# Molecular atlas of root dentinogenesis and spatiotemporal signaling pathways: A systematic review

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**Abstract.** The present systematic review aimed to combine the evidence on rodent models on molecular regulators of root dentinogenesis across the temporal phases and spatial zones, and evaluate the translation of this map for human dental development and regenerative therapies. A PRISMA 2020-guided systematic review of experimental studies through the major electronic databases was performed. Data on models, molecules, techniques, spatiotemporal expression and the functional outcomes were extracted. The ARRIVE guidelines and SYRCLE's risk of bias tool were used to assess the risk of bias in animal studies. The evidence form rodent studies supports an organized network that begins with initiation at the cervical loop that requires the downregulation of mesenchymal fibroblast growth factor (FGF)10 and the activation of epithelial Sonic hedgehog (SHH) and mesenchymal bone morphogenetic protein (BMP)2/4. During elongation, the cervical zone exhibits high nuclear factor IC (NFIC), BMP/TGF-β and dentin sialoprotein (DSPP) activity associated with differentiation, whereas the apical zone maintains proliferation through SHH, FGF2 and Wnt signaling. Maturation involves the upregulation of dentin sialophosphoprotein (DSPP) and dentin matrix protein 1 (DMP1), followed by Hertwig's epithelial root sheath (HERS) disintegration. The signaling crosstalk indicates that NFIC modulates Hh through Hhip, BMP/TGF-β inhibits Wnt to prevent ossification and RUNX2 activates the Wnt inhibitor, Notum. The rodent-derived spatiotemporal framework reveals evidence of conservation for selected molecular pathways in human genetic and cellular studies, while the extent to which the complete spatial and temporal organization is conserved in human root development remains incompletely defined. The synthesis therefore provides a conceptual basis for further mechanistic and preclinical investigation of biomimetic regenerative strategies.

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## Introduction

Root dentin forms the bulk of the tooth root, providing structural support and anchorage for the tooth within the jawbone. It is vital for tooth function and integrity, and any defects in root dentin formation, arrested root development, short root anomaly and dentin dysplasia can lead to tooth loss. Although critical, root dentinogenesis has received less attention than crown development, even though it is essential for occlusion, periodontal health and sensory function. The understanding of root development at the molecular level is crucial for the diagnosis of congenital root defects and for designing regenerative endodontic therapies (1).

Anatomically, once crown formation is complete, a new epithelial structure, the Hertwig's epithelial root sheath (HERS), appears. HERS is formed from the fusion of inner and outer enamel epithelia at the cervical loop and extends apically. It functions as a temporary scaffold and its signals induce the underlying neural crest-derived mesenchyme (dental papilla) to condense and differentiate into pre-odontoblasts and odontoblasts that deposit root dentin; HERS then disintegrates to permit cementum and ligament formation. When HERS continuity is disrupted experimentally, odontoblast differentiation fails and roots are malformed (1).

Furthermore, HERS itself secretes signaling and growth factors that function as a local signaling center to orchestrate root formation (2,3). Simultaneously, the apical papilla [the undifferentiated mesenchyme at the root tip that contains the stem cells of the apical papilla (SCAPs)] also contributes progenitor cells for dentinogenesis. Therefore, root development depends on coordinated epithelial-mesenchymal interactions involving HERS and apical stem cells (1,2). Different regions along the root axis (cervical, middle and apical thirds) and different developmental stages (initiation, elongation and maturation) feature distinct signaling environments (4,5). The molecular gradient along the tooth root is increasingly recognized, and certain growth and transcription factors are upregulated in early HERS growth, but are subsequently downregulated thereafter, while others peak in mid-root. For instance, Wnt10a exhibits a dynamic epithelial and mesenchymal expression pattern during tooth-root development, with stage-dependent

changes associated with root furcation morphogenesis (4), and bone morphogenetic protein (BMP) and Sonic hedgehog (SHH) are present at the onset of root formation in the inner enamel epithelium and dental mesenchyme (5). Therefore, it was hypothesized that dynamic spatial and temporal patterns of signaling molecules, rather than a uniform environment, regulates root patterning.

Animal models, particularly mouse molars, provide key experimental systems for investigating the cellular and molecular mechanisms of tooth-root development, including the spatiotemporal regulation of HERS, dental mesenchymal progenitors and odontoblast differentiation (1). The findings from these models provide a basis for investigating the relevance of selected developmental pathways to human root development and regeneration.

The present systematic review aimed to integrate all available evidence from rodent models on the molecular regulation of root dentinogenesis, organized along both temporal and spatial axes. Moreover, a detailed spatiotemporal map of signaling pathways [e.g., nuclear factor IC (NFIC)/TGF-β, BMP/Smad, Wnt/β-catenin, SHH, fibroblast growth factor (FGF) and dentin sialoprotein (DSPP)] during root formation was constructed, and the extent to which this rodent-based map can be translated to human dental development and applied in dental regeneration was evaluated.

## Data and methods

The PRISMA 2020 guidelines for systematic reviews were followed. A comprehensive full literature search was performed using the PubMed, Scopus and Web of Science databases from database inception to December, 2025. The database search used three predefined concept blocks: i) Root development and related anatomical/developmental terms; ii) molecular, gene-expression, signaling pathway, transcription factor and growth factor terms; and iii) rodent species terms. The Boolean structure was [('root development' OR 'root formation' OR 'root dentinogenesis' OR 'Hertwig's epithelial root sheath' OR 'odontoblast differentiation' OR 'apical papilla development') AND (molecular OR 'gene expression' OR 'signaling pathway' OR BMP OR Wnt OR FGF OR SHH OR NFIC OR RUNX2 OR DSPP OR DMP1 OR 'transcription factor' OR 'growth factor') AND (rat OR mouse OR rodent OR murine)].

*Inclusion criteria*. Eligibility was defined using the Population, Exposure, Comparator, and Outcome (PECO) criteria. The population comprised developing root tissues of permanent teeth, including HERS, dental papilla/apical papilla and odontoblasts. The exposure comprised experimentally investigated molecules or signaling pathways, including gene expression studies, genetic manipulation and pathway inhibition. Comparators included different developmental time points or spatial regions and, where available, wild-type vs. mutant or experimentally manipulated conditions. Outcomes included root dentin histology, molecular expression patterns and dentin measurements or histomorphometric findings. Only original experimental studies providing interpretable spatial or temporal information and a molecular mechanism relevant to root development were eligible.

*Exclusion criteria*. Studies limited to crown development, primary teeth, non-mammalian species, *in vitro* systems without an eligible *in vivo* root development component, reviews, editorials, conference abstracts and studies lacking interpretable spatial/temporal or mechanistic information were excluded.

*Study selection*. The identified records were imported into Rayyan software (https://new.rayyan.ai/reviews). Duplications were removed automatically and verified manually. Moreover, two reviewers MHA and BAG, independently checked titles and abstracts for relevance, then reviewed full texts of potentially qualified articles.

The data were extracted into a table and the extracted items included the following: Author, year of publication; species and model, the key molecule/pathway, the experimental technique and the spatiotemporal expression pattern with the functional role/outcome and any reported human correlation.

The results were then organized into spatial zones and temporal phases. The spatial zones covered the regions involved in root elongation and maturation; cervical (near the enamel junction), middle and apical (root tip) thirds of the root were considered. Furthermore, the temporal phases were initiation (root patterning and onset of HERS), elongation (active odontoblast differentiation and dentin deposition) and maturation (dentin mineralization and root apex closure).

*Assessment of reporting quality and risk of bias*. Reporting quality was assessed using an adaptation of the ARRIVE 2.0 Essential 10 framework and, as the ARRIVE 2.0 guidelines do not prescribe a numerical scoring system, a descriptive scoring approach was applied to the 10 Essential 10 items: 1 point for fully reported, 0.5 points for partially reported, and 0 points for not reported. This scoring approach was based on a previously published ARRIVE reporting-quality assessment that used the same 1/0.5/0 scoring system to distinguish fully reported, partially reported and unreported information (6,7). In the present systematic review, the score was restricted to the 10 ARRIVE Essential 10 items, and the total score was expressed as a percentage of the maximum possible score.

Risk of bias was assessed using the Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) tool for animal studies (8). The risk-of-bias tool is comprised of 10 items as follows: D1, sequence generation; D2, baseline characteristics; D3, allocation concealment; D4, random housing; D5, blinding of investigators; D6, random outcome assessment; D7, blinding of outcome assessment; D8, incomplete outcome data; D9, selective outcome reporting; D10, other sources of bias. For each item, the judgment was 'low', 'high', or 'unclear' risk of bias.

## Results

*Study selection*. The database search identified 1,922 records (PubMed, 398; Scopus, 431; Web of Science, 1,093). Following the removal of 150 duplicates and 806 records for other reasons (non-English and reviews), 966 records remained for title/abstract screening. Of these, 687 were excluded and 279 full-text articles were assessed for eligibility. A total of 215 full-text articles were excluded for the following reasons:

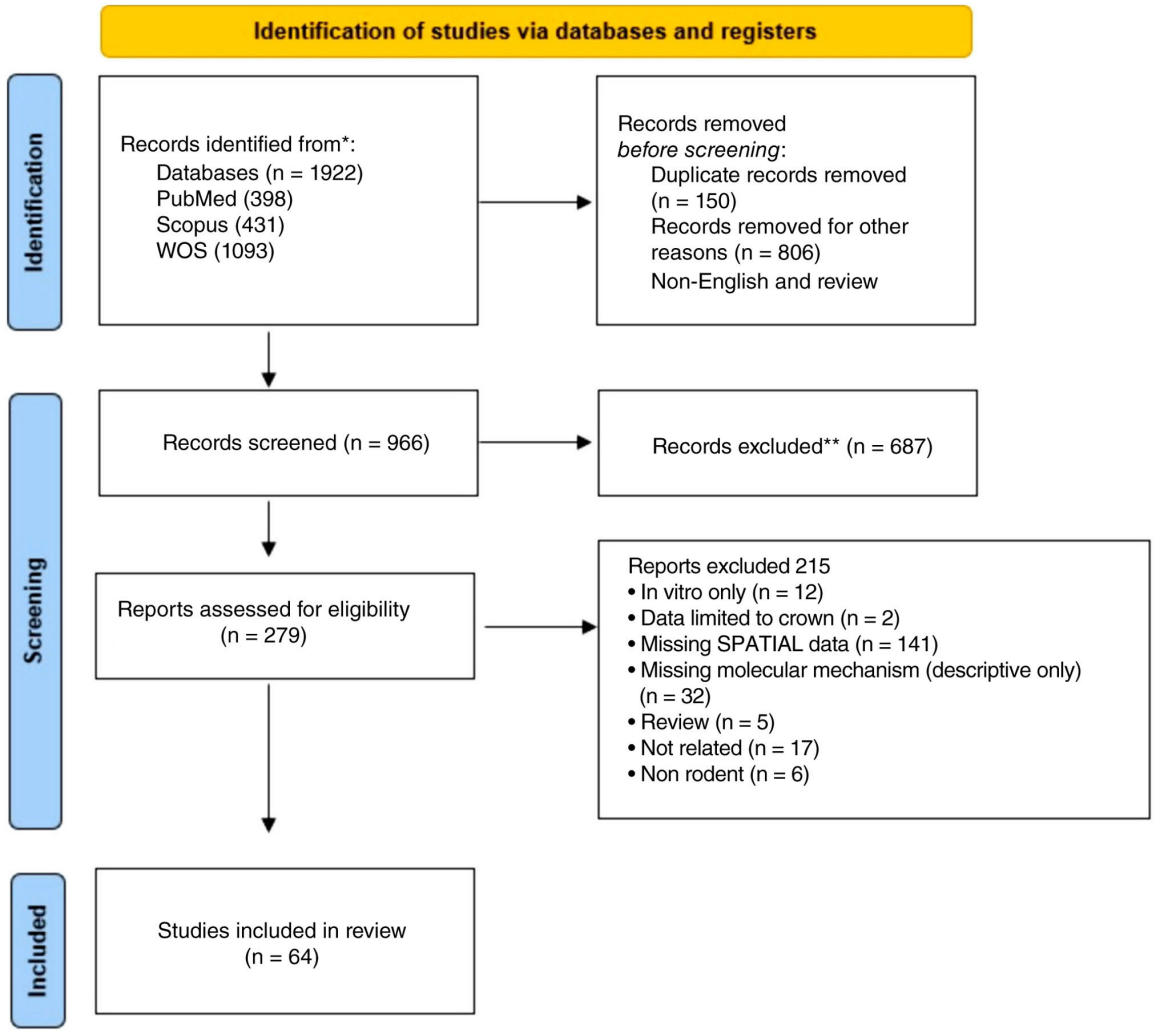


Figure 1. PRISMA 2020 flow diagram outlining the systematic search and selection process, yielding 64 eligible studies from 1,922 initial records.

*In vitro* only (n=12), data limited to crown (n=2), missing spatial/temporal data (n=141), missing molecular mechanism (descriptive only) (n=32), reviews (n=5), not related to root development (n=17), non-rodent (n=6). Finally, 64 studies met the inclusion criteria and were included in the qualitative synthesis, as illustrated in the PRISMA flow diagram (Fig. 1).

*Study characteristics*. A total of 64 studies (3-5,9-69) met the inclusion criteria and were included in the qualitative synthesis. The evidence was predominantly derived from *in vivo* mouse studies (n=61), with three studies using rats. Common experimental approaches included genetic knockout or conditional deletion models and pathway-specific manipulation. The reported techniques included immunohistochemistry, *in situ* hybridization, micro-CT and RNA-based analyses. In total, 18 studies also reported human correlative evidence, including human genetic findings, histological observations, or experiments using human stem cells from the apical papilla. Detailed characteristics of all the included studies, including model, developmental phase, spatial comparison and principal findings, are presented in Table I. Molecular interactions and functional validation are summarized in Table SI, while rodent findings and reported human evidence are summarized in Tables II and SII.

*Spatial and temporal patterning of root development*

*The initiation phase of root development*. Root initiation was characterized by a transition from the crown-forming program to the root-forming program at the cervical loop. The reviewed experimental evidence consistently implicated cessation of FGF10 signaling together with epithelial BMP/SMAD4 and SHH activity in this transition. BMP/SMAD4 signaling was linked to SHH induction, which subsequently contributed to mesenchymal NFIC activation and odontoblast-lineage specification. These findings identify coordinated epithelial-mesenchymal signaling as a central feature of root initiation (3,9-11).

*The elongation phase of root development*. During root elongation, the evidence supported a spatially organized signaling environment along the apical-cervical axis. The apical region was characterized by signaling associated with progenitor maintenance and proliferation, including SHH/Gli1, Wnt/β-catenin and FGF pathways, whereas the cervical-to-midroot region exhibited greater involvement of BMP/TGF-β signaling and NFIC-dependent odontoblast differentiation (5,12,13). The experimental disruption of these pathways produced region-specific abnormalities, including impaired proliferation, shortened roots, defective odontoblast differentiation and abnormal dentin formation (14-16). The

Table I. The 64 studies that met the inclusion criteria.

| First author, year of publication | Model | Temporal phase | Spatial zones compared | Key spatial finding | (Refs.) |
|---|---|---|---|---|---|
| Steele-Perkins, 2003 | NFIC KO Mouse | Initiation | Labial, lingual | $NFIC^{-/-}$ molars have normal crowns but completely lack roots. Incisors show asymmetric dentin formation (labial normal, lingual absent). Alveolar bone fails to form specifically around missing roots. | (9) |
| Shimamura, 2025 | Chd3 KO mouse | Initiation | Cervical width vs. Crown width; Apical papilla vs. other dental papilla | Cervical width significantly narrowed at PN8; $Ki\text{-}67^{+}$ cells decreased specifically in apical papilla at PN8. | (10) |
| Yokohama-Tamaki, 2006 | Mouse incisor ($Fgf10^{-/-}$ transplant), mouse molar culture | Initiation | Labial vs. lingual side; IEE vs. OEE/stellate reticulum; crown analog vs. root analog | Loss of Fgf10 causes labial side (normally crown-forming) to develop root-like structures with HERS and fragmented epithelium, mimicking molar root development. | (11) |
| Sun, 2024 | K14-Cre; Wnt10a mouse (M1) | Initiation | HERS in presumptive root furcation region (buccal vs. lingual, elongation direction) | Wnt10a ablation impairs horizontal elongation of HERS; increases angle of elongation vs. horizontal plane. | (12) |
| Fujiwara, 2009 | Mouse ddY, lower first molar | Initiation | Cervical loop (IEE, OEE, SR) vs. HERS; Crown vs. root apex | Reduction of Egf signaling in the cervical loop is necessary for SR disappearance and subsequent HERS formation, initiating root development. | (13) |
| Yu, 2020 | K14-Cre; Wnt10a fl/fl mouse molars | Initiation/ elongation | Cervical loop/furcation region epithelium vs. mesenchyme; furcation vs. non-furcation (mesial) region | Loss of epi-Wnt10a decreases epithelial proliferation in presumptive furcation at PN0 but increases mesenchymal proliferation in the furcation at PN4/7, leading to failed furcation formation. | (4) |
| Hirose, 2013 | C57BL/6 mouse, PN10-20 | Initiation/ elongation | HERS basal vs. apical tip | AMBN localized in basal HERS, absent at tip; siRNA causes multilayered basal HERS | (17) |
| Ihn, 2021 | Bbx KO mouse | Initiation/ elongation | Crown vs. root; mesial vs. distal root; dental epithelium vs. mesenchyme; odontoblasts vs. HERS cells | Bbx expressed in both epithelium and mesenchyme during development. KO leads to shorter mesial and distal roots but normal crown length. | (18) |
| Hosoya, 2008 | Mouse (ICR) first molar | Initiation/ elongation | HERS vs. surrounding dental papilla/ mesenchyme vs. odontoblast layer | BMP4 is expressed in mesenchyme surrounding HERS; BMP receptors localized in HERS cells. BMP4 from mesenchyme signals to HERS to inhibit its elongation. | (19) |

Table I. Continued.

| First author, year of publication | Model | Temporal phase | Spatial zones compared | Key spatial finding | (Refs.) |
|---|---|---|---|---|---|
| Huang, 2019 | BMP9-KO mouse | Initiation/ elongation | Whole-root comparison (KO vs. WT): Root length, mid-root dentin thickness, apical foramen width; no explicit cervical vs. apical comparison within roots | BMP9 deficiency leads to globally shorter roots, thinner dentin, and wider apical foramen. | (20) |
| Gama, 2020 | Mouse (C57BL/6J), Rankl$^{-/-,+/-}$, Tg; Anti-RANKL Ab | Initiation/ elongation | Lingual vs. buccal; HERS vs. dental pulp vs. apical follicle vs. alveolar bone | Bone matrix deposition preferentially interrupts follicle-papilla boundary in buccal region in Rankl$^{-/-}$. HERS cell number differs between lingual/buccal regions and genotypes. | (21) |
| Nagata, 2025 | Mouse (C57BL/6); Cxcl12-creER lineage tracing; Ctnnb1 cKO | Initiation/ elongation | AP vs. coronal dental papilla; root dentin (inside) vs. cementum (outside) | CXCL12$^{+}$ cells emerge specifically in the hypoxic AP at root onset (P3). These progenitors give rise to odontoblasts (inner dentin) and cementoblasts (outer root surface). | (22) |
| Mu, 2021 | K14-cre; Bmp2/4 dKO mouse | Initiation/ elongation | HERS (epithelium) vs. root mesenchyme (odontoblasts/dental papilla) | Epithelial Bmp2/4 deficiency disrupts signaling in adjacent mesenchyme, suppressing odontoblast differentiation and dentin formation. | (23) |
| Liu, 2023 | Mouse (Fam20a epi-cKO) | Initiation/ elongation | HERS; cervical vs. apical periodontium; coronal eruption path | HERS is disorganized and persists longer in cKO; cervical and apical periodontal fiber orientation is altered in cKO at P16. | (24) |
| Bae, 2013 | Mouse WT & β-catenin cKO | Initiation/ elongation | Crown odontoblasts vs. apical odontoblasts (root apex) | Identifies 'apical odontoblasts' (AOds) as a distinct population located at the apical side of developing roots, responsible for root formation. | (25) |
| Kim, 2015 | Nfic KO mouse | Initiation/ elongation | Elongation region vs. furcation region | In mutants, cell proliferation decreased in elongation region but increased in furcation region; leads to short roots and abnormal/delayed furcation (taurodontism-like). | (26) |
| Romero, 2017 | Eda/Edar mutant mice | Initiation/ elongation | Bifurcation region vs. outside; buccal vs. lingual HERS; mesenchymal zones adjacent to HERS | Mutant HERS extends at a wider, more vertical angle in the bifurcation region; increased mesenchymal proliferation adjacent to HERS in non-bifurcating mutants. | (27) |
| Chen, 2014 | SD rat, WT | Initiation/ elongation | HERS cells vs. adjacent DPCs vs. distant DPCs/DFCs | Nfic expression is highest in DPCs immediately adjacent to HERS; absent in HERS itself. | (28) |

Table I. Continued.

| First author, year of publication | Model | Temporal phase | Spatial zones compared | Key spatial finding | (Refs.) |
|---|---|---|---|---|---|
| Ma, 2021 | Mouse mesenchymal Ror2 conditional knockout (Osr2-Cre) | Initiation/ elongation | Apical dental mesenchyme vs. epithelium; crown vs. root; furcation vs. elongation region; odontoblast differentiation in apical region | Ror2 in dental mesenchyme regulates cell proliferation specifically in the apical region, affecting root elongation and furcation formation. Crown development is unaffected. | (14) |
| Wen, 2020 | Mouse mandibular first molar; Gli1-CreERT2;Runx2 <sup>fl/fl</sup> conditional KO | Initiation/ elongation | Apical dental mesenchyme vs. other regions; HERS vs. adjacent dental papilla; preodontoblast region | RUNX2$^{+}$ cells are a subpopulation of GLI1$^{+}$ MSCs in the apical mesenchyme. NOTUM expression is restricted to preodontoblasts adjacent to HERS. Runx2 ablation disrupts cellular patterning and differentiation in this specific zone. | (29) |
| Pei, 2024 | Mouse (Gli1-CreER; Fgfr2fl/fl) | Initiation/ elongation | Apical/middle/coronal papilla; dental follicle; HERS; odontoblast layer; PDL | Sensory nerves and FGF1 enriched in apical papilla. Fgfr2 expressed in Gli1$^{+}$ progenitors in papilla/follicle. Loss of Fgfr2 disrupts proliferation/differentiation in these zones. | (15) |
| Huang, 2010 | K14-Cre; Smad4fl/fl and Nfic$^{-/-}$ mouse molars | Initiation/ elongation | Crown vs. root; HERS (epithelium) vs. dental papilla/follicle (mesenchyme) | Without Smad4, HERS enlarges at the crown apex but fails to elongate apically to guide root formation. | (3) |
| Lav, 2023 | Mouse Gli1creERT2; Wls cKO | Initiation/ elongation | Apex vs. crown base; apical HERS vs. mesenchyme; radicular vs. periodontal tissues | Wnt-responsive Axin2$^{+}$ stem/progenitors shift from crown base to root apex during development. Loss of apical Wnts disrupts HERS integrity and apical mesenchymal organization. | (30) |
| Kim, 2013 | Mouse β-catenin cKO (odontoblast) | Initiation/ elongation | Crown vs. cervix vs. apical region; HERS inner vs. outer layer; odontoblast lineage stages | β-catenin loss disrupts odontoblast differentiation specifically in the cervical region, preventing root dentin formation despite HERS extension. | (31) |
| Lohi, 2010 | Axin2-lacZ mouse | Initiation/ elongation | Cervical (cusp/ ameloblast-free zone) vs. apical (root); Epithelium (enamel knots) vs. mesenchyme (papilla); crown vs. root | Canonical Wnt activity (via Axin2) is excluded from ameloblasts, high in enamel-free cusp tips and root-forming regions (HERS, dental papilla, inter-radicular zone). | (32) |
| Liu, 2015 | Mouse 1st mandibular molar (WT & Nfic$^{-/-}$) | Initiation/ elongation | HERS vs. Apical Papilla; Gradient within AP (proximal vs. distal | Shh ligand expressed in HERS. Hh activity (Gli1) highest in HERS, forms a diminishing | (5) |

Table I. Continued.

| First author, year of publication | Model | Temporal phase | Spatial zones compared | Key spatial finding | (Refs.) |
|---|---|---|---|---|---|
| | | | to HERS) | gradient into the AP. Proliferation highest in AP cells nearest HERS. | |
| Liu, 2026 | Mouse Bmp9-KO and adenovirus silencing | Initiation/ elongation/ maturation | Apical foramen width, root dentin thickness, HERS, odontoblast layer | Bmp9 deficiency leads to shorter roots, wider apical foramen, thinner dentin, impaired odontoblast differentiation, and reduced HERS proliferation. | (33) |
| Li, 2023 | Sox2-Cre; Fam20c cKO mouse | Initiation/ elongation/ maturation | Crown vs. root region; focus on root odontoblasts and apical papilla | Defects (morphological, differentiation, proliferation) were more severe in the root region compared to the crown in cKO mice. | (34) |
| Xu, 2016 | MT1-MMP KO (mouse) | Initiation/ elongation/ maturation | Cervical vs. apical root; buccal vs. lingual aspects; HERS vs. papilla/follicle; PDL vs. bone interface | HERS structure altered apically; Dentin thinner in roots; PDL disorganized with absent Sharpey's fiber insertion into bone; reduced alveolar bone formation. | (35) |
| Du, 2021 | Mouse Gli1-CreER; Arid1afl/fl | Initiation/ elongation/ maturation | Apical progenitor region vs. differentiated root regions (furcation, lateral) | Loss of Arid1a in apical Gli1$^{+}$ progenitors leads to overactivated proliferation in apical region but impaired differentiation into odontoblasts and PDL throughout root. | (36) |
| Park, 2007 | Nfic KO mouse | Initiation/ elongation/ maturation | Cervical root vs. apical root; HERS vs. odontoblast layer | Nfic disruption does not affect HERS morphology but causes disorganized, non-polarized odontoblasts specifically in the root, leading to short, abnormal roots resembling osteodentin. | (37) |
| Ono, 2016 | Mouse genetic models (PPR cKO) | Initiation/ elongation/ maturation | Dental follicle vs. papilla; cervical (CEJ) to apex; root surface (cementum/PDL) vs. dentin/pulp; interradicular area | Oss$^{+}$ progenitors in dental follicle/papilla give rise to all root lineages. PPR signaling in these cells is essential for proliferation at HERS and formation of organized PDL/ acellular cementum. PTHrP is expressed on the root surface in cementoblasts/PDL cells. | (38) |
| Yun, 2016 | Mouse (Osr2-Cre; Smad4fl/fl, OC-Cre; Smad4fl/fl) | Initiation/ elongation/ maturation | Crown dentin vs. root dentin (particularly cervical region) | Smad4 loss leads to thinner crown dentin and replacement of root/cervical dentin with ectopic bone-like tissue. | (39) |
| Zhang, 2013 | Mouse OC-Cre; Ctnnb1 cKO | Initiation/ elongation/ maturation | Crown vs. root; cervical vs. apical root; labial vs. lingual incisor; | Wnt/β-catenin signaling is active in apical pre-odontoblasts and HERS. Its loss disrupts root/ | (40) |

Table I. Continued.

| First author, year of publication | Model | Temporal phase | Spatial zones compared | Key spatial finding | (Refs.) |
|---|---|---|---|---|---|
| | | | HERS vs. papilla | lingual dentin and periodontium formation, but crown/labial structures remain intact. | |
| Lapthanasupkul, 2012 | Mouse; Ring1a$^{-/-}$; Ring1bcko/cko (conditional KO) | Elongation | Cervical vs. apical (molar root); HERS vs. dental papilla (Bmp4 expression). | Expression of Ring1a, Ring1b, Nspc1, Fbxl10 and Skp1 were all found to be localized in postnatal molars in apical areas at the early stages of root formation, particularly in root odontoblasts. | (41) |
| Zheng, 2024 | Mouse (K14-Cre; Axin1 cKO) | Elongation | HERS vs. apical mesenchyme | Axin1 expression and function is restricted to HERS epithelium; its loss disrupts signaling to adjacent odontoblasts. | (16) |
| Huang, 2018 | RANKL KO mouse | Elongation | HERS vs. dental pulp; radicular odontoblast region (whole root) | HERS elongation and radicular odontoblast differentiation are disrupted in the mutant. | (42) |
| Wang, 2023 | Atp6i KO mouse | Elongation | HERS vs. dental papilla; odontoblast layer | HERS truncation in mutants; p-Smad2/3 attenuation in odontoblast layer. | (43) |
| Cui, 2024 | Mouse incisor/ molar; human DPSCs | Elongation | Lingual (root) vs. labial (crown); cervical loop, papilla-pulp, dental follicle; apical/coronal/ middle papilla | HMCN1 expression is higher on the root-forming (lingual) side in cervical loop and pulp-papilla, and is concentrated in the root-side dental pulp and odontoblasts. | (44) |
| Zhang, 2015 | Mouse odontoblast-specific Ctnnb1 conditional knockout | Elongation | HERS structure along the developing root (cervical to apical progression) | Loss of β-catenin in odontoblasts leads to premature and excessive HERS fenestration/fragmentation, disrupting normal root elongation. | (45) |
| Sheng, 2021 | Mouse (C57BL6/J) conditional KO; human DPCs | Elongation | Crown vs. root | METTL3 expression differs between crown and root. METTL3 loss causes root-specific defects: short/thin root, sparse odontoblast processes in radicular but not coronal dentin. | (46) |
| Bae, 2013 | Mouse [OC-Cre: Catnb$^{+}$/lox(ex3)] | Elongation | Cervical region (300 and 100 $\mu$m apical to CEJ) | Mutants have thin, hypomineralized root dentin and excessive cementum deposition along the root surface compared to WT. | (47) |
| Lee, 2009 | Nfic KO mouse | Elongation | Incisor: Labial crown analog vs. lingual root analog; odontoblast layer organization | Nfic deficiency causes dentin formation failure in the lingual root analog and abnormal dentin/odontoblast dissociation in the labial analog. Loss of odontoblast polarity and sheet-like arrangement. | (48) |

Table I. Continued.

| First author, year of publication | Model | Temporal phase | Spatial zones compared | Key spatial finding | (Refs.) |
|---|---|---|---|---|---|
| Khan, 2007 | Mouse (CD-1) wild-type | Elongation | Cervical margin vs. early root dentine vs. apical HERS; HERS epithelium vs. adjacent papilla/follicle mesenchyme vs. peripheral mesenchyme | SHH signaling is active only in HERS epithelium and adjacent mesenchyme within a short range (few cell diameters). Differentiated root odontoblasts show no SHH pathway activity. | (49) |
| Nakatomi, 2006 | Mouse Ptc<sup>mes</sup> mutant | Elongation | HERS vs. adjacent dental mesenchyme (pulp proliferation zone); epithelium vs. mesenchyme; apical vs. coronal regions | Shh signaling molecule expression and cell proliferation markers extensively overlap in the mesenchyme adjacent to HERS. Loss of Shh signaling represses proliferation in this zone. | (50) |
| Yang, 2021 | Inducible β-catenin CKO/stabilization in mouse HERS | Elongation | HERS bilayer vs. dental papilla; Root apex | β-catenin loss disrupts HERS bilayer integrity prematurely; β-catenin stabilization prevents HERS dissociation. Altered signaling from HERS affects adjacent papilla cells. | (51) |
| Hosoya, 2025 | Lewis rat (wild-type and injury) | Elongation/ maturation | Apical vs. coronal root odontoblasts; cervical loop vs. differentiated zone in incisor | Bmi1, nuclear β-catenin and p-Smad1/5/8 show strong apical-to-weak coronal gradient in root odontoblasts. | (52) |
| Wang, 2021 | Mouse M1 (BRE-LacZ, BAT-gal) | Elongation/ maturation | Dental sac, crown pulp vs. root pulp, apical papilla, HERS, mesenchyme below cusps | BMP activity shifts coronally to apically; Wnt activity initiates under cusps, expands around root, then disappears. | (53) |
| Rakian, 2013 | Bmp2-cKO (Sp7-Cre) mouse | Elongation/ maturation | Cervical loop vs. apical papilla; pulp vs. odontoblast layer vs. periodontium; CIFC vs. AEFC | Bmp2 deletion in $Sp7^{+}$ cells disrupts terminal differentiation in root odontoblasts and organization of the periodontium and cementum. | (54) |
| Bae, 2015 | Mouse odontoblast-specific Wls CKO | Elongation/ maturation | Crown vs. root; cervical vs. apical; odontoblast layer; HERS | Dentin thickness reduced more severely in roots; Root elongation impaired due to reduced cell proliferation at apex; HERS fragmentation delayed. | (55) |
| Li, 2018 | Mouse Ift140 cKO | Elongation/ maturation | Future cusp vs. root area; Furcation/ Interradicular dentin; root vs. crown dentin | IFT140 expressed in root odontoblasts; Deletion causes thin interradicular dentin, short roots, but normal crown dentin. | (56) |
| Sun, 2010 | CaR KO and double KO mice | Elongation/ maturation | Apical pulp, Hertwig's epithelial root sheath (HERs), predentin vs. | In $CaR^{-/-}$ mice: $PTHrP^{+}$ and $PCNA^{+}$ cells decreased in apical pulp and HERs; | (57) |

Table I. Continued.

| First author, year of publication | Model | Temporal phase | Spatial zones compared | Key spatial finding | (Refs.) |
|---|---|---|---|---|---|
| | | | mineralized dentin, dental alveolar bone | predentin area increased; mineralized dentin and alveolar bone volume decreased. Rescued in $CaR^{-/-}$; $Pth^{-/-}$ mice. | |
| Nakatomi, 2013 | Rat incisor and molar (developmental + injury) | Elongation/ maturation | Incisor (apical bud to mature zone) vs. molar (crown vs. root dentin formation); Intact vs. injured pulp | Lef1 expression precedes Dspp in all spatial contexts. Markers are downregulated in resting molar odontoblasts but not in continuously growing incisors. | (58) |
| Gao, 2014 | Mouse (P1-P20), human SCAPs *in vitro* and *in vivo* transplant | Elongation/ maturation | Odontoblasts/ preodontoblasts vs. pulp vs. apical papilla vs. PDL vs. alveolar bone vs. HERS; coronal vs. root pulp | NFIC expression strongest in odontoblasts/preodontoblasts, weak in pulp/apical papilla, absent in HERS. Higher in coronal vs. root pulp. | (59) |
| Zhang, 2015 | Osx cKO and Nfic KO mice | Elongation/ maturation | Crown dentin vs. root dentin; Incisor crown-analog vs. root-analog | OSX is essential for establishing normal dentin tubule architecture and thickness in the root, but not in the crown. | (60) |
| Kim, 2015 | Mouse conditional Osx KO (Col1a1-Cre; OC-Cre) | Elongation/ maturation | i) Crown vs. root; ii) root apex (elongation) vs. interradicular (furcation) dentin | Osx is required in root, but not crown odontoblasts. Root shortening and severe interradicular dentin hypoplasia. | (61) |
| Wang, 2017 | Bmp1/Tll1 conditional dKO mouse | Elongation/ maturation | Crown vs. root; central vs. lateral root | Root defects more severe than crown. Predentin expansion greater in lateral vs. central root. | (62) |
| Foster, 2013 | $Alpl^{-/-}$ mouse | Elongation/ maturation | Crown vs. root; buccal vs. lingual root dentin | Root dentin mineralization defective (esp. lingual aspect); crown dentin spared. | (63) |
| Lin, 2023 | Mouse (Ogn KO) | Elongation/ maturation | Cervical (CEJ) vs. middle vs. apical; apical papilla vs. dental follicle | Root hard tissue (dentin/cementum) thicker at all zones in $Og^{n-/-}$ mice; Hh pathway activity spatially localized to AP/DF at PN15. | (64) |
| Foster, 2018 | $Spp1^{-/-}$, $Ank^{-/-}$ mice | Elongation/ maturation | Dentin/cementum, alveolar bone (buccal/ lingual, cervical/mid/ apical), pulp, PDL | $Spp1^{-/-}$ increases dentin/ alveolar bone volume/density, decreases pulp/PDL volume. Acellular cementum thickness unchanged. | (65) |
| Jeong, 2024 | Mouse (inducible β-catenin stabilization in HERS; Catnb <sup>lA5hh</sup>) | Elongation/ maturation | Cervical vs. apical (HERS dissociation front) | Stabilization of β-catenin in HERS prevents its apical dissociation into epithelial rests of Malassez (ERM), leading to arrested root elongation and hypomineralized apical dentin. | (66) |

Table I. Continued.

| First author, year of publication | Model | Temporal phase | Spatial zones compared | Key spatial finding | (Refs.) |
|---|---|---|---|---|---|
| Niibe, 2025 | Hdac3-CKOosx mice (C57BL/6) | Maturation | Crown vs. root; mesial vs. distal roots; root apex; cervical loop; dentin/cementum thickness gradients | CKO mice have shorter roots, smaller apices; cementum grows inward closing apex; dentin/cementum structure disorganized and thinner. | (67) |
| Kim, 2015 | Smad4 cKO mice (Dspp, OC, Col1a1-Cre) | Maturation | Crown, cervical region, root furcation | Dentin defects vary by zone; cervical region highly responsive to Smad4 during secondary dentin formation. | (68) |
| Zhang, 2019 | Mouse (P14), human SCAPs | Maturation | HERS vs. surrounding mesenchyme | GNAI3 expressed in HERS and surrounding mesenchyme during root development. | (69) |

individual experimental models and spatial comparisons are summarized in Table I.

*The functional maturation and termination of root development*. Root maturation involved continued odontoblast differentiation, dentin matrix production, mineralization and the remodeling of HERS. Sustained NFIC activity and expression of dentin-associated matrix genes, including DSPP and DMP1, were associated with functional dentin maturation (25,53,61,63). The evidence also indicated that HERS remodeling is an active developmental process, with inappropriate persistence or premature disruption of epithelial signaling associated with abnormal root development (30,51). These findings support HERS remodeling as an integral component of root maturation rather than a passive terminal event.

*Integrated signaling associations*. Across the included studies, multiple pathways exhibited evidence of interaction rather than independent activity. The principal associations identified included BMP/SMAD4-SHH-NFIC signaling (3,23), Wnt/β-catenin regulation by RUNX2-NOTUM (29), epithelial WNT10A interactions with mesenchymal Wnt signaling (4,12), and reciprocal epithelial-mesenchymal regulation involving BMP/TGF-β and HERS (19,23). Detailed interaction evidence and functional validation are provided in Table SI.

*Translational relevance of the rodent evidence*. The available human evidence supports the biological conservation of selected pathways identified in rodent models; however, it does not establish direct equivalence between rodent and human root development. Human genetic findings, concordant dental phenotypes and experimental observations in human dental stem-cell systems provide evidence that selected regulatory mechanisms are conserved. However, the complete spatial and temporal organization of these pathways during human root development remains incompletely defined.

However, the findings revealed that WNT10A mutations are associated with taurodontism in humans, while Wnt10a deficiency in mice disrupts root furcation morphogenesis through altered epithelial-mesenchymal signaling during root development (4). Additionally, other genes included in the present synthesis, including RUNX2, FAM20A, PTH1R, ROR2, AXIN2 and IFT140, have reported human or rodent associations with dental or craniofacial phenotypes (14,24,29,32,38,56).

Accordingly, the present rodent-based framework should be regarded as a translationally informative model for hypothesis generation and preclinical research rather than as a direct representation of human root development. The translational validation of rodent phenotypes and their relevance to human root-development pathways is summarized in Tables II and SII.

*Functional conservation in human dental stem cells*. Human stem-cell studies provide additional evidence that selected regulatory mechanisms identified in rodent models are conserved in human dental cells. Human SCAPs express NFIC, respond to FGF2 and TGF-β1 and activate the same NFIC-TGF-β1 feedback loop identified *in vivo* (43,59). Moreover, the RUNX2-NOTUM axis operates in human cells, confirming the conservation of Wnt attenuation mechanisms (29). These findings support the biological relevance of selected pathways identified in rodent root-development studies. However, the cellular conservation of individual signaling mechanisms does not demonstrate that the complete spatial and temporal signaling network identified in rodent models is reproduced during human root development. Further human developmental and translational studies are therefore required.

*Preclinical models for interventions*. Several experimental studies have provided preclinical proof-of-concept that selected molecular pathways can be modified to influence root-associated phenotypes (29,63,70,71). Enzyme replacement with a mineral-targeting tissue-nonspecific alkaline phosphatase prevented dental hypomineralization and defects in dentin and cementum in Akp2$^{-/-}$ mice, providing preclinical proof-of-concept for enzyme replacement therapy

Table II. Translational validation from rodent phenotypes to humans.

| Molecule/ pathway | Category | Source | Target cells | Function in rodent root formation | Human relevance/notes | (Refs.) |
|---|---|---|---|---|---|---|
| TGF-β (incl. Smad4)/BMPs | Initiator | HERS epithelium/ basal lamina | Dental papilla (odontoblast precursors) | Induces odontoblast differentiation and matrix secretion; patterns differentiation along the root axis | Smad4 disruption → short roots in rodents; candidate in human root dysplasia | (3,19,23, 54,68,71, 75) |
| SHH (Sonic hedgehog) | Spatial organizer | HERS/apical epithelium | Surrounding mesenchyme (Ptch/Gli-expressing cells) | Controls proliferation at root apex and contributes to root length and patterning; gradient-dependent effects on root number/shape | Implicated in furcation patterning models | (3,5,49, 50) |
| FGF10 | Initiation | Apical mesenchyme (cervical loop-associated) | HERS and mesenchyme | High FGF10 maintains crown program; downregulation required to permit root initiation; exogenous FGF10 delays root formation | Likely relevant in humans for crown-root transition timing | (11) |
| Wnt/β-catenin (Wnt10a etc.) | Growth and differentiation | Epithelium and mesenchyme | Odontoblasts, HERS | Promotes odontoblast differentiation and Dspp expression; influences root length and furcation; Wnt dysregulation → taurodont-like phenotypes | WNT10A variants associated with human dental anomalies (e.g., taurodontism) | (4,29,30,31, 47,51,55) |
| NFIC (nuclear factor IC) | Mesenchymal master regulator | Dental papilla (odontoblast lineage) | Odontoblast differentiation | Essential for root dentinogenesis; knockout → normal crowns but severely defective/short roots (fails to produce proper dentin) | Human NFIC perturbation linked to radicular dentin defects; strong translational candidate | (3,5,9,48, 59) |
| DSPP (dentin sialophosphoprotein) | Matrix/ effector | Odontoblasts (secreted) | Dentin matrix formation; ECM signaling | Major structural and regulatory dentin matrix protein. Its cleavage products modulate mineralization and cell behavior | DSPP mutations cause dentinogenesis imperfecta in humans | (58,60,61, 62) |
| Runx2/Osx (Sp7) | Periodontal lineage regulators | Dental follicle/ mesenchyme | Cementoblasts, PDL fibroblasts, alveolar osteoblasts | Direct osteo/cementogenic differentiation of follicle cells; loss → short roots and defective PDL | Runx2 mutations → bone/tooth phenotypes | (29,37,38, 60,61) |
| Wnt antagonists (DKK1, SFRP, | Modulators | Epithelium and | Wnt-responsive | Establish spatiotemporal Wnt | Fine-tune furcation and root width | (29,47) |

Table II. Continued.

| Molecule/ pathway | Category | Source | Target cells | Function in rodent root formation | Human relevance/notes | (Refs.) |
|---|---|---|---|---|---|---|
| Notum) | | mesenchyme | cells (HERS, follicle) | gradients necessary for correct root timing and patterning | | |
| Notch, Hippo-YAP, PI3K/AKT | Emerging regulators | Epithelium and mesenchyme | Proliferation, cell fate, survival | Modulate progenitor activity, epithelial-mesenchymal transitions, and cytoskeletal/growth responses during root formation; data still emerging in rat | Candidate pathways for translating complex human phenotypes and regeneration | (12,16,42) |

in hypophosphatasia (63,70). Moreover, pathway modulation is similarly effective: NOTUM protein partially rescues RUNX2 deficiency (29), the inhibition of Wnt signaling attenuates the ectopic osteogenic differentiation associated with Tgfbr2 deletion in root pre-odontoblasts, supporting functional cooperation between TGF-β and Wnt signaling during root odontoblast differentiation (71), and FGF signaling contributes to progenitor cell regulation during tooth root development (15), while NFIC is involved in the odontogenic differentiation of human stem cells from the apical papilla (59). Finally, emerging targets for intervention include $CXCL12^{+}$ apical progenitors (22), the OGN-Hedgehog axis (64) and HMCN1-mediated extracellular matrix signaling (44).

*Quality assessment of selected studies*. According to an adaptation of the ARRIVE 2.0 guidelines, the quality scoring system was applied to included studies (Y=1, P=0.5, N/NA=0). Overall, the quality percentages ranged from 30 to 75%, and the majority of studies were within the average-quality range (~50-75%). However, 14 studies scored <50%, reflecting substantial methodological or reporting deficiencies. As detailed in the study-level heatmap (Fig. 2) and summarized by the average compliance per criterion (Fig. 3), outcome reporting, the description of experimental procedures, presentation of results and the reporting of experimental animals were commonly rated as fully or partially adequate. This indicates that the majority of studies clearly describe what was measured, how experiments were conducted and what was observed. On the other hand, items of study design, sample size reporting and statistical analysis were partially addressed. The partial scoring suggests that methods were often mentioned, but lacked justification, transparency or sufficient detail (e.g., absence of power calculations or incomplete statistical descriptions). However, the items that were not reported (inclusion/exclusion criteria, randomization and blinding) directly increased the risk of bias, performance and detection bias.

*Risk of bias in studies*. Based on the SYRCLE risk of bias assessment, the overall pattern of the included studies indicated a low to unclear risk of bias, with relatively few items consistently reported as high risk. In particular, baseline characteristics (D2), incomplete outcome data (D8), selective outcome reporting (D9) and (D10) any other potential sources of bias, were rated as low risk, suggesting that outcome evaluation and reporting were generally handled in a transparent and reliable manner. By contrast, a higher risk of bias was observed and was confined to specific items, the blinding of caregivers or investigators (D5) and blinding of outcome assessment (D7), where several studies exhibited insufficient safeguards. The detailed results of the SYRCLE risk-of-bias assessment are presented in Fig. 4.

## Discussion

The present systematic review synthesized experimental rodent evidence on the molecular regulation of root dentinogenesis and organized the findings according to developmental phase and spatial region. Across the included studies, root formation emerged as a coordinated epithelial-mesenchymal process involving HERS, the apical progenitor compartment, odontoblast-lineage cells, and multiple interacting signaling pathways (1,3,5,31,51). The principal pattern identified was a transition from signaling associated with root initiation and progenitor maintenance toward pathways involved in odontoblast differentiation, dentin matrix deposition, mineralization and HERS remodeling (3,5,9,31,51).

Root initiation was associated with a transition at the cervical loop from the crown-forming program toward the root-forming program. The reviewed experimental evidence implicated the cessation of FGF10 signaling together with epithelial BMP/SMAD4 and SHH activity in this transition. BMP/SMAD4 signaling was linked to SHH induction, followed by mesenchymal NFIC activation and odontoblast-lineage specification (3,9). These findings support the interpretation that root initiation depends on coordinated signaling between the epithelium and adjacent mesenchyme rather than on an isolated molecular event (3,11).

During root elongation, the evidence supported a spatial organization of signaling along the apical-cervical axis. The apical region was associated with progenitor maintenance and


Figure 2. Heatmap of ARRIVE 2.0 reporting quality for the 64 included studies (Y=1, P=0.5, N/NA=0). The overall compliance ranged from 30 to 75%, with the majority of studies within the average range.

proliferation involving SHH/Gli1, Wnt/β-catenin and FGF signaling (30,32,55), whereas the cervical-to-mid-root region exhibited greater involvement of BMP/TGF-β signaling and NFIC-dependent odontoblast differentiation (9,60,61,71). The disruption of these pathways was associated with region-specific phenotypes, including impaired proliferation, shortened roots, defective odontoblast differentiation and abnormal dentin formation (5,14-16,31,55). The detailed experimental evidence underlying these associations is presented in Tables I and SI.

Root maturation involved continued odontoblast differentiation, dentin matrix production, mineralization and the remodeling of HERS. Sustained NFIC activity and the expression of dentin-associated matrix genes, including DSPP and DMP1, were associated with functional dentin maturation (9,60,61). The evidence also indicated that HERS remodeling is an active developmental process. The appropriate regulation of epithelial β-catenin signaling is associated with controlled HERS dissociation and fragmentation into the epithelial rests of Malassez, whereas the disruption of β-catenin activity can lead to premature HERS disruption or the failure of HERS dissociation and abnormal root development (51).

The principal contribution of the present systematic review is the systematic organization of experimental rodent evidence across spatial and temporal dimensions. The present

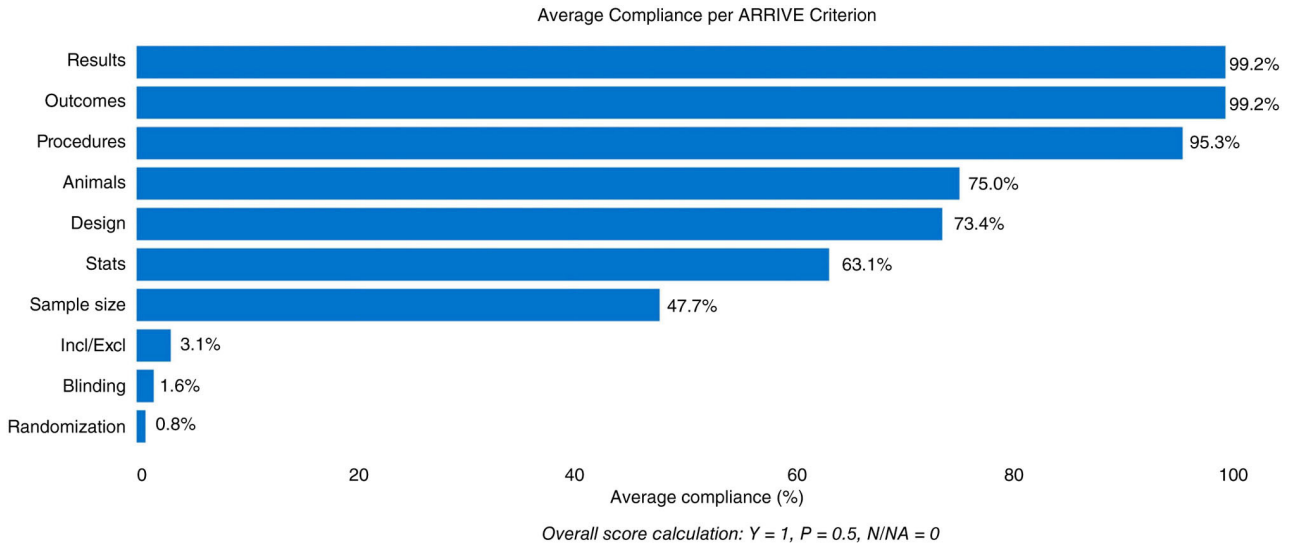


Figure 3. Mean ARRIVE 2.0 compliance per criterion. Outcomes and results were highly reported (>99%), while randomization, blinding and inclusion/exclusion criteria exhibited minimal reporting (<5%).

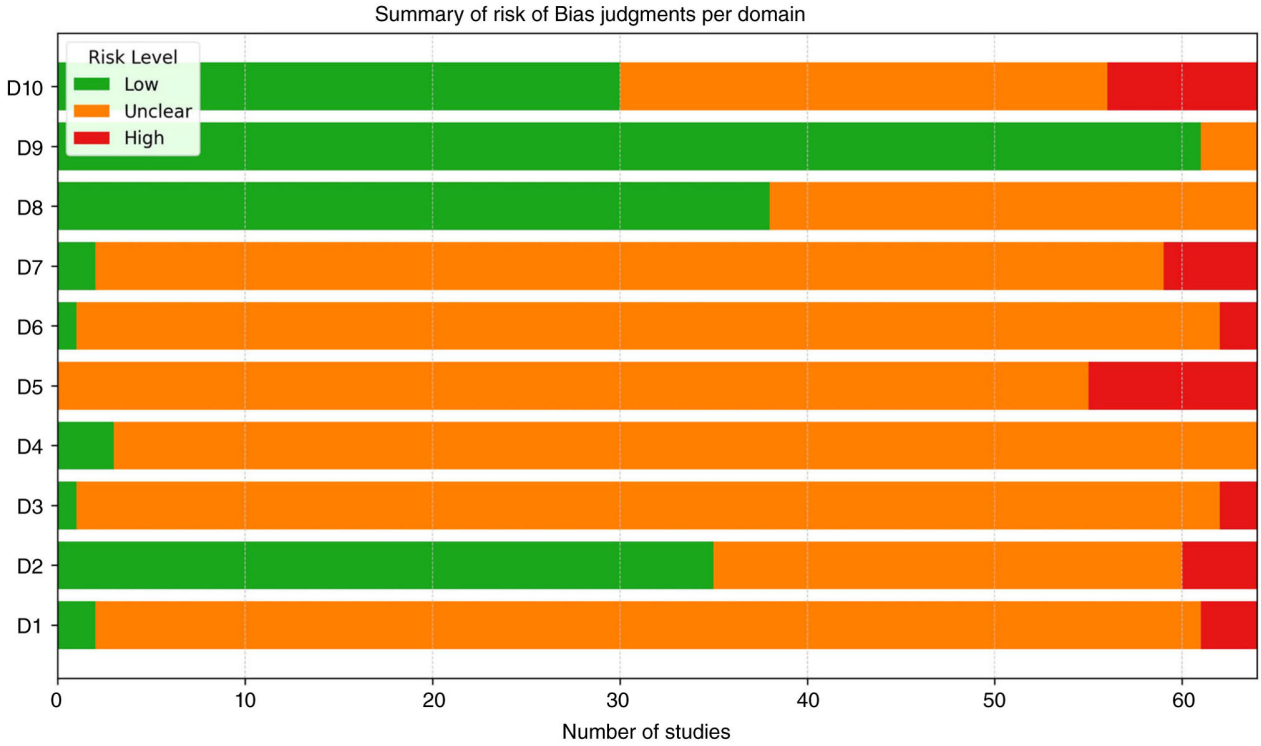


Figure 4. SYRCLE risk-of-bias judgments (low/unclear/high) across 10 domains (D1-D10) for all 64 studies. The highest risk was confined to blinding domains (D5 and D7), whereas outcome reporting (D8-D9) was consistently low risk. SYRCLE, Systematic Review Centre for Laboratory animal Experimentation. The domains are as follows: D1, sequence generation; D2, baseline characteristics; D3, allocation concealment; D4, random housing; D5, blinding of investigators; D6, random outcome assessment; D7, blinding of outcome assessment; D8, incomplete outcome data; D9, selective outcome reporting; D10, other sources of bias.

systematic review integrates predefined eligibility criteria with the structured extraction of developmental phase, spatial region, molecular perturbation, experimental technique, functional outcome and reported human correlation. This framework complements previous reviews of tooth-root development (72), while providing a structured synthesis focused specifically on experimentally investigated molecular mechanisms of root dentinogenesis. The aim was to identify reproducible associations and patterns across the available experimental evidence.

A key finding of this synthesis is that canonical Wnt/β-catenin signaling does not exert a uniformly promotive or inhibitory effect on root development. Its effects depend on the cellular compartment, developmental stage and interaction with other signaling pathways (4,12,31,47,51,55). Epithelial Wnt10a loss was associated with impaired HERS elongation and altered furcation patterning, whereas excessive β-catenin activity in odontoblast-lineage cells impaired root formation and was associated with abnormal differentiation and matrix

formation (47). In HERS itself, β-catenin inactivation caused premature HERS disruption, whereas β-catenin stabilization prevented normal HERS dissociation (51). These opposing phenotypes indicate that both insufficient and excessive pathway activity can be detrimental. However, the available evidence does not establish a universal quantitative concentration threshold for Wnt activity, but the findings support the concept that an appropriate level of Wnt pathway activity is required within a specific cellular and developmental context.

The context dependence of Wnt signaling is further supported by pathway integration. The disruption of TGF-β signaling in root pre-odontoblasts increased Wnt activity and was associated with ectopic osteogenic differentiation and osteodentin formation (71), whereas RUNX2-dependent induction of the Wnt antagonist NOTUM provides a mechanism for restricting Wnt activity during odontoblast differentiation (29). Thus, Wnt signaling is better interpreted as one component of an interacting epithelial-mesenchymal regulatory network than as an independent linear pathway. The functional consequences of Wnt modulation therefore depend not only on the direction of pathway alteration, but also on where and when the alteration occurs.

The reviewed evidence similarly demonstrates that BMP signaling is context-dependent. Mesenchymal BMP4 can inhibit HERS elongation through BMP receptors expressed by HERS cells (19), whereas epithelial BMP2/4 signaling contributes to HERS development and subsequent root formation (23). TGF-β/BMP signaling also contributes to odontoblast maturation and dentin formation in a stage- and site-dependent manner (68). These apparently different effects emphasize the importance of cellular source and anatomical location when interpreting pathway function. They also illustrate why broad genetic manipulations may produce phenotypes that differ from those obtained when the same pathway is manipulated in a defined cellular compartment.

Taken together, the evidence supports a model of root dentinogenesis in which signaling pathways operate through coordinated spatial and temporal interactions, rather than as independent linear mechanisms. HERS, the apical progenitor compartment and differentiating odontoblasts participate in reciprocal signaling associations that are altered during root initiation, elongation and maturation (3,5,30,51). The systematic organization of these associations provides a framework for interpreting apparently divergent experimental findings and for identifying questions that require further mechanistic investigation.

From a translational perspective, the human evidence supports the biological conservation of selected molecular pathways; however, it does not establish direct equivalence between rodent and human root development. Human genetic findings and studies of human dental stem-cell systems support the relevance of selected pathways, while the complete spatial and temporal organization of these signals during human root development remains incompletely characterized (4,59,73). The findings should therefore be regarded as a conceptual framework for hypothesis generation and preclinical investigation rather than evidence of direct therapeutic efficacy.

The reviewed experimental models suggest that the successful modulation of root development may require appropriate spatial and temporal control of interacting pathways, rather than non-specific delivery of a single growth factor (30,51). However, methods capable of reproducing these developmental conditions in engineered tissues remain investigational. Preclinical rescue experiments provide proof-of-concept that selected molecular pathways can be experimentally modified, but they do not establish clinical efficacy, safety, or the feasibility of reproducing the complete developmental signaling environment (29,70).

*Practical and clinical implications*. From a clinical perspective, the findings suggest that numerous congenital and acquired root defects arise from the disruption of spatial signal coordination rather than from failure of odontogenesis. Developmental root malformations, such as short root anomaly and single-root agenesis are related to specific disorders in signaling pathway interactions between BMP, Wnt/β-catenin, SHH and the transcription regulators NFIC (4,23). Moreover, the shortened roots are associated with impaired apical growth of HERS due to the failure of coordination of epithelial-mesenchymal reciprocal interaction (73).

Furthermore, root defects associated with hypophosphatasia result from tissue-nonspecific alkaline phosphatase (TNAP) deficiency, which compromises the root dentin and cementum mineralization (70). In fact, the understanding that these phenotypes are failures in specific developmental modules, such as the apical progenitor niche or HERS degeneration aids in the early diagnosis and management of pediatric and orthodontic patients. Short and abnormal root development may predispose the individual to orthodontic complications and may require force modification during treatment (73,74).

For regenerative endodontic therapy, the evidence suggests that successful root regeneration requires recreating the spatially restricted signaling and targeting the apical apex. The collected data from the pre-clinical experimental rodent models indicate that the gradient of SHH, Wnt/β-catenin, BMP and other pathways control the proliferation and differentiation along the apical to cervical axis during root formation (5,53). Therefore, the non-specific growth factor delivery may not recapitulate the target developmental patterning.

Accordingly, targeting the SHH and Wnt dependent progenitor niche with simultaneously promoting BMP/TGF/β-catenin-NFIC promote the differentiation in cervical region are necessary to achieve functional root elongation and maturation (50,75). However, the specific approaches to spatially constrain these signals in engineered tissues remain investigational.

Another approach is enzyme replacement strategies, the supplementation of TNAP in case of hypophosphatasia models demonstrates correction of the pathway deficits and can rescue the root dentin mineralization, which provides a proof-of-concept for targeted molecular therapies. As previously demonstrated, in TNAP-null ($Alpl^{-/-}$) mouse models, treatment with mineral-targeted TNAP prevented the dental hypo-mineralization and corrected defects of dentin and cementum formation (70), thereby supporting the concept that molecularly tailored therapy can restore critical aspects of root formation.

*Implications for developmental and regenerative biology research*. Theoretically, the present systematic review

advances the understanding of tooth root development by framing it as a modular and gradient-driven process analogous to other organ elongation systems. Moreover, the morphogen gradients regulate not only root elongation, but also patterning and growth in diverse biological contexts, where the graded distributions of signaling molecules coordinate cell fate and proliferation during organogenesis (76). The identification of HERS as both a structural guide and a dynamic signaling center corresponds to the known role of epithelial organizers in other systems, such as the limb bud organizers as apical ectodermal ridge signaling and gut epithelial patterning (77,78). These organizers serve as sites of concentrated signaling activity that instruct and direct adjacent tissues with respect to spatial patterning and growth.

Furthermore, the integration of transcription factors, signaling pathways and the epigenetic regulators in root development suggest that root dentinogenesis is controlled by a multilayered regulatory network rather than a linear pathway. The developmental biology has established that epithelial-mesenchymal interactions and layered signaling modules, such as SHH, Wnt/β-catenin, BMP/TGF-β and downstream transcription factors are essential for coordinated morphogenesis across organs (77,79).

Notably, the repeated disruption of normal pathway activation across multiple genetic models supports the concept that regenerative success depends on restoring developmental patterning cues rather than simply inducing differentiation. In fact, signals such as SHH and BMP function as true morphogens with diffusible patterning cues that form gradients interpreted by cells to adopt distinct fates depending on concentration thresholds (76,80). Taken together, these principles indicate that tooth root regeneration research could benefit from gradient-based engineering models.

Several limitations should be considered when interpreting this synthesis. First, the majority of the included studies used mouse models, with only three studies using rats, which limits direct extrapolation to human root development. Second, substantial heterogeneity existed among studies in genetic models, developmental stages, experimental interventions, spatial regions, and outcome measures. Third, the incomplete reporting of randomization and blinding was common, contributing to uncertainty in some risk-of-bias domains. Finally, although the systematic synthesis identifies consistent spatial and temporal patterns, the available studies do not permit establishment of quantitative pathway thresholds or a definitive causal hierarchy among all signaling pathways. Accordingly, the proposed framework should be interpreted as an evidence-based synthesis of current experimental findings, rather than as a complete or definitive model of human root development.

In conclusion, the present systematic review supports a model in which root dentinogenesis is regulated by a spatially and temporally organized network of epithelial-mesenchymal interactions involving HERS, the apical progenitor compartment, odontoblast-lineage cells and multiple signaling pathways. The evidence indicates that FGF, SHH, Wnt/β-catenin, BMP/TGF-β, NFIC, RUNX2-NOTUM and dentin-matrix pathways contribute to distinct stages of root initiation, elongation and maturation. The context-dependent effects of Wnt/β-catenin emphasize the importance of cellular location, developmental timing, and pathway interaction. Human genetic and cellular findings support conservation of selected molecular mechanisms; however, the complete spatial and temporal framework identified in rodent models remains insufficiently characterized in humans. The present synthesis therefore provides an evidence-based conceptual framework for future developmental and preclinical studies of root formation and regeneration.

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**Availability of data and materials**

The data generated in the present study may be requested from the corresponding author.

**Authors' contributions**

MHA conceptualized the study, was involved in the study methodology and provided software (Rayyan for screening; Microsoft Excel for data extraction/management). BA and MHA were involved in data curation, and in the writing and preparation of the original draft of the manuscript. MMFAH was involved in visualization (including figures and graphical presentation of the findings) and in the screening/investigation of included studies, the extraction of relevant evidence, and the assessment of study characteristics. BA supervised the study. MHA and MMFAH provided software (Rayyan for screening; Microsoft Excel for data extraction/management) and were involved in the validation of the extracted data and study findings. MHA was involved in the writing, reviewing and editing of the manuscript. MHA and BA confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**Use of artificial intelligence tools**

During the preparation of this work, AI tools (ChatGPT and Paperpal) were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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