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Mesenchymal Progenitor Regulation of Tooth Eruption: A View from PTHrP

M. Nagata[1], N. Ono[1], and W. Ono[1]

Abstract

Tooth eruption is a unique biological process by which highly mineralized tissues emerge into the outer world, and it occurs concomitantly with tooth root formation. These 2 processes have been considered independent phenomena; however, recent studies support the theory that they are indeed intertwined. Dental mesenchymal progenitor cells in the dental follicle lie at the heart of the coupling of these 2 processes, providing a source for diverse mesenchymal cells that support formation of the highly functional tooth root and the periodontal attachment apparatus, while facilitating formation of osteoclasts. These cells are regulated by autocrine signaling by parathyroid hormone–related protein (PTHrP) and its parathyroid hormone/PTHrP receptor PPR. This PTHrP-PPR signaling appears to crosstalk with other signaling pathways and regulates proper cell fates of mesenchymal progenitor cell populations. Disruption of this autocrine PTHrP-PPR signaling in these cells leads to defective formation of the periodontal attachment apparatus, tooth root malformation, and failure of tooth eruption in molars, which essentially recapitulate primary failure of eruption in humans, a rare genetic disorder exclusively affecting tooth eruption. Diversity and distinct functionality of these mesenchymal progenitor cell populations that regulate tooth eruption and tooth root formation are beginning to be unraveled.

Keywords: mesenchymal progenitor cells, dental follicle, PTH1R, tooth eruption, signaling pathway, primary failure of eruption

Introduction

Tooth eruption is essential for survival of humans and mammals in general, with direct impact on the fundamental functions of the craniofacial structure, such as growth and development of the lower face, mastication for nutrition and energy intake, speech, and aesthetics for effective communication. Tooth eruption is a unique biological process by which highly mineralized tissues emerge into the outer world. This process involves the movement of a tooth from its site of development within bones to its functional position in the oral cavity so that it can occlude with its opposing teeth. Several theories of tooth eruption have been proposed; however, the regulatory mechanism remains largely unknown (Marks and Schroeder 1996; Wise and King 2008; Kjaer 2014).

Tooth eruption occurs concomitantly with formation of the tooth root, which is a critical component of the tooth anchored to surrounding alveolar bones through the periodontal ligament (PDL). Traditionally, tooth eruption has been considered a separate and distinct process from tooth root formation, as teeth can emerge into the oral cavity without roots or PDLs (Cahill and Marks 1980; Wang 2013). However, evidence from recent studies supports the emerging theory that these 2 processes are indeed intertwined (Ono et al. 2016; Takahashi et al. 2019). Formation of the highly functional tooth root and the periodontal attachment apparatus (i.e., cementum, PDL, and alveolar cryptal bones) requires deliberate coordination of mesenchymal cell differentiation. Mesenchymal progenitor cells, the precursor of these differentiated skeletal lineage cells, reside in dental mesenchymal tissues, such as the dental follicle (DF) and dental papilla (DP), and contribute to tooth root formation (Li et al. 2017; Wang and Feng 2017). Diversity and functionality of these mesenchymal progenitor cell populations at the heart of tooth root formation are beginning to be unraveled.

The purpose of this review is to summarize the current understanding on the mechanism of tooth eruption and how dental mesenchymal progenitor cells regulate this important biological process.

Root Cause of Tooth Eruption

Tooth eruption is executed through 3 defined stages: 1) pre-eruptive tooth movement, 2) eruptive tooth movement, and 3) post-eruptive tooth movement (Nanci 2017; Richman 2019; Fig. 1).

The first stage (pre-eruptive tooth movement) begins at the end of the early bell stage and lasts until the beginning of tooth

[1]Department of Orthodontics and Pediatric Dentistry, School of Dentistry, University of Michigan, Ann Arbor, MI, USA

Corresponding Author:
W. Ono, Department of Orthodontics and Pediatric Dentistry, School of Dentistry, University of Michigan, 1011 N University Ave, Ann Arbor, MI 48109, USA.
Email: wono@umich.edu

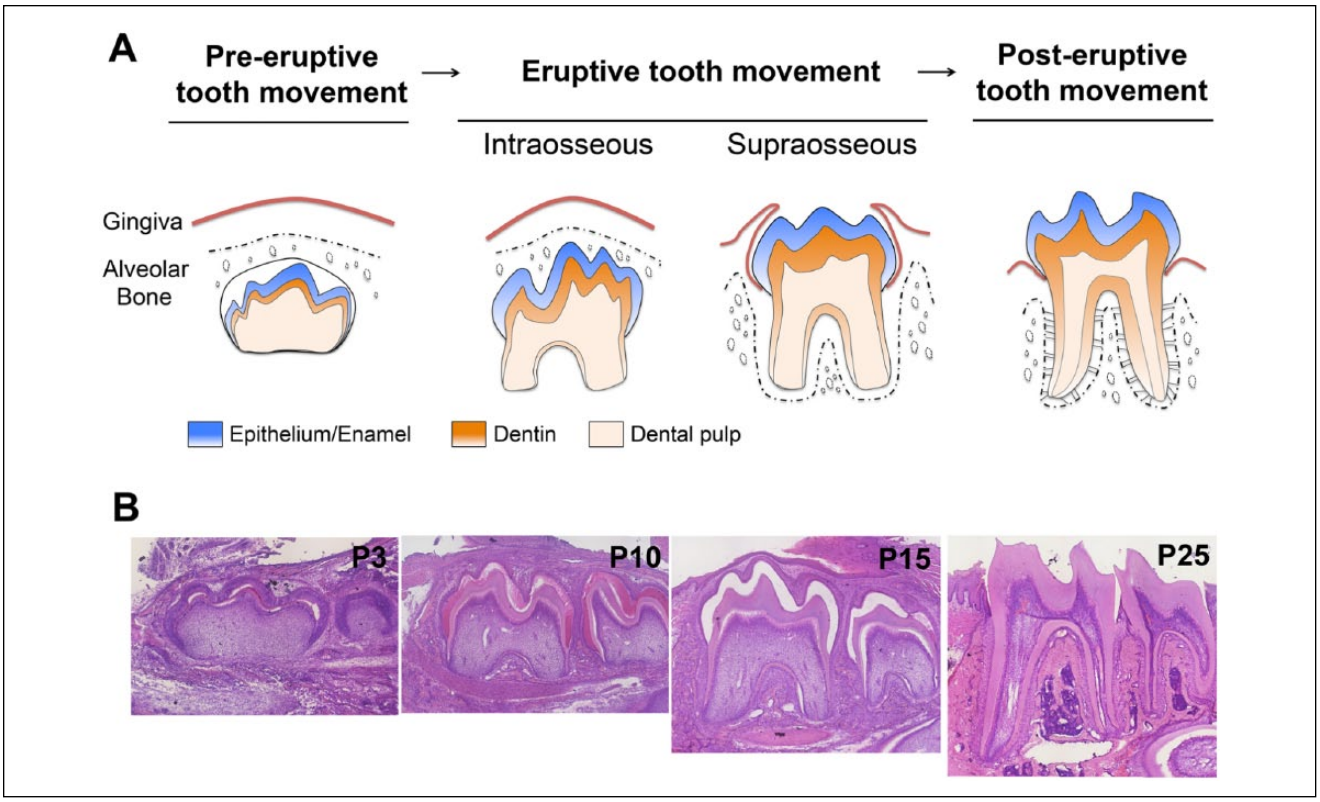

Figure 1. Three stages of tooth eruption. (**A**) Schematic diagrams of tooth eruption in mice during tooth root formation. Pre-eruptive tooth movement: tooth germs within alveolar bone before beginning to erupt. Eruptive tooth movement: movement from its position within the alveolar bone to its functional position in occlusion. This phase is subdivided into intra- and supraosseous phases. Posteruptive tooth movement: tooth maintains its fully erupted functional position in occlusion, while the jaws continue to grow. Tooth also compensates its loss of functional position caused by occlusal and proximal tooth wear. (**B**) Histologic sections of molars at different time points during tooth root formation in mice. Hematoxylin and eosin staining of the mandible at postnatal days 3, 10, 15, and 25.

root formation. In this stage, dental epithelial cells located at the apical region of the enamel organ in the developing tooth proliferate and invade further apically, sending signals to recruit DP mesenchyme inside the tooth bud to become odontoblasts that produce the dentin. Growth of the tooth bud owing to formation of the enamel and dentin at this stage continues until the tooth crown is complete, preparing the tooth to emerge into the oral cavity.

The second stage (eruptive tooth movement) begins with the onset of tooth root formation and lasts until the crown appears in the oral cavity and reaches the occlusal plane. Eruptive tooth movement is subdivided into 2 phases: intra- and supraosseous. In this stage, the epithelial structure termed Hertwig's epithelial root sheath (HERS) and the dental mesenchyme (i.e., DF and DP) signal each other to achieve rapid elongation of the tooth root. Subsequent bone resorption of the cortical shell on the coronal portion of the tooth bud by osteoclasts facilitates the tooth to emerge into the oral cavity.

The third stage (posteruptive tooth movement) starts when the tooth reaches its occlusion and maintains its position within the alveolar bone to achieve proper occlusion. This stage requires continuous maturation of the periodontal attachment apparatus and maintenance of its related structures.

Distinct Regulation of Tooth Crown and Root Formation

The tooth is made of 2 functionally distinct components: the crown and the root (Thesleff 2003; Balic and Thesleff 2015). Transcription factors nuclear factor I C (NFIC) and osterix (Osx) play a critical role in tooth root formation, which follows tooth crown formation (Kim et al. 2013; Kim, Bae, Lee, et al. 2015; Kim, Bae, Yang, et al. 2015; Zhang et al. 2015; Wang and Feng 2017). NFIC is expressed by odontoblasts of the crown and the root; however, NFIC-knockout mice showed a rootless tooth with no apparent change in the molar crowns (Steele-Perkins et al. 2003). Osx is a one of the major downstream molecules of NFIC, and it plays an essential role in tooth root formation but not crown formation (Zhang et al. 2015). These studies provide evidence that tooth crown and root formation are separately regulated.

DF and Its Mesenchymal Progenitor Cell Populations

The DF, a sac-like membranous tissue surrounding the developing tooth bud, plays central roles in tooth eruption and tooth root

formation. It has been known for several decades that surgical removal of the DF prevents tooth eruption, but the ability of the DF to support tooth eruption does not depend on tooth root formation (Cahill and Marks 1980). Osteoclast activities are particularly important during the second stage of tooth eruption, through which the tooth emerges into the oral cavity. However, formation of the periodontal tissue is equally important for the latter stage of tooth eruption (Gorski and Marks 1992; Wise and King 2008).

It has been postulated from histologic studies that the DF includes precursor cells for cementoblasts, PDL cells, and alveolar bone osteoblasts (Ten Cate 1997). More recent in vivo lineage-tracing experiments with tamoxifen-inducible *creER* lines in mice unambiguously demonstrated that the DF contains a variety of mesenchymal progenitor cell populations, including cells expressing glioma-associated oncogene homolog 1 (Gli1), Osx, and parathyroid hormone–related protein (PTHrP; Liu et al. 2015; Ono et al. 2016; Takahashi et al. 2019). Dental mesenchymal cells are derived from cranial neural crest cells and differentiate into dental pulp cells and odontoblasts (Chai et al. 2000; Li et al. 2017). Gli1 is expressed by mesenchymal cells and epithelial cells of HERS. After tooth root formation, descendants of $Gli1^+$ cells contribute to all the tooth root structures and their surrounding alveolar bone (Fig. 2A; Liu et al. 2015). Osx is exclusively expressed by mesenchyme cells, such as apical papilla and DF around HERS. Osx^+ cells differentiate into a majority of the odontoblasts, dental pulp cells, cementoblasts, and a small number of PDL fibroblasts (Fig. 2B; Ono et al. 2016). PTHrP is specifically expressed in DF, and $PTHrP^+$ DF cells differentiate into PDL fibroblasts, cementoblasts on acellular cementum, and osteoblasts of alveolar cryptal bone (Takahashi et al. 2019; Fig. 2C). These studies suggest that Osx^+ cells and $PTHrP^+$ cells are subpopulations of $Gli1^+$ cells. These different classes of DF cells with potential overlaps can become cementoblasts, PDL cells, and alveolar bone osteoblasts during tooth root formation (Fig. 2). Additionally, so-called mesenchymal stem cells have been isolated from the DF of wisdom teeth in humans with in vitro culture condition (Yao et al. 2008; Bai et al. 2011), although the properties of these cells in vivo remain incompletely known (Sharpe 2016).

Therefore, DF contains important mesenchymal progenitor cell populations that orchestrate tooth eruption and tooth root formation through common or distinct mechanisms. Further characterization of each population of DF mesenchymal progenitor cells will shed further light on the mechanism of mesenchymal regulation on tooth eruption.

An Enigmatic Genetic Disease Exclusively Affecting Tooth Eruption

Lessons from rare genetic diseases give us substantial insight into molecular mechanisms of tooth eruption. In humans, loss-of-function mutations in parathyroid hormone receptor 1 (*PTHR1*), also known as parathyroid hormone (PTH)/PTHrP receptor (*PPR*), are associated with primary failure of tooth eruption (PFE; Decker et al. 2008; Frazier-Bowers et al. 2010; Yamaguchi et al. 2011; Risom et al. 2013; Frazier-Bowers et al. 2014; Roth et al. 2014; Jelani et al. 2016; Grippaudo et al. 2018). PFE is a rare autosomal dominant nonsyndromic disorder with a prevalence of 0.06% (Baccetti 2000). In this condition, molars are partially erupted but submerged, with moderate anomalies in tooth roots. PFE is defined as incomplete eruption of the initially nonankylosed tooth despite the presence of a clear eruption pathway, which results in a posterior unilateral or bilateral open bite. PFE can affect primary and permanent teeth and most commonly affects posterior teeth (Proffit and Vig 1981).

PPR is a G protein–coupled receptor with 7 transmembrane-spanning helixes, and it binds to PTH and PTHrP in an equivalent affinity (Jüppner et al. 1991; Dean et al. 2008). Upon ligand binding, PPR activates at least 2 second messenger signaling systems: the adenylyl cyclase/protein kinase A pathway and the phospholipase C/protein kinase C pathway (Mannstadt et al. 1999). PPR mediates a number of important biological processes, such as endochondral bone formation (Kronenberg 2006). In humans, homozygous loss-of-function mutations in *PPR* result in embryonic lethal Blomstrand-type chondrodysplasia (Karaplis et al. 1998; Zhang et al. 1998), while gain-of-function mutations in *PPR* lead to Jansen-type metaphyseal chondrodysplasia (Schipani et al. 1995). Interestingly, PFE is the only known genetic disease associated with haploinsufficiency in the *PPR* gene in humans, which shows phenotypes only in molars but not in other skeletal elements. Interestingly, PPR haploinsufficiency does not cause any PFE phenotype in mice; however, complete loss of PPR in Osx-lineage mesenchymal cells with *Osx-cre* and *PPR*-floxed alleles leads to complete failure of tooth eruption with significantly truncated roots lacking PDL (Ono et al. 2016).

Therefore, PFE is a unique genetic condition that can give us precious insight into the mechanism on tooth eruption, highlighting the indispensable role of PPR in tooth eruption.

PTHrP Regulation of Tooth Eruption and Tooth Root Formation

A group of mesenchymal cells in the DF, particularly those adjacent to the dental epithelium, abundantly expresses PTHrP. PTHrP, a locally acting autocrine/paracrine ligand, exerts pleiotropic effects on cell proliferation and differentiation; in organogenesis, PTHrP regulates epithelial-mesenchymal interactions in various organs, such as skin, hair follicle, mammary gland, pancreas, and developing teeth (Wysolmerski et al. 1994; Wysolmerski et al. 1995; Vasavada et al. 1996; Foley et al. 1998; Philbrick et al. 1998). In endochondral bone development, PTHrP maintains chondrocyte proliferation and inhibits its differentiation into prehypertrophic and hypertrophic chondrocytes through the PTHrP–Indian hedgehog (Hh) feedback loop (Kronenberg 2003). In addition, $PTHrP^+$ chondrocytes within the resting zone of the postnatal growth plate behave as skeletal stem cells (Mizuhashi et al. 2018), indicating that mesenchymal cells expressing PTHrP might share some features with skeletal stem/progenitor cells.

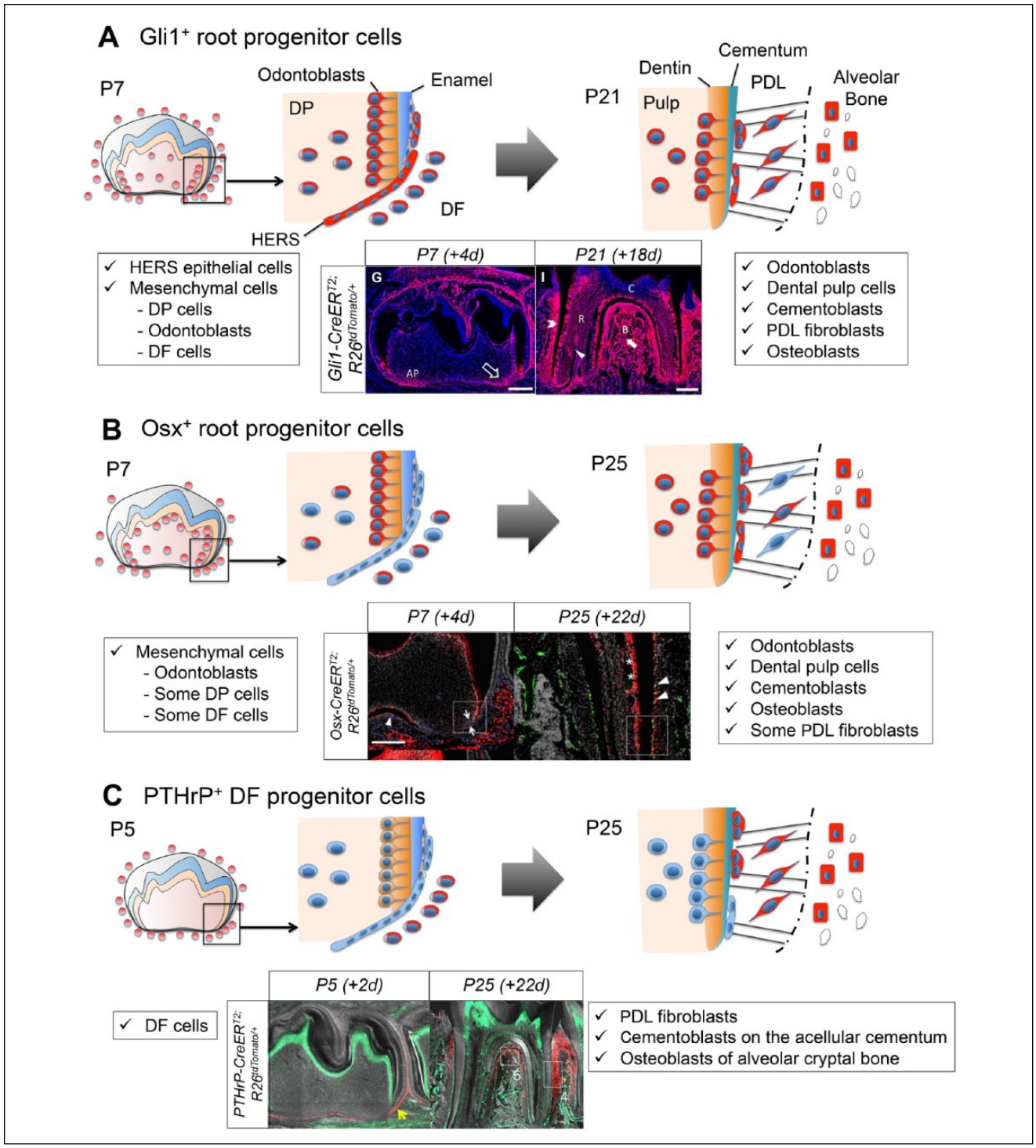

Figure 2. Mesenchymal progenitor cell populations for tooth root formation in mice. (**A**) Schematic diagrams of the fate of Gli1$^+$ root progenitor cells during tooth root formation. Gli1$^+$ cells pulsed with tamoxifen at postnatal day 3 (P3) of *Gli1-CreER^{T2}* mice. Gli1$^+$ cells are found in HERS, apical papilla, and dental follicle. After tooth root formation, descendants of Gli1$^+$ cells were located in all the root structures, including the root pulp, PDL, and surrounding alveolar bone (Liu et al. 2015). DF, dental follicle; DP, dental papilla; HERS, Hertwig's epithelial root sheath; PDL, periodontal ligament. Histologic images reproduced and adapted with permission from Liu et al., *Development*, 2015, copyright the Company of Biologists. (**B**) Schematic diagrams of the fate of Osx$^+$ root progenitor cells during tooth root formation. Osx$^+$ cells pulsed with tamoxifen at P3 of *Osx-CreER^{T2}* mice. Osx$^+$ cells are found in apical papilla and dental follicle around HERS. After tooth root formation, Osx$^+$ cells differentiate into a majority of the odontoblasts, dental pulp cells, cementoblasts, and some PDL fibroblasts (Ono et al. 2016). Histologic images reproduced and adapted with permission from Ono et al., *Nature Communications*, 2016. (**C**) Schematic diagrams of the fate of PTHrP$^+$ DF mesenchymal progenitor cells during tooth root formation. PTHrP$^+$ cells pulsed tamoxifen at P3 of *PTHrP-CreER^{T2}* mice. PTHrP$^+$ cells are specifically found in DF around tooth bud. After tooth root formation, PTHrP$^+$ DF cells differentiate into PDL fibroblasts, some cementoblasts on acellular cementum, and osteoblasts of alveolar cryptal bone (Takahashi et al. 2019). Histological images reproduced and adapted with permission from Takahashi et al., *Proceedings of the National Academy of Sciences of the United States of America*, 2019.

During tooth development, PTHrP is required for tooth eruption. PTHrP-null mice die at birth due to a chondrodystrophic phenotype characterized by premature chondrocyte differentiation and accelerated bone formation. Philbrick et al. (1998) restored PTHrP expression in chondrocytes in PTHrP-null mice, but not in the teeth, to rescue early lethality. However, it led to complete failure of tooth eruption and tooth root formation in the surviving animals that lacked PTHrP in the dental tissues. While Philbrick et al. originally reported that *PTHrP* mRNA is expressed in the stellate reticulum of the enamel organ, *PTHrP* mRNA is also abundantly expressed in DF mesenchymal cells adjoining the HERS (Ono et al. 2016; Takahashi et al. 2019). Our in vivo lineage-tracing experiments with *PTHrP-creER* demonstrated that $PTHrP^+$ DF cells can readily differentiate into cementoblasts on the acellular cementum, PDL cells, and alveolar cryptal bone osteoblasts during tooth root formation; when PPR was removed in these $PTHrP^+$ DF cells, it led to a failure of tooth eruption (Takahashi et al. 2019). In contrast, injection of PTHrP (1-34) accelerates tooth eruption and inhibits osteogenesis of the DF cells by inactivating the Wnt/β-catenin pathway (Zhang et al. 2019). Possible downstream signaling of the PTHrP-PPR system is histone deacetylase 4 (HDAC4; Ono et al. 2016) and salt-inducible kinase 3 (SIK3; Nishimori et al. 2019).

Therefore, PTHrP is an indispensable autocrine/paracrine cytokine that regulates tooth eruption and tooth root formation, which is highly expressed by a group of DF mesenchymal progenitor cells contributing to formation of the periodontal attachment apparatus.

PTHrP-PPR Autocrine Signaling Regulates Tooth Eruption and Tooth Root Formation

During tooth development, PPR is expressed by dental mesenchymal cells, particularly by cells in the DF as well as the DP and odontoblasts of the coronal portion (Ono et al. 2016). Interestingly, PPR is abundantly expressed by $PTHrP^+$ DF mesenchymal cells (Takahashi et al. 2019). This raises an intriguing hypothesis that PTHrP-PPR autocrine signaling plays important roles in directing proper differentiation of $PTHrP^+$ DF mesenchymal cells during tooth root formation. To test this hypothesis, our group disturbed this autocrine signaling by conditionally deleting PPR in $PTHrP^+$ DF cells based on *PTHrP-creER* and *PPR*-floxed alleles. PPR deficiency induced a cell fate shift of $PTHrP^+$ DF mesenchymal cells to nonphysiologic cementoblast-like cells precociously forming the cellular cementum on the root surface, which was associated with upregulation of Mef2c and matrix proteins. Mef2c is a transcription factor located downstream of the PPR-Gsα-cAMP-protein kinase A pathway (Kozhemyakina et al. 2009). This resulted in loss of the proper periodontal attachment apparatus without any apparent alteration in osteoclasts around molars or ankylosis. Interestingly, this phenotype further developed into malformation of molar roots associated with undereruption particularly severe in the first molars in adult mice, essentially recapitulating human PFE conditions (Takahashi et al. 2019).

Therefore, these mouse genetic experiments provide the experimental evidence that defective formation of the periodontal attachment apparatus and PFE are closely related, at least in the mouse model of PFE. It remains to be determined why the first molars are the most affected in human and mouse PFE conditions. Our recent study based on a series of 3-dimensional analyses of mouse PFE molars demonstrated that PFE molars, particularly the first molars, could indeed continue to erupt but at a much slower rate than normal molars, contributing to the most pronounced phenotype in first molars (Tokavanich et al., unpublished data). These findings shed light on the potential pathophysiology of PFE. It requires further investigations regarding the mechanism underlying this selective phenotype.

Other Major Signaling Pathways Involved in Tooth Eruption

A plausible hypothesis is that PTHrP-PPR signaling interacts with other major signaling pathways with DF mesenchymal progenitor cells to facilitate tooth eruption and tooth root formation. As mentioned earlier, PPR is a G protein–coupled receptor. Gαs is the stimulatory subunit of a G protein complex and transduces G protein–coupled receptor signaling. Gαs-mediated signaling induced by the PTHrP-PPR ligand-receptor interaction crosstalks with Wnt and Hh signaling pathways (Cong et al. 2019). Here, we focus on Wnt/β-catenin, Hh, and TGF-β/BMP signaling as auxiliary pathways that potentially interact with PTHrP-PPR signaling during tooth eruption.

Wnt/β-catenin Signaling

Wnt/β-catenin signaling plays essential roles in skeletal development and homeostasis (Logan and Nusse 2004; Glass et al. 2005; Holmen et al. 2005). β-catenin is expressed in dental epithelium and dental mesenchyme during tooth root formation (Kim et al. 2011). Roles of Wnt/β-catenin signaling in DF mesenchymal progenitor cells are not known; however, their roles in more mature skeletal cells have been reported. Constitutive activation of β-catenin signaling in osteoblasts and odontoblasts (*Col1a1-cre; Ctnnb*$^{+/lox(ex3)}$) leads to disturbance in tooth eruption for incisor and molars with increase of alveolar bone mass (Kim et al. 2012). This is due to disruption of osteoclast activities resulting from activation of Wnt/β-catenin signaling in mature osteoblasts. Moreover, constitutive activation of β-catenin in osteocytes (dentin matrix protein 1–cre [*Dmp1-cre*]; *Ctnnb*$^{+/lox(ex3)}$) leads to disturbance of tooth eruption in incisors (Wu et al. 2019). In contrast, inactivation of β-catenin signaling in osteoblasts and odontoblasts (osteocalcin-cre [*Oc-cre*]; *Ctnnb1*$^{fl/fl}$) leads to normal emergence of incisor and molars into the oral cavity despite complete failure of root formation (Kim et al. 2013). In bone, deletion of β-catenin in mature osteoblasts by *Col1a1-cre, Oc-cre*, or *Dmp1-cre* causes an increase in osteoclasts and low

bone mass with normal bone formation (Glass et al. 2005; Holmen et al. 2005; Kramer et al. 2010).

Therefore, excessive osteoclast activities might account for normal emergence of these molars into the oral cavity despite the absence of the tooth root. These studies demonstrate that the Wnt/β-catenin signaling in mature osteoblasts regulates tooth eruption indirectly through regulating osteoclast formation. How Wnt/β-catenin signaling functions in more immature mesenchymal progenitor cell populations and regulates tooth eruption and tooth root formation remain to be studied.

Hedgehog Signaling

Hedgehog (Hh) signaling is a developmentally conserved pathway for embryonic and postnatal development in a number of organs (Hammerschmidt et al. 1997; Chuang and McMahon 1999; Ingham and McMahon 2001; Briscoe and Therond 2013). Hh signaling is involved in the process of epithelial-to-mesenchymal transition and essential for tooth root formation (Dassule et al. 2000; Jernvall and Thesleff 2000; Khan et al. 2007). In the developing teeth, HERS abundantly expresses Shh (sonic hedgehog) during tooth root formation (Nakatomi et al. 2006; Khan et al. 2007). Apical mesenchymal cells of the DP and the DF surrounding HERS express the Hh receptor patched 1 (Ptch1), which has an inhibitory function for Smo (smoothened) signaling. Binding of Hh ligands to Ptch1 receptors releases this inhibition. In fact, loss-of-function spontaneous mutations in *Ptch1* in homozygous mesenchymal dysplasia (*Ptch1*^{mes}) mice, which express an abnormal C-terminus of Ptch1 protein, lead to delay in tooth eruption and short roots due to inhibited proliferation of dental mesenchymal cells around HERS (Nakatomi et al. 2006).

Gli1, a canonical transcriptional target of Hh signaling, is expressed in the apical mesenchyme adjacent to the HERS that abundantly expresses Shh. Inhibition of Hh signaling by pharmacologic Hh inhibitors and constitutive activation of Hh signaling by *Gli1-creER; Rosa26-lsl-SmoM2* mouse models lead to shorter roots and normal tooth eruption (Liu et al. 2015). Interestingly, Gli1 appears to be highly expressed in dental mesenchymal progenitor cells. In the developing incisor, Gli1^{+} mesenchymal cells are slow cycling and behave as mesenchymal stem cells of the continuously growing mouse incisor (Zhao et al. 2014). NFIC, a transcription factor mentioned earlier, activates Hh attenuator Hhip in the dental mesenchyme and fine-tunes Hh signaling activities in these cells (Liu et al. 2015). These studies demonstrate that Hh signaling in DF mesenchymal progenitor cells may play important roles in tooth root formation but potentially also in tooth eruption.

TGF-β/BMP Signaling

Transforming growth factor β (TGF-β) signaling is important for epithelial-to-mesenchymal transition (Xu et al. 2009). Deletion of *Tgfr2* in Osx^{+} mesenchymal cells (*Osx-cre; Tgfbr2*$^{fl/fl}$) leads to failure of tooth eruption and tooth root formation, with disruption of osteoblast differentiation and reduction of osteoclasts in alveolar bone surrounding the tooth bud (Wang et al. 2013). Bone morphogenetic protein (BMP) signaling plays a major role of osteoblastic differentiation and bone formation and interacts intricately with TGF-β signaling (Beederman et al. 2013; Wu et al. 2016). In the developing tooth, BMP signaling actively regulates cell fate decisions of epithelial and mesenchymal cells (Aberg et al. 1997; Rakian et al. 2013). Moreover, conditional deletion of BMP1 and mammalian tolloid like 1 (TLL1; *Ubc-creER*^{T2};*Bmp1*$^{fl/fl}$; *Tll1*$^{fl/fl}$) leads to delay in tooth eruption due to reduction in osteoclast formation (Wang et al. 2017). BMP1 and TLL1 belong to a small family of extracellular metalloproteinases that share a similar structure (Ge and Greenspan 2006). Msx2 (muscle segment homeobox-like 2) is a bona fide target of BMP signaling and transiently expressed in postmigratory mesenchymal cells in cranial neural crest–derived tissues (Semba et al. 2000; Brugger et al. 2004). Msx2-null mice showed amelogenesis imperfecta with failure of tooth eruption (Aïoub et al. 2007). Msx2-expressing cells behave as early mesenchymal progenitor cells in craniofacial bone development (Sakagami et al. 2018). These studies suggest that TGF-β/BMP signaling in dental mesenchymal progenitor cells may play a role in tooth eruption and tooth root formation.

Roles of Osteoclasts in Tooth Eruption

Osteoclasts, bone-resorbing multinucleated cells belonging to the monocyte-macrophage lineage, have been traditionally considered the central regulator of tooth eruption. They play essential roles in clearing the eruption pathway for unerupted teeth encased in the alveolar bone (Wise et al. 2002) by resorbing the overlaying cortical shell of the alveolar bone. Indeed, inhibition of osteoclast formation and function results in delay of tooth eruption (Yoda et al. 2004). Osteoclastogenesis is tightly regulated by important factors such as CSF-1 (colony-stimulating factor 1), receptor activator of nuclear factor-κB ligand (RANKL), and OPG (osteoprotegerin; Heinrich et al. 2005). These factors are predominantly expressed by mesenchymal cells; osteoclasts need signals from their adjacent dental mesenchymal cells, specifically DF cells, to facilitate tooth eruption during eruptive tooth movement (stage 2). Failure to perforate the cortical shell during eruptive tooth movement is detrimental to subsequent tooth root formation. RANKL-deficient mice (*RANKL*$^{-/-}$) show failure of tooth eruption with disorganization of HERS (Huang et al. 2018). In addition, osteocytes express much higher levels of RANKL than osteoblasts, indicating that osteocytes are likely one of the major regulators in tooth eruption by regulating osteoclast formation and bone homeostasis (Nakashima et al. 2011; Xiong et al. 2011). Osteopetrosis in *ntl* mice induces failure of tooth eruption with developing odontoma-like proliferations near the proximal ends of the incisor (Lu et al. 2009). *c-Fos* is a component of the AP-1 (activator protein 1) complex that lies downstream of the RANKL/RANK signaling pathway (Asagiri and Takayanagi 2007). *c-Fos* homozygous mutant mice (*c-Fos*$^{-/-}$) show failure of tooth eruption and tooth root formation associated with lack of osteoclast formation (Alfaqeeh et al. 2015).

Table. Transgenic Mouse Lines Used for the Analysis of Tooth Eruption.

Mouse Genotype	Cre Transgenic Line	Tooth Eruption	Emergence	Root Formation	Reference	How Gene Manipulation Affects Root and Alveolar Bone
Osx-Cre;Tgfbr2$^{fl/fl}$	*Osx-Cre*	Delay	Infraerupted	Short roots	Wang et al. 2013	Reduced number of osteoclasts, reduced odontoblast and osteoblast differentiation marker genes
Osx-Cre;PPR$^{fl/fl}$	*Osx-Cre*	Failure	No emergence	Short roots	Ono et al. 2016	Ankylosis of cementum to bone, no PDL
Osx-CreER;PPR$^{fl/fl}$	*Osx-CreER*	Failure	Infraerupted	Short roots	Ono et al. 2016, Takahashi et al. 2019	Increased cementum thickness
PTHrP-CreER;PPR$^{fl/fl}$	*PTHrP-CreER*	Failure	Infraerupted	Short roots	Takahashi et al. 2019	A cell fate shift of PTHrP^{+} dental follicle cells to cementoblast-like cells
UBC-CreER; Bmp1$^{fl/fl}$;*Tll1*$^{fl/fl}$	*UBC-CreER*	Delay	Infraerupted	Short roots	Wang et al. 2017	Decreased number of odontoblasts and osteoclasts with reduced DMP and DSPP expression
Col1a1-Cre; Ctnnb$^{+/lox(ex3)}$	*Col1a1-Cre*	Failure	No emergence	Short roots	Kim et al. 2012	Increased alveolar bone mass
Gli1-CreER;R26SmoM2	*Gli1-CreER*	Normal	Normally erupted	Short roots	Liu et al. 2015	Decreased proliferation of apical papilla cells
Oc-Cre;Ctnnb1$^{fl/fl}$	*Oc-Cre*	Normal	Normally erupted	No roots	Kim et al. 2013	Lack of odontoblasts and dentin in roots due to disruption in odontoblast differentiation
Col2-Cre;Sik3$^{fl/fl}$;*PTHrP*$^{-/-}$	*Col2-Cre*	Failure	No emergence	Short roots	Nishimori et.al. 2019	Not listed
Ptch1$^{mes/mes}$	—	Delay	Infraerupted	Short roots	Nakatomi et al. 2006	Increased proliferation of apical cells
Ntl$^{-/-}$	—	Delay	No emergence	No roots	Lu et al. 2009	Malformed osteoclasts and formation of odontoma-like structures
c-Fos$^{-/-}$	—	Failure	No emergence	No roots	Alfaqeeh et al. 2015	Reduced osteoclast formation with the HERS unable to extend downward due to the presence of bone
Msx2$^{-/-}$	—	Failure	Infraerupted (M1, M2), no emergence (M3)	Short roots	Aïoub et al. 2007	Decreased osteoclast formation with reduced RANKL expression in alveolar bone
Runx2/Cbf1$^{-/-}$	—	Delay	Infraerupted	Not listed	Yoda et al. 2004	Suppressed osteoclast formation.
PTHrP$^{-/-}$; *Col2-PTHrP*	—	Failure	No emergence	No roots	Philbrick et al. 1998	Unabsorbed alveolar bone surrounding tooth bud despite abundant osteoclasts
NFIC$^{-/-}$	—	Not listed	Infraerupted but extracted at P190	No roots	Steele-Perkins et al. 2003	Decreased alveolar bone formation with reduced DSPP expression

DMP, dentin matrix protein; DSPP, dentin sialophosphoprotein; HERS, Hertwig's epithelial root sheath; M1 to M3, first to third molars; P190, postnatal day 190; PDL, periodontal ligament; PTHrP, parathyroid hormone–related protein.

Therefore, failure in tooth root formation in these mice is a secondary consequence due to the lack of space available to the tooth caused by failure to remove the surrounding bone. Importantly, dental mesenchymal cells play intrinsic roles in facilitating pre-eruptive tooth movement (stage 1), as well as posteruptive movement (stage 3), with little involvement with osteoclasts (Wise and King 2008; Fleischmannova et al. 2010; Richman 2019).

Challenges and Future Directions

The emerging concept that tooth eruption is regulated by a diverse group of dental mesenchymal progenitor cells is supported by new mouse genetic approaches. The majority of our current and previous knowledge on molecular regulation of this process has been derived from global knockout/knock-in mice and cell type–specific conditional gene deletion experiments based on conventional *cre-loxP* transgenic systems. The limitation of these approaches is that roles of a particular gene or cell population tend to be overestimated without the ability to temporally control gene manipulation and/or target a single population of mesenchymal progenitor cells.

Tooth eruption occurs during the stages of postnatal tooth development. Therefore, studying this process requires a highly specific inducible approach that allows temporal labeling and gene manipulation during a specific window of time within a specific population of mesenchymal progenitor cells. Moreover, there is a need to thoroughly characterize subpopulations of mesenchymal progenitor populations through more rigorous emerging single-cell technologies. There is a hope that these more detailed analyses will lead to identification of new marker genes that enable us to perform more detailed functional characterization of distinct subsets of mesenchymal progenitor cell populations, particularly through generation of new inducible transgenic lines. Furthermore, functional analyses of tooth eruption have been largely hampered by lack of standardization for the phenotype assessment. The use of 3-dimensional imaging analyses will be instrumental for a more objective standard for the assessment of tooth eruption.

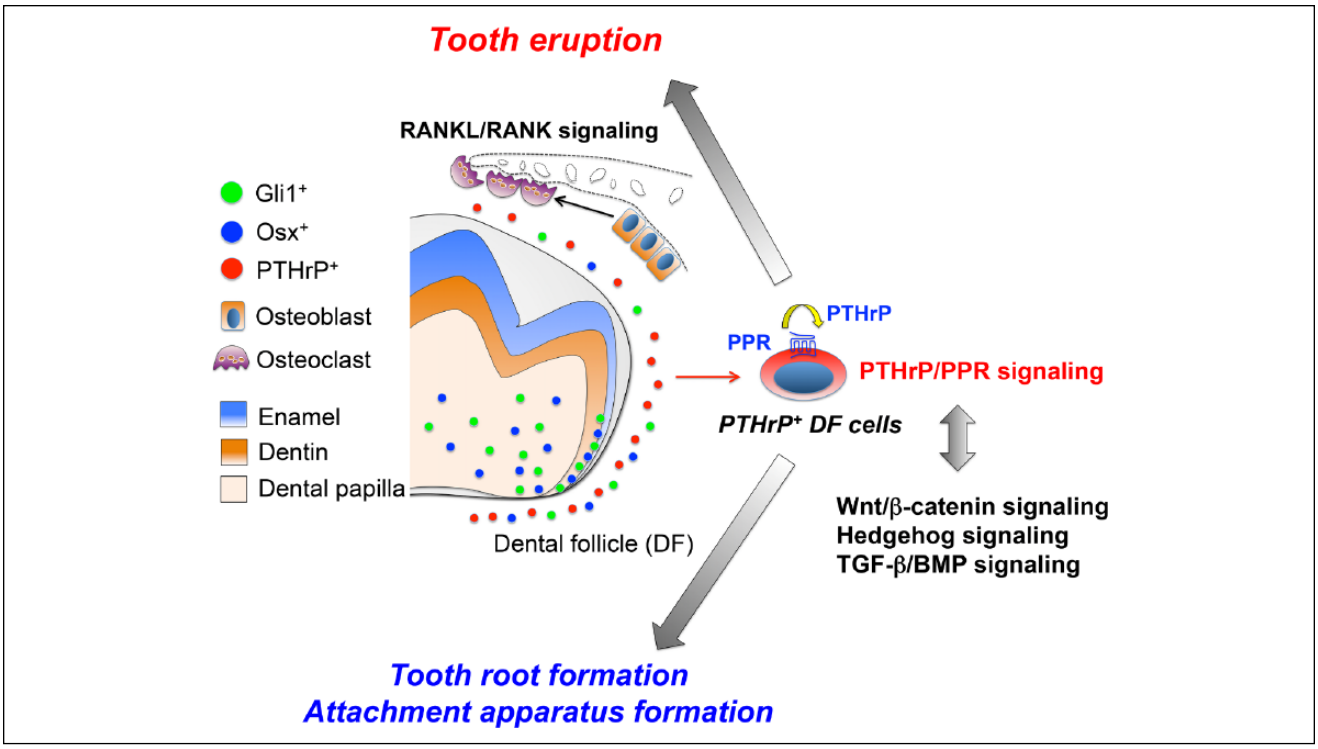

Figure 3. Role of mesenchymal progenitor cells in tooth eruption. PTHrP^{+} DF mesenchymal progenitor cells are required for tooth eruption and formation of tooth root and proper attachment apparatus via autocrine PTHrP/PPR signaling. PTHrP/PPR signaling may interact with other molecular signaling, such as Wnt/β-catenin, hedgehog, TGF-β/BMP, and RANKL/RANK signaling. DF, dental follicle; PPR, parathyroid hormone/PTHrP receptor; PTHrP, parathyroid hormone–related protein.

Conclusion

Tooth eruption is a continuous biological process that occurs during postnatal tooth development, which is closely intertwined with tooth root formation. Dental mesenchymal progenitor cells contributing to tooth root formation can directly and indirectly regulate tooth eruption. Thanks to insight from the rare human genetic disease exclusively affecting tooth eruption (PFE) and continuous progress in mouse genetics, we are now beginning to understand that PTHrP-PPR autocrine signaling functions as the linchpin for tooth eruption and tooth root formation, with potential involvement of the major signaling pathways, such as Wnt/β-catenin, Hh, and TGF-β/BMP (Table and Fig. 3). For better understanding of this important biological process, we need to develop more specific genetic tools that allow functional analysis of specific groups of dental mesenchymal progenitor cells. We expect that further understanding of dental mesenchymal progenitor cells and how they regulate tooth eruption will facilitate development of innovative dental regenerative approaches in the future.

Author Contributions

M. Nagata, contributed to conception and design, drafted the manuscript; N. Ono, W. Ono, contributed to conception and design, drafted and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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ORCID iD

W. Ono https://orcid.org/0000-0002-0358-1897

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