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Calcium Signaling and Growth Factors in Oral Tissue Homeostasis and Regeneration: A Narrative Review

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ABSTRACT

Background: Calcium ions (Ca^{2+}) function not only as structural components of mineralized tissues but also as intracellular signaling molecules involved in proliferation, migration, differentiation, and tissue repair. Their relationship with growth-factor signaling in oral tissue regeneration remains insufficiently understood.

Objective: This narrative review aimed to summarize evidence on calcium signaling and growth-factor pathways in oral tissue homeostasis and regeneration, with emphasis on their potential signaling convergence.

Methods: Literature was identified through Scopus using keywords related to calcium signaling, calcium dynamics, growth factors, oral tissue regeneration, dental pulp, dentin, periodontal tissues, and oral wound healing. Original research articles were prioritized, while review articles were used for contextual background. Studies were qualitatively synthesized according to signaling mechanisms and regenerative outcomes.

Results: Experimental studies indicate functional associations between calcium signaling and growth-factor pathways in oral regeneration. Calcium silicate-based materials were associated with FGFR/ERK signaling and odontogenic differentiation, while calcium dynamics induced by tricalcium silicate-based cements were associated with TGF-β/BMP2 expression and mineralization. FGF-2 regulated dental pulp-cell proliferation, migration, and mineralizing differentiation. Calcium-regulated signaling was also implicated in oral wound healing through modulation of keratinocyte behavior and Wnt signaling. However, direct molecular evidence of calcium–growth factor crosstalk remains limited.

Conclusion: Calcium signaling may function as an important regulatory component of oral tissue regeneration and may converge with growth-factor pathways to coordinate cellular responses. Further mechanistic studies are needed to establish causal interactions and their therapeutic potential in regenerative dentistry.

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INTRODUCTION

Oral tissues are continuously exposed to mechanical, microbial, and chemical challenges that require tightly regulated mechanisms to maintain tissue integrity and function. Homeostasis within the oral cavity depends on coordinated interactions among epithelial

cells, fibroblasts, immune cells, endothelial cells, mesenchymal stem/progenitor cells, and mineralized tissue-forming cells. Following tissue injury, these cellular populations must sequentially and coordinately regulate inflammation, proliferation, migration, differentiation, extracellular matrix deposition, angiogenesis, and, in mineralized tissues, matrix mineralization. These processes are not controlled by a single signaling pathway but rather by a complex network of extracellular mediators and intracellular signaling mechanisms. Among these, growth factors and calcium-dependent signaling have emerged as important regulators of oral tissue homeostasis, repair, and regeneration [1–3]. Growth factors are extracellular signaling proteins that regulate fundamental cellular processes, including proliferation, migration, differentiation, survival, extracellular matrix production, and tissue remodeling. Several growth-factor families, including transforming growth factor-beta (TGF-β), bone morphogenetic proteins (BMPs), fibroblast growth factors (FGFs), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF), have been implicated in the maintenance and regeneration of oral tissues [1,2]. In regenerative dentistry, these factors have been investigated in periodontal regeneration, dental pulp repair, dentinogenesis, alveolar bone regeneration, wound healing, and implant osseointegration. Recent evidence indicates that growth-factor-based approaches may facilitate tissue repair by modulating cell recruitment, proliferation, differentiation, angiogenesis, and extracellular matrix remodeling [1,4]. In particular, FGF-2 has been shown experimentally to regulate the behavior of human dental pulp cells, supporting its potential role in dentin-pulp complex repair [5].

The biological effects of growth factors, however, do not occur independently of intracellular second-messenger systems. Calcium ions (Ca^{2+}), traditionally recognized as structural components of mineralized tissues, also function as highly versatile intracellular signaling molecules. Changes in intracellular Ca^{2+} concentration, amplitude, frequency, and duration can encode extracellular stimuli and regulate diverse cellular processes, including proliferation, migration, differentiation, cytoskeletal organization, gene transcription, secretion, and cell survival. Therefore, calcium should not be regarded solely as a passive mineral substrate but also as an active signaling mediator capable of translating extracellular environmental cues into cellular responses. This signaling function is particularly relevant to oral tissues because calcium is abundant within the extracellular environment of mineralized tissues and is released during tissue injury, demineralization, and interaction with calcium-containing biomaterials. Dental pulp cells and dental pulp stem cells are capable of sensing changes in extracellular calcium and responding through intracellular calcium signaling. In regenerative endodontics, calcium-releasing materials such as tricalcium silicate-based cements have attracted considerable interest because they provide both a source of mineral ions and a biologically active microenvironment. Experimental evidence demonstrates that calcium released from tricalcium silicate-based materials can alter intracellular Ca^{2+} dynamics in human dental pulp stem cells and is associated with changes in genes related to mineralization and tissue regeneration, including TGF-β and BMP2 [6]. Importantly, the relationship between calcium signaling and growth factors appears to be bidirectional rather than independent. Growth-factor receptors can activate intracellular signaling cascades that converge on calcium-dependent mechanisms, whereas changes in intracellular Ca^{2+} can modulate downstream pathways involved in growth-factor-mediated cellular responses. Several signaling pathways relevant to oral regeneration—including mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), protein kinase C (PKC), calcium/calmodulin-dependent protein kinases, and nuclear factor of activated T cells (NFAT)—provide potential points of convergence between extracellular growth-factor stimulation and calcium signaling. Through these interactions, cells may integrate biochemical signals from growth factors with ionic signals originating from the extracellular microenvironment. More direct evidence for calcium-mediated regulation of regenerative signaling has emerged from studies using calcium-releasing dental biomaterials. Rathinam et al. investigated human dental pulp stem cells stimulated with tricalcium silicate-based materials and simultaneously evaluated extracellular calcium concentration, intracellular Ca^{2+} dynamics, gene expression, cytotoxicity, and mineralization [6]. The study demonstrated that biomaterial-induced calcium responses were associated with changes in regenerative and mineralization-related markers, including TGF-β and BMP2, together with Alizarin Red and Von Kossa-positive mineral deposition [6]. These findings provide an important mechanistic basis for considering Ca^{2+} not merely as a component of mineralized matrix formation but as a signaling cue that may influence growth-factor-related regenerative responses. The interaction between calcium signaling and other developmental pathways further supports the concept of signaling crosstalk in oral regeneration. Wnt signaling, for example, plays important roles in tooth development, dental pulp homeostasis, stem-cell maintenance, and dentin regeneration [7]. Calcium-dependent signaling may influence several of these cellular behaviors through regulation of cytoskeletal dynamics, adhesion, migration, and gene transcription. Consequently, the local regenerative microenvironment may provide simultaneous protein-mediated and ion-mediated signals that determine the magnitude and direction of cellular responses.

Nevertheless, the existing literature remains fragmented. Most studies have focused either on the biological effects of individual growth factors or on the mineralizing and regenerative properties of calcium-containing materials. Reviews of growth factors in oral regeneration have extensively discussed TGF-β, BMPs, FGFs, VEGF, PDGF, and related signaling molecules [2–4], while other reviews have focused on Wnt signaling and dental pulp regeneration [7]. However, the mechanistic relationship between calcium signaling and growth-factor pathways across different oral tissues has received comparatively less integrated attention. Importantly, evidence from original research suggests that calcium dynamics can be associated with changes in regenerative growth-factor pathways, providing a rationale for examining these signaling systems together [5,6]. Therefore, this narrative review aims to

synthesize current evidence regarding the roles of calcium signaling and growth factors in oral tissue homeostasis and regeneration, with particular emphasis on their molecular interactions and potential points of pathway convergence. Finally, the potential therapeutic implications of integrating calcium-mediated and growth-factor-mediated signals in regenerative dentistry will be discussed, together with current knowledge gaps and future directions for translational research.

METHODS

This study employed a narrative review approach to summarize and critically analyze current evidence regarding the roles and potential interplay of calcium signaling and growth factor-mediated pathways in oral tissue homeostasis and regeneration. Relevant literature was identified through searches of the Scopus databases using combinations of keywords related to calcium signaling, growth factors, oral tissues, and tissue regeneration. The primary search terms included *calcium signaling*, *Ca2+ signaling*, *intracellular calcium*, *calcium dynamics*, *calcium-releasing materials*, *calcium silicate*, *growth factors*, *growth factor signaling*, *oral tissue regeneration*, *oral mucosa*, *dental pulp*, *dental pulp stem cells*, *dentin regeneration*, *periodontal tissue*, *periodontal ligament*, *alveolar bone*, and *oral wound healing*. Additional relevant articles were identified by screening the reference lists of key publications.

Peer-reviewed original research articles investigating calcium-related signaling, growth-factor pathways, or their potential convergence in oral tissues were prioritized as the primary evidence for this review. Experimental studies using relevant cellular, animal, or tissue models were considered eligible when they evaluated molecular signaling, cellular responses, tissue repair, differentiation, mineralization, or regeneration. Review articles were used selectively to provide conceptual background, identify relevant signaling pathways, and contextualize findings from original research studies. Duplicate, non-English, and publications unrelated to calcium signaling, growth-factor pathways, or oral tissue homeostasis and regeneration were excluded.

The selected literature was analyzed qualitatively and synthesized according to the major themes of the review. These themes included: (1) the fundamental mechanisms of calcium sensing and intracellular Ca2+ signaling; (2) growth-factor signaling pathways involved in oral tissue homeostasis and regeneration; (3) the convergence and potential crosstalk between calcium signaling and growth-factor pathways, including TGF-β/BMP, FGF/FGFR, EGF/EGFR, VEGF/VEGFR, and PDGF/PDGFR signaling; (4) the role of these signaling networks in dental pulp–dentin, periodontal tissues, alveolar bone, and oral mucosal regeneration; and (5) the therapeutic implications of calcium-containing or calcium-releasing biomaterials and growth-factor-based strategies for regenerative dentistry. Particular attention was given to distinguishing direct experimental evidence of calcium–growth factor interactions from indirect evidence involving shared downstream signaling pathways or functional associations.

RESULT AND DISCUSSION

Several original research studies demonstrated associations between calcium-containing or calcium-releasing stimuli and growth factor-related signaling, particularly involving FGFR/ERK, TGF-β/BMP, and other intracellular pathways regulating cell proliferation, migration, differentiation, and mineralization. However, the strength of evidence varied among studies, with some demonstrating a direct mechanistic relationship between calcium-related signals and growth factor pathways, whereas others provided indirect evidence through shared downstream signaling or regenerative outcomes. The main experimental findings are summarized in Table 1.

Tabel 1. Summarized Data Extraction

No.	Reference/ year	Experimental Model	Calcium-Related Component	Growth Factor / Receptor	Main Finding	Relevance
1	Liu et al. — *Odontogenic differentiation of human dental pulp cells by calcium silicate materials stimulating via FGFR/ERK signaling pathway/ 2014*	Human dental pulp cells	Calcium silicate materials	FGFR	Calcium silicate materials stimulated FGFR-related signaling and enhanced odontogenic differentiation and mineralized matrix formation.	High, direct connection between calcium-containing material and growth-factor receptor signaling

2	Shimabukuro et al. — *Fibroblast Growth Factor-2 Regulates the Cell Function of Human Dental Pulp Cells/ 2009*	Human dental pulp cells	Calcium deposition/ mineralization	FGF-2	FGF-2 regulated proliferation and migration and affected the timing of odontogenic differentiation and calcified nodule formation.	High, links FGF signaling with mineralization in dental pulp
3	Rathinam et al. — *The calcium dynamics of human dental pulp stem cells stimulated with tricalcium silicate-based cements determine their differentiation and mineralization outcome/ 2021*	Human dental pulp stem cells	Extracellular and intracellular Ca^{2+} dynamics	TGF-β, BMP2	Calcium stimulation altered intracellular Ca^{2+} dynamics and regenerative/mineralization-related gene expression, including TGF-β and BMP2, with subsequent mineral deposition.	Very high, strongest evidence for calcium signaling associated with growth-factor pathways
4	Lin et al. — *Platelet-derived growth factor-B gene delivery sustains gingival fibroblast signal transduction/ 2008*	Gingival fibroblasts	—	PDGF-B	PDGF-B gene delivery sustained growth-factor signal transduction in gingival fibroblasts and promoted a regenerative cellular response.	Moderate, useful for periodontal growth-factor signaling, but calcium link is indirect
5	Park et al. — *Bone morphogenetic protein-2 associated multiple growth factor delivery for bone tissue regeneration/ 2018*	Experimental bone-regeneration model	—	BMP-2 + multiple growth factors	Combined growth-factor delivery enhanced bone tissue regeneration compared with individual factor approaches.	Moderate, supports coordinated signaling in mineralized tissue regeneration
6	Li et al. — *DAPK1 Ablation Promotes Wound Healing by Keratinocyte Modulation/ 2026*	Oral keratinocytes and experimental oral wound model	Ca^{2+}/calmodulin-regulated DAPK1	Wnt signaling	DAPK1 ablation enhanced keratinocyte proliferation/migration and accelerated oral wound healing while modulating Wnt signaling.	High for calcium signaling, but not a classical growth-factor study

Several original research studies demonstrate that calcium-related signals and growth-factor pathways are functionally interconnected in oral tissue homeostasis and regeneration. The strongest evidence was observed in dental pulp and dentin regeneration, where calcium-containing or calcium-releasing materials were associated with activation of growth-factor-related

signaling pathways and subsequent odontogenic differentiation. Additional evidence from oral mucosal wound healing and periodontal tissues indicates that calcium-dependent intracellular signaling and growth-factor-mediated responses may contribute to cellular proliferation, migration, differentiation, and tissue repair. However, the available evidence remains heterogeneous, and direct mechanistic evidence of calcium–growth factor crosstalk in oral tissues is still limited.

The strongest evidence for an association between calcium-related stimuli and growth factor signaling in oral tissue regeneration comes from studies of dental pulp and dentin. Liu et al. demonstrated that calcium silicate materials promoted odontogenic differentiation of human dental pulp cells and were associated with activation of fibroblast growth factor receptor (FGFR)-related signaling, particularly the ERK/MAPK and p38 pathways [11]. These findings suggest that calcium-containing biomaterials may function as more than passive sources of mineral ions; rather, they may create a bioactive microenvironment capable of modulating growth-factor receptor-associated signaling. Nevertheless, this study should not be interpreted as definitive evidence that extracellular Ca^{2+} directly activates FGFR, because calcium silicate materials can simultaneously alter pH, ionic composition, and other physicochemical properties of the cellular environment. Thus, the findings are better interpreted as evidence of functional convergence between calcium-containing biomaterials and growth-factor-related signaling.

This concept is further strengthened by the work of Rathinam et al., who directly investigated calcium dynamics in human dental pulp stem cells exposed to tricalcium silicate-based cements [12]. The study demonstrated that different calcium-silicate materials produced distinct extracellular calcium concentrations and intracellular Ca^{2+} responses. Importantly, changes in intracellular calcium dynamics were associated with alterations in regenerative and mineralization-related gene expression, including TGF-β and BMP2, as well as subsequent mineral deposition [12]. These findings support the concept that Ca^{2+} acts as an active signaling mediator rather than merely serving as a structural component of mineralized matrix. However, because the study primarily demonstrated an association between altered calcium dynamics and TGF-β/BMP2 expression, it does not establish that these growth factors are direct downstream targets of Ca^{2+} signaling. Instead, the findings suggest that calcium signaling and growth-factor-associated pathways may converge during odontogenic differentiation and mineralization. This distinction is important because it prevents an overinterpretation of the current evidence while still supporting the biological rationale for calcium–growth factor interaction.

The relationship between growth-factor signaling and mineralization is also supported by Shimabukuro et al., who investigated the effects of FGF-2 on human dental pulp cells [13]. FGF-2 enhanced cellular proliferation and migration but initially suppressed alkaline phosphatase activity and calcified nodule formation. Interestingly, following withdrawal of FGF-2, pretreated cells subsequently demonstrated increased alkaline phosphatase activity and calcified nodule formation [13]. These findings indicate that FGF-2 may regulate the temporal sequence of pulp-cell responses, initially supporting proliferation and migration before allowing progression toward differentiation and mineralization. Although intracellular calcium signaling was not directly investigated in this study, the findings provide an important functional connection between growth-factor activity and calcium-dependent mineralization processes in the dentin-pulp complex. This temporal relationship may be particularly relevant during regeneration, in which cellular recruitment and proliferation must precede organized extracellular matrix formation and mineral deposition.

Evidence from oral mucosal healing further expands the potential role of calcium-related signaling beyond mineralized tissues. Li et al. recently demonstrated that DAPK1, a Ca^{2+}/calmodulin-regulated kinase, participates in oral wound healing through modulation of keratinocyte behavior [14]. DAPK1 ablation enhanced keratinocyte proliferation and migration and accelerated oral wound closure, while transcriptomic analyses indicated modulation of Wnt-related signaling. Although Wnt is not a classical growth factor, this study illustrates how a calcium-regulated intracellular signaling component can interact with another major regenerative signaling network to influence tissue repair. These findings suggest that the biological significance of calcium signaling extends beyond mineralization and may include regulation of soft-tissue homeostasis, epithelial migration, and wound closure. The observation is particularly relevant to oral tissues, where epithelial and mesenchymal cells must rapidly respond to injury while simultaneously integrating signals from growth factors, extracellular matrix components, and ionic changes within the wound microenvironment.

Collectively, the studies summarized in Table 1 support a model in which calcium signaling and growth-factor pathways function as interconnected rather than independent regulatory systems. In dental pulp and dentin, calcium-containing materials can influence FGFR/ERK signaling and odontogenic differentiation [11], while intracellular Ca^{2+} dynamics are associated with TGF-β/BMP2 expression and mineralization [12]. Conversely, FGF-2 regulates cellular proliferation, migration, and subsequent mineralizing differentiation [13]. These findings suggest that calcium and growth-factor signals may converge at several levels, including receptor activation, intracellular second messengers, kinase cascades, transcriptional regulation, and cellular phenotype. Potential points of convergence include MAPK/ERK, PI3K/Akt, PKC, calcium/calmodulin-dependent signaling, and Wnt-associated pathways. Such convergence may allow oral cells to integrate biochemical signals provided by growth factors with physicochemical cues derived from calcium-rich extracellular environments.

From a regenerative perspective, this interaction has important implications for the design of bioactive materials and therapeutic strategies. Growth-factor-based approaches provide potent biological signals for proliferation, migration, differentiation, angiogenesis, and matrix remodeling, whereas calcium-containing or calcium-releasing materials can provide both mineral ions and signaling cues. The findings of Liu et al. and Rathinam et al. suggest that calcium-silicate-based materials can influence cellular

signaling in addition to promoting mineral deposition [11,12]. This raises the possibility that future regenerative materials could be designed to control both the temporal release of Ca^{2+} and the presentation of growth factors, thereby more closely mimicking the dynamic signaling environment of naturally regenerating tissues. Such strategies may be particularly relevant to dental pulp regeneration, periodontal regeneration, alveolar bone repair, and oral mucosal wound healing. The available evidence indicates that calcium signaling and growth factors are important and potentially interconnected regulators of tissue repair, although direct molecular evidence demonstrating their interaction during wound healing remains limited. Calcium signaling regulates fundamental cellular processes involved in tissue repair, including cell migration, proliferation, differentiation, and re-epithelialization, while growth factors such as epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor-beta (TGF-β) coordinate cellular communication throughout the different phases of wound healing [15-19]. Following tissue injury, transient intracellular calcium elevations and intercellular calcium waves can propagate from the injured region to surrounding cells, providing a rapid mechanism for transmitting information about tissue damage and coordinating migratory and proliferative responses [16,20].

CONCLUSION

Calcium signaling and growth-factor-mediated signaling represent interconnected regulatory systems that contribute to oral tissue homeostasis and regeneration. Current experimental evidence, particularly from dental pulp and dentin models, demonstrates that calcium-containing or calcium-releasing stimuli can influence regenerative responses and are associated with growth-factor-related pathways, including FGFR/ERK and TGF-β/BMP signaling. Growth factors such as FGF-2 also regulate cellular proliferation, migration, differentiation, and mineralization, indicating that calcium-dependent and growth-factor-mediated signals may converge to coordinate different stages of tissue repair. Evidence from oral mucosal wound healing further suggests that calcium-regulated intracellular signaling can interact with other regenerative pathways, including Wnt signaling.

Nevertheless, the current literature remains heterogeneous, and direct molecular evidence demonstrating causal calcium–growth factor crosstalk in oral tissues is still limited. Therefore, the available evidence supports functional convergence and potential crosstalk rather than a universal direct interaction between calcium and individual growth factors. Future research should investigate the temporal and spatial characteristics of Ca^{2+} signaling together with growth-factor receptor activation and downstream molecular pathways. A better understanding of these interactions may facilitate the development of next-generation regenerative strategies that combine controlled calcium signaling with growth-factor modulation for dental pulp, periodontal, alveolar bone, and oral mucosal regeneration.

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