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REVIEW ARTICLE

Regulatory Pathways Governing Odonto/Osteogenic Differentiation in Dental Pulp Stem Cells

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ABSTRACT

Background: The ability of dental pulp stem cells (DPSCs) to undergo differentiation into odonto/osteogenic lineages is governed by complex cell signalling regulatory networks and interactions between cells and the extracellular matrix (ECM).

Aim: This article provides a comprehensive evaluation of cell signalling pathways and ECM that modulate odonto/osteogenic differentiation of DPSCs.

Methods: A comprehensive narrative review method was utilised to examine the key cell signalling mechanisms that govern odonto/osteogenic differentiation in DPSCs, aiming to clarify their significance and critically evaluate their prospective implications for future applications in dentine/pulp repair and regenerative strategies.

Results: Current literatures demonstrate that transforming growth factor-β (TGF-β), Wnt, Notch, and fibroblast growth factor (FGF) signalling, both individually and through interactions, influence stem cell fate. TGF-β1 is essential in regulating DPSC differentiation toward odonto/osteogenic lineages. Wnt signalling crucially contributes to reparative dentine formation, evidenced by its upregulation in animal models following pulp capping. Wnt activators significantly promote dentine regeneration. Notch signalling activates in the dental pulp niches, facilitating reparative dentinogenesis post-injury. Interactions between Notch and other pathways influence DPSC odonto/osteogenic differentiation. Basic fibroblast growth factor (bFGF) regulates DPSC stemness and differentiation, with factors such as dosage and exposure time influencing its biological impact. Furthermore, ECM components play a significant role in differentiating stem cells by enhancing biological factors in the microenvironment and providing physical support, thereby promoting dentine and pulp repair.

Conclusion: A comprehensive understanding of these regulatory mechanisms has the potential to augment insights into the control of DPSC differentiation and facilitate their utilisation in repair and regenerative therapies for the dentine–pulp complex.

1 | Introduction

Dental pulp tissues are loose connective tissues inside the pulp cavity, surrounded by the dentine. This tissue comprises a heterogeneous population of cells, including fibroblasts, odontoblasts, endothelial cells, glial cells, lymphocytes, mononuclear macrophages, resident immunocompetent cells, proliferating cells, and mesenchymal cells. It also includes cellular constituents derived from nerves and blood vessels (Ren et al. 2022). Among these, a subpopulation of mesenchymal stem cells (MSCs), known as

dental pulp stem cells (DPSCs), has attracted considerable attention in regenerative dentistry. DPSCs are multipotent stem cells capable of differentiating into various cell types, including odontoblasts, osteoblasts, endothelial cells, adipocytes, insulin-producing cells, and neuronal cells (Osathanon et al. 2011; Sawangmake et al. 2014; Ganapathy et al. 2024; Kornsuthisopon et al. 2025). These cells express several MSC markers while lacking the expression of haematopoietic markers. These cells can be induced to become odontoblast-like cells that contribute to reparative dentinogenesis by depositing dentine matrix and participating in pulp tissue regeneration (Ledesma-Martínez et al. 2016).

Given their accessibility, robust proliferative capacity, multilineage differentiation particularly toward odontogenic and osteogenic lineages, immunomodulatory properties, and ability to regenerate mineralised tissues, DPSCs represent a promising cell source for cell-based therapies targeting not only the dentine-pulp complex but also broader therapeutic applications in regenerative endodontics, bone regeneration, and craniofacial tissue reconstruction (Gronthos et al. 2002; Huang et al. 2009; Chansaenroj et al. 2024). The capacity of DPSCs to differentiate into odontogenic and osteogenic lineages is orchestrated by intricate regulatory pathways involving growth factors, transcription factors, epigenetic modifications, and cell–matrix interactions. Understanding these regulatory mechanisms is critical for optimising DPSC-based regenerative therapies.

Although several reviews have previously addressed the odonto/osteogenic differentiation of DPSCs; however, important gaps remain. Many studies have investigated individual signalling pathways, yet their stage-specific and sometimes contradictory effects are not fully understood. Similarly, the interplay between major pathways such as Wnt, Notch, and FGF, and their integration with inflammatory and hypoxic signals, remains insufficiently explored. Beyond this, a translational gap persists. Although DPSCs have been widely studied in vitro, challenges such as the stability of signalling proteins, the design of efficient delivery systems, and the influence of ECM properties on clinical outcomes have not been comprehensively addressed in previous reviews. By focusing on unresolved controversies, recent bioinformatic insights, and novel translational strategies, this article aims to provide a more holistic understanding of the regulatory networks governing DPSC differentiation, emphasising the interplay of signalling cascades with ECM dynamics, mechanotransduction, and small-molecule modulators to inform the rational design of next-generation regenerative approaches for the dentine–pulp complex.

2 | Methodology

This narrative review approach was employed to provide a comprehensive evaluation of cell signalling pathways and extracellular matrix (ECM) components that regulate the odonto/osteogenic differentiation of DPSCs. In compiling this review, relevant literature was identified through electronic searches in PubMed and Scopus databases, limited to English-language articles published between 2000 and 2025. The search emphasised studies addressing DPSCs, key signalling pathways, mainly transforming growth factor-β (TGF-β), Wnt, Notch, and fibroblast growth factor (FGF), extracellular matrix (ECM), and regenerative approaches in dentistry. Additional publications were identified by examining the reference lists of selected papers. Only peer-reviewed original research articles and reviews focusing on molecular mechanisms, differentiation, or the regenerative potential of DPSCs were included.

2.1 | Regulatory Pathways Governing Odontogenic/Osteogenic Differentiation of Human Dental Pulp Stem Cells

Since multiple signalling pathways have been reported to synchronise and orchestrate proliferation, migration, lineage commitment, and ECM deposition, a comprehensive understanding of the molecular signals that govern DPSC fate is crucial for harnessing the full therapeutic potential of these stem cells. Among these, TGF-β, Wnt, Notch, and FGF signalling are recognised as master regulators of stem cell behaviour and tissue-specific differentiation toward the odontogenic/osteogenic lineage (Aval et al. 2017; Liu et al. 2021; Figure 1). Beyond their individual contributions, these signalling pathways engage in complex crosstalk, forming a complex and dynamic regulatory network that precisely orchestrates the odontogenic/osteogenic differentiation of DPSCs during development and repair. Therefore, understanding the roles and interactions of these key signalling pathways that guide their osteogenic differentiation offers critical insights into developing targeted strategies for dental tissue regeneration. Building upon the above discussion, this article aims to critically evaluate the roles of the TGF-β, Wnt, Notch, and FGF signalling pathways in regulating the odontogenic and osteogenic differentiation of DPSCs. By synthesising current evidence from recent literature, we seek to provide an integrative overview of how these signalling cascades, individually and through crosstalk, govern stem cell fate decisions.

2.2 | TGF-β Signalling

TGF-β signalling is a multifaceted pathway integral to regulating various cellular processes. The TGF-β superfamily encompasses a diverse array of ligands, including TGF-βs, bone morphogenetic proteins (BMPs), activins, and growth differentiation factors (Morikawa et al. 2016). Its complexity arises from the interplay between canonical (Smad-dependent) and noncanonical (Smad-independent) signalling cascades, each contributing to diverse physiological and pathological outcomes. The canonical TGF-β signalling pathway is initiated when TGF-β ligands bind to a heteromeric receptor complex composed of specific type I (TβRI) and type II (TβRII) serine/threonine kinase receptors on the cell surface, which in turn phosphorylates receptor-regulated Smads (R-Smads). These phosphorylated R-Smads form a complex with the common mediator Smad (Co-Smad), Smad4, and translocate into the nucleus to modulate the expression of target genes. Negative regulation of this pathway is mediated by inhibitory Smads (I-Smads), such as Smad7, which can prevent R-Smad phosphorylation and promote receptor degradation through the recruitment of E3 ubiquitin ligases, including Smurf1 and Smurf2 (Lin and Souchelnytskyi 2011; Tzavlaki and Moustakas 2020).

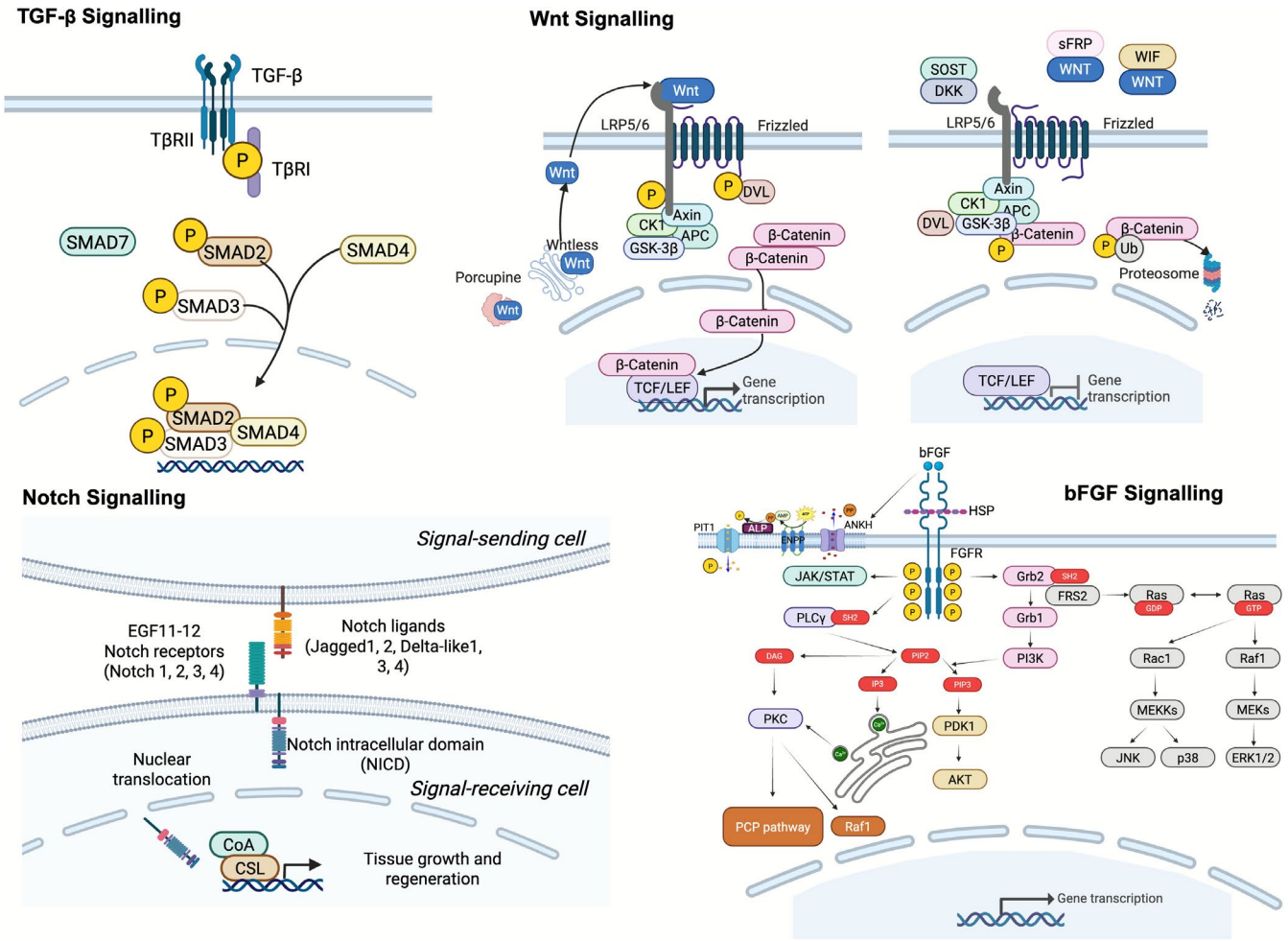

FIGURE 1 | Schematic diagrams illustrate the intracellular pathway for TGF-β, Wnt, Notch, and bFGF signalling. Created in BioRender. https://BioRender.com/tt3wtze.

In non-canonical pathways, TGF-β activates the mitogen-activated protein kinase (MAPK) signalling, which is involved in regulating cell proliferation, differentiation, and responses to cellular stress (Qian et al. 2021). Additionally, the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (also known as PKB or AKT) pathway is activated by TGF-β, leading to AKT phosphorylation and promoting cell survival and metabolic activity (Hamidi et al. 2017). The Rho-like GTPase pathways (including RhoA, Rac1, and Cdc42) control cytoskeletal organisation and cell motility, processes critical for migration and morphogenesis. Furthermore, TGF-β can activate the nuclear factor-κB (NF-κB) pathway, which plays a crucial role in immune regulation and inflammatory responses (Zhang 2009).

TGF-β signalling facilitates both proliferation and early osteogenic differentiation but inhibits bone formation during later stages (Lin et al. 2018). Activation of the TGF-β signalling pathway promotes the expression of key osteogenic transcription factors and genes involved in ECM synthesis (Wu et al. 2016). In later stages of differentiation, TGF-β signalling shifts toward inhibiting osteogenesis. TGF-β mediates its activity through SMAD2/3 to suppress osteoblast activity by promoting Runx2 degradation via histone deacetylase (HDAC) 4 and 5 recruitment (Kang et al. 2005). Additionally, TGF-β upregulates vimentin and HDAC6, both of which negatively influence osteogenic regulators such as ATF4 and primary cilia-mediated mechanotransduction. It also increases Smurf1 expression, antagonising BMP signalling, and downregulates insulin-like growth factor (IGF)-1, a crucial anabolic factor (Zhang et al. 2009).

TGF-β, particularly TGF-β1, plays a pivotal role in regulating the odontogenic and osteogenic differentiation of DPSCs. Under growth conditions, dental pulp cells (DPs) express *TGFB1*, *TGFB2*, and *TGFB3*, with *TGFB1* being most abundant, and their levels further increase during osteogenic induction, especially *TGFB1* and *TGFB3* at later stages (Manokawinchoke et al. 2021). This evidence suggests that TGF-β1 exerts a dual-phase effect. Similarly, previous studies demonstrate that TGF-β1 promotes lineage commitment by enhancing markers such as alkaline phosphatase (ALP), collagen type I alpha 1 chain (COL1A1), runt-related transcription factor 2 (RUNX2), and dentine matrix protein 1 (DMP1) through activation of AKT, extracellular signal-regulated kinase (Erk1/2), and p38 MAPK. Inhibition of these pathways diminishes TGF-β1-induced odontogenic differentiation, underscoring their significance in this process (Bai et al. 2023). Another study confirms that TGF-β1 acts as a positive regulator during the early stages of odontogenic differentiation, enhancing the expression of early odontoblastic markers such as ALP, RUNX2, and COL1A1, and promoting cellular commitment toward the odontoblastic

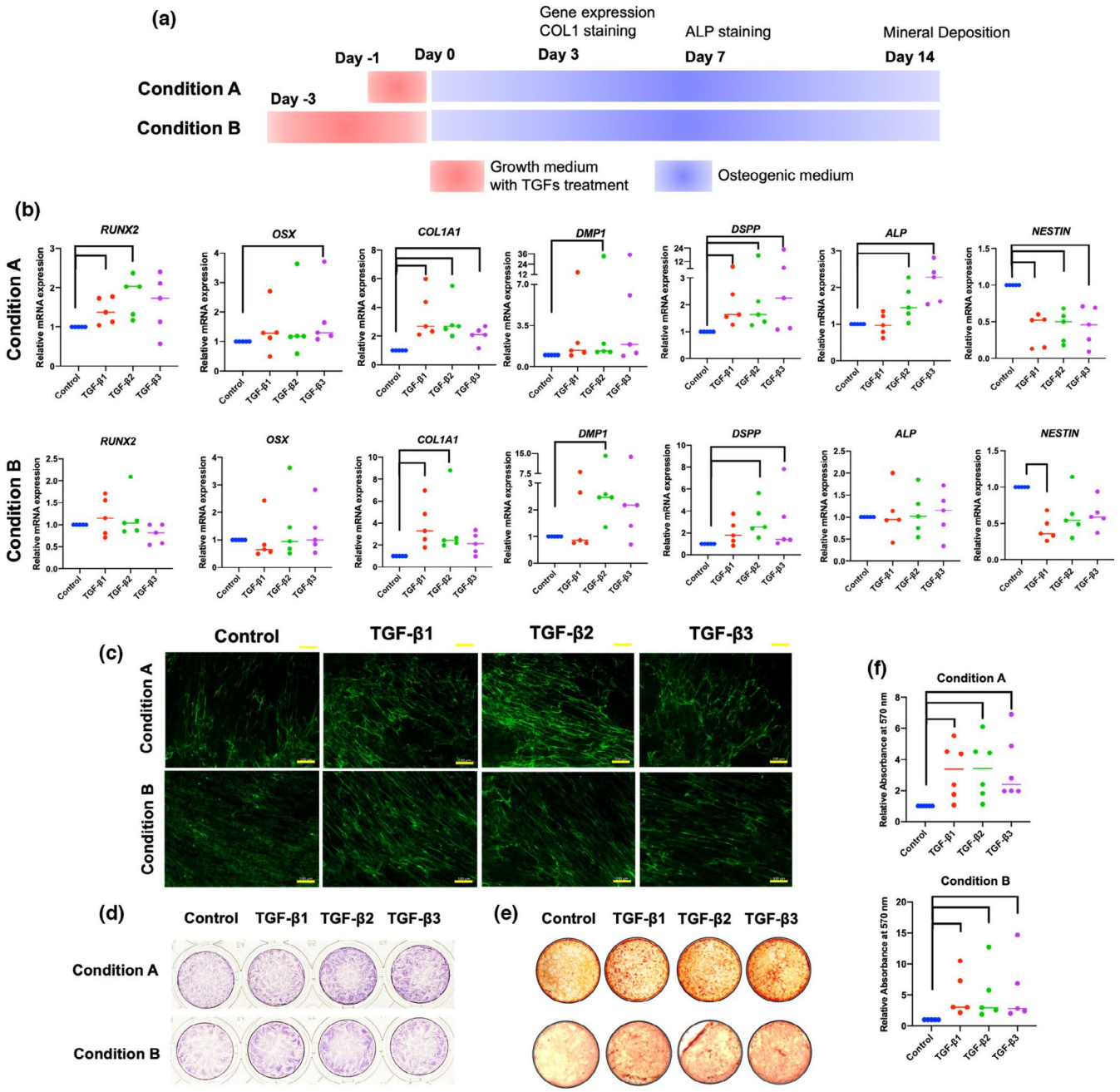

FIGURE 2 | Short-term TGF-βs priming promoted osteogenic differentiation in hDPs. Schematic diagram of experimental plan (a). Osteogenic marker gene expression was determined using real-time polymerase chain reaction (b). COL1 protein expression was examined using immunofluorescence staining (c). ALP enzymatic activity and mineral deposition were examined using ALP staining (d) and alizarin red S staining (e), respectively. Graphs demonstrated the optical density at 570 nm of solubilised alizarin red dye (f). Bars indicate the significant differences. Reprinted from Manokawinchoke J, et al. Dorsomorphin attenuates Jagged1-induced mineralisation in human dental pulp cells. *Int Endod J* 2021; 54:2229–2242. with permission from John Wiley & Sons Ltd. (Manokawinchoke et al. 2021).

lineage. However, late-stage mineralisation is suppressed as demonstrated by reduced ARS staining and downregulation of mineralisation-related genes (Bai et al. 2022). Notably, short-term pretreatment with TGF-β1, TGF-β2, or TGF-β3 before osteogenic induction markedly enhanced odontogenic/osteogenic marker expression, including *COL1A*, *RUNX2*, osterix (*OSX*), dentine sialophosphoprotein (*DSPP*), and *DMP1*, which corresponded with increased ALP activity and mineral deposition in hDPs (Manokawinchoke et al. 2021; Figure 2). These findings indicate that transient TGF-β signalling effectively primes hDPs toward an odontoblast/osteoblast-like phenotype, thereby accelerating matrix production and mineralisation. Similar effects of TGF-β isoforms on early lineage commitment and mineralised tissue formation have been reported in MSCs and dental pulp-derived cells, supporting their regulatory role through Smad-dependent and non-Smad pathways (Niwa et al. 2018; Li, Ge, et al. 2022). Collectively, these results underscore the importance of TGF-β priming in fine-tuning odontogenic differentiation and highlight its translational potential in dentine–pulp tissue engineering.

In vivo odontogenic assay shows that TGF-β1-treated cells produce abundant collagen but lack mineralised tissue. These findings suggest that TGF-β1 promotes early odontogenic differentiation of DPSCs but inhibits terminal mineralisation (Bai et al. 2022). A systematic review and meta-analysis further support the role of TGF-β in promoting DPSC proliferation and osteogenic differentiation. The analysis revealed significant increases in proliferation indices and the expression of osteogenic markers, including bone sialoprotein (*BSP*), *COL1A1*, *OCN*, and *RUNX2*. However, the effect of TGF-β1 on mineralised nodule formation remains inconclusive, indicating that TGF-β signalling may play a complex and stage-specific role in the regulation of mineralisation during odontogenic differentiation (Gao et al. 2023). The synergistic effects of TGF-β1 with other growth factors, including FGF2, have been explored. Co-treatment with TGF-β1 and FGF2 enhances odontoblastic differentiation, as evidenced by increased ALP activity, mineralised nodule formation, and upregulation of dentine-specific proteins (He et al. 2008). This synergy suggests that combinatorial growth factor therapies may optimise DPSC differentiation outcomes.

Innovative delivery strategies for TGF-β1 have shown significant promise in enhancing the odontogenic and osteogenic potential of DPSCs. One such approach involves liposome-encapsulated TGF-β1, which enables the sustained and localised release of the growth factor, thereby enhancing the expression of odontogenic markers and promoting mineralised nodule formation in vitro (Jiang et al. 2020). Complementing this, the therapeutic potential of secretomes derived from TGF-β1-transfected DPSCs is investigated in comparison to non-transfected controls. Proteomic analysis identifies a distinct protein signature in the TGF-β1 secretome that favours osteogenic differentiation and wound healing, while suppressing adipogenic pathways. Functional assays support these findings, showing enhanced osteogenesis, improved cell migration, and reduced adipogenesis in treated cells (Salkin et al. 2022). These findings underscore the therapeutic versatility of TGF-β1 as a direct bioactive molecule, a scaffold-enhancing factor, and a potent modulator of the DPSC secretome, highlighting its multifaceted role in promoting odontogenic and osteogenic differentiation for regenerative applications.

Another promising strategy to enhance odontogenic and osteogenic differentiation involves the use of decellularised extracellular matrix (dECM) derived from DPSCs. Proteomic profiling of this dECM has revealed an enrichment of key matrisome proteins, including those associated with the TGF-β superfamily, specifically TGF-β1 and TGF-β2, highlighting the potential role of TGF-β in signalling regulation. When used as a biological scaffold, this DPSC-derived dECM not only provides a biomimetic microenvironment but also actively promotes the differentiation of seeded stem cells. Bioinformatic analyses, including gene set enrichment and pathway interaction mapping, suggest that this enhanced differentiation capacity is at least partly mediated through the activation of the TGF-β signalling pathway (Kornsuthisopon et al. 2024). The scaffold thus acts not merely as a structural support, but also as a bioactive matrix that modulates cellular behaviour and differentiation ability.

2.3 | Wnt Signalling

Wnt signalling pathway is a crucial regulatory cascade involved in embryonic development and adult tissue homeostasis (Komiya and Habas 2008). Wnt activation requires components, including Wnt proteins, Wnt receptors, modulatory molecules, and transcription factors, which are present in the target tissues (MacDonald et al. 2009). Following translation, Wnt proteins are transported to the rough endoplasmic reticulum (RER), where they undergo palmitoylation mediated by the enzyme Porcupine, a modification that facilitates their secretion (Proffitt and Virshup 2012). Wnt proteins initiate signalling by binding to frizzled (FZD) receptors and low-density lipoprotein receptor-related protein (LRP)-5/6 co-receptors on the cell surface, thereby triggering a cascade of intracellular events (Croce and McClay 2008; MacDonald and He 2012).

The canonical Wnt pathway, also known as the Wnt/β-catenin pathway, is activated when Wnt ligands bind to FZD receptors and LRP5/6 co-receptors, forming a complex that inhibits the activity of the destruction complex, which consists of axin, adenomatous polyposis coli (APC), glycogen synthase kinase 3 beta (GSK-3β), and casein kinase 1 (CK1). This inhibition causes cytoplasmic β-catenin accumulation and subsequent nuclear translocation, which interacts with T-cell factor/lymphoid enhancer factor (TCF/LEF) transcription factors, leading to the activation of Wnt target genes (MacDonald et al. 2009). This pathway is crucial for dictating the lineage commitment of MSCs toward osteoblasts. This intricate signalling pathway orchestrates the differentiation of bone marrow progenitor cells into osteoblasts by modulating the expression of adipocyte and osteoblast transcription factors, either individually or in concert (Chen et al. 2016). Concurrently, Wnt/β-catenin activation influences the balance of osteoclastogenic regulators by downregulating receptor activator of nuclear factor kappa-B ligand (RANKL) and upregulating osteoprotegerin (OPG), thereby suppressing bone resorption (Glass et al. 2005). This distinction highlights the upstream cytoskeletal regulation versus the downstream functional effects on bone metabolism.

On the contrary, the non-canonical Wnt pathway operates through a β-catenin-independent mechanism. The Wnt/calcium pathway, a prominent branch of non-canonical Wnt signalling, is vital for regulating many physiological events, including cytoskeletal rearrangements, cellular adhesion, and other developmental processes (Kühl 2004; Kohn and Moon 2005). Another key non-canonical Wnt signalling pathway is planar cell polarity (Devenport 2014; Yang and Mlodzik 2015). After activation, this pathway is controlled by core PCP proteins, including Van Gogh (VANG), FZD, tyrosine kinase-like orphan receptor (ROR), and Dvl. Activation of JNK/p38 MAPK, small GTPase, and Rho-associated kinase (ROCK) signalling is presented, leading to various consequences, including actin polymerisation and microtubule stabilisation.

Several Wnt ligands, including Wnt3a, Wnt5a, Wnt6, Wnt10a, Wnt10b, and Wnt16, have been shown to stimulate osteogenic differentiation of MSCs through the canonical Wnt/β-catenin

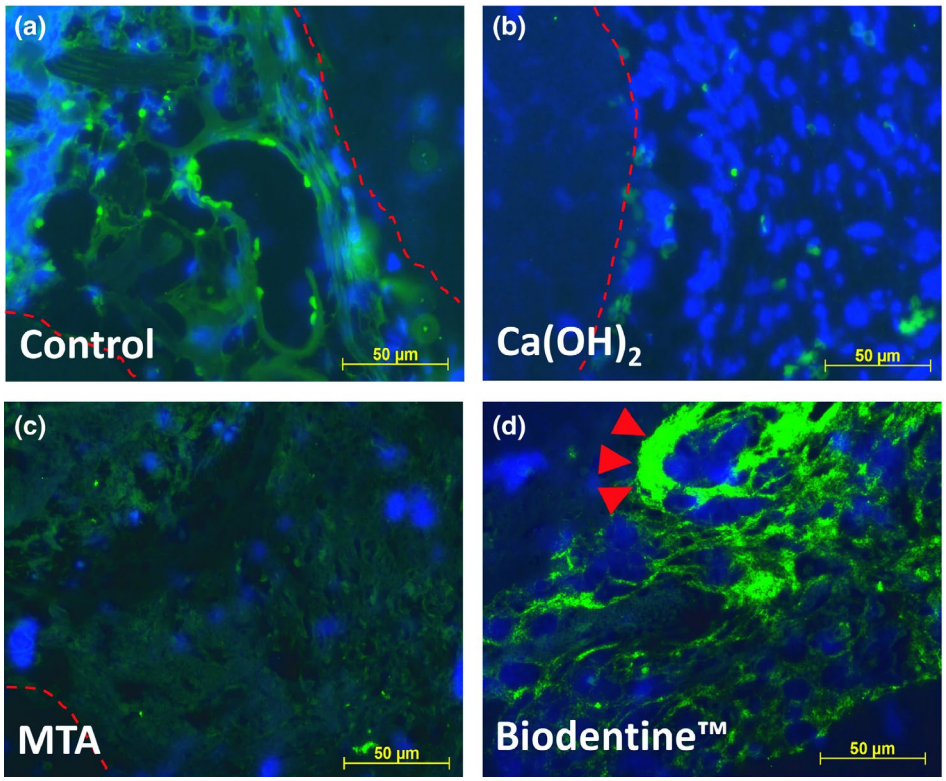

FIGURE 3 | Representative images demonstrating the immunofluorescence staining of β-catenin. The red dashed lines indicate the dentine wall of the pulp chamber. The red arrows indicate the β-catenin in the cells adjacent to the reparative dentine. Reprinted from Yaemkleebbua K, et al. Analysis of hard tissue regeneration and Wnt signalling in dental pulp tissues after direct pulp capping with different materials. *Int Endod J* 2019;52:1605–1616. with permission from John Wiley & Sons Ltd. (Yaemkleebbua et al. 2019).

pathway (Visweswaran et al. 2015; Liang et al. 2021). Mechanistically, Wnt3a promotes the formation and deposition of bone matrix by activating Runx2 through synergistic interactions with BMP9 (Liang et al. 2020). Wnt5a plays a critical role in sustaining the osteogenic potential of MSCs, in part by regulating the activity of the four and a half LIM domains protein 2 (FHL2), a member of the LIM-only subclass of the LIM protein superfamily that influences MSC osteogenic differentiation (Brun et al. 2013). Elevated levels of Wnt6, Wnt10a, and Wnt10b have been shown to enhance β-catenin expression, inhibit adipogenic differentiation in 3T3-L1 cells, and promote their transition toward an osteogenic lineage (Cawthorn et al. 2012).

Wnt signalling represents an alternative pathway involved in reparative dentine formation. Activation of this pathway has been demonstrated in animal studies following direct pulp capping treatments (Han et al. 2014; Angelova Volponi et al. 2018; Yaemkleebbua et al. 2019). Notably, direct pulp capping with Biodentine induces canonical Wnt signalling, as indicated by nuclear localisation of β-catenin in odontoblast-like cells and dental pulp cells near the injury site (Figure 3). This observation highlights the functional role of canonical Wnt signalling in promoting odontoblast differentiation and subsequent reparative dentinogenesis. Consistent with these findings, another study using a genetic mouse model demonstrated that activation of Wnt/β-catenin signalling aligns with peak cell proliferation during reparative dentinogenesis, indicating its role in post-injury cellular expansion. Also, genetic lineage tracing revealed that *Axin2*-expressing cells proliferate after damage, with some differentiating into odontoblast-like cells. By the end of the observation period, these cells were closely associated with the dentine bridge and exhibited elongated processes characteristic of mature odontoblasts (Babb et al. 2017). Collectively, these data suggest that Wnt signalling acts as a key regulatory mechanism linking injury-induced signals to odontoblast lineage commitment. Accordingly, Figure 3 provides a visualisation of pathway activation and further underscores the mechanistic contribution of canonical Wnt signalling to pulp repair and dentine regeneration.

Wnt activation is acquired either through Wnt protein-receptor binding or small-molecule Wnt agonists. Distinct Wnt ligands contribute to various aspects of dental pulp cell behaviour and differentiation. The upregulation of transcripts associated with the WNT signalling pathway, such as cyclin D1 (CCND1) and TCF7, has been shown to coincide with enhanced expression of osteogenic markers, morphological alterations indicative of osteogenic differentiation, and mineralised nodule formation in DPSCs (Guo et al. 2018). Wnt1 promotes neurogenic differentiation, potentially aiding pulp innervation during development (Feng et al. 2013). Liposome-encapsulated Wnt3a enhances the proliferation of undifferentiated pulp cells and boosts alkaline phosphatase activity in odontoblasts following molar pulp injury (Hunter et al. 2015; Zhao et al. 2018). Wnt10a enhances the proliferation and self-renewal of DPSCs, supporting its role in early dentine formation and repair (Zhang et al. 2014). Moreover, Wnt10a stimulates Wnt/β-catenin signalling to enhance the

repair of various dentine-pulp injuries (Li et al. 2023). Wnt4 restores odontogenic potential under inflammatory conditions by increasing mineralisation and expression of odonto/osteogenic markers (Zhong et al. 2019). WNT5A stimulates inflammatory cytokine release and macrophage migration, facilitating infection control and tissue repair (Zhao et al. 2014). Predicted mRNA and pathways targeted by extracellular vesicles derived miRNA of helioxanthin derivative-treated DPSCs revealed WNT5A as one of the target genes. Additionally, upstream regulator analysis suggests that WNT3A may drive the gene expression changes and promote osteogenic differentiation observed in DPSCs following helioxanthin stimulation (Fujii et al. 2024). Collectively, these findings underscore the therapeutic potential of specific Wnt proteins in dentine regeneration, particularly in pulp capping strategies under inflammatory conditions.

Despite their versatile effect on pulp tissue regeneration, Wnt proteins face significant challenges in clinical translation owing to poor stability and difficult delivery. Their required lipid modification for receptor binding makes them hydrophobic and unstable (Janda et al. 2012). While solubilising agents like 3-[(3-cholamidopropyl) dimethylammonio]-1-propanesulfonate or CHAPS can aid delivery, they may negatively impact stem cell viability (Tüysüz et al. 2017). Lipid-based carriers such as liposomes have been investigated but are costly and inconsistent (Tüysüz et al. 2017). Due to the limitations of Wnt proteins, small-molecule Wnt agonists, with greater stability, show more promise for clinical applications in reparative dentinogenesis. These molecules mainly target GSK-3β, a crucial regulator of the Wnt/β-catenin pathway. By inhibiting GSK-3β this prevents the phosphorylation of β-catenin, leading to the stabilisation of β-catenin and further initiating Wnt signalling. Small-molecule inhibitors of GSK-3β include lithium chloride (LiCl), arylimidazoles 95 (CHIR 99021) and 96 (CHIR 98014), 6-Bromoindirubin-3′-Oxime (BIO), and tideglusib (Kramer et al. 2012; Law and Zheng 2022).

Previous studies have indicated the promising role of small-molecule GSK-3β antagonists in enhancing dentine regeneration. LiCl mimics Wnt pathway activation by promoting β-catenin accumulation in DPSCs, leading to enhanced calcium nodule formation, increased matrix mineralisation, and elevated expression of odonto/osteogenic gene expression (Han et al. 2014). When incorporated into pulp-capping materials, LiCl improves dental pulp cell migration, differentiation, and mineralisation in vitro compared to untreated controls (Ali et al. 2019). In vivo studies further support these findings, with LiCl-containing materials promoting tertiary dentine formation and facilitating dentine bridge development in mechanically injured rat teeth (Ishimoto et al. 2015; Sukarawan et al. 2023; Figure 4). Mechanistically, LiCl enhances the survival and expansion of αSMA^+ progenitor cells, thereby promoting their differentiation into odontoblasts and osteoblasts through activation of the Wnt/β-catenin signalling pathway (Vijaykumar and Mina 2021). Figure 4, therefore, demonstrates dentine bridge formation induced by LiCl-containing materials and further highlights the pivotal role of canonical Wnt signalling in promoting progenitor cell differentiation and reparative dentinogenesis.

Similarly, other small-molecule Wnt activators, including CHIR, BIO, and tideglusib, significantly enhance dentine regeneration at injury sites compared to collagen sponge alone (Neves et al. 2017). Another study demonstrates that both tideglusib and CHIR99021 promote mineralisation in DPSCs; however, CHIR99021 more robustly upregulates key odontoblastic markers, including DSPP and DMP1, which are indicative of odontoblast differentiation (Hanna et al. 2023). BIO and tideglusib enhance odontogenic and osteogenic differentiation of DPSCs in vitro (Kornsuthisopon, Rochanavibhata, et al. 2022; Kornsuthisopon et al. 2023). In particular, global gene profiling of tideglusib-treated DPSCs exhibits upregulation of FGF5, suggesting the complex interaction between cell signalling to synergistically govern the odonto/osteogenic differentiation ability of these cells (Kornsuthisopon et al. 2023). Moreover, pathway enrichment analysis revealed that downregulated genes were associated with interleukin (IL)-17 and TNF signalling pathways, supporting the notion that Wnt signalling may contribute to immunomodulation and the maintenance of pulp vitality (Kornsuthisopon et al. 2023). Given its original development for neurodegenerative diseases such as Alzheimer's and progressive supranuclear palsy (currently in phase II clinical trials; del Ser et al. 2013; Lovestone et al. 2015), tideglusib's commercial availability, stability, and established safety profile make it a promising candidate for incorporation into pulp-capping materials to enhance dentine repair. Taken together, these findings highlight the therapeutic potential of Wnt pathway agonists in promoting pulp healing, especially considering the manufacturing limitations of native Wnt proteins due to their hydrophobic nature. Consequently, small-molecule activators represent a more practical and scalable alternative for clinical use in regenerative endodontics.

In organoid-like microspheroids, treatment with cannabidiol (CBD) demonstrated the highest in vitro and in vivo bone regenerative capacity, particularly in a calvarial defect model in nude mice. Transcriptomic and bioinformatic analyses identified *WNT6* upregulation as a key contributor to their elevated osteogenic potential (Liu et al. 2024). For further development as a cell-free therapeutic approach, dECM derived from DPSCs has been shown to enhance the odonto/osteogenic differentiation potential of human gingival fibroblasts (hGFs), which inherently possess limited regenerative capacity in this context. Results reveal that this enhancement is mediated via activation of the Wnt and Hippo signalling pathways. Matrisome profiling revealed upregulation of WNT5A and WNT5B, while pathway enrichment analysis of RNA sequencing data from hGFs cultured on DPSC-derived ECM indicated increased expression of genes associated with Wnt and Hippo pathway activation (Kornsuthisopon et al. 2024). Cumulatively, these findings underscore the role of Wnt signalling as a key regulatory pathway in promoting the odonto/osteogenic differentiation of DPSCs, supporting its potential utility in both cell-based and cell-free approaches for regenerative dentistry and bone tissue engineering.

2.4 | Notch Signalling

Notch signalling pathway is a highly conserved mechanism of direct cell-to-cell communication, comprising a ligand-expressing cell and a receptor-expressing receiving cell. Notch receptors are single-pass transmembrane proteins characterised by extracellular epidermal growth factor (EGF)-like repeats,

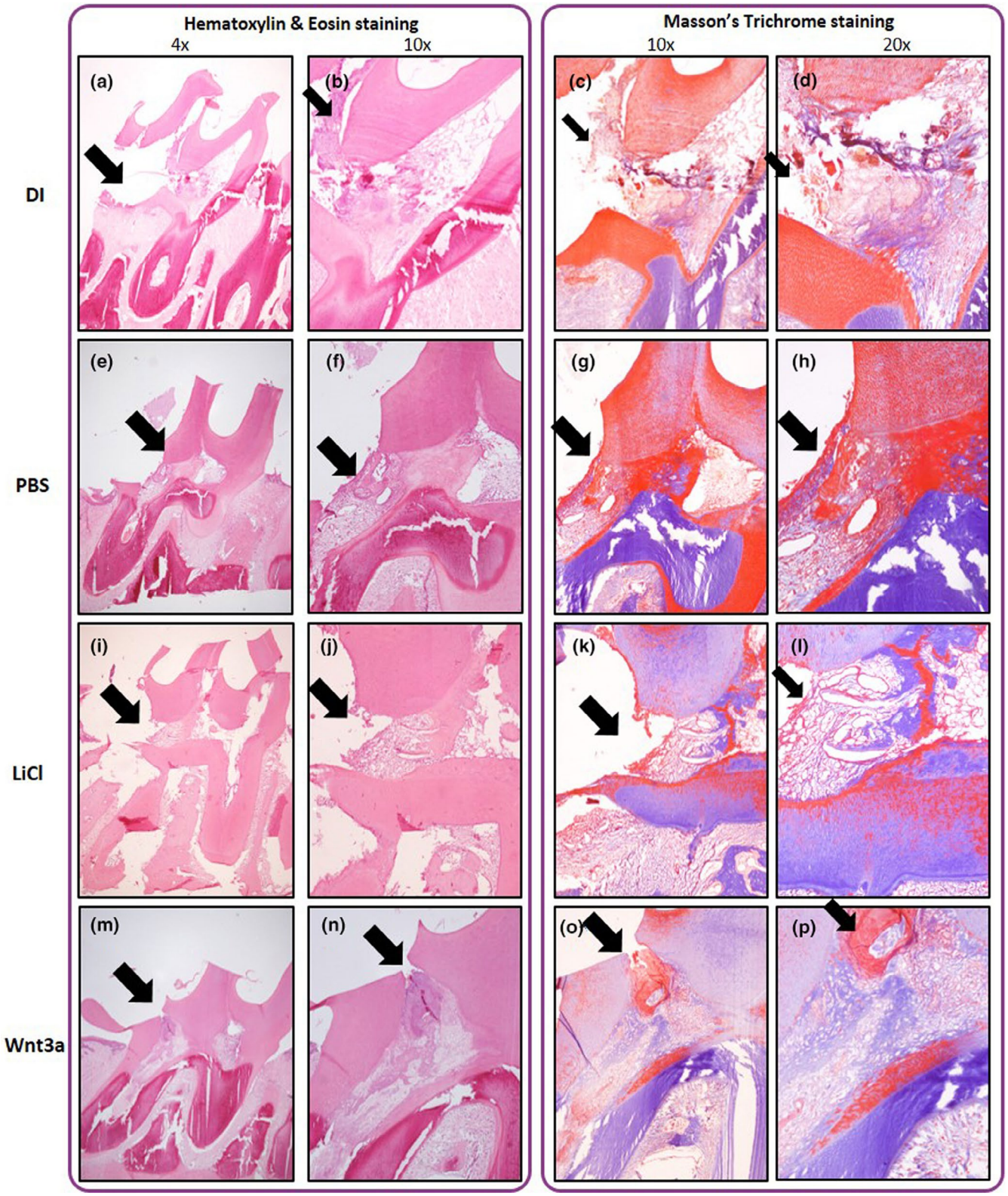

FIGURE 4 | Wnt3a promotes tertiary dentine formation in vivo. Dental pulp injury in rat molars was treated with distilled water (DI; a–d), phosphate-buffered saline (PBS; e–h), lithium chloride (LiCl; i–l), and recombinant human Wnt3a (m–p). After 4 weeks, specimens were decalcified and processed for histological evaluation. In the first and second columns, sections were stained with haematoxylin and eosin. Sections in the third and fourth columns were stained with Masson's Trichrome. Black arrows indicate the exposure sites, $n = 6$ teeth per group. Reprinted from Sukarawan et al. Wnt3a promotes odonto/osteogenic differentiation in vitro and tertiary dentine formation in rat model. *Int Endod J* 2023;56:514–529. With permission for John Wiley & Sons Ltd. (Sukarawan et al. 2023).

transmembrane components, and intracellular domains that mediate signal transduction. Notch ligands contain a conserved Delta/Serrate/Lag-2 (DSL) domain essential for receptor binding with EGF repeats 11–12 (Vanorny and Mayo 2017). Unlike other cell-signalling pathways that rely on second messengers for signal transduction, Notch signalling activation occurs through ligand-receptor interactions, which facilitate direct cell-to-cell interaction with neighbouring cells.

For canonical Notch signalling, ligand-receptor binding triggers a conformational change in the Notch receptor, exposing a cleavage site for a disintegrin and metalloprotease (ADAM). Subsequent proteolytic cleavage processing by γ-secretase releases the Notch intracellular domain (NICD), which translocates into the nucleus to further incorporate with DNA-binding protein CBF1/RBP-Jκ/Suppressor of Hairless/LAG-1 (CSL) and co-activators like Mastermind-like (MAML) proteins. This event activates transcription of downstream target genes, including hairy and enhancer of split (HES) and hairy and enhancer of split-related to YRPW motif (HEY) families, which are transcription factors that regulate the expression of genes involved in cell fate determination and differentiation (Dontu et al. 2004).

Regarding non-canonical Notch signalling, Notch receptors can be activated without ligand engagement, often through interactions with other membrane proteins or mechanical stress, leading to cleavage and the release of NICD. Non-canonical Notch can be triggered in a CSL-independent manner by interacting with other transcription factors or co-regulators, thereby modulating alternative gene networks. Additionally, full-length Notch receptors or their fragments interact with pathways such as the Wnt/β-catenin, NF-κB, and mammalian target of rapamycin (mTOR) pathways. This process expands the versatility of Notch signalling, allowing context-dependent responses and crosstalk with other signalling networks to influence biological processes (Andersen et al. 2012).

Notch signalling has emerged as a critical regulator of osteogenic differentiation, with its role being context-dependent and varying based on cell type, developmental stage, and the presence of other signalling cues. Activation of Notch signalling enhances osteogenic differentiation in certain cell types, such as MSCs and pre-osteoblasts, while inhibiting the terminal differentiation of osteoblasts has been reported (Zieba et al. 2020). As a positive regulator, Notch signalling promotes osteogenic differentiation of MSCs by upregulating the expression of key osteogenic transcription factors, such as RUNX2 and OSX, which are essential for the differentiation of MSCs into osteoblasts. In addition, Notch signalling has been shown to interact with other signalling pathways, such as BMP (Tezuka et al. 2002; Lin and Hankenson 2011) and Wnt signalling (Kornsuthisopon, Chansaenroj, et al. 2022), to synergistically promote osteogenic differentiation, highlighting the intricate interplay and complexity of the regulatory network governing this process. Serving as a negative modulator of osteogenesis, Notch signalling inhibits Runx2 transcriptional activity through the action of Hey1, a protein encoded by a Notch target gene (Zamurovic et al. 2004). Transient expression of NICD, Hes, or Hey in MSCs reduces Runx2 transactivity, with co-immunoprecipitation confirming that Hes and Hey directly bind to Runx2 (Hilton et al. 2008). Additionally, NICD itself can associate with Runx2 to block terminal osteoblast differentiation in vitro (Engin et al. 2008). Notch signalling is activated in osteochondroprogenitor cells to maintain the multipotency and promote the proliferation of pre-osteoblasts, preventing them from differentiating into mature osteoblasts (Chen et al. 2014). During intramembranous bone healing, a temporospatial separation between Notch and Wnt signalling activation has been observed. Notch is activated during the early stages of bone regeneration to promote the proliferation of osteoprogenitor cells. This phase is subsequently followed by the activation of canonical Wnt signalling, which initiates osteogenic differentiation by inhibiting Notch activity, thereby leading to the termination of the proliferative phase. These results suggest a molecular switch responsible for the transition of progenitor cell proliferation to differentiation during bone regeneration (Lee et al. 2021). Attenuation of Notch1 signalling in bone marrow mesenchymal stem cells (BMSC) has been demonstrated to promote the osteogenic differentiation capacity of these cells (He and Zou 2019). Altogether, this evidence supports the multifaceted role of Notch during osteogenesis.

Given that the effects of Notch signalling on cellular behaviour are highly context-dependent, its functional outcomes vary according to the cellular microenvironment and developmental stage. Although the four Notch receptors share considerable structural and functional similarities, each exerts distinct roles owing to differences in their spatial and temporal expression patterns, receptor-ligand affinities, and downstream signalling dynamics. These variations influence how Notch signalling modulates cell fate, either promoting self-renewal, maintaining an undifferentiated state, inhibiting lineage commitment, or, conversely, facilitating terminal differentiation (Canalis 2018). During tooth development, the dental papilla and apical papilla ultimately differentiate into dental pulp tissue located in the crown and root apex regions of the tooth, respectively. Although sharing a common origin from the neural crest, comparative analyses of DPSCs and stem cells from apical papilla (SCAPs) have revealed notable differences in Notch-related gene expression patterns, potentially influencing their cell fate decisions and differentiation capabilities. Coronal pulp expressed a higher gene expression profile than that of apical pulp tissue, including *NOTCH3*, *NOTCH4*, *DLL1*, *JAG2*, *MAML3*, *HES*, and *HEY* (Damrongsri et al. 2021). Specifically, SCAPs have demonstrated higher colony formation efficiency and cell proliferation rates compared to DPSCs, hinting at a more robust proliferative capacity and possibly less osteogenic differentiation potential owing to the fact that terminal differentiation is typically associated with the cessation of proliferation and the irreversible withdrawal from the cell cycle (Ruijtenberg and van den Heuvel 2016). These findings suggest that disparities in Notch-related gene expression profiles significantly influence the differentiation behaviours of cells.

Notch signalling is implicated in the activation of putative dental pulp niches, contributing to reparative dentinogenesis following dental injury. Studies have demonstrated that Notch signalling is upregulated in MSCs within the pulp tissue of carious or injured adult teeth, resulting in mineral deposition while concurrently inhibiting cellular proliferation (About and Mitsiadis 2001). Following dental injury, the main population of cells within the sub-odontoblastic layer expresses the Notch

2 receptor and can differentiate into odontoblast-like cells to replace apoptotic odontoblasts. However, severe stress can lead to the elimination of these sub-odontoblastic cells via apoptosis, significantly reducing the number of neighbouring cells available for differentiation into odontoblast-like cells (Mitsiadis and Rahiotis 2004). This necessitates the activation of alternative sources of pulp stem/progenitor cells to ensure effective dental tissue repair. Another study reports that Notch 2-positive cells are strongly expressed in MSCs at the apical pulp, correlating with enhanced proliferation and migration of stem/progenitor cells toward the injury site, thereby supporting dentine/pulp regeneration (Mitsiadis et al. 2003). Notch 1 and Notch 3 are primarily detected in vascular-associated cells, suggesting their roles in maintaining vasculature, regulating stem/progenitor cell dynamics, and activating specific pulpal perivascular niches (Mitsiadis et al. 2017; Pagella et al. 2021). Thus, the dynamic interplay of these Notch receptors suggests a finely tuned balance between maintaining a proliferative pool of progenitor cells and controlling differentiation, which is critical for successful dental tissue repair.

Specific ligand binding also plays a crucial role in regulating Notch activity on DPSC odontogenic and osteogenic differentiation. Notch activation driven by DLL1 promotes the self-renewal capacity and odonto/osteogenic differentiation potential of these cells (He et al. 2009; Wang et al. 2011). Importantly, the efficacy of Notch activation depends not only on ligand type but also on the mode of ligand presentation. Multivalent or immobilised ligands, which allow multiple extracellular domains to engage the receptor simultaneously, elicit stronger signalling than monomeric, soluble forms (Kovall et al. 2017). Clustered DLL1 constructs with multiple ligand extracellular domains being available for Notch activation have been shown to potentiate Notch signalling more effectively than their monomeric counterparts (Kovall et al. 2017). Given that Notch signalling requires cell-to-cell contact and mechanical pulling to facilitate NICD release, indirect immobilisation of JAG1 via protein G optimises ligand orientation, facilitating effective receptor engagement and NICD release, resulting in robust activation of downstream targets such as *HES1* and *HEY1*, and inducing cell cycle arrest (Manokawinchoke et al. 2017). This strategy additionally enhances DPSC odonto/osteogenic differentiation, as visualised in Figure 5 (Kornsuthisopon, Chansaenroj, et al. 2022). Figure 5, therefore, illustrates the functional consequence of ligand presentation strategy, emphasising that effective Notch pathway activation requires both appropriate ligand selection and structural presentation. These findings are consistent with reports demonstrating that multivalent or immobilised Notch ligands potentiate differentiation outcomes more effectively than soluble or directly coated ligands (Hansamuit et al. 2020), highlighting a practical approach to harnessing Notch signalling for regenerative dentistry applications.

Crosstalk between Notch and other key signalling directs the osteogenic differentiation potential of DPSCs. Bioinformatic and enrichment pathway analysis show that Notch signalling interacts with BMP and FGF signalling to synergistically promote odontogenic differentiation in DPSCs (Manokawinchoke et al. 2017). Upon stimulation with immobilised JAG1, bioinformatic analysis of genes within the bone mineralisation ontology revealed significant upregulation of *TGFB1* and *TGFB3*, suggesting potential crosstalk between the Notch and TGF-β signalling pathways (Hansamuit et al. 2020). The interplay between Notch and noncanonical Wnt signalling mediated by WNT5A orchestrates the intricate process of mineralisation in DPSCs (Kornsuthisopon, Chansaenroj, et al. 2022). The study has also investigated the participation of IL-15 in JAG1-induced mineral deposition in DPSCs (Kornsuthisopon et al. 2021). These findings highlight the complex interactions of Notch signalling in the differentiation of these cells.

Notch signalling can be activated and modulated by a diverse array of factors, including chemical cues, microenvironmental conditions, including ECM, and biological processes such as post-transcriptional modifications. CBD has been shown to restore the osteogenic differentiation ability of DPSCs under *Porphyromonas gingivalis* (*P. gingivalis*) lipopolysaccharide (LPS)-induced inflammatory milieus (Kornsuthisopon et al. 2025). Bioinformatic analysis suggests that CBD exerts the induction effect on odontogenesis and osteogenesis of DPSCs partly through NOTCH1 signalling activation (Kornsuthisopon et al. 2025). The matrisome profile from the membrane compartment of indirectly immobilised JAG1-treated hDPSCs reveals proteins related to odontogenesis, suggesting that Notch-activating cells can deliver signals to potentiate odontogenic and osteogenic differentiation both through intracellular signalling cascades and by modulating the extracellular microenvironment, including the composition and organisation of the ECM (Chansaenroj et al. 2022). Post-transcriptional modification via succinylation, mediated by succinylases KAT2A, plays a crucial role in enhancing Notch1 activation. KAT2A activates Notch1 signalling by succinylating Notch 1 at the K2177 site, leading to increased protein levels of Notch1 in DPSCs, thereby promoting odontogenic differentiation ability in these cells (Ye et al. 2024). MicroRNAs (miRNAs), highly conserved non-coding RNA molecules, have been documented to regulate Notch-related gene expression. miR-146a-5p targeting Notch 1 inhibition leads to increased mineralisation of STRO-1^{+} DPSCs (Lin et al. 2018). On the contrary, miRNA expression profiling following indirect JAG1-induced Notch activation in DPSCs revealed the significant upregulation of miR-296-3p and miR-450b-5p. Overexpression of these miRNAs further enhanced mineralisation and promoted the upregulation of odontogenic and osteogenic marker genes (Kulthanaamondhita et al. 2024). These findings further confirm the bidirectional role of Notch signalling in osteogenic differentiation, which is highly dependent on cellular context, ligand-receptor specificity, and environmental factors.

To enhance the clinical applicability of Notch signalling, various strategies have been explored, particularly focusing on JAG1 delivery systems. Functionalised hydrogels incorporating indirectly immobilised JAG1 have demonstrated pro-angiogenic effects and promoted both odontogenic and osteogenic differentiation of DPSCs (Zhang, Yu, et al. 2024). Similarly, affinity-immobilised JAG1 on PCL-incorporated hydroxyapatite (PCL/HA) membranes upregulated Notch target gene expression in human periodontal ligament stem cells (f) and significantly increased ALP activity following osteogenic induction. However, this approach requires further validation in DPSCs (Nowwarote, Chanjavanakul, et al. 2018). Another study elucidates that surface-immobilised JAG1 has been shown to enhance odonto/osteogenic differentiation in DPSCs, together with supporting

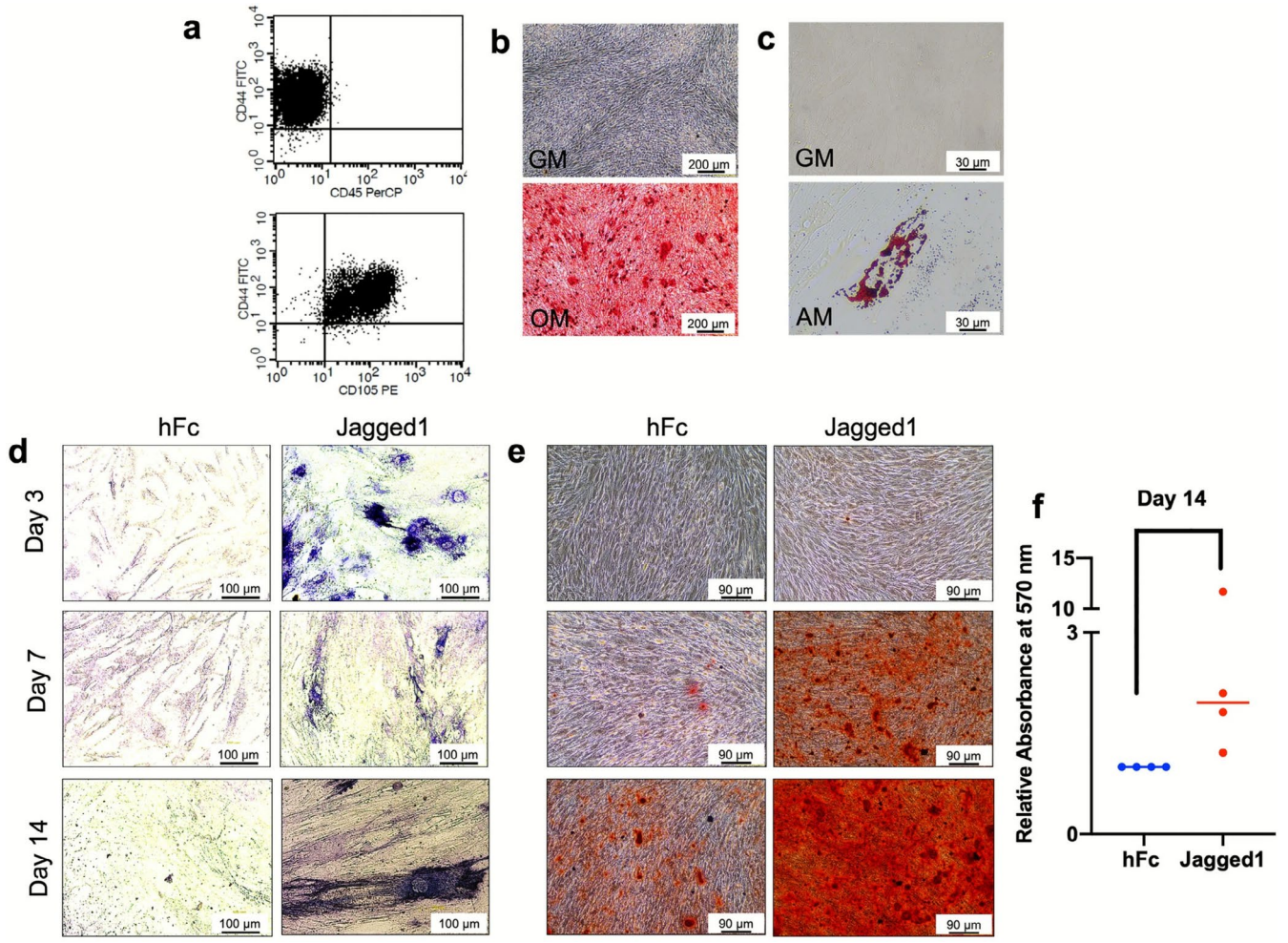

FIGURE 5 | Indirect immobilised Jagged1 promotes hDPSC osteo/odontogenic differentiation. MSC surface markers were examined using (a) flow cytometry. Multilineage differentiation toward the osteo/odontogenic and adipogenic lineages was examined using (b) alizarin red S staining and (c) oil red O staining, respectively. Cells were seeded on Jagged1 immobilised surface and maintained in osteo/odontogenic medium. Cells on hFc-immobilised surfaces were used as the control. The cells were cultured in osteo/odontogenic medium for 3, 7, and 14 days. Osteo/odontogenic differentiation was evaluated by (d) ALP staining and (e) in vitro mineral deposition using alizarin red S staining. The alizarin red S staining was solubilised, and (f) the absorbance was measured at 570 nm. Bars indicate a significant difference between groups ($p < 0.05$). Reprinted from Kornsuthisopon C, et al. Non-canonical Wnt signalling participates in Jagged1-induced osteo/odontogenic differentiation in human dental pulp stem cells. *Sci Rep* 2022; 12:7583. under a Creative Commons Attribution 4.0 International Licence. (Kornsuthisopon, Chansaenroj, et al. 2022).

cell viability, attachment, and spreading. In contrast, its soluble form fails to activate Notch target genes, underscoring the necessity of an immobilised delivery system for effective in vivo application (Manaspon et al. 2020). Furthermore, dECM derived from JAG1-treated hDPSCs has been shown to be biocompatible with stem cells from the SCAP and to enhance their odonto/osteogenic differentiation, highlighting its potential as a Notch-activating scaffold for regenerative applications (Phothichailert et al. 2022).

2.5 | FGF Signalling

Basic fibroblast growth factor (bFGF, or FGF-2) is widely recognised as a potent mitogen for a variety of cell types, including stem cells of mesenchymal origin (Liu et al. 2021). In the context of dental pulp, bFGF has been shown to significantly enhance DPSC proliferation and survival (Sukarawan et al. 2014; Nowwarote et al. 2020; Luo et al. 2021). In vitro, bFGF treatment leads to higher cell numbers and an extended lifespan of the cells, partly by upregulating cell cycle promoters and anti-apoptotic proteins (Morito et al. 2009; Nowwarote et al. 2020). Correspondingly, bFGF treatment of human dental pulp tissue increased expression of cyclins and reduced caspase-3 activity, consistent with improved proliferative capacity and cell survival (Kim et al. 2010). Indeed, bFGF appears to maintain stem cell stemness while expanding cell numbers. bFGF upregulates cell-cycle drivers (cyclin B1, cdc2) via FGFR–MEK/ERK signalling and concurrently enhances stemness-associated genes (like *REX1, OCT4, NANOG*) in dental stem cells (Chang et al. 2017; Nowwarote et al. 2020). This dual effect is valuable for regenerative endodontics, where a sufficient pool of multipotent DPSCs is needed to rebuild pulp tissues. In practical terms, bFGF has been shown to significantly increase the number of colony-forming units and enhance the migration capacity of SHEDs (stem cells derived from deciduous pulp), further evidence of its ability to expand the effective stem cell pool. Notably, bFGF's augmentation

of stemness may involve secondary signalling mediators; for instance, bFGF elevates IL-6 in SHEDs, which in turn helps sustain expression of the pluripotency gene *REX1* under conditions of mechanical stress (Govitvattana et al. 2013; Nowwarote et al. 2017). Such crosstalk between growth factor and cytokine pathways likely contributes to a supportive niche that balances rapid cell expansion with the maintenance of stem cell identity. Together, these findings underscore the dual benefit of bFGF in pulp regeneration. It not only expands the local population of stem cells through mitogenic effects but also actively attracts additional progenitor cells into the regenerative site. Such a mechanism ensures a dense and responsive cellular environment that supports both early tissue repair and long-term pulp regeneration.

Clinically, the ability of bFGF to stimulate cell proliferation could accelerate the repopulation of a disinfected pulp canal with reparative cells. Beyond its mitogenic role, bFGF also functions as a powerful chemoattractant. Following pulp injury, bFGF released from dentine or produced by inflammatory cells can establish a local concentration gradient that guides DPSCs and other progenitor cells toward the damaged site (Howard et al. 2010; Suzuki et al. 2011). Experimental studies have shown that bFGF is among the most effective chemotactic agents for dental stem cells (Fayazi et al. 2017). In comparative analyses, bFGF nearly doubled the number of cells migrating to engineered scaffolds compared to untreated controls (Fayazi et al. 2017). Remarkably, its cell-homing efficacy was found to be on par with granulocyte colony-stimulating factor (G-CSF), a well-established mobilising agent (Takeuchi et al. 2015). The underlying mechanism involves activation of the AKT/PKB signalling pathway, which plays a crucial role in MSC migration (Schmidt et al. 2006). Collectively, these findings support bFGF as a key player in mobilising endogenous cells for regenerative endodontic therapies.

The combinatorial effect of bFGF as a proliferative and migratory cue means it can help accumulate a critical mass of regenerative cells at the site of pulp damage in a short time frame. However, it is noteworthy that the microenvironment (especially the ECM context discussed above) can modulate how effectively bFGF exerts these functions; for instance, an ECM rich in heparan sulfate can bind bFGF and present it to cells in a sustained manner, whereas a proteoglycan-poor environment might diminish bFGF gradient formation. From a therapeutic standpoint, although the clinical applicability remains to be fully established, studies in animal models suggest that delivering bFGF (e.g., via an injectable hydrogel or a scaffold) into a root canal can enhance pulp-like tissue regeneration compared to controls (Elnawam, Thabet, Mobarak, Abdallah, and Elbackly 2024; Elnawam, Thabet, Mobarak, et al. 2024). bFGF's role as a trophic factor thus sets the stage for subsequent phases of regeneration by ensuring adequate DPSCs are present and active. Any opinion on regenerative strategy would strongly favour harnessing this aspect, for instance, pre-conditioning DPSCs with bFGF before implantation or including bFGF in the scaffold to enhance initial cell engraftment and proliferation.

The effect of bFGF on the differentiation of DPSCs into odontoblasts and, more broadly, into mineralising cells is complex and highly dependent on timing. Although studies have reported conflicting outcomes, the current consensus is that these differences stem from the timing and duration of bFGF application. Research has shown that short-term exposure to bFGF during the early proliferative phase encourages odontoblast commitment and supports (Sagomonyants and Mina 2014a, 2014b). In contrast, continuous or late-stage exposure suppresses final differentiation (Sagomonyants and Mina 2014a, 2014b; Sagomonyants et al. 2017). For example, a brief early application of bFGF enhanced dentine matrix formation, while ongoing exposure inhibited the expression of key markers such as DMP1 and DSPP. Mechanistically, persistent FGFR signalling maintains high ERK activity while downregulating TGF/BMP-SMAD pathways, effectively inhibiting maturation. Strong evidence supports that a knockdown endogenous level of bFGF rescues mineralisation, providing clear evidence that endogenous bFGF functions to restrain terminal differentiation (Nowwarote, Pavasant, and Osathanon 2015).

This biphasic behaviour was also confirmed in animal models. When bFGF was delivered briefly after pulp exposure, it promoted the formation of a well-organised dentine bridge composed of DSPP-positive cells, favouring odontogenesis over osteogenesis (Sagomonyants et al. 2017). However, when bFGF was applied continuously or introduced too late, the pulp tissue remained in a proliferative state, often leading to disorganised or excessive calcification rather than true dentine formation. These findings underscore the double-edged nature of bFGF. It is highly beneficial in the early regenerative window to stimulate cell recruitment and expansion. Still, it must be withdrawn to allow proper differentiation and mineralisation. From a clinical standpoint, regenerative strategies using bFGF must carefully control its timing and concentration (Nowwarote, Sawangmake, et al. 2015). Fast-release hydrogels or materials that degrade quickly after releasing bFGF may be ideal (Kataoka et al. 2021). Alternatively, combining bFGF with switchable inhibitors could offer temporal control over its effects. Dose also matters, while low to moderate doses may strike a balance between cell proliferation and differentiation (Nowwarote, Sawangmake, et al. 2015), high doses risk overwhelming the pulp environment with prolonged proliferation and angiogenesis (Kanda et al. 1999), potentially disrupting tissue architecture. Furthermore, bFGF does not act in isolation. Its effects on DPSC fate are shaped by interactions with other pathways, such as BMP, Wnt (via PI3K/AKT), and phosphatase/pyrophosphate regulatory genes (Sagomonyants and Mina 2014a, 2014b; Nowwarote, Sukarawan, et al. 2018). These signalling crosstalks can fine-tune whether cells stay in a progenitor state or proceed toward mature odontoblasts.

In addition to its effects on odontoblast-lineage cells, bFGF has a notable influence on alternative lineage pathways of dental stem cells. For example, bFGF is essential for the neurogenic differentiation of both DPSC and SHEDs. Addition of exogenous bFGF in neurobasal media is required to induce neuron-like cells from these stem cells, an effect mediated through the PLCγ (phospholipase C-gamma) signalling (Osathanon et al. 2011). This underscores the pleiotropic role of bFGF; it not only guides odontogenic vs. non-odontogenic fate decisions depending on context, but also highlights that

within a regenerating pulp, bFGF might support the development of neural elements (which could be beneficial for pulp innervation and function).

In summary, bFGF plays a stage-specific role in dental pulp regeneration, priming the process but ultimately yielding to other signals for complete tissue development. A promising direction is the sequential delivery of bioactive cues, starting with bFGF to activate and expand the cell population, followed by morphogens, such as BMP-2 or Wnt, to drive terminal odontoblast differentiation. While this approach remains to be validated clinically, it offers a rational framework for designing next-generation regenerative therapies.

2.6 | Additional Signalling Pathways and Crosstalk in DPSC Differentiation

In addition to TGF-β, Wnt, Notch, and FGF, several other signalling pathways contribute to the regulation of odonto/osteogenic differentiation of DPSCs. These include NF-κB, hypoxia-inducible factor (HIF), and PI3K/AKT pathways, which exert important and often context-dependent effects on lineage specification. Activation of the NF-κB pathway under inflammatory conditions tends to suppress odontoblastic maturation, whereas inhibition of NF-κB signalling enhances the expression of odontogenic markers and collagen matrix formation (Hozhabri et al. 2015; Pei et al. 2016). Mechanistically, NF-κB drives transcription of pro-inflammatory mediators, thereby antagonising odontogenic transcription factors and matrix synthesis (Hozhabri et al. 2015). Modulating NF-κB, therefore, alters the inflammatory set-point that permits DSPP/DMP1 upregulation and mineral deposition.

As for the HIF signalling pathway, HIF-1α is a master transcription factor that influences MSC and DPSC survival, paracrine activity, and differentiation through metabolic reprogramming and the induction of angiogenic factors (Razban et al. 2012; Shi et al. 2019). HIF-1α stabilisation increases cell viability in ischemic microenvironments, promotes vascular endothelial growth factor (VEGF) and other pro-angiogenic/metabolic targets, and can indirectly favour odontogenic outcomes by improving cell survival and vascular support required for matrix mineralisation (Han et al. 2022). Similarly, HIF-1α activation in hypoxic culture conditions detrimentally affects the osteogenic differentiation potential of porcine DPs (Agata et al. 2008). Thus, HIF-1α shapes the niche permissive for DSPP/DMP1 expression by coupling metabolism, survival, and angiogenesis.

PI3K/AKT signalling exerts context-dependent effects on proliferation, migration, and odontogenesis of DPSCs (Zhang et al. 2020). PI3K/AKT activation supports proliferation and early commitment, while pharmacologic inhibition (e.g., LY294002) reduces DSPP levels, highlighting its role in odontoblastic marker regulation (Park et al. 2022). Interestingly, the same study demonstrates that downstream branching to mTOR (noted as PI3K/AKT/mTOR signalling pathways) produces opposite outcomes, promoting stemness, thereby attenuating DPSC osteogenic differentiation potential (Park et al. 2022). Apart from mTOR, PI3K/AKT crosstalks with Wnt/β-catenin (via AKT-mediated GSK3β inhibition) allows amplification of DSPP/DMP1 transcriptional programs (Rajasekar et al. 2025). TGF-β can also activate the PI3K/AKT pathway, resulting in AKT phosphorylation, which enhances cellular survival and metabolic functions of DPSCs (Hamidi et al. 2017).

Taken together, integrating modulation of NF-κB (to limit deleterious inflammation), stabilisation of HIF-1α (to enhance survival/angiogenesis), and transient activation of PI3K/AKT (to support commitment and survival), while preserving pro-odontogenic cues such as Wnt and TGF-β, may provide a mechanistic basis for promoting DSPP/DMP1-driven mineralisation.

3 | Extracellular Matrix Cues in Pulp Regeneration

3.1 | ECM Composition and Odontogenic Differentiation

The native dental pulp ECM is a complex meshwork of collagens (types I and III being predominant), non-collagenous glycoproteins (e.g., fibronectin, laminin), and proteoglycans (e.g., decorin, biglycan) that together create the niche for dental pulp tissue. Beyond structural support, this composition provides biochemical cues that regulate stem cell fate (Cosgrove et al. 2016; Alqahtani et al. 2018; Bakhtiar et al. 2020). By binding growth factors, mediating cell adhesion, and activating receptors such as integrins, ECM molecules initiate intracellular signalling cascades in DPSCs (Ivaska and Heino 2011; Assal et al. 2013). Specific ECM components exert distinct effects. Fibronectin promotes robust upregulation of odontoblastic markers ALP and DSPP, whereas laminin-5 or laminin-332 induces ALP but not DSPP, indicating differential effects of basement membrane proteins on lineage commitment (Lee et al. 2023). In line with this, laminin loss during pulp decellularisation disrupts odontoblast layer formation, while its reintroduction enhances adhesion and restores odontogenic differentiation in vivo (Fu et al. 2020). Proteoglycans such as heparan sulfate and decorin further support regeneration by modulating the availability of growth factors, sequestering bFGF and presenting it to FGFRs, thereby creating localised morphogen reservoirs that guide cell fate (Kresse and Schonherr 2001). Collectively, collagens provide scaffolding, fibronectin and laminin regulate differentiation via adhesion receptors, and proteoglycans modulate growth factor availability, together orchestrating a microenvironment conducive to dentine regeneration.

On a mechanistic level, ECM molecules engage integrin receptors on DPSCs, triggering signalling pathways (such as FAK, MAPK, and Wnt pathways) that converge on the nucleus to regulate genes involved in differentiation (Shih et al. 2011; Rahman et al. 2018). Moreover, the ECM acts as a reservoir for growth factors, including TGF-β1, VEGF, and bFGF itself, which can be retained and gradually released (Alqahtani et al. 2018; Li et al. 2020; Gross et al. 2023). By sequestering such factors, the ECM prolongs their availability to cells and ensures spatially localised signals that guide DPSCs toward odontoblast lineage commitment. The dual role of ECM components, providing structural scaffolding and presenting biochemical signals,

makes them indispensable in strategies aiming to regenerate a well-organised dentine–pulp complex.

3.2 | DPSC-Derived Matrices and Bioactive Scaffolds

DPSCs not only respond to ECM cues but can also produce a bioactive extracellular matrix of their own that can be leveraged for regenerative therapy. When DPSCs are cultured under suitable conditions (e.g., in osteogenic medium with ascorbic acid), they secrete a rich matrix that can be decellularised to yield a DPSC-derived ECM scaffold. This DPSC-secreted ECM has been shown to recapitulate much of the native pulp microenvironment's inductive potential. For instance, decellularised matrices from DPSCs contain a "matrisome" enriched in collagens and other proteins associated with mineralisation, especially if the DPSCs were driven toward an odontogenic/osteogenic phenotype during matrix production (Nowwarote et al. 2021, 2024; Chansaenroj et al. 2022; Phothichailert et al. 2022, 2024; Kornsuthisopon et al. 2024). A recent proteomic analysis compared ECM from DPSCs versus gingival stem cells (GSCs) and found that DPSC-derived ECM harbours unique osteogenic signature proteins (e.g., BMP-2, periostin, LEF1) that are less abundant in GSC-derived ECM (Kornsuthisopon et al. 2024). Functionally, when GSCs were reseeded onto DPSC-derived ECM, they showed upregulation of Hippo and Wnt signalling pathways and markedly enhanced osteogenic differentiation (Nowwarote et al. 2021; Kornsuthisopon et al. 2024). This underscores the instructive power of pulp cell-derived matrices in guiding stem cell fate. Moreover, decellularised dental pulp ECM has been tested in vivo and shown to support the regeneration of pulp-like tissue. Hydrogels from decellularised bovine dental pulp ECM retained critical growth factors, including TGF-β1, VEGF, and bFGF, which were released in a sustained manner (Elnawam, Thabet, Mobarak, Abdallah, and Elbackly 2024; Elnawam, Thabet, Mobarak, et al. 2024). Such growth factor retention likely underpins the scaffold's bioactivity. In animal studies, implanted decellularised pulp scaffolds promoted well-organised connective tissue ingrowth and odontoblastic layer formation in canal spaces (Hu et al. 2017). One study noted that adding hyaluronic acid to a pulp ECM hydrogel further sustained growth factor release and potentially enhanced the regenerative outcome (Elnawam, Thabet, Mobarak, Abdallah, and Elbackly 2024; Elnawam, Thabet, Mobarak, et al. 2024). Together, these findings highlight that ECM-based scaffolds—especially those derived from pulp cells—can faithfully mimic the native niche by providing both the physical framework and the molecular signals needed for dentine–pulp regeneration. Going forward, optimising decellularisation methods to preserve delicate ECM cues and possibly augmenting them with specific components (like laminin or fibronectin supplementation) could yield off-the-shelf scaffolds that reliably induce DPSCs or recruited host cells to regenerate pulp tissue.

3.3 | Matrix Stiffness and Topography as Regulatory Signals

Beyond composition, the biophysical properties of the ECM—its stiffness (elastic modulus) and topographical features—critically regulate DPSC behaviour via mechanotransduction (Li

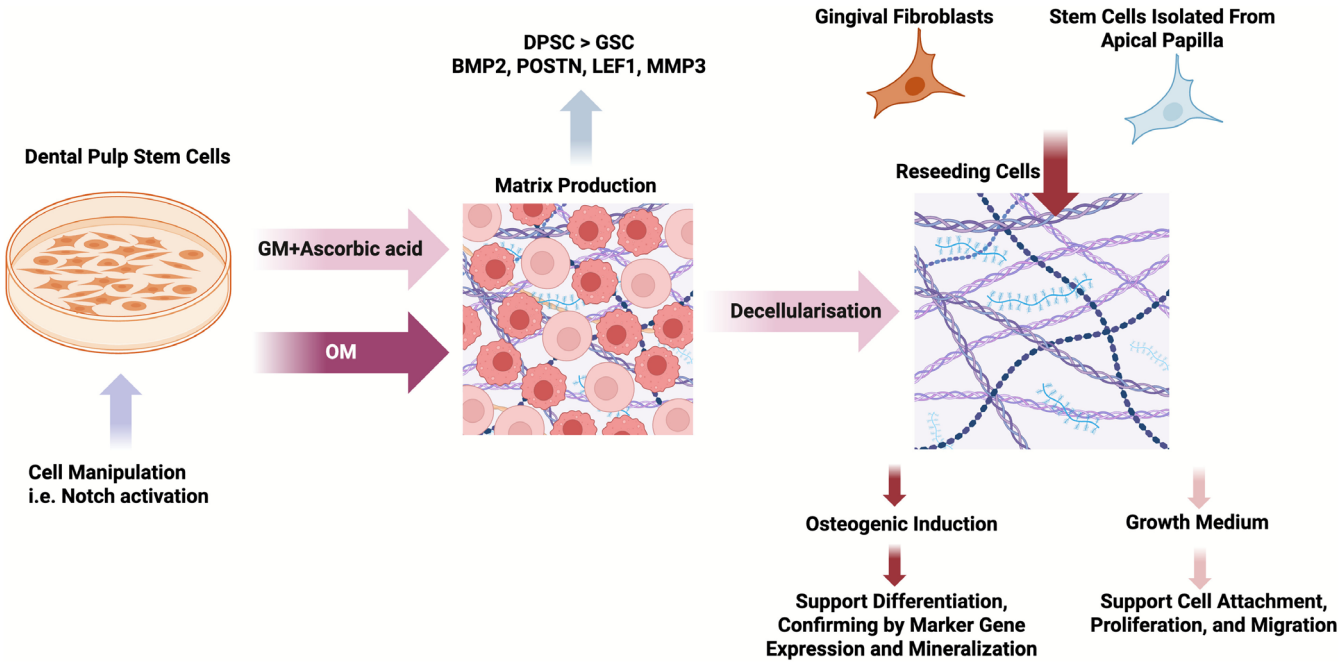

FIGURE 6 | Influence of DPSC-derived ECM on oral cells' behaviour and regenerative outcomes. DPSCs are cultured under growth medium supplemented with ascorbic acid (GM + ascorbic acid) or osteogenic medium (OM) to produce ECM. Following decellularisation, the resulting matrix retains bioactive components that influence recipient cells, including GFs and SCAPs. DPSC-derived ECM supports proliferation and mineralisation. Proteomic analysis of the matrix (matrisome) reveals the enrichment of collagens and elastic fibres in native ECM (N-ECM), while OM-ECM contains affiliated proteins mediated in part through Hippo and Wnt signalling pathways. DPSCs produce matrices richer in osteogenic-associated proteins (BMP2, POSTN, LEF1, MMP3) compared to gingival stem cells (GSC). Created in BioRender. https://BioRender.com/tt3wtze.

TABLE 1 | Summary table of regulatory pathways and extracellular matrix components governing odontogenic and osteogenic differentiation of dental pulp stem cells.

Component	Target/mechanism	Functional outcomes	Conflicting evidence/ Concerns	References
TGF-β signalling				
TGF-β1/2/3	Canonical (Smad activation) and non-canonical (PI3K/ AKT, MAPK)	Early: promotes proliferation, odontogenic commitment. Late: inhibits mineralisation	Stage-specific biphasic effect; transient exposure beneficial, prolonged exposure suppressive	Wu et al. (2016); Lin et al. (2018); Kang et al. (2005); Zhang et al. (2009); Manokawinchoke et al. (2021); Bai et al. (2022)
TGF-β delivery (liposomes, dECM)	Sustained release/ ECM delivery	Enhances migration, odontogenic markers, and mineralisation	Multiple cues act; difficult to ascribe to TGF-β alone; exposure timing critical	Jiang et al. (2020); Salkin et al. (2022); Kornsuthisopon et al. (2024)
Wnt signalling (canonical and non-canonical)				
Tideglusib (Small molecule Wnt agonist)	GSK-3β inhibitor activates Wnt/β-catenin	Enhances odontogenic/ osteogenic marker expression, mineralisation in DPSCs; dentine regeneration in injury models	Compared with CHIR99021, tideglusib increases mineralisation but may be less potent; dose/ delivery vehicle matters	Neves et al. (2017); Hanna et al. (2023); Kornsuthisopon et al. (2023)
CHIR99021 (Small molecule Wnt agonist)	GSK-3β inhibitor activates Wnt/β-catenin	Robust upregulation of odontoblastic markers and mineralisation; dentine regeneration	Often stronger marker induction than tideglusib; potency may increase off-target risk	Neves et al. (2017); Hanna et al. (2023)
BIO (Small molecule Wnt agonist)	GSK-3β inhibitor activates Wnt/β-catenin	Enhances odonto/osteogenic differentiation, mineralisation	—	Neves et al. (2017); Kornsuthisopon et al. (2023)
LiCl (Small molecule Wnt agonist)	GSK-3β inhibitor activates Wnt/β-catenin	Enhances β-catenin, mineralisation; improves dentine bridge formation in animal models	—	Neves et al. (2017); Han et al. (2014); Ishimoto et al. (2015); Ali et al. (2019); Vijaykumar and Mina (2021); Sukarawan et al. (2023)

(Continues)

TABLE 1 | (Continued)

Component	Target/mechanism	Functional outcomes	Conflicting evidence/ Concerns	References
Wnt proteins (Wnt1, Wnt3a, WNT3A, Wnt4 Wnt10a, and WNT5A)	Native ligands, canonical/ non-canonical Wnt	Promote reparative dentinogenesis; enhance proliferation, mineralisation, and expression of odonto/osteogenic markers.	Delivery/stability challenges for native Wnts due to hydrophobicity	Feng et al. (2013); Zhang et al. (2014); Zhao et al. (2014); Hunter et al. (2015); Zhao et al. (2018); Zhong et al. (2019); Li et al. (2023); Fujii et al. (2024)
Notch signalling				
Immobilised JAG1	Activates Notch receptors NICD release, HES/HEY induction; Crosstalk with non-canonical Wnt, BMP, FGF, and IL-15 signalling	Promotes odonto/osteogenic differentiation and mineralisation	Ligand identity and presentation (immobilised vs. soluble) are critical	Manokawinchoke et al. (2017); Hansamuit et al. (2020); Kornsuthisopon et al. (2021); Kornsuthisopon, Chansaenroj, et al. 2022
DLL1	Notch activation (ligand-dependent)	Promotes self-renewal and odonto/ osteogenic potential in DPSCs	Ligand type and cell context yield variable outcomes	He et al. (2009); Wang et al. (2011)
FGF signalling				
bFGF (FGF-2)	FGFR MEK/ERK, PLCγ pathways	Potent mitogen and chemoattractant; expands DPSC pool, enhances migration and stemness; short-term promotes odontoblast commitment	Time-dependent effect: beneficial only during the early regenerative window; sustained exposure can prevent maturation and lead to disorganised calcification; Dose-dependent effect: low–moderate doses balance proliferation and differentiation, whereas high doses cause excessive proliferation/ angiogenesis that may disrupt tissue architecture	Kanda et al. (1999); Sagomonyants and Mina (2014a); Sagomonyants and Mina (2014b); Nowwarote, Pavasant, and Osathanon (2015); Sagomonyants et al. (2017)

(Continues)

TABLE 1 | (Continued)

Component	Target/mechanism	Functional outcomes	Conflicting evidence/ Concerns	References
bFGF delivery (hydrogels/sequential)	Localised release strategies	Early release helps recruitment; sequential delivery proposed for regeneration.	Release kinetics determine the effect	Kataoka et al. (2021)
ECM				
Fibronectin	Integrin FAK/MAPK	Upregulates odontoblastic markers (*ALP* and *DSPP*) and supports odontoblastic differentiation	Different ECM proteins have selective effects	Lee et al. (2023)
Laminin	Basement membrane cue via integrins	Induces *ALP* (not *DSPP*) expression; restores odontoblast layering	Different ECM proteins have selective effects	Fu et al. (2020)
Proteoglycans (heparan sulfate, decorin)	Growth factor sequestration/ presentation	Modulate growth factor activity and DPSC fate	Composition highly variable by protocol	Kresse and Schonherr (2001)
DPSC-derived dECM	Biomimetic matrisome delivering multiple proteins	Promotes mineralisation, activates Hippo and Wnt signalling pathways, enhances osteogenesis	Multiple factors contribute; preservation of cues is crucial	Nowwarote et al. (2021); Kornsuthisopon et al. (2024)
ECM mechanics	Mechanotransduction (YAP/TAZ, FAK)	Stiffer substrates favour differentiation	Optimal stiffness depends on species/culture	Lin et al. (2018); Wang et al. (2022); Zhang, Li, et al. (2024); Li et al. (2025)
Other modulators				
NF-κB inhibitors	Block inflammatory transcription	Improves odontoblastic marker expression under inflammation	Inflammation status strongly alters outcomes	Hozhabri et al. (2015)
HIF-1α stabilisation	Metabolic/angiogenic reprogramming	Increases survival, VEGF; supports vascularisation	Context-dependent effects	Agata et al. (2008); Han et al. (2022)
PI3K/AKT modulators	PI3K/AKT activation; Crosstalk with Wnt/β-catenin and TGF-β	Promotes proliferation, migration, and odontogenesis	Context-dependent effects; Downstream branches to mTOR produce opposite outcomes	Hamidi et al. (2017); Zhang et al. (2020); Park et al. (2022); Rajasekar et al. (2025)
CBD	Modulates Wnt and Notch signalling (Identified by transcriptomic analysis)	Enhances odonto/osteogenic differentiation, mineralisation; Restores osteogenic differentiation under inflammation	Mechanisms partially defined; more validation needed	Liu et al. (2024); Kornsuthisopon et al. (2025)

et al. 2025). In the confined pulp chamber, the stiffness of dentine and the predentin layer provides a mechanical context that pulp cells can sense (Gross et al. 2023). DPSC responds to substrate stiffness; a rigid matrix (approximating mineralised dentine) can encourage osteogenic/odontoblastic differentiation. Whereas a softer matrix (resembling pulp tissue) may maintain stemness or favour other lineages (Wang et al. 2022). ECM stiffness influences cell shape and cytoskeletal tension, which in turn governs the activity of mechanosensitive transcriptional regulators such as YAP/TAZ (Li, Raghunathan, et al. 2022). Indeed, it has been shown that when DPSCs are cultured on substrates of varying stiffness, their lineage-specific gene expression shifts accordingly, with higher stiffness upregulating osteo/odontogenic markers and very low stiffness maintaining a more quiescent or fibroblastic phenotype (Liu et al. 2018). Recent work also identified YAP-dependent mechanotransduction as a key pathway by which the "young" (compliant) versus "old" (stiffer) microenvironment influences pulp cell regenerative capacity (Zhang, Li, et al. 2024). Similarly, nano- and micro-scale topography of scaffolds (such as aligned fibres or patterned surfaces) can modulate DPSC differentiation (Rahman et al. 2018; Diana et al. 2020). For regenerative endodontics, these insights suggest that an ideal scaffold must strike a balance in stiffness, rigid enough to encourage odontoblast-like differentiation to form dentine, yet compliant enough to permit cell infiltration and angiogenesis. Hydrogels or decellularised matrices can be cross-linked to adjust stiffness, a key factor in regenerative performance. Insufficient stiffness or rapid degradation of pulp ECM hydrogels has been shown to impair their efficacy (Elnawam, Thabet, Mobarak, Abdallah, and Elbackly 2024; Elnawam, Thabet, Mobarak, et al. 2024). Decellularised DPSC-derived matrices not only support the proliferation and differentiation of SCAP, but with activation of Notch signalling in DPSCs, the mineralisation ability is enhanced (Song et al. 2017; Phothichailert et al. 2022), suggesting potential for development into novel allografts for regenerative endodontic therapies or pulp capping applications (Figure 6). Thus, engineering the mechanical niche in tandem with biochemical signals is essential for guiding DPSCs. Future investigations using tunable biomaterials and 3D culture systems will further delineate how specific ranges of stiffness and defined topographies correlate with optimal dentine formation, and how mechanotransductive signalling pathways could be targeted to enhance regeneration.

Taken together, the present study highlights the intricate signalling pathways and ECM components and characteristics that regulate the odontogenic and osteogenic differentiation of DPSCs, as summarised in Table 1. Crosstalk between major pathways is depicted in Figure 7.

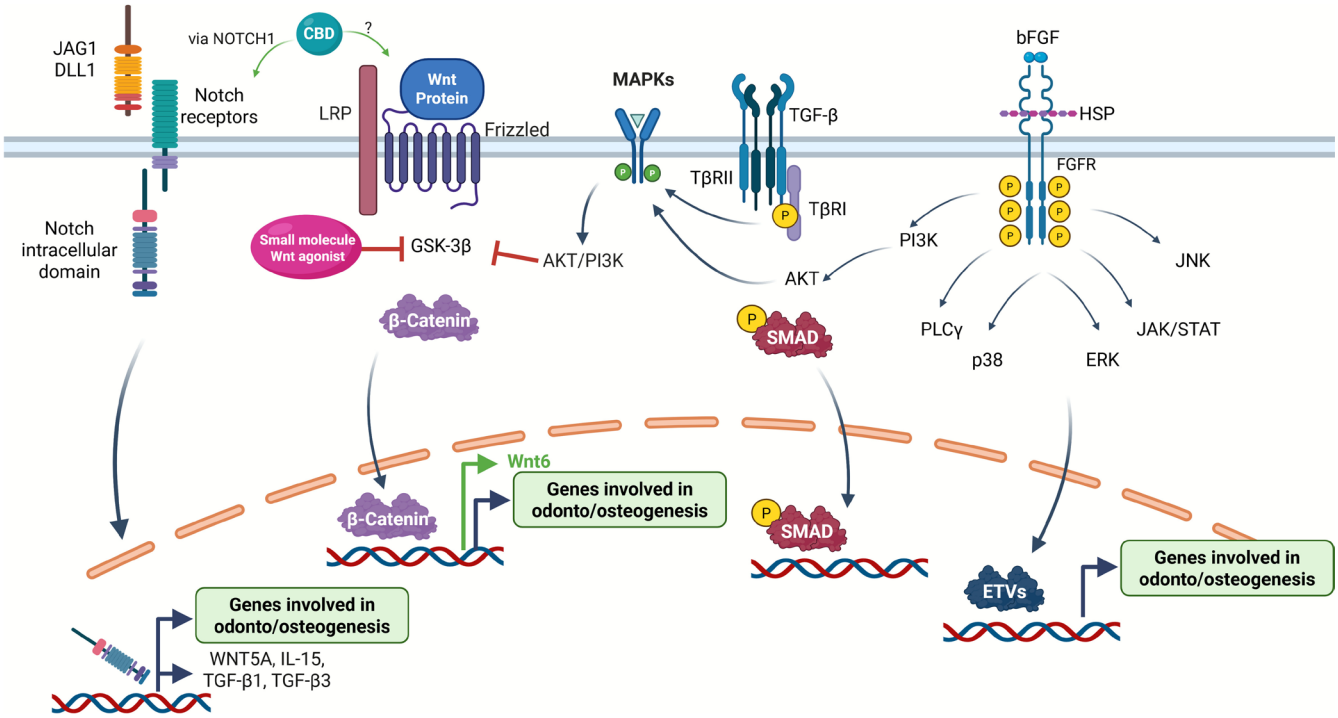

FIGURE 7 | Crosstalk among Notch, Wnt, TGF-β, and bFGF signalling pathways regulating odonto/osteogenic differentiation of DPSCs. Notch activation occurs when membrane-bound ligands (e.g., DLL or Jagged) bind to the Notch receptor on neighbouring cells, leading to proteolytic cleavage and release of NICD. The NICD translocates into the nucleus, where it interacts with transcriptional regulators to control genes involved in lineage-specific differentiation. The Wnt/β-catenin pathway is activated either by Wnt proteins binding to Frizzled/LRP receptors or through inhibition of GSK-3β by small molecules, resulting in β-catenin stabilisation, nuclear translocation, and subsequent activation of genes involved in odonto/osteogenesis. Wnt signalling further interacts with the MAPK and AKT/PI3K cascades, creating a regulatory feedback loop. TGF-β/SMAD signalling, through receptor-mediated phosphorylation of SMAD proteins, synergistically regulates odontogenic and osteogenic gene expression, working in conjunction with Wnt-driven β-catenin activity. FGF signalling results in several downstream activations, including the PI3K/AKT pathway, which further initiates Wnt activation by targeting GSK-3β. Other components, such as CBD, are suggested to modulate Notch (via NOTCH 1) as well as Wnt6 gene expression. Created in BioRender. - https://BioRender.com/vwst0x8.

4 | Conclusion

A thorough understanding of the regulatory mechanisms governing DPSC differentiation is fundamental for advancing therapeutic strategies. Beyond the well-characterised pathways, additional regulatory cascades continue to emerge, reflecting the complexity of dentine–pulp biology. Evidence highlights that effective dentine–pulp repair and regeneration depend not on isolated signals but on recreating the natural microenvironment, where biochemical cues act synergistically with ECM support to guide lineage commitment and tissue organisation. While these insights provide a strong foundation for next-generation therapies, successful clinical translation will require careful assessment of feasibility, cost, and comparative effectiveness relative to existing material-based dental methodologies.

Author Contributions

Chatvadee Kornsuthisopon: conceptualisation, methodology, data curation, writing – original draft, writing – review and editing. **Nunthawan Nowwarote:** methodology, data curation, writing – original draft, writing – review and editing. **Tanida Srisuwan:** data curation, writing – review and editing. **Waruna Lakmal Dissanayaka:** data curation, writing – review and editing. **Thanaphum Osathanon:** project administration, conceptualisation, methodology, data curation, writing – review and editing. All authors have contributed significantly and agree with the manuscript.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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