Tooth Root Development and Homeostasis during Eruptive and Post-eruptive Movement

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Tooth eruption is the process whereby the developing tooth moves to its functional position in the occlusal plane and it occurs concomitantly with formation of the tooth root, which is a critical component of the tooth anchored to surrounding alveolar bone through the periodontal ligament. Post-eruptive tooth movement ensues that once occlusion is achieved, the teeth maintain their alignment within the alveolar bone to facilitate proper bite function through periodontium remodelling. Tooth overeruption presents a clinically significant issue, yet the precise mechanisms by which alterations in occlusal forces are translated into periodontal remodelling remain largely unexplored. In this review, the present authors aim to outline the latest progress on the potential mechanisms governing tooth root formation and homeostasis during tooth eruptive and post-eruptive movement. Based on recent findings using various mouse models, we provide an overview of the collaborative intercellular interaction during root formation, including Hertwig's epithelial root sheath, dental papilla and dental follicle. Moreover, we summarise the potential mechanism underlying post-eruptive movement mainly in view of the responses of periodontal tissues to vertical mechanical stimuli. In sum, the precise regulatory mechanisms during tooth eruption throughout life will shed light on disease treatment of tooth eruption defects and overeruption.

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The tooth, which comprises two functionally distinct components, the crown and the root, is critical for mastication, digestion and phonation.[1,2] Tooth development begins with the dental lamina and underlying dental mesenchyme, and involves sequential, reciprocal epithelial-mesenchymal interactions. The dental lamina derives from thickened oral epithelium, giving rise to the enamel organ (epithelial component). The condensed dental mesenchyme is derived from cranial neural crest cells after their migration into the oral region of the first pharyngeal arch, and diversifies into dental papilla (DP) and dental follicle (DF) (mesenchymal components). DP gives rise to dental pulp and odontoblasts, whereas DF differentiates into periodontal tissues including the periodontal ligament (PDL), cementum and alveolar bone.[2-4]

Tooth eruption refers to the movement of the tooth from its developmental location within the arch to its functional position in the oral cavity,[2,5] a process that occurs concomitantly with root formation.[6] The process of tooth eruption can be divided into three distinct phases: pre-eruptive tooth movement (phase 1), eruptive tooth movement (phase 2) and post-eruptive tooth movement (phase 3).[6] Pre-eruptive tooth movement is a series of intricate biological events that take place for the preparation of tooth emergence into the oral cavity, which mainly consists of the early stages of tooth development until the onset of tooth root formation.[6] Eruptive tooth movement occurs accompanied by tooth

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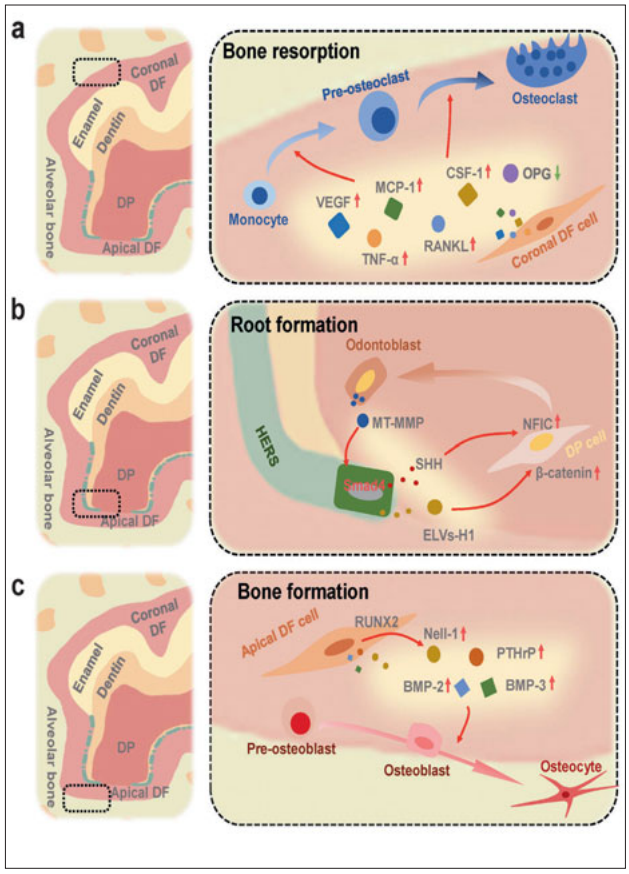

Fig 1a to c Cellular interactions during tooth eruption and tooth root formation. Coronal DF regulates osteoclastic bone resorption during eruptive tooth movement **(a)**. The interaction between HERS and DP participates in tooth root formation **(b)**. Basal DF regulates osteoblastic bone formation during eruptive tooth movement **(c)**.

root formation, and lasts until the tooth crown reaches the occlusal plane. This phase can be divided into two stages: intra- and supraosseous eruptive tooth movement.[6] It involves the formation of Hertwig's epithelial root sheath (HERS), root dentine, the PDL, cementum, alveolar bone in the apical tooth region, and osteoclast-mediated bone resorption of the cortical shell overlaying the tooth crown for eruptive path formation, which jointly facilitate the emergence of the tooth into the oral cavity.[5,7-9] Once the tooth reaches its occlusal position, occlusal force starts to stimulate the continuous maturation of the periodontal attachment apparatus of the tooth.[10] Physiological post-eruptive movement in a vertical direction happens throughout life, which compensates for coronal wear and maintains the position of the tooth within the alveolar bone to achieve proper occlusion.[10] Vertical post-eruptive movement leads to the concerning issue of tooth overeruption after the loss of the opposing occlusion.[6,10,11] Post-eruptive tooth movement in a horizontal direction happens mainly due to adjacent tooth loss or under orthodontic force.[12-14] The potential mechanisms that govern tooth root formation and homeostasis during eruptive and post-eruptive tooth movement remain largely unexplored.

In this review, the present authors summarised the potential mechanisms underlying eruptive and post-eruptive tooth movement (Table 1), specifically highlighting the collaborative intercellular interaction involved in tooth eruption, including HERS, DP and DF (Fig 1). For post-eruptive tooth movement, we focused on the responses of periodontal tissues to vertical mechanical stimuli (Fig 2). Additionally, we described various mouse models used to study occlusal hypofunction or hyperfunction, including molar extraction,[15-22] dietary modifications,[23-25] induction of masticatory muscle atrophy[26,27] and the use of intraoral bite blocks or other devices (Table 2).[16,28-31]

Eruptive tooth movement

Pre-eruptive tooth movement consists of the early stages of tooth development until the onset of tooth root formation. The development of the tooth crown begins from the dental lamina, followed by a series of bud, cap and bell stages. At the interface between the dental epithelium and mesenchyme, odontoblasts and ameloblasts differentiate to form dentine and enamel, respectively.[32]

The process of tooth eruption can be regarded as the result of increments of basal tissue and subtractions of coronal tissue, which are mediated by intricated cellular interactions between HERS, DP, DF and so on (Table 1 and Fig 1).[6,7,11,33-37] The increments mainly include root formation, PDL formation and osteogenesis in the root region, providing motive forces for coronal eruption. Meanwhile, the decrement refers to the formation of the eruption pathway through osteoclastic activities above the tooth crown region. After the bone overlying the erupting tooth is resorbed, the reduced dental epithelium and the oral epithelium fuse, degenerate and form an epithelial canal through which the tooth erupts, thus preventing bleeding during supraosseous tooth eruption. Then the tooth gradually reaches its functional position and achieves occlusal contact with the opposite tooth.[2,3]

HERS

Tooth root initiation and shaping

Once crown formation is completed, epithelial cells of the inner and outer enamel epithelium proliferate

Table 1 Mechanisms of tooth root development and homeostasis during eruptive and post-eruptive movement.

Phase	Cell type	Genotype/model	Mechanism	Phenotype/function
Eruptive tooth movement	HERS	*K14-Cre; Wnt10a*$^{fl/fl}$	Ablation of epithelial *Wnt10a* resulted in the elevation of *Wnt4* and *Axin2* in DP	Loss of *Wnt10a* led to an absence of or apically located root furcation in mouse molars[42]
		K14-Cre; Wnt10a$^{fl/fl}$	Epithelial deletion of *Wnt10a* resulted in decreased *Notch2* and *Jag1* expression in HERS, which might suppress the Notch signalling transduction	Loss of epithelial *Wnt10a* presented enlarged pulp chamber and apical displacement of the root furcation of multi-rooted teeth[43]
		Krt5-rtTA; tetO-Cre; Alk3$^{fl/fl}$	Epithelial *Bmpr1a* knockout promoted Wnt/β-catenin signalling	Cessation of epithelial BMP signalling by *Bmpr1a* depletion during the differentiation stage switched differentiation of crown epithelium into the root lineage and formed ectopic cementum-like structures[49]
		Krt14-rtTA; tetO-Cre; Smad4$^{fl/fl}$*; Shh*$^{fl/fl}$	Loss of *Smad4* resulted in ectopic Shh-Gli1 signalling and maintenance of Sox2+ cells	Loss of *Smad4* in the dental epithelium of developing molars prolonged the maintenance of the cervical loop and molar crown development[50]
		K14-Cre; Smad4$^{fl/fl}$	TGF-b/BMP signalling relied on a Smad-dependent mechanism in regulating *Nfic* expression via Shh signalling to control root development	Loss of *Smad4* in HERS led to abnormal enamel and dentine formation 14 d after kidney capsule transplantation[59]
		Shh-CreER; Ctnnb$^{fl/fl}$*; R26R*	The inactivation of β-catenin in HERS increased EMT of HERS cells and regulated the odontogenic differentiation of DP through inducing the expression of morphogenetic regulators such as *Osx* and *Nfic*	The inactivation of β-catenin in HERS led to failure of odontogenic differentiation of DP cells and interrupted root elongation due to premature disruption of HERS at P10[39]
		Cell culture	ELVs-H1 activated Wnt/β-catenin signalling	ELVs-H1 promoted the migration and proliferation of DP cells and induced odontogenic differentiation[86]
	DP	*Nfic*$^{-/-}$	*Nfic* regulated Hh signalling in dental mesenchyme through upregulation of *Hhip*, contributing to apical DP growth and proper root formation	Loss of *Nfic* led to short and malformed roots and decreased alveolar bone formation[55,59,60]
		Col1-Cre; Osx$^{fl/fl}$	Loss of *Osx* resulted in a decrease in expression of DMP1 and DSPP	Loss of *Osx* led to inhibition in odontoblast differentiation, and short thin root dentine with few dentine tubules at 2 wk[61]
		OC-Cre; Ctnnb1$^{fl/fl}$*; R26R*	Disruption of β-catenin in odontoblasts and cementoblasts diminished expression of Col1α1, OC and DSPP	Inactivation of β-catenin in developing odontoblasts led to normally extended HERS, impaired root odontoblast differentiation and failed root formation from P5-28[62,63]
		Osr2-Cre; Ezh2$^{fl/fl}$	Interplay between EZH2 and ARID1A epigenetically modulated Cdkn2a expression in the dental mesenchyme, influencing root patterning and growth	Mesenchyme lacking *Ezh2* resulted in too few roots, and abnormality in the "bridge" region between the roots; epithelium lacking *Ezh2* led to an incorrect number of roots and lately developed bridges between the roots from P6-28[67]
		Gli1-CreER; Arid1a$^{fl/fl}$	Loss of ARID1A disturbed the differentiation-associated cell cycle arrest of tooth root progenitors through Hh signalling regulation	Loss of ARID1A led to shortened roots and delayed eruption[68]
		Ogn$^{-/-}$	SCAPs secreted OGN to inhibit the Hh pathway to regulate DFSC differentiation and pluripotency	Loss of *Ogn* accelerated root elongation and dentine deposition from P0-30[93]
		Osx-Cre; MT1-MMP$^{fl/fl}$	MT1-MMP mediated matrix remodelling in tooth eruption through effects on bone formation, soft tissue remodelling and organisation of the DF/PDL region	Absence of MT1-MMP in Osx-expressing mesenchymal cells led to altered HERS structure, short roots, impaired dentine formation and mineralisation, and decreased alveolar bone formation at P10, P76-79[96]
		Prx1-Cre; PTH1Rfl/fl	Loss of *PTH1R* in Prx1+ progenitors mutant mice led to reduced alveolar bone formation and decreased expression of key regulators of osteogenesis	Conditional deletion of *PTH1R* using the Prx1 promoter exhibited delayed molar eruption[97]

Table 1 (cont.) Mechanisms of tooth root development and homeostasis during eruptive and post-eruptive movement.

Phase	Cell type	Genotype/model	Mechanism	Phenotype/function
	DF	*PTHrP-CreER; PPR*$^{fl/fl}$; *R26R*$^{tdT/+}$	PPR deficiency induced a cell fate shift of PTHrP+ DF mesenchymal progenitor cells to nonphysiological cementoblast-like cells precociously forming the cellular cementum on the root surface associated with up-regulation of Mef2c and matrix proteins	Loss of PPR in PTHrP+ DF cells resulted in defective formation of the periodontal attachment apparatus, tooth root malformation and failure of tooth eruption in molars from P3-182[69]
		Lepr-Cre; Igf1$^{fl/fl}$; *Slc1a3-CreER; Igf1r*$^{fl/fl}$	Igf1-Igf1r signalling mediated cell-cell interaction between lateral and apical DF domains	Loss of *Igf1* or *Igf1r* led to a larger PDL area at P16.5[58]
		Osr2-Cre; Foxp4$^{fl/fl}$	*Foxp4* partly regulated lineage contribution of the apical DF	Deletion of *Foxp4* in the dental mesenchyme led to an increased PDL area and diminished periostin expression at P16.5[58]
		Runx2 mutation	*Runx2* mutation impaired osteogenesis through inhibiting osteoblast-associated genes, including *Runx2*, *Alpl*, *Osx*, *OC* and *Col1a1*	*Runx2* mutation resulted in cleidocranial dysplasia (CCD) hindered alveolar bone formation and led to eruption failure[74]
		Cell culture	*Runx2* directly interacts with the OSE2 elements to transactivate the human *Nell-1* promoter	Transfection of *Runx2* into rat osteoblasts resulted in the upregulation of *Nell-1* expression, and in Runx2-null calvarial cells, the expression of *Nell-1* was restored[77]
		Harlan Sprague-Dawley rats; cell culture	TNF-α enhances the expression of BMP-2 and BMP-3, with a more pronounced effect on BMP-2	BMP-2, BMP-3 and TNF-α are notably expressed in the basal DF at P3 and P9[72,78]
Post-eruptive tooth movement	Cementoblast	*Rsk2*$^{-/y}$	*Rsk2* was a critical regulator of cementoblast function	Loss of *Rsk2* led to cementum hypoplasia, detachment and disorganisation of the PDL and significant alveolar bone loss with age[102]
		Cell co-culture	*PTHrP* influenced the balance of OPG and RANKL production by cementoblasts	Cementoblasts had the capability to inhibit osteoclast differentiation[105]
		Cell co-culture	Cementoblasts upregulated osteoclastogenesis associated chemokines/cytokines and RANKL through the TLR-2 signaling pathway in response to LPS	Cementoblasts contributed to the recruitment of osteoclastic precursor cells[106]
		Cell culture	Force-loaded cementocytes regulated osteoclastogenesis and osteoclastic root resorption in cell-to-cell communication using the S1P/S1PR1/Rac1 axis during this process	IDG-CM6 cells under compression force regulated osteoclast precursors/osteoclasts[133]
	PDL fibroblast	*Mkx*$^{-/-}$	Mkx upregulated the expression of collagens such as *Col1α1* and *Col1α2*, and inhibited PDL degeneration through the suppression of osteogenic-related gene expression including *Osx*, *Alpl* and Run*x2* in PDL fibroblasts	Loss of Mkx led to changes in PDL properties including expansion of the PDL, collagen fibril degeneration and morphological changes in PDL cells at 6 and 12 mo[113]
		Bgn$^{-/0}$*Fmod*$^{-/-}$	SLRPs regulated TGF-β/BMP signalling, matrix turnover and collagen organisation	Deletion of *Bgn* and *Fmod* resulted in abnormal collagen fibrils in PDL, altered remodelling of alveolar bone and elevated numbers of osteoclasts at 4 to 8 wk[116]
		Cell co-culture	Co-cultures of PBMCs with human primary PDL fibroblasts resulted in a marked increase in ICAM-1 and osteoclastogenesis-related markers (RANKL, RANK, TNF-α)	Cell–cell adhesion between osteoclast precursors and PDL fibroblasts led to a significant rise in osteoclast-like cell numbers[117]
		Unloading model	Unloading led to decreased PLAP-1 in PDL fibroblasts which inhibited *Col1* expression while promoted Osx and OC expression, thus suppressing collagen synthesis and triggering osteogenesis	Unloading resulted in a decrease in collagen disorder in PDL, enhanced osteogenic activity on PDL–bone border, aggravated osteoclast activity in alveolar bone inner part, increase in alveolar bone height, and a gain in the mandibular width[17]

		Unloading model (patient)	Unloading led to a downregulation of BBS7 in PDL of unopposed teeth and occlusal force influenced the expression of BBS7 to mediate Shh signalling activity	Occlusal hypofunction led to a dynamic alternation in PDL, including the cells, fibres, primary cilia and blood vessels[130]
		Unloading model	PDL plays a pivotal role in mechanotransduction by translating physical forces into the intracellular signalling axis Piezo1/Ca^{2+}/HIF-1α/SLIT3, which promotes type H angiogenesis and OSX+ cell-related osteogenesis	Occlusal hypofunction induced periodontal disuse atrophy characterized by a progressive decrease in BV/TV and mineral density, enlargement of the medullary space in the interradicular area, decreased PDL width and increasingly sparse collagen bundles in the furcation areas[20]
		Cell co-culture (vertical force)	Vertical mechanical stress resulted in dose- and time-dependent upregulation of RANKL expression via increased PGE2 production	Vertical mechanical stress led to a notable rise in osteoclast-like cell formation[118]
		Hyper-loading model	Hyper-occlusion predominantly induced CCL2 expression in PDL tissues and promoted chemotaxis and osteoclastogenesis	Mechanical stress-dependent alveolar bone destruction[31]
		CCL2$^{-/-}$ or *CCR2*$^{-/-}$ mice	Hyper-occlusion induced compensatory CCL3 expression and promoted osteoclastogenesis to counterbalance deficient CCL2/CCR2 signalling	Mechanical stress-dependent alveolar bone destruction[30]
	PDLSC	*Gli1-CreER; Ai14* (unloading)	Gli1+ cells in the PDL were MSCs and could contribute to alveolar bone regeneration	Unloading led to a decrease in the activities of PDLSCs, lower alveolar bone height (CEJ-ABC) and lower bone density, which were more dramatic in the furcation and interdental septum regions from 14 to 60 d post[18]
		Lepr-CreER; tdT (unloading and hyper-loading)	Modulation on activation and osteogenic differentiation of Lepr+ PDLSCs under hyper-loading and unloading of occlusal forces depends on Piezo1-mediated mechanosensing	Unloading led to impaired osteogenic differentiation of Lepr+ cells from 1 to 35 d; hyper-loading resulted in osteogenic differentiation of Lepr+ cells from 0 d to 28 d post[16]
		Axin2-CreER; R26R$^{mT-mG/+}$ (hyper-loading)	Wnt-responsive stem/progenitor cells coordinate the functional adaptation of PDL and alveolar bone to hyper-loading	Hyper-loading resulted in increased collagen deposition, a thicker, stiffer PDL, activated bone resorption, the peak of which was followed by a bone formation phase, leading ultimately to an accelerated rate of mineral apposition and an increase in alveolar bone density at hyper-loading 7 to 28 d[19]
	Osteocytes	*Gli1-CreER; Ai14; Sost*$^{-/-}$ (unloading)	Alveolar bone osteocytes negatively regulated Gli1+ PDLSCs activity through Sost in response to unloading	Knockout of Sost eliminated the response of Gli1+ PDLSCs to unloading on 14/30 d post[18]
	Osteoblasts	*Piezo1-CreER; Rosa26-Ai47* (unloading)	PIEZO1 may promote osteoclastic apoptosis through osteoblast-secreted FasL through a PIEZO1-STAT3/ESR1-FasL pathway	Piezo1 activation prevented occlusal force loss-induced alveolar bone loss[22]

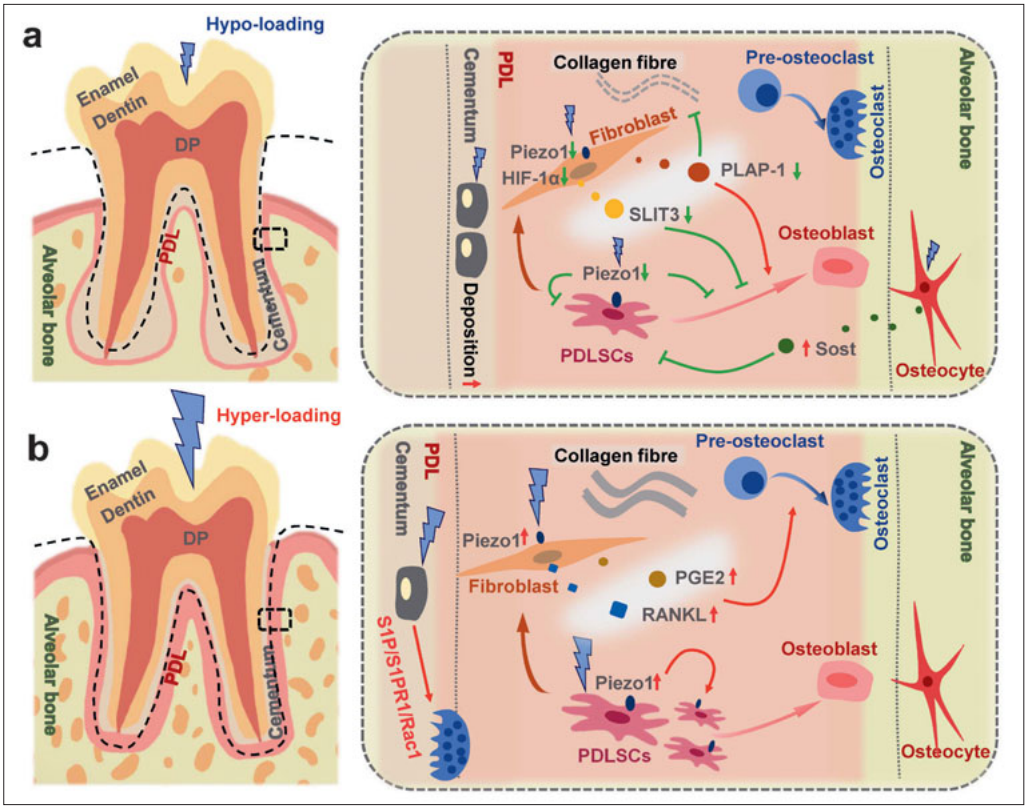

Fig 2a and b Mechanisms of periodontium response to mechanical stimuli. Hypo-loading leads to apical cellular cementum deposition, sparse and disorganised collagen fibres, enhanced osteogenic activity in the PDL-bone border with a gain in alveolar bone height, and aggravated osteoclast activity in alveolar bone marrow with progressive decrease in BV/TV and mineral density **(a)**. Hyper-loading leads to enhanced cementum hardness and resorption, thicker and stiffer collagen fibres and activated bone resorption, followed by a bone formation phase, leading ultimately to increased alveolar bone density **(b)**. The dotted lines represent the normal tooth border.

from the cervical loop of the enamel organ to form a double layer of cells known as HERS.[2,38,39] HERS cells express strong epithelial cell markers Keratin 14 (K14) and E-cadherin.[39,40] HERS elongates apically, acting as a template for root morphology and guiding the emergence of multi-rooted structures in posterior teeth. It invaginates inwards towards the pulp at the location of future root furcation, thus forming multiple roots. Deviations in this process lead to a variety of morphological root variances such as supernumerary roots, pyramidal-shaped roots and taurodontism.[41] For example, researchers found that loss of Wnt10a in the HERS, which is a ligand in canonical Wnt signalling, inhibits cell proliferation and horizontal elongation, leading to taurodontism with the absence of or apically located pulp floor and pulp chamber enlargement.[42,43]

Regulatory mechanism of HERS

The formation and function of HERS are regulated by multiple classical signalling pathways, such as sonic hedgehog (Shh), Wnt/β-catenin and bone morphogenic protein (BMP)/transforming growth factor-beta (TGF-β) signalling pathways.[44] Shh, a member of the vertebrate Hh family and expressed in the apical HERS, is crucial for epithelial-mesenchymal interactions at the root apex. Nakatomi et al[45] identified *Ptc1* as Shh target genes mainly expressed in DP adjacent to the HERS, whose loss leads to inhibited cell proliferation, root elongation and disturbed eruption in homozygous Ptc^{mes} mutants at 4 weeks. β-catenin, expressed in HERS during tooth root formation, is a key mediator of canonical Wnt signalling. Yang et al[39] reported that the inactivation of β-catenin in HERS leads to interrupted root elongation due to premature disruption of HERS. In addition, it has been reported that loss of Wnt ligands results in a breakdown of the epithelial integrity of HERS with aberrant cellular projections.[46] BMP/TGF-β signalling is a key regulator for stem cell fate determination in many epithelial tissues, such as the hair and intestine.[47,48] BMP signalling is actively involved in regulating cell fate decisions during the formation of HERS. Yang et al[49] showed that cessation of the epithelium BMP signalling switches differentiation of crown epithelia into the root lineage, forming ectopic cementum-like structures using a *Krt5-rtTA;tetO-Cre;Alk3*$^{fl/fl}$ mouse model. Li et al[50] found that loss of *Smad4* in the dental epithelium prolongs the maintenance of the cervical loop and molar crown development through BMP-SMAD4-Shh signalling using a *Krt14rtTA;tetO-Cre;Smad4*$^{fl/fl}$*;Shh*$^{fl/fl}$ mouse model.

Table 2 Comparison between different models of occlusal hypofunction/ hyperfunction.

Model	Surgery	Animal	Age	Site/methods	Analysis time	Phenotype
Hypo-loading	Extraction	Swiss Webster mice	35 d	Maxillary molars	6/21 d after surgery	Increased cellular cementum; larger cementocytes[15]
		Gli1-CreER; tdT mice	4 wk	3 maxillary molars	14/30/60 d after surgery	Lower alveolar bone height (CEJ-ABC); lower bone density[18]
		Lepr-CreER; tdT mice	6 wk	Maxillary first molar	14 d after surgery	Impaired osteogenic differentiation of Lepr+ cells[16]
		C57BL/6J mice	4 wk	3 maxillary molars	2/4/6 wk	Decrease in BV/TV and mineral density, bone resorption in the medullary space and PDL atrophy[20]
		C57BL/6J mice	4 wk	3 maxillary molars	1/4/12 wk	Collagen disorder in PDL, enhanced osteogenic activity on the PDL–bone border, aggravated osteoclast activity in alveolar bone inner part, increase in alveolar bone height, gain in mandibular width[17]
		Sprague-Dawley rats	5 wk	Mandibular molars	4 wk after surgery	Active bone formation on the PDL–bone border, expansion in bone marrow and decrease in bone volume[21]
		Sprague-Dawley rats; *Piezo1-CreER; Rosa26-Ai47* mice	6 wk (rats)	3 maxillary/mandibular molars	12 wk after surgery (rats); 3 wk after surgery (mice)	Decreased alveolar bone loss in the Piezo1 activated group[22]
	Diet	*Axin2-CreER; R26Rm*$^{T\text{-}mG/+}$ mice	P15	Soft diet	P15-65	PDL atrophy[23]
		Sprague-Dawley rats	21 wk	Soft diet	27 wk	Higher and wider alveolar process[25]
	Muscle atrophy (single side botulinum toxin [BTX] injection)	Sprague-Dawley rats	18 wk	Masseter and temporal muscles	4 wk after surgery	Masseter and temporal muscle atrophy and alveolar bone loss in injected side[26]
		New Zealand white rabbits	5 mo	Masseter muscle	4/12 wk after surgery	Decreased bone volume in molar regions of both sides[27]
	Devices	Mice	5 wk	Maxilary first molar (flatten cusps)	6 wk after surgery	mx M1: elongation of both the mesial root and its surrounding alveolar bone; mn M1: overeruption of the mesial side of the tooth[28]
		Wistar-strain rats	5 wk	Bite-raising appliance	16 wk	Longer and narrower roots especially the mesial root, a decrease in root area and PDL thickness and area[29]
Hyper-loading	Molar extraction	*Axin2-CreER; R26R*$^{mT\text{-}mG/+}$ mice	5 wk	Maxillary second and third molar	7/14/28/56 d after surgery	Increased collagen deposition, a thicker, stiffer PDL, activated bone resorption followed by bone formation, leading ultimately to mineral apposition and increased alveolar bone density[19]
	Diet	C57BL/6 J mice	3 wk	Hard diet	14 wk	Osteocytes balanced the cytokine expression to enhance jaw bone formation[24]
		Axin2-CreER; R26Rm$^{T\text{-}mG/+}$ mice	P15	Hard diet	P15-65	Mastication-induced strain maintained the PDL fibres[23]
	Devices	*Lepr-CreER; tdT* mice	6 wk	Maxillary first molar(adhere composite resin)	14 d after surgery	Promoted osteogenic differentiation of Lepr+ cells[16]
		Wistar rats/ddY mice	8 wk/ 5 wk	3 mx molars (bond stainless steel wire)	4–7 d after surgery	Upregulated expression of CCL2 in PDL, CCR2 in pre-osteoclasts, and tartrate-resistant acidphosphatase-positive cells in alveolar bone[31]
		CCL2$^{-/-}$ or *CCR2*$^{-/-}$ mice	5 wk	3 maxillary molars	4–7 d after surgery	Increased expression of CCL3 and TRAP-positive cells[30]

P, postnatal day.

DP

Tooth root pulp and dentine formation

At the cap stage, the DP is formed underlying the invaginated dental lamina. Subsequently, DP cells develop into dental pulp cells and odontoblasts.[2,51] It is well documented that stem cells that exist in the apical DP could contribute to tooth root formation.[52] Using lineage tracing mice models, researchers have validated that various markers can be utilised to identify stem cells in the DP in vivo, such as Wnt1,[53] osterix (OSX),[54] Gli1,[55] Axin2[56] and α-smooth muscle actin (α-SMA).[57] Recently, utilising single-cell transcriptome profiling of the mouse molar at postnatal day 3.5 (P3.5), Jing et al[58] revealed that apical DP cells (Aox3+/Tac1+) are progenitor cells with a highly proliferative capacity and give rise to odontoblasts and the dental pulp lineage.

Regulatory mechanism of DP

The development and differentiation of DP are regulated by multiple molecular factors. Nuclear factor I-C (NFIC) is a transcription factor (TF) that binds to DNA through CAATT-boxes. The function of NFIC during postnatal root development has been confirmed using the *Nfic*$^{-/-}$ mouse model, which exhibits short and malformed root morphology but displays normal crowns.[59,60] Besides, Liu et al[55] proved that *Nfic* regulates Hh signalling in the dental mesenchyme by upregulating *Hhip*, an Hh attenuator, thus contributing to apical DP growth and proper root formation. Zhang et al[61] suggested that OSX, a mesenchymal TF involved in osteogenesis and odontogenesis, promotes odontoblast and cementoblast differentiation and root elongation using a *Col1-Cre;Osx*$^{fl/fl}$ mouse model. Beyond its role in HERS, Wnt/β-catenin signalling activity in odontoblast-lineage cells is also indispensable for root formation. Root odontoblast differentiation has been found to be impeded with diminished expression of collagen type I, alpha 1 (Col1α1), osteocalcin (OC) and dentine sialophosphoprotein (DSPP), leading to failed root formation with conditional knockout β-catenin in developing odontoblasts.[62,63]

Epigenetic regulation has also been implicated in the processes of root formation. EZH2, the catalytic subunit of the polycomb repressive complex 2, silences its target genes by generating the lysine 27 trimethylation epigenetic mark on histone H3.[64] ARID1A contains a DNA-binding domain and mediates the chromatin remodelling function of the SWI/SNF complex, playing a role in cell cycle regulation, metabolic reprogramming and epithelial-mesenchymal transition.[65,66] Jing et al[67] revealed that the interplay between EZH2 and ARID1A epigenetically modulates *Cdkn2a* (a cell cycle inhibitor) expression in the dental mesenchyme, influencing root patterning and growth through targeted deletion of EZH2 in the dental mesenchyme using *Osr2-Cre;Ezh2*$^{fl/fl}$ mouse models. Using a *Gli1-CreER;Arid1a*$^{fl/fl}$ mouse model, Du et al[68] showed that loss of ARID1A impairs the differentiation-associated cell cycle arrest of tooth root progenitors through Hh signalling regulation, leading to shortened roots and delayed eruption.

DF

Periodontal tissues and eruption pathway formation

The DF, outside both the enamel organ and DP, contributes to the periodontal attachment apparatus including the cementum, PDL and alveolar bone.[6] It has been demonstrated that distinct cellular domains within the DF function differently during tooth crown and root development.[8,35,58] It has been confirmed that the lateral and apical DF domains contain precursors that can differentiate into PDL fibroblasts, cementoblasts and alveolar bone osteoblasts.[6,58,69] Thus, the removal of the basal half of the DF results in no bone accrual and tooth eruption[11], whereas coronal DF participates in the regulation of osteoclastic bone resorption,[8] and the removal of the coronal DF could result in failed alveolar bone resorption and tooth eruption.[11]

Regulatory mechanism of DF

Parathyroid hormone-related protein (PTHrP)-PTHrP receptor (PPR) autocrine signalling has been found to be critical for root formation and tooth eruption. PPR knockout in PTHrP+ DF cells was shown to cause failed tooth eruption, which may be induced by a lack of motive forces.[7,69-71] In addition, it is reported that Igf1-Igf1r signalling mediates the cell-cell interaction between lateral and apical DF, which is crucial for PDL development, with its absence resulting in an enlarged PDL area but not affecting root length at P16.5 using *Lepr-Cre;Igf1*$^{fl/fl}$ and *Slc1a3-CreER;Igf1r*$^{fl/fl}$ mouse models where *Igf1* and *Igf1r* were specifically knocked out from the lateral and apical DF.[58] In *Osr2-Cre;Foxp4*$^{fl/fl}$ mice, loss of *Foxp4* in DF leads to an increased PDL area and diminished periostin expression, suggesting that the lineage contribution of the apical DF is regulated in part by *Foxp4*.[58]

The cellular expression of factors involved in bone remodelling varies within different DF domains and

stages, reflecting the coordination of osteogenesis and osteoclastogenesis during eruption.[35,72] RUNX2 is a pivotal TF imperative for the differentiation of osteoblasts. RUNX2 mutations result in cleidocranial dysplasia (CCD), which impairs osteogenesis by inhibiting osteoblast-associated genes, including alkaline phosphatase (*Alpl*), *Osx*, *OC* and *Col1α1*, thereby hindering alveolar bone formation, which functions as a motive force for tooth eruption.[73,74] Tang et al[75] identified that Nel-like molecule type 1 (*Nell-1*) protein is restricted to the odontoblasts and endothelial cells of blood vessels during tooth eruption, and it has been revealed that *Runx2* directly regulates the expression of *Nell-1* by binding to osteoblast-specific binding element 2 sites in the *Nell-1* promoter in vitro experiment.[76,77] Thus, the Runx2/Nell-1 axis in the basal DF may act as one of the key regulatory pathways during alveolar bone formation.[8] BMP-2, BMP-3 and tumour necrosis factor-alpha (TNF-α) are notably expressed in the basal DF, correlating with the onset of alveolar bone formation at P3 and accelerated bone growth at P9 in the alveolar bony crypt of the mandibular first molar in rats.[72,78] Yao et al[72] established that TNF-α enhances the expression of BMP-2 and BMP-3, with a more pronounced effect on BMP-2.

Furthermore, the coronal DF plays a prominent role in modulating osteoclast activity through the upregulation of receptor activator of nuclear factor kappa B ligand (RANKL) and downregulation of osteoprotegerin (OPG), thereby creating the eruption pathway.[35,79-81] The crucial modulation of DF on osteoclastogenesis shows two bursts in the rat mandibular molar development model. At P3, it triggers a significant increase in osteoclast formation with the expression of chemotactic protein-1 (MCP-1) and colony-stimulating factor-1 (CSF-1) at peak levels, attracting osteoclast precursors and stimulating their differentiation.[11,35,82] By P9-11, the expression of CSF-1 and MCP-1 dips, while TNF-α and vascular endothelial growth factor (VEGF) peak. VEGF can also recruit osteoclasts and upregulate RANK expression in endothelial cells and osteoclast precursors, suggesting a role in osteoclastogenesis beyond recruiting precursors.[83,84]

Interaction between HERS, DP and DF

HERS, DP and DF interact closely during tooth root development. In addition to its foundational role in root shaping, HERS also plays a vital role during the differentiation of root odontoblasts in DP during root dentine formation.[41] Mullen et al[85] proved that HERS secretes laminin 5 to induce the growth, migration and differentiation of dental mesenchymal cells in the DP. Huang et al[59] demonstrated that tissue-specific knockout of *Smad4* in HERS, the common mediator of BMP/TGF-β signalling, results in abnormal enamel and dentine formation because of the absence of SMAD4-Shh-NFIC signalling. Yang et al[39] indicated that β-catenin plays roles in cell-cell adhesion of HERS to maintain its structural integrity as well as affect epithelial-mesenchymal transition (EMT), and also regulates the odontogenic differentiation of DP through inducing the expression of morphogenetic regulators such as *Osx* and *Nfic*, using *Shh-CreER;Ctnnb*$^{fl/fl}$*;R26R* mice. Zhang et al[86] demonstrated that HERS-derived exosome-like vesicles (ELVs-H1) promote the migration and proliferation of DP cells and also induce odontogenic differentiation and activation of Wnt/β-catenin signalling.

Concurrently, HERS is also essential for the differentiation of DF cells into periodontal tissues.[87] PDL formation starts with the migrated DF cells in contact with the HERS between root dentine and alveolar bone, coinciding with the beginning of HERS perforation.[80,88] Luan et al[89] demonstrated that although HERS itself did not produce cementum, its fenestration was an essential requirement for the onset of cementogenesis. This finding is consistent with Heretier's hypothesis that the absence rather than presence of HERS epithelial cells was critical for cementogenesis, but they did not exclude the possibility of HERS playing an inductive role during the initiation of acellular cementogenesis.[89,90] Recently, some research has shown that HERS cells may have the capability to transform into PDL fibroblasts and cementoblasts in the development of the periodontal tissues.[91,92] Although it is still questionable whether participation is autonomous or non-autonomous, it is undeniable that HERS plays a crucial role in the formation of cementum.

DF development could also be regulated by the adjacent apical DP. Lin et al[93] proved that stem cells from apical DP (SCAPs)-secreted osteoglycin (OGN) inhibits the differentiation and maintains the stemness of DF stem cells (DFSCs) via the OGN-HH pathway during root development by employing a transwell coculture system. Meanwhile, partial SCAP differentiation markers were upregulated after DFSC coculture. They also demonstrated that OGN knockout leads to accelerated root elongation and dentine deposition from P0 to P30 in *Ogn*$^{-/-}$ mice, probably due to upregulated HH signalling in the apical DP and DF.[93]

The precise regulatory mechanism of tooth eruption is widely debated. Tooth eruption and tooth root formation had been considered independent since teeth can emerge into the oral cavity without roots or PDL.[94,95] Xu et al[96] found that the absence of mem-

brane-type matrix metalloproteinase 1 (MT1-MMP) in mesenchyme leads to malformed roots and decreased alveolar bone formation but with teeth erupted into the oral cavity. Cui et al[97] identified deletion of PTH1R in Prx1+-progenitors results in delayed tooth eruption due to reduced alveolar bone formation despite unaffected molar root and PDL development. Controversy remains over the relationship between tooth root formation and tooth eruption, with some other studies supporting the idea that the processes of tooth eruption and root formation are intertwined.[6,70] Tooth eruption is accompanied by root development and periodontal tissue formation, and the direction of crown movement is consistent with that of root growth.[11,70] In addition, in patients with primary failure of eruption (PFE), defective tooth eruption is likely to be caused by a lack of motive forces, as the eruption path is normal.[70]

Post-eruptive tooth movement

Normal homeostasis

The tooth eruption process does not stop upon reaching the occlusal plane but continues throughout life. In humans, mastication involves cyclic loading by forces ranging from tens to occasionally hundreds of Newtons on the teeth. With each chewing cycle, the teeth may move up to several tens of microns.[98] In homeostasis, continuous remodelling and homeostasis of the cementum and PDL of the tooth root, as well as the alveolar bone, are sophisticatedly maintained (Table 1).[6,10,99]

Cementum physiological apposition

Cementum is a mineralised tissue enveloping the roots of teeth, formed by cementoblasts, marked with ALPL, bone sialoprotein (BSP) and OC, and plays a key role in the periodontal attachment apparatus.[2,100] Xie et al[101] identified that Axin2+ PDL cells are primary progenitor cell sources for cementum formation. Koehne et al[102] demonstrated that ribosomal S6 kinase RSK2 is a critical regulator of cementoblast function. They found cementum hypoplasia in Rsk2-deficient mice, which results in detachment and disorganisation of the PDL and is associated with significant alveolar bone loss with age.[102] Cementocytes, the embedded cells within cellular cementum, exhibit mechanoresponsive properties in response to mechanical forces.[103] Cellular cementum primarily exists on the cervical portions of the root, contributing to tooth anchorage. It extends over the apical root dentine and facilitates continuous occlusal adjustment. While similar to bone in composition, cementum is avascular, does not undergo physiological remodelling and grows by continuous apposition throughout life.[103,104] Boabaid et al[105] demonstrated that cementoblasts inhibit osteoclast differentiation by producing and releasing OPG, suggesting that cementoblasts may play a role in maintaining lower levels of osteoclastic activity at the root surface compared to the adjacent alveolar bone in vitro research. Meanwhile, Nemoto et al[106] reported that cementoblasts contribute to the recruitment of osteoclastic precursor cells through the upregulation of osteoclastogenesis associated chemokines/cytokines and RANKL through the TLR-2 signalling pathway in response to Porphyromonas gingivalis lipopolysaccharide in vitro experiments.

Collagen organisation and maintenance in PDL

PDL is made up of collagen fibre bundles located between the cementum and the inner wall of the alveolar bone.[2,107] It functions not only as a cushion against masticatory pressure but also as a transducer that perceives physical signals and converts them into biological responses within the alveolar bone.[20] Stem/progenitor cells within the PDL termed PDLSCs, which can be marked with Axin2+,[19,23] Gli1+[18,108] and Lepr+ cells,[16,109] have robust self-renewal and multilineage differentiation capacities and are critical for the mechanical response of periodontal tissue.[16,18,109-111] PDL fibroblasts are spindle-shaped and elongated connective tissue cells derived from PDLSCs. They can play an essential role in the mechanical response through primary cilia, which are non-motile sensory organelles.[112-115] Koda et al[113] reported that Mohawk homeobox (*Mkx*), a tendon-specific TF, regulates PDL homeostasis by upregulating the expression of collagens such as *Col1α1* and *Col1α2*, and suppressing osteogenic-related gene expression including *Osx*, *Alpl* and *Runx2* in PDL fibroblasts. Small leucine-rich proteoglycans (SLRPs) are extracellular matrix molecules, suggested to regulate collagen organisation and cell signalling. Wang et al[116] demonstrated the importance of SLRPs in maintaining periodontal homeostasis through regulation of TGF-β/BMP signalling, matrix turnover and collagen organisation using a $Bgn^{-/0}Fmod^{-/-}$ mouse model.

The interaction between PDL fibroblasts and osteoclast precursors profoundly influences periodontal homeostasis. Various mechanical forces to PDL fibroblasts could alter their capacity to produce osteoclastogenesis-related molecules.[112,117,118] Bloemen et al[117] reported a marked increase in the expression of intercellular adhesion molecule-1 (ICAM-1) and osteoclas-

togenesis-related markers (RANKL, RANK, TNF-α), as well as a significant rise in osteoclast-like cell numbers in co-cultures of blood mononuclear cells (PBMCs) with human primary PDL fibroblasts, compared to PBMCs cultured alone.

Continuation of remodelling in alveolar bone

Tooth roots are embedded in the alveolar bone by PDL and the alveolar bone continues remodelling in its physiological state through coupled osteoclast-osteoblast actions.[26,119,120] Osteocytes, the most abundant cells in bone, possess mechanosensing appendices stretching through bone canaliculi.[121] These cells regulate local bone remodelling by directing osteoblast and osteoclast activity in response to mechanical stimuli.[104] In addition, when stimulated by occlusal force, osteocytes have the capability to regulate periodontium tissue turnover by activating PDLSCs that surround the neurovascular bundle, contributing to periodontal homeostasis upon mechanical force,[18,110,122-124] for example sclerostin (SOST) from the osteocyte is a negative feedback regulator for Gli1+ PDLSC activity.[18] Yang et al[22] identified Piezo1 as the pivotal mediator of occlusal force in osteoblasts, thereby sustaining alveolar bone homeostasis through the facilitation of osteogenesis and the orchestration of catabolic pathways via Fas ligand (FasL)-mediated osteoclastic apoptosis.

Hypo-loading condition

It is common to employ an unopposed mouse molar model to investigate axial tooth movement. A hypofunctional state leads to augmented area and thickness in apical regions, suggesting that apposition responds to occlusal load changes with neo-cementogenesis adapting to maintain occlusal height.[15,125,126] Significant cementum formation is associated with elevated extracellular matrix gene expression such as *Col1*, *integrin β5* and *osteonectin* gene expression.[15,125,126] The notable changes following the loss of an opposing tooth highlight the significant role of cementum; however, the mechanisms by which cementum responds to alterations in occlusal forces require further investigation.

The collagen fibre density within the PDL decreases with compromised structural integrity under a hypofunctional state.17,23 PDL-associated protein-1 (PLAP-1)/asporin is an extracellular proteoglycan uniquely localized in the PDL. Chen et al17 demonstrated that unloading reduces PLAP-1 levels in PDL fibroblasts significantly, resulting in inhibited Col1 expression while promoting the expression of Osx and OC, thereby suppressing collagen synthesis and inducing osteogenesis. Bardet-Biedl syndrome 7 (BBS7) is an indispensable constituent of a protein complex named the BBSome, and plays a crucial role in ciliogenesis and regulating Shh signalling activity.127-129 Chang et al130 found that the expression of BBS7 is downregulated in PDL of unopposed teeth in vivo and in vitro, and they reported that occlusal force influences the expression of BBS7 to mediate Shh signaling activity, which is vital for cell migration and thus maintaining proper PDL homeostasis. In a recent study, CD31+ Endomucin+ type H endothelium, especially abundant at the root furcation regions, plays a pivotal role in mechanotransduction in PDL through an intracellular Piezo1/Ca2+/HIF-1α/SLIT3 signalling axis.20 Following occlusal unloading, the density of type H vasculature and coupled OSX+ osteoprogenitors decline significantly.20 Gli1+ PDLSCs, predominantly localised within the apical PDL space and surrounding the neurovascular bundle, are responsible for periodontal tissue turnover and damage repair. Men et al18 demonstrated that unloading inhibits Gli1+ PDLSC activation by upregulating SOST secreted by osteocytes in alveolar bone. Zhang et al16 proved that Lepr+ PDLSCs, located in the perivascular niche, are reduced significantly in hypo-loading, resulting in impaired osteogenic differentiation through Piezo1-mediated mechanosensing in the periodontium.

However, opinions differ on the issue of bone mass in unloading models, with some stating that there is an increase and others a decrease. This disagreement may be due to the different detective sites in the alveolar bone and measurement methods. For the resorption or formation of alveolar bone, the PDL–bone border is characterised by enhanced osteogenic activity, whereas the medullary space of the alveolar bone is typical of aggravated osteoclast activity, which contributes to a progressive decrease in volume fraction (bone volume/total volume index, BV/TV) and mineral density.[17,20,21] Regarding alveolar bone height, two kinds of measurements yield divergent outcomes: the distance from the cementoenamel junction to the alveolar bone crest (CEJ-ABC) indicates an increase, suggesting bone loss in the unloading model,[18] while the distance from the mandibular canal level to the alveolar bone beneath the root furcation, defined as mandibular height, also shows an increase, suggesting bone formation in the unloading model.[17] Current studies mainly focus on the effect of osteocytes and PDL on alveolar bone in the presence of disrupted homeostasis. Studies revealing the molecular mechanisms of how these phenotypes are formed remain scarce, especially regarding how osteoclasts accumulate in hypo-loading.

Hyper-loading condition

Trauma from occlusion can be initiated when the magnitude of forces exceeds the adaptive capacity of periodontal supporting tissues (primary trauma) or when the adaptive threshold is compromised, rendering the remaining tissues incapable of withstanding physiological occlusal forces (secondary trauma).[131] Clinically, premature occlusal contacts and lateral displacement of abutment teeth in partial dentures lead to excessive force application on periodontal tissues. Nonaxial forces (lateral or horizontal and torque or rotational) are more likely to damage periodontal tissues compared to axial forces.[131] Consequently, research focuses primarily on orthodontic movement rather than vertical movement. Xu et al[19] developed a finite element (FE) model and an in vivo murine model by extracting the maxillary second molar (mxM2) and maxillary third molar (mxM3), thereby directing the total force onto the mandibular first molar (mnM1). This study aimed to analyse stress distributions within the periodontium under normal and hyper-occlusion conditions. The results indicated that compressive strains are present in all three periodontal tissues, with strain magnitudes increasing fourfold under hyper-loading conditions.[19]

Niver et al1[32] noted that excessive loading significantly enhances cementum hardness while promoting apical cementum resorption. Wang et al[133] demonstrated that force-loaded cementocytes modulate osteoclastogenesis and osteoclastic root resorption through cell-to-cell communication via the Sphingosine-1-phosphate (S1P)/S1PR1/Rac1 pathway.

Hyper-loading leads to increased collagen deposition and a thicker, stiffer PDL.[19,23] Utilising FE modelling, it was illustrated that occlusal hyper-loading could lead to mitotically active Axin2+ PDLSCs in stressed PDL areas, resulting in collagen increase and a stiffer PDL adapted to increased load finally using *Axin2-CreER;R26R*$^{mTmG/+}$ mice.[19,23] Besides, it has also been found that the declined adaptive function of the PDL to masticatory force during aging might be relative to the diminished number of the Axin2+ PDLSCs.[23] Lepr+ PDLSCs are sustained as a quiescent population but can be activated by mechanical stimulation. Zhang et al[16] proved that hyper-loading promotes Lepr+ PDLSCs osteogenic differentiation through Piezo1-mediated mechanosensing in the periodontium.

Hyper-loading activates bone resorption, the peak of which is followed by a bone formation phase partly due to the responses of Wnt-responsive stem/progenitor cells in the alveolar bone, leading ultimately to an accelerated rate of mineral apposition and an increase in alveolar bone density.[19] Kanzaki et al[118] observed that vertical compressive forces on PDL fibroblasts, dose- and time-dependently upregulates RANKL expression via increased prostaglandin E2 (PGE2) production, leading to a notable rise in osteoclast-like cell formation in vitro. Goto et al[30,31] demonstrated that hyper-occlusion elevates C-C chemokine ligand (CCL) 2 expression in PDL, enhancing chemotaxis and osteoclastogenesis and synergistic function of CCL3 and CCL2 in mechanical stress-dependent alveolar bone destruction.

In summary, unloading leads to tooth elongation by apical cellular cementum deposition; sparse and disorganised collagen fibres in the PDL; enhanced osteogenic activity in the PDL-bone border with a gain in alveolar bone height; and aggravated osteoclast activity in alveolar bone marrow with a progressive decrease in BV/TV and mineral density. On the other hand, hyper-loading leads to enhanced cementum hardness and resorption; thicker and stiffer collagen fibres in the PDL; and activated bone resorption, followed by a bone formation phase, leading ultimately to increased alveolar bone density.

Conclusion and prospects

In this review, we systemically summarised the cellular interaction and molecular mechanism that play key roles in regulating tooth root development and homeostasis in the tooth eruption and post-eruption stages mainly based on the mice models. In summary, following the formation of the tooth crown, eruption commences, characterised by axial movement and initiation of root development until the tooth reaches its final position in the oral cavity in contact with the opposing tooth. This process involves cellular interactions within the HERS, DP and DF that govern the development of the tooth crown, root, periodontal tissues and osteogenic and osteoblastic activity, thus contributing to tooth eruption. Even after a tooth attains its functional position, eruptive movement persists due to the remodelling of cementum, PDL and alveolar bone, which are essential for maintaining periodontium homeostasis. Mechanical stimuli, such as occlusal hypofunction, or hyperfunction, can disrupt this homeostasis, and potentially lead to overeruption or occlusal trauma. To understand the cellular mechanism mediating the post-eruptive tooth movement under hypo-loading and hyper-loading conditions, we summarized the advanced findings in recent studies using the transgenic rodent molar models.

Although transgenic rodent molar models are useful tool for studying the mechanisms of tooth eruption, additional large animal models and human subjects are needed to determine the mechanism underlying these phenotypes in the future. For example, the miniature pig model has a diphyodont dentition similar to that of humans. Using a miniature pig model, Wu et al[134,135] validated that tooth eruption could release the accumulated mechanical stress inside the mandible, and the permanent tooth did not develop until the primaryd tooth began to erupt. Using FE analysis models of human teeth, Sarrafpour et al[136,137] proposed that both eruptive and post-eruptive tooth movements result from bone remodelling in the bony crypt and lamina dura, driven by biomechanical forces. These new findings enrich knowledge relating to tooth development and eruption and suggest the significance of interdisciplinary methods, such as biomechanical models, in achieving a more comprehensive understanding of tooth development and maintenance mechanisms.

Eruption disorders are commonly observed in the human population, presenting as either isolated conditions or part of complex syndromes, and invariably lead to impaired mastication, speech, facial aesthetics and social interaction.[4,74] Delayed tooth eruption (DTE), the most frequent deviation from normal eruption timing, occurs when a tooth emerges into the oral cavity at a time that diverges significantly from established norms for various races, ethnicities and sexes.[138] DTE may signal a systemic condition such as cleidocranial dysplasia (CDD) or reflect altered craniofacial physiology, such as physical obstruction due to premature loss of primary teeth.[138,139] Surgical exposure combined with orthodontic intervention is the predominant treatment approach. In orthodontic therapy, the technique of removing impediments and exposing the crown is termed fenestration. By affixing a bracket to the tooth surface at the exposed "window" and employing orthodontic traction, the impacted tooth can gradually return to the normal dental arch, thereby restoring function.[140] Conventional surgery, which involves direct tissue cutting with a surgical blade, often results in bleeding, infection and postoperative trauma. Consequently, the development of early molecular diagnosis and a therapeutic strategy for eruption disorders are crucial and advantageous for affected populations.

Furthermore, it has been reported that up to 31% of adults with occlusal disharmony or bruxism suffer from disrupted periodontal equilibrium due to irregular force loading.[131] When teeth are no longer in occlusal contact, such as after the extraction of an opposing tooth, the balance of forces is disrupted, leading to overeruption, which can cause occlusal interferences and malocclusion, posing challenges for restoration.[141] Lindskog-Stokland et al[14] observed that both unopposed and opposed teeth exhibit overeruption over a 12-year period, with statistically significant greater overeruption in unopposed teeth. Craddock and Youngson[142] noted that 83% of unopposed teeth are prone to overeruption of up to 5.39 mm. Over-erupted teeth necessitate treatment with an orthodontic intrusive force, which is typically generated through the elastic deformation of the archwire.[143] This treatment poses a significant clinical challenge due to its requirement for high technical precision and potential side effects, including root resorption and reactive loading on anchorage teeth.

A detailed understanding of the molecular and cellular mechanisms underlying tooth eruption and overeruption in pathological states is essential not only for elucidating these biological processes but also for guiding potential clinical interventions. Enhancing comprehension of dental tissue development, disease and dental stem cell biology is crucial for establishing a robust foundation for future strategies and clinical therapies in dental medicine.

Conflicts of interest

The authors declare no conflicts of interest related to this study.

Author contribution

Dr En Hui Yao contributed to the literature search, data analysis and manuscript draft; Drs Xin Quan JIANG and Jia Hui DU contributed to the idea for the article. All authors revised the paper critically for intellectual content and approved the final version.

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References

1. Friedlander L, Berdal A, Cormier-Daire V, Lyonnet S, Garcelon N. Determinants of dental care use in patients with rare diseases: a qualitative exploration. BMC Oral Health 2023;23:413.
2. Nanci A. Development, Structure, and Function, ed 9. St. Louis: Elsevier, 2018.
3. Nibali L. Development of the gingival sulcus at the time of tooth eruption and the influence of genetic factors. Periodontol 2000 2018;76:35–42.
4. Fleischmannova J, Matalova E, Sharpe PT, Misek I, Radlanski RJ. Formation of the tooth-bone interface. J Dent Res 2010;89:108–115.

5. Marks SC Jr, Schroeder HE. Tooth eruption: Theories and facts. Anat Rec 1996;245:374–393.
6. Nagata M, Ono N, Ono W. Mesenchymal progenitor regulation of tooth eruption: A view from PTHrP. J Dent Res 2020;99:133–142.
7. Richman JM. Shedding new light on the mysteries of tooth eruption. Proc Natl Acad Sci U S A 2019;116:353–355.
8. Zeng L, He H, Sun M, et al. Runx2 and Nell-1 in dental follicle progenitor cells regulate bone remodeling and tooth eruption. Stem Cell Res Ther 2022;13:486.
9. Kjær I. Mechanism of human tooth eruption: review article including a new theory for future studies on the eruption process. Scientifica (Cairo) 2014;2014:341905.
10. Craddock HL, Youngson CC. Eruptive tooth movement--the current state of knowledge. Br Dent J 2004;197:385–391.
11. Wise GE, King GJ. Mechanisms of tooth eruption and orthodontic tooth movement. J Dent Res 2008;87:414–434.
12. Walker CG, Dangaria S, Ito Y, Luan X, Diekwisch TG. Osteopontin is required for unloading-induced osteoclast recruitment and modulation of RANKL expression during tooth drift-associated bone remodeling, but not for super-eruption. Bone 2010;47:1020–1029.
13. Craddock HL, Youngson CC, Manogue M, Blance A. Occlusal changes following posterior tooth loss in adults. Part 2. Clinical parameters associated with movement of teeth adjacent to the site of posterior tooth loss. J Prosthodont 2007;16:495–501.
14. Lindskog-Stokland B, Hansen K, Tomasi C, Hakeberg M, Wennström JL. Changes in molar position associated with missing opposed and/or adjacent tooth: a 12-year study in women. J Oral Rehabil 2012;39:136–143.
15. Lira Dos Santos EJ, Salmon CR, Chavez MB, et al. Cementocyte alterations associated with experimentally induced cellular cementum apposition in Hyp mic. J Periodontol 2021;92:116–127.
16. Zhang D, Lin W, Jiang S, et al. Lepr-expressing PDLSCs contribute to periodontal homeostasis and respond to mechanical force by Piezo1. Adv Sci (Weinh) 2023;10:e2303291.
17. Chen Y, Luo M, Xie Y, Xing L, Han X, Tian Y. Periodontal ligament-associated protein-1 engages in teeth overeruption and periodontal fiber disorder following occlusal hypofunction. J Periodontal Res 2023;58:131–142.
18. Men Y, Wang Y, Yi Y, et al. Gli1+ periodontium dtem cells are regulated by osteocytes and occlusal force. Dev Cell 2020;54:639–654.e6.
19. Xu Q, Yuan X, Zhang X, et al. Mechanoadaptive responses in the periodontium are coordinated by Wnt. J Dent Res 2019;98:689–697.
20. Chen Y, Yin Y, Luo M, et al. Occlusal force maintains alveolar bone homeostasis via Type H sngiogenesis. J Dent Res 2023;102:1356–1365.
21. Ejiri S, Toyooka E, Tanaka M, Anwar RB, Kohno S. Histological and histomorphometrical changes in rat alveolar bone following antagonistic tooth extraction and/or ovariectomy. Arch Oral Biol 2006;51:941–950.
22. Yang Y, Dai Q, Gao X, et al. Occlusal force orchestrates alveolar bone homeostasis via Piezo1 in female mice. J Bone Miner Res 2024;39:580–594.
23. Zhang X, Yuan X, Xu Q, et al. Molecular basis for periodontal ligament adaptation to in vivo loading. J Dent Res 2019;98:331–338.
24. Inoue M, Ono T, Kameo Y, et al. Forceful mastication activates osteocytes and builds a stout jawbone. Sci Rep 2019;9:4404.
25. Mavropoulos A, Odman A, Ammann P, Kiliaridis S. Rehabilitation of masticatory function improves the alveolar bone architecture of the mandible in adult rats. Bone 2010;47:687–692.
26. Kün-Darbois JD, Libouban H, Chappard D. Botulinum toxin in masticatory muscles of the adult rat induces bone loss at the condyle and alveolar regions of the mandible associated with a bone proliferation at a muscle enthesis. Bone 2015;77:75–82.
27. Rafferty KL, Liu ZJ, Ye W, et al. Botulinum toxin in masticatory muscles: Short- and long-term effects on muscle, bone, and craniofacial function in adult rabbits. Bone 2012;50:651–662.
28. Star H, Chandrasekaran D, Miletich I, Tucker AS. Impact of hypofunctional occlusion on upper and lower molars after cessation of root development in adult mice. Eur J Orthod 2017;39:243–250.
29. Motokawa M, Terao A, Karadeniz EI, et al. Effects of long-term occlusal hypofunction and its recovery on the morphogenesis of molar roots and the periodontium in rats. Angle Orthod 2013;83:597–604.
30. Tsutsumi T, Kajiya H, Goto KT, Takahashi Y, Okabe K. Hyperocclusion up-regulates CCL3 expression in CCL2- and CCR2-deficient Mice. J Dent Res 2013;92:65–70.
31. Goto KT, Kajiya H, Nemoto T, et al. Hyperocclusion stimulates osteoclastogenesis via CCL2 expression. J Dent Res 2011;90:793–798.
32. Jernvall J, Thesleff I. Tooth shape formation and tooth renewal: evolving with the same signals. Development 2012;139:3487–3497.
33. He YD, Sui BD, Li M, Huang J, Chen S, Wu LA. Site-specific function and regulation of Osterix in tooth root formation. Int Endod J 2016;49:1124–1131.
34. Thomas HF, Kollar EJ. Differentiation of odontoblasts in grafted recombinants of murine epithelial root sheath and dental mesenchyme. Arch Oral Biol 1989;34:27–35.
35. He M, Wang P, Li B, et al. Rodent incisor and molar dental follicles show distinct characteristics in tooth eruption. Arch Oral Biol 2021;126:105117.
36. Proffit WR, Frazier-Bowers SA. Mechanism and control of tooth eruption: overview and clinical implications. Orthod Craniofac Res 2009;12:59–66.
37. Wise GE. Cellular and molecular basis of tooth eruption. Orthod Craniofac Res 2009;12:67–73.
38. Huang X, Bringas P Jr, Slavkin HC, Chai Y. Fate of HERS during tooth root development. Dev Biol 2009;334:22–30.
39. Yang S, Choi H, Kim TH, et al. Cell dynamics in Hertwig's epithelial root sheath are regulated by β-catenin activity during tooth root development. J Cell Physiol 2021;236:5387–5398.
40. Bi F, Tang H, Zhang Z, et al. Hertwig's epithelial root sheath cells show potential for periodontal complex regeneration. J Periodontol 2023;94:263–276.
41. Wright T. The molecular control of and clinical variations in root formation. Cells Tissues Organs 2007;186:86–93.
42. Yu M, Liu Y, Wang Y, et al. Epithelial Wnt10a is essential for tooth root furcation morphogenesis. J Dent Res 2020;99:311–319.
43. Sun K, Yu M, Wang J, et al. A Wnt10a-Notch signaling axis controls Hertwig's epithelial root sheath cell behaviors during root furcation patterning. Int J Oral Sci 2024;16:25.
44. Li J, Parada C, Chai Y. Cellular and molecular mechanisms of tooth root development. Development 2017;144:374–384.
45. Nakatomi M, Morita I, Eto K, Ota MS. Sonic hedgehog signaling is important in tooth root development. J Dent Res 2006;85:427–431.
46. Lav R, Krivanek J, Anthwal N, Tucker AS. Wnt signaling from Gli1-expressing apical stem/progenitor cells is essential for the coordination of tooth root development. Stem Cell Reports 2023;18:1015–1029.

47. Oshimori N, Fuchs E. Paracrine TGF-β signaling counterbalances BMP-mediated repression in hair follicle stem cell activation. Cell Stem Cell 2012;10:63–75.
48. He XC, Zhang J, Tong WG, et al. BMP signaling inhibits intestinal stem cell self-renewal through suppression of Wnt-beta-catenin signaling. Nat Genet 2004;36:1117–1121.
49. Yang Z, Hai B, Qin L, et al. Cessation of epithelial Bmp signaling switches the differentiation of crown epithelia to the root lineage in a β-catenin-dependent manner. Mol Cell Biol 2013;33:4732–4744.
50. Li J, Feng J, Liu Y, et al. BMP-SHH signaling network controls epithelial stem cell fate via regulation of its niche in the developing tooth. Dev Cell 2015;33:125–135.
51. Nagata M, Ono N, Ono W. Unveiling diversity of stem cells in dental pulp and apical papilla using mouse genetic models: a literature review. Cell Tissue Res 2021;383:603–616.
52. Sonoyama W, Liu Y, Fang D, et al. Mesenchymal stem cell-mediated functional tooth regeneration in swine. PloS One 2006;1:e79.
53. Collignon AM, Castillo-Dali G, Gomez E, et al. Mouse Wnt1-CRE-RosaTomato dental pulp stem cells directly contribute to the calvarial bone regeneration process. Stem Cells 2019;37:701–711.
54. Ono W, Sakagami N, Nishimori S, Ono N, Kronenberg HM. Parathyroid hormone receptor signalling in osterix-expressing mesenchymal progenitors is essential for tooth root formation. Nat Commun 2016;7:11277.
55. Liu Y, Feng J, Li J, Zhao H, Ho TV, Chai Y. An Nfic- hedgehog signaling cascade regulates tooth root development. Development 2015;142:3374–3382.
56. Babb R, Chandrasekaran D, Carvalho Moreno Neves V, Sharpe PT. Axin2-expressing cells differentiate into reparative odontoblasts via autocrine Wnt/β-catenin signaling in response to tooth damage. Sci Rep 2017;7:3102.
57. Vidovic-Zdrilic I, Vining KH, Vijaykumar A, Kalajzic I, Mooney DJ, Mina M. FGF2 enhances odontoblast differentiation by αSMA+ progenitors in vivo. J Dent Res 2018;97:1170–1177.
58. Jing J, Feng J, Yuan Y, et al. Spatiotemporal single-cell regulatory atlas reveals neural crest lineage diversification and cellular function during tooth morphogenesis. Nat Commun 2022;13:4803.
59. Huang X, Xu X, Bringas P Jr, Hung YP, Chai Y. Smad4-Shh-Nfic signaling cascade-mediated epithelial-mesenchymal interaction is crucial in regulating tooth root development. J Bone Miner Res 2010;25:1167–1178.
60. Steele-Perkins G, Butz KG, Lyons GE, et al. Essential role for NFI-C/CTF transcription-replication factor in tooth root development. Mol Cell Biol 2003;23:1075–1084.
61. Zhang H, Jiang Y, Qin C, Liu Y, Ho SP, Feng JQ. Essential role of osterix for tooth root but not crown dentin formation. J Bone Miner Res 2015;30:742–746.
62. Kim TH, Bae CH, Lee JC, et al. β-catenin is required in odontoblasts for tooth root formation. J Dent Res 2013;92:215–221.
63. Zhang R, Yang G, Wu X, Xie J, Yang X, Li T. Disruption of Wnt/β-catenin signaling in odontoblasts and cementoblasts arrests tooth root development in postnatal mouse teeth. Int J Biol Sci 2013;9:228–236.
64. Wu S, Fatkhutdinov N, Fukumoto T, et al. SWI/SNF catalytic subunits' switch drives resistance to EZH2 inhibitors in ARID1A-mutated cells. Nat Commun 2018;9:4116.
65. Jin F, Yang Z, Shao J, et al. ARID1A mutations in lung cancer: biology, prognostic role, and therapeutic implications. Trends Mol Med 2023;29:646–658.
66. Zhou W, Liu H, Yuan Z, et al. Targeting the mevalonate pathway suppresses ARID1A-inactivated cancers by promoting pyroptosis. Cancer Cell 2023;41:740–756.e10.
67. Jing J, Feng J, Li J, et al. Antagonistic interaction between Ezh2 and Arid1a coordinates root patterning and development via Cdkn2a in mouse molars. Elife 2019;8:e46426.
68. Du J, Jing J, Yuan Y, et al. Arid1a-Plagl1-Hh signaling is indispensable for differentiation-associated cell cycle arrest of tooth root progenitors. Cell Rep 2021;35:108964.
69. Takahashi A, Nagata M, Gupta A, et al. Autocrine regulation of mesenchymal progenitor cell fates orchestrates tooth eruption. Proc Natl Acad Sci U S A 2019;116:575–580.
70. Yamaguchi T, Hosomichi K, Shirota T, Miyamoto Y, Ono W, Ono N. Primary failure of tooth eruption: Etiology and management. Jpn Dent Sci Rev 2022;58:258–267.
71. Philbrick WM, Dreyer BE, Nakchbandi IA, Karaplis AC. Parathyroid hormone-related protein is required for tooth eruption. Proc Natl Acad Sci U S A 1998;95:11846–11851.
72. Yao S, Prpic V, Pan F, Wise GE. TNF-alpha upregulates expression of BMP-2 and BMP-3 genes in the rat dental follicle--implications for tooth eruption. Connect Tissue Res 2010;51:59–66.
73. Liu Y, Wang Y, Sun X, et al. RUNX2 mutation reduces osteogenic differentiation of dental follicle cells in cleidocranial dysplasia. Mutagenesis 2018;33:203–214.
74. Ge J, Guo S, Fu Y, et al. Dental follicle cells participate in tooth eruption via the RUNX2-MiR-31-SATB2 loop. J Dent Res 2015;94:936–944.
75. Tang R, Wang Q, Du J, Yang P, Wang X. Expression and localization of Nell-1 during murine molar development. J Mol Histol 2013;44:175–181.
76. Zhang X, Ting K, Bessette CM, et al. Nell-1, a key functional mediator of Runx2, partially rescues calvarial defects in Runx2(+/-) mice. J Bone Miner Res 2011;26:777–791.
77. Truong T, Zhang X, Pathmanathan D, Soo C, Ting K. Craniosynostosis-associated gene nell-1 is regulated by runx2. J Bone Miner Res 2007;22:7–18.
78. Wise GE, Yao S. Regional differences of expression of bone morphogenetic protein-2 and RANKL in the rat dental follicle. Eur J Oral Sci 2006;114:512–516.
79. Ruan X, Zhang Z, Aili M, et al. Activin receptor-like kinase 3: a critical modulator of development and function of mineralized tissues. Front Cell Dev Biol 2023;11:1209817.
80. Zhou T, Pan J, Wu P, et al. Dental follicle cells: Roles in development and beyond. Stem Cells Int 2019;2019:9159605.
81. Ma Y, Xu Y, Zhang Y, Duan X. Molecular mechanisms of craniofacial and dental abnormalities in osteopetrosis. Int J Mol Sci 2023;24:10412.
82. Wise GE, Fan W. Changes in the tartrate-resistant acid phosphatase cell population in dental follicles and bony crypts of rat molars during tooth eruption. J Dent Res 1989;68:150–156.
83. Wise GE, Yao S. Expression of vascular endothelial growth factor in the dental follicle. Crit Rev Eukaryot Gene Expr 2003;13:173–180.
84. Wise GE, Yao S. Expression of tumour necrosis factor-alpha in the rat dental follicle. Arch Oral Biol 2003;48:47–54.
85. Mullen LM, Richards DW, Quaranta V. Evidence that laminin-5 is a component of the tooth surface internal basal lamina, supporting epithelial cell adhesion. J Periodontal Res 1999;34:16–24.
86. Zhang S, Yang Y, Jia S, et al. Exosome-like vesicles derived from Hertwig's epithelial root sheath cells promote the regeneration of dentin-pulp tissue. Theranostics 2020;10:5914–5931.

87. Xiong J, Gronthos S, Bartold PM. Role of the epithelial cell rests of Malassez in the development, maintenance and regeneration of periodontal ligament tissues. Periodontol 2000 2013;63:217–233.
88. Guo Y, Guo W, Chen J, Chen G, Tian W, Bai D. Are Hertwig's epithelial root sheath cells necessary for periodontal formation by dental follicle cells? Arch Oral Biol 2018;94:1–9.
89. Luan X, Ito Y, Diekwisch TG. Evolution and development of Hertwig's epithelial root sheath. Dev Dyn 2006;235:1167–1180.
90. Heritier M. Experimental induction of cementogenesis on the enamel of transplanted mouse tooth germs. Arch Oral Biol 1982;27:87–97.
91. Bertin TJC, Thivichon-Prince B, LeBlanc ARH, Caldwell MW, Viriot L. Current perspectives on tooth implantation, attachment, and replacement in amniota. Front Physiol 2018;9:1630.
92. Nam H, Kim J, Park J, et al. Expression profile of the stem cell markers in human Hertwig's epithelial root sheath/Epithelial rests of Malassez cells. Mol Cells 2011;31:355–360.
93. Lin X, Li Q, Hu L, Jiang C, Wang S, Wu X. Apical papilla regulates dental follicle fate via the OGN-Hh pathway. J Dent Res 2023;102:431–439.
94. Cahill DR, Marks SC Jr. Tooth eruption: evidence for the central role of the dental follicle. J Oral Pathol 1980;9:189–200.
95. Wang XP. Tooth eruption without roots. J Dent Res 2013;92: 212–214.
96. Xu H, Snider TN, Wimer HF, et al. Multiple essential MT1-MMP functions in tooth root formation, dentinogenesis, and tooth eruption. Matrix Biol 2016;52-54:266–283.
97. Cui C, Bi R, Liu W, et al. Role of PTH1R signaling in Prx1+ mesenchymal progenitors during eruption. J Dent Res 2020;99:1296–1305.
98. Naveh GR, Lev-Tov Chattah N, Zaslansky P, Shahar R, Weiner S. Tooth-PDL-bone complex: response to compressive loads encountered during mastication - a review. Arch Oral Biol 2012;57:1575–1584.
99. Luan X, Zhou X, Trombetta-eSilva J, et al. MicroRNAs and periodontal homeostasis. J Dent Res 2017;96:491–500.
100. Komaki M, Iwasaki K, Arzate H, Narayanan AS, Izumi Y, Morita I. Cementum protein 1 (CEMP1) induces a cementoblastic phenotype and reduces osteoblastic differentiation in periodontal ligament cells. J Cell Physiol 2012;227:649–657.
101. Xie X, Wang J, Wang K, et al. Axin2+-mesenchymal PDL cells, instead of K14+ epithelial cells, play a key role in rapid cementum growth. J Dent Res 2019;98:1262–1270.
102. Koehne T, Jeschke A, Petermann F, et al. Rsk2, the kinase mutated in Coffin-Lowry syndrome, controls cementum formation. J Dent Res 2016;95:752–760.
103. Lira Dos Santos EJ, de Almeida AB, Chavez MB, et al. Orthodontic tooth movement alters cementocyte ultrastructure and cellular cementum proteome signature. Bone 2021;153:116139.
104. Zhao N, Foster BL, Bonewald LF. The cementocyte-An osteocyte relative? J Dent Res 2016;95:734–741.
105. Boabaid F, Berry JE, Koh AJ, Somerman MJ, McCcauley LK. The role of parathyroid hormone-related protein in the regulation of osteoclastogenesis by cementoblasts. J Periodontol 2004;75:1247–1254.
106. Nemoto E, Darveau RP, Foster BL, Nogueira-Filho GR, Somerman MJ. Regulation of cementoblast function by P. gingivalis lipopolysaccharide via TLR2. J Dent Res 2006;85:733–738.
107. Seo BM, Miura M, Gronthos S, et al. Investigation of multipotent postnatal stem cells from human periodontal ligament. Lancet 2004;364:149–155.
108. Shalehin N, Seki Y, Takebe H, et al. Gli1+-PDL cells contribute to alveolar bone homeostasis and regeneration. J Dent Res 2022;101:1537–1543.
109. Mizoguchi T. In vivo dynamics of hard tissue-forming cell origins: Insights from Cre/loxP-based cell lineage tracing studies. Jpn Dent Sci Rev 2024;60:109-119.
110. Zhang W, Yelick PC. Tooth repair and regeneration: Potential of dental stem cells. Trends Mol Med 2021;27:501–511.
111. Pakpahan ND, Kyawsoewin M, Manokawinchoke J, et al. Effects of mechanical loading on matrix homeostasis and differentiation potential of periodontal ligament cells: A scoping review [epub ahead of print 12 May 2024]. J Periodontal Res doi: 10.1111/jre.13284.
112. Sokos D, Everts V, de Vries TJ. Role of periodontal ligament fibroblasts in osteoclastogenesis: a review. J Periodontal Res 2015;50:152–159.
113. Koda N, Sato T, Shinohara M, et al. The transcription factor mohawk homeobox regulates homeostasis of the periodontal ligament. Development 2017;144:313–320.
114. Donnelly E, Williams R, Farnum C. The primary cilium of connective tissue cells: Imaging by multiphoton microscopy. Anat Rec (Hoboken) 2008;291:1062–1073.
115. Jeon HH, Teixeira H, Tsai A. Mechanistic insight into orthodontic tooth movement based on animal studies: A critical review. J Clin Med 2021;10:1733.
116. Wang L, Foster BL, Kram V, et al. Fibromodulin and biglycan modulate periodontium through TGFβ/BMP signaling. J Dent Res 2014;93:780–787.
117. Bloemen V, Schoenmaker T, de Vries TJ, Everts V. Direct cell–cell contact between periodontal ligament fibroblasts and osteoclast precursors synergistically increases the expression of genes related to osteoclastogenesis. J Cell Physiol 2010;222:565–573.
118. Kanzaki H, Chiba M, Shimizu Y, Mitani H. Periodontal ligament cells under mechanical stress induce osteoclastogenesis by receptor activator of nuclear factor kappaB ligand up-regulation via prostaglandin E2 synthesis. J Bone Miner Res 2002;17:210–220.
119. Choi H, Yang L, Liu Y, Jeong JK, Cho ES. Npp1 prevents external tooth root resorption by regulation of cervical cementum integrity. Sci Rep 2022;12:21158.
120. Hathaway-Schrader JD, Novince CM. Maintaining homeostatic control of periodontal bone tissue. Periodontol 2000 2021;86:157–187.
121. Galli C, Passeri G, Macaluso GM. Osteocytes and WNT: the mechanical control of bone formation. J Dent Res 2010;89:331–343.
122. Wang K, Xu C, Xie X, et al. Axin2+ PDL cells directly contribute to new alveolar bone formation in response to orthodontic tension force. J Dent Res 2022;101:695–703.
123. Li Y, Zhan Q, Bao M, Yi J, Li Y. Biomechanical and biological responses of periodontium in orthodontic tooth movement: up-date in a new decade. Int J Oral Sci 2021;13:20.
124. Takimoto A, Kawatsu M, Yoshimoto Y, et al. Scleraxis and osterix antagonistically regulate tensile force-responsive remodeling of the periodontal ligament and alveolar bone. Development 2015;142:787–796.
125. Luan X, Ito Y, Holliday S, et al. Extracellular matrix-mediated tissue remodeling following axial movement of teeth. J Histochem Cytochem 2007;55:127–140.
126. Holliday S, Schneider B, Galang MT, Fukui T, Yamane A, Luan X, Diekwisch TG. Bones, teeth, and genes: a genomic homage to Harry Sicher's "Axial Movement of Teeth". World J Orthod 2005;6:61–70.
127. Zaghloul NA, Katsanis N. Mechanistic insights into Bardet-Biedl syndrome, a model ciliopathy. J Clin Invest 2009;119: 428–437.

128. Seo S, Zhang Q, Bugge K, et al. A novel protein LZTFL1 regulates ciliary trafficking of the BBSome and Smoothened. PLoS Genet 2011;7:e1002358.
129. Jin H, White SR, Shida T, et al. The conserved Bardet-Biedl syndrome proteins assemble a coat that traffics membrane proteins to cilia. Cell 2010;141:1208–1219.
130. Chang PE, Li S, Kim HY, Lee DJ, Choi YJ, Jung HS. BBS7-SHH signaling activity regulates primary cilia for periodontal homeostasis. Front Cell Dev Biol 2021;9:796274.
131. Passanezi E, Sant'Ana ACP. Role of occlusion in periodontal disease. Periodontol 2000 2019;79:129–150.
132. Niver EL, Leong N, Greene J, Curtis D, Ryder MI, Ho SP. Reduced functional loads alter the physical characteristics of the bone-periodontal ligament-cementum complex. J Periodontal Res 2011;46:730–741.
133. Wang H, Li T, Jiang Y, et al. Force-loaded cementocytes regulate osteoclastogenesis via S1P/S1PR1/Rac1 axis. J Dent Res 2023;102:1376–1386.
134. Wu X, Hu J, Li G, et al. Biomechanical stress regulates mammalian tooth replacement via the integrin β1-RUNX2-Wnt pathway. EMBO J 2020;39:e102374.
135. Li G, Li Q, Shen Z, et al. Fibulin-1 regulates initiation of successional dental lamina. J Dent Res 2023;102:1220–1230.
136. Sarrafpour B, Rungsiyakull C, Swain M, Li Q, Zoellner H. Finite element analysis suggests functional bone strain accounts for continuous post-eruptive emergence of teeth. Arch Oral Biol 2012;57:1070–1078.
137. Sarrafpour B, El-Bacha C, Li Q, Zoellner H. Roles of functional strain and capsule compression on mandibular cyst expansion and cortication. Arch Oral Biol 2019;98:1–8.
138. Suri L, Gagari E, Vastardis H. Delayed tooth eruption: Pathogenesis, diagnosis, and treatment. A literature review. Am J Orthod Dentofacial Orthop 2004;126:432–445.
139. Yoon H, Kim HJ, Shin HR, et al. Nicotinamide improves delayed tooth eruption in Runx2+/- mice. J Dent Res 2021;100:423–431.
140. Xu D, Wang P, Liu H, Gu M. Efficacy of three surgical methods for gingivectomy of permanent anterior teeth with delayed tooth eruption in children. Head Face Med 2022;18:23.
141. Luan X, Diekwisch TG. Vienna-Chicago: the cultural transformation of the model system of the un-opposed molar. Bioessays 2007;29:819–830.
142. Craddock HL, Youngson CC. A study of the incidence of overeruption and occlusal interferences in unopposed posterior teeth. Br Dent J 2004;196:341–348; discussion 337.
143. Wang D, Turkkahraman H, Chen J, Li B, Liu Y. Quantification of orthodontic loads on teeth in the correction of canine overeruption using different archwire designs. Am J Orthod Dentofacial Orthop 2023;163:e13–e21.