou, X. D., Zheng, L. W., & Zhou, X. (2019). Dental Follicle Cells: Roles in Development and Beyond. *Stem Cells International, 2019*. https://doi.org/10.1155/2019/9159605

Zibandeh, N., Genç, D., Duran, Y., Banzragch, M., Sokwala, S., Göker, K., Atug, O., & Akkoç, T. (2020). Human dental follicle mesenchymal stem cells alleviate T cell response in inflamed tissue of Crohn's patients. *Turkish Journal of Gastroenterology, 31*(5), 400–409. https://doi.org/10.5152/tjg.2020.19358