# Molecular mechanisms underlying tooth root development

Liu Yang, Eui-Sic Cho<sup>†</sup>

Cluster for Craniofacial Development and Regeneration Research, Institute of Oral Biosciences, Jeonbuk National University School of Dentistry

접수: 2020년 11월 4일/ 수정접수: 2020년 12월 3일/ 계재 승인: 2020년 12월 4일/ 출간: 2020년 12월 31일

Root is a crucial and functional part of tooth for mammals, and tooth root development begins after the completion of tooth crown. Although bioengineered tooth has been extensively researched in animal studies recently, it is still impossible to regenerate new tooth in humans. Moreover, the intricate molecular networks that regulate root development, which are the cornerstone of tooth regeneration, still remain largely unknown. Therefore, fully understanding tooth root development is of great interest to aid further research in the field of regenerative medicine. Herein, we review the advances in the understanding of processes and mechanisms of root development using different mouse models. In this review, we start with the Hertwig's epithelial root sheath (HERS) formation, which marks the initiation of root development. We then highlight root development. In addition, we summarize the complicated molecular interactions between epithelium and mesenchyme during root development. Finally, this review also features a list of various root abnormalities using gene deletion or overexpression mouse models to provide an overview of root malformations.

Keywords: root development, epithelium, mesenchyme, dentinogenesis, cementogenesis

<sup>†</sup> Corresponding author: Eui-Sic Cho

Laboratory for Craniofacial Biology, Jeonbuk National University School of Dentistry 567 Baekje-Daero, Deokjin-Gu, Jeonju 54896, South Korea

Phone: 82-63-270-4045, Fax: 82-63-270-4004, E-mail: oasis@jbnu.ac.kr

# Introduction

In mammals, root is an indispensable part of the whole tooth. In mice, crown continues to develop after birth and reaches to its full size until postnatal day 4 (P4). Then root starts to form and lasts 3 weeks<sup>1)</sup>. At P4, the outer enamel epithelium (OEE) and inner enamel epithelium (IEE) at the cervical loop elongate and form a continuous double layer structure named Hertwig's epithelial root sheath (HERS), which marks the commencement of the root development<sup>2)</sup>. Morphologically, HERS is a structural boundary of two dental ectomesenchymal tissues: dental papilla and dental follicle which will form the pulp, dentin and periodontium. Following tooth root development and elongation, tooth finally erupts into the oral cavity and then establishes occlusal contacts with opposing teeth.

During the whole process of root development, epithelium and mesenchyme is tightly interacted and mutual influenced. Until now, there have been a lot of studies related to root development defects by application of transgenic mouse models, but most of these studies focused on a few molecules or signaling pathways and still we did not elucidate the mechanism of root development. Here, in this review, we divide the completed root development into three main parts: (1) The formation of HERS associated with the transition from crown to root; (2) Apically growth of the HERS and dentinogenesis; (3) The disintegration of the HERS and cementogenesis. This review will provide an overview of recent studies related to root development by using mouse models, in order to get a more comprehensive understanding of the regulatory mechanisms for root development.

# **HERS** formation

In mice, during molar root development, the transition from dental cervical loop to HERS is regarded as the initiation of root formation. And it was generally accepted that root development proceeds under the control of HERS. Hence, it is of particular importance to figure out the formation and development of HERS since the precise mechanism underlying HERS development and growth remain to be elucidated. HERS originated from the stellate reticulum and/or OEE, and HERS formation is regulated by sequential and reciprocal interactions between epithelium and mesenchyme<sup>3)</sup>. Similar to other organogenesis, the functional form of HERS is the result of precise coordination between the processes of cell proliferation, differentiation and apoptosis<sup>4)</sup>. A widely accepted theory of HERS formation is the differences of cell dynamics between IEE and OEE. At beginning, growth factors like insulin-like growth factor I and hepatocyte growth factor (Hgf) secreted by the surrounding mesenchymal tissues are capable of increasing cell proliferation in the OEE but not IEE<sup>5, 6)</sup>, so it was believed that more active cell proliferation in the outer epithelium layer of HERS results in the HERS elongation. In consistent with this theory, disordered cell proliferative activity in IEE and OEE due to sustained Egf signaling and Fgf3/10 expression result in inhibited HERS formation<sup>7, 8)</sup>. Subsequently, HERS formed a continuous bi-layer of flat, cuboidal cells, with extension in root apical direction. During this process, transforming growth factor- $\beta$  (TGF- $\beta$ )/BMP signaling is especially crucial for the fate of HERS. It has been demonstrated that exogenous Bmp4, a member of TGF- $\beta$  superfamily, inhibits HERS development by preventing its

proliferation and elongation during root formation<sup>9)</sup>. Furthermore, deletion of epithelial BMP signaling by Bmp receptor1a (Bmpr1a) conditional knockout mice promotes the differentiation of crown epithelial into HERS<sup>10</sup>. So this may suggest that BMP signaling pathway control the transition from crown to root. Smad4 is a central intracellular effector of both TGF- $\beta$  and BMP signaling. Inactivation of TGF- $\beta$ / Smad4 signaling by using K14-Cre:  $Smad4^{n/n}$  mice also resulted in abnormal HERS which enlarges but could not elongate to guide root development, so root development halts at the initiation step<sup>11)</sup>. In addition, Shh, a member of the hedgehog family, is also expressed in dental epithelium, has been suggested to be induced or inhibited by BMP/TGF-B/Smad4 signaling<sup>12)</sup>. Shh is a secreted protein which has been showed to be an important regulator for the initiation of tooth formation at the early stage of tooth development. At the beginning of root development, Shh transcripts were restricted to the HERS cells and were related to the regulation of proliferative activity of HERS cells<sup>13)</sup>. Moreover, the expression of Shh needs Smad4 in the dental epithelium during the epithelial-mesenchymal interaction, and either deletion or activation of the hedgehog signaling in the dental mesenchyme results in shorter molars. Therefore, HERS-derived Shh is important not only in HERS formation but also in root elongation.

Different from incisor which has only one root, molars have two or three roots. Over the past decades, most of the researches were related with root elongation area, but little was known about the root furcation formation. In mouse mandibular molar, at P4, two tongue-shaped epithelial protrusions grow toward each other and at P8, both the lingual and buccal epithelial protrusions were almost in contact. Until now, the epithelial protrusions were considered to be HERS since the structure and morphology is same as that in elongation area. During the process of furcation development, there were mainly three different activities of HERS observed. Firstly, invagination of epithelial protrusions, then horizontally extension, and finally connection and dissociation of HERS. Recently, the formation of furcation was contributed to proliferative differences between mesenchymal cells in different areas. By comparing cell proliferation of the mesenchyme in the mesial-root-forming (MRF) regions and the bifurcation-forming regions, one study found that the mesenchymal cells in the MRF showed relatively higher proliferation<sup>14)</sup>. So it may indicate that the bifurcation-formation region was passively formed. Consistent with this view, other researchers also found that the occurrence of taurodont teeth which is characterized by elongated root trunk or unformed root trunk at furcation area is related to changed proliferative activity in the neighboring root mesenchyme<sup>15, 16, 17)</sup>. Although these studies may suggest that the mesenchyme is the driver of single- and multi-rooted root patterning, the molecule or signaling pathway which regulate the proliferative activity is still undecided. Since the interaction between epithelium and mesenchyme is especially important for root development, the furcation development is most likely regulated by both. Our point of view is that the formation of furcation is mainly controlled by epithelium. Firstly, it has been reported that deletion of Smo or Smad4 by K14-Cre in dental epithelium made the HERS fail to form, resulting in rootless molar. Secondly, during the horizontally extension of HERS, we found that

more proliferative activity around HERS, but less or even no proliferative cells in the mesenchyme between the HERS. So it is likely that more active HERS and passive mesenchyme allow the HERS to invaginate toward the center of teeth. Thirdly, signaling factors secreted from HERS are expressed in the mesenchyme around HERS during the furcation development. For example, Axin2 which is a target gene of Wnt signaling, is highly express in the mesenchyme around HERS, and our research found that loss and activation of Wnt signaling pathway lead to root defects<sup>18,19</sup>. In keeping with this idea, loss of *Wnt10a* both in mice and human can also lead to taurodontism<sup>20</sup>.

### **Root elongation and dentinogenesis**

After formation, HERS then elongates apically and guides root formation under the sequential and reciprocal regulation of epithelium and mesenchyme. During root elongation, the epithelial cells of HERS gradually enclose the expanding dental papilla. Then. HERS starts to induce the differentiation of odontoblasts from ectomesenchymal cells at the periphery of the dental papilla, resulting in pre-dentin and dentin formation <sup>21)</sup>. The basement membrane of HERS is secreted by both dental epithelial and mesenchymal cells and acts as an inducer for odontoblast differentiation. HERS secretes extracellular matrix components, such as laminin 5 and TGF- $\beta$ to induce differentiation of dental papilla into root odontoblasts. In turn, odontoblasts produce signaling molecules such as BMPs to regulate the growth and morphogenesis of HERS<sup>22, 23, 24, 25)</sup>. In the developing root, odontoblast lineage cells have been tradition-

secreting and mineralizing cells with a tall, columnar shape. Preodontoblasts are the precursors of odontoblasts with a cuboidal shape. Particularly, our lab firstly identified and characterized the "apical odontoblasts" (Aods) as new population of odontoblasts which were responsible for root elongation<sup>26)</sup>. Aods were always present on the apical side of developing roots and moved downward together with HERS. Normal differentiation and maintenance of odontoblasts is the prerequisite for root development and disturbed odontoblast differentiation will result in various root abnormalities. Analysis of the expression patterns of growth factors during odontogenesis suggests that members of the TGF- $\beta$  superfamily, IGFs, WNTs, FGFs and other molecules contribute to odontoblast terminal differentiation. During root development, Bmp 2, 3 and 7 are expressed in early odontoblasts in the apical region, but Bmp4 is expressed in pre-odontoblasts and its expression is down-regulated after odontoblasts differentiation<sup>27)</sup>. Inhibition of TGF-β signaling in *Wnt1-Cre*; *Tgfbr2*<sup>#/</sup> <sup>fl</sup> mice and Osterix-Cre; Tgfbr2<sup>fl/fl</sup> mice results in abnormal dentin formation <sup>25, 28)</sup>. Ablation of Smad4 in the dental mesenchyme by using Osr2-Ires Cre and odontoblast specific knockout of Smad4 resulted in disturbed odontoblast differentiation and abnormal root development<sup>29)</sup>. This disruption not only impaired the mesenchymal BMP signaling pathways but also consequently altered the fate of HERS. So intact TGF-β/BMP communication between dental epithelial and ectomesenchymal tissues was required for the normal development of tooth roots.

ally classified as odontoblasts and preodontoblasts

according to their status of differentiation. Odonto-

blasts are a type of terminally differentiated matrix

Besides, canonical Wnt/β-catenin signaling pathway is of great importance in developing molar roots mainly based on the observation that Axin2, a direct target of canonical Wnt/ β-catenin signaling pathway, highly expressed in the root odontoblasts<sup>30)</sup>. Also, some Wnts, such as Wnt5a and Wnt10a, as well as Wnt signaling mediator, Lef1, are expressed in developing odontoblasts. Dkk1, an inhibitor of Wnt signaling, is strongly expressed in pre-odontoblasts. The Wntless, is specially required for the secretion of Wnt proteins, and tissue-specific deleted in odontoblasts leads to impaired molar root elongation<sup>31, 32,</sup> <sup>33)</sup>. Moreover, disruption of Wnt signaling in mesenchyme either by  $\beta$ -catenin deletion or overexpression of Dkk1 resulted in disrupted differentiation of root odontoblasts and severely retarded molar root<sup>34</sup>). However, constitutive stabilization of  $\beta$ -catenin leads to shortened roots with excessively deposited dentin<sup>18)</sup>. These reports therefore suggest that modulation of Wnt signaling play an important role during odontoblast differentiation and dentin formation.

Other transcriptional factors such as Nuclear Factor I C (Nfic) and Osterix (Osx) also play important role in odontoblast differentiation. Nfic, which belongs to the nuclear factor I family of transcriptional factors, is primarily expressed in odontoblasts. Deletion of *Nfic* has been shown to leads to short and abnormal root due to suppression of odontoblast proliferation and differentiation by activating Shh signaling pathway. However, no major changes were noticed in molar crown formation in the *Nfic*-deficient mice, which indicating that Nfic is a transcription factor exclusively related to root development <sup>35,</sup> <sup>36, 37)</sup>. Osx, a key mesenchymal transcriptional factor participating in the differentiation and mineralization of odontoblasts. Recent studies revealed that Osx is capable of promoting expression and secretion of dentine sialophosphoprotein (DSPP), contributing to dentinogenesis. Additionally, a series of reports have uncovered site-specific function of Osx in tooth root development. Both odontoblastic conditional *Osx* knockout mice and conventional *Osx* knockout mice showed severe disrupted odontoblast differentiation and finally resulted in short molars<sup>38, 39, 40)</sup>.

It is worth mentioning that normal initiation of HERS can be followed by disturbed root elongation because of abnormal mesenchymal modulation. Our previous data showed that disrupted differentiation of apical odontoblasts lead to rootless molar in the *OC-Cre; Ctnnb1*<sup>co/co</sup> mouse with normal initiation extension of HERS<sup>19)</sup>. In addition, it is still questionable whether the signaling molecules and growth factors remain effective during root elongation process in light of the observation that HERS structures appeared in impaired molar roots of several gene target mice<sup>19, 41, 42)</sup>. Therefore, although HERS maybe indispensable for root initiation, optimal differentiation of odontoblasts is necessary for root elongation and formation.

## Cementogenesis

At P10, HERS started to dissociate. Subsequently, the root continued development and HERS cells became increasingly dissociated. If the epithelial root sheath fails to become interrupted at the correct developmental stage (postnatal day 7 or later in mice) and remains attached to the surface of the root, the dental follicle mesenchymal cells cannot penetrate the HERS to contact the dentin and cannot be in-

duced to become cementoblasts to form cementum.

As root formation is completed, HERS divides into epithelial nests and cords and remains quiescent in the periodontal ligament, known as epithelial rests of Malassez (ERM). According to observations in histological sections, the number of epithelial cells decreases during the epithelial sheath fragmentation. So this phenomenon arouses the thinking of the reason or the fates of the disappeared epithelial cells. It has been controversial for decades about the relative contribution of HERS cells and dental follicle cells to cementogenesis. Previously, the widely accepted theory of cementogenesis suggests that cementum is a dental follicle-derived tissue that the dental follicle cells become cementoblasts and secret cementum subsequent to HERS disintegration<sup>43)</sup>. However, now more and more researchers suggested that HERS cells underwent epithelial-mesenchymal transition (EMT) to differentiate into cementoblasts, directly participating in the formation of cementum<sup>11)</sup>. Additionally, some researchers also proposed an epithelial origin for acellular cementum and a mesenchymal origin for cellular cementum<sup>44, 45)</sup>. EMT was believed to be the conversion of epithelial cells into mesenchymal cells, and it is indispensable for embryogenesis and tissue development. Meanwhile, EMT can also explain why HERS cells decrease in number even though some cells may die by apoptosis. Some in vitro experiments by direct co-culture of HERS cells and dental follicle cells showed that HERS cells were corroborated to own the ability of mineralization and they acted as an indispensable inductive factor for the differentiation of dental follicle cells during formation of the periodontal structures<sup>46</sup>. By using K14-Cre; R26R mouse, Huang et al found that HERS cells on the surface of the root can also express cementoblast markers, such as collagen I and bone sialoprotein. In the root apical region, HERS cells are embedded in the cellular cementum, which indicated that HERS cells might participate in the formation of the cementum<sup>2</sup>. Moreover, some more recent findings showed that activation of TGF- $\beta$  signaling induces HERS fragmentation through EMT and the fragmented HERS cells contribute to the formation of PDL and acellular cementum through periostin and fibronectin expression<sup>47</sup>.

The mature mammalian tooth root is covered by cementum on its surface and is stabilized by periodontal ligament fibers which are embedded in both the cementum and alveolar bone. The cementum can be broadly classified into acellular and cellular cementum based on its cellular components. The thin and flat acellular cementum covers the cervical portion of the root, which is essential for tooth attachment. And the thicker and rough cellular cementum occupies the apical portion of the root. According to the functionality of cementum in the periodontal ligament attachment, the acellular type is more important for the cementum regeneration. Nevertheless, for decades, the regulation and formation of cementum types during cementum development are largely unknown. Our findings suggest that cementum type is not determined by its specific location, and Wnt signaling might be important for the determination of cementum type during cementum formation<sup>48)</sup>. In addition, compared to cellular cementum, acellular cementum is more hypersensitive to regulators of mineralization which mainly refer to extracellular levels of inorganic phosphate (P<sub>i</sub>) and pyrophosphate  $(PP_{i})^{49}$ 

# Conclusions

Unlike crown formation that has been studied with a substantial progress, root development remains poorly understood. All the recent studies we mentioned above are still far enough to reveal the intricate regulations during root development. It is though clear that reciprocal and sequential interactions between the epithelium and mesenchyme eventually leads to the formation of root dentin, cementum and other periodontal tissues during root development (Fig. 1). To date, there has been considerable studies with the application of gain- or lossof-function of different genes which have made great progress in the root development field (Table 1). However, several important questions related to the mechanisms of root development are still controversial and unsolved. (1) How does the change in expression of genes result in the transition from crown morphogenesis to root development? (2) What is the mechanism that regulates the furcation development and how is the number of tooth roots determined? (3) What are drive factors for root elongation? (4) What is the origin of cementoblasts? In this review, we focus on molecule regulations during the progress of root development, hoping that knowledge related to the mechanisms of root development will pave the way to the development of tooth regeneration in the future.

www.k



Figure 1. Schematic of main molecules and signaling pathway between epithelium and mesenchyme during root development. (A) At HERS formation stage, Egf, Smad4. Shh. Notch2 express in the epithelium, and laf. Hgf, Fgf, Bmp4, TGF- $\beta$  secreted from mesenchyme to epithelium also take part in the formation of HERS. For the furcation formation, Eda and Evc from the epithelium, and Wnt10a, G9a, Ezh2, Bmp2 from the mesenchyme can regulate the proliferation of mesenchymal cells around HERS, leading to the Furcation formation. (B) During root elongation, HERS secreted laminin 5, Shh and  $TGF-\beta$  to mesenchyme and induce the differentiation of odontoblasts. In turn, odontoblasts can produce BMPs to regulate the growth of HERS. The other molecules like *Nfic*, and *Osx* and signaling pathway like *TGF-* $\beta$  and Wnt/B-Catenin in mesenchyme also regulate the odontoblast differentiation. (C) During cementogenesis, HERS on the one side divides into ERM, and on the other side undergoes EMT to differentiate into cementoblasts under the regulation of  $TGF-\beta$  and Wnt signaling for the cellular cementum formation. Another key transcription factor for the differentiation of cementoblast is Osx during cellular cementum formation. For acellular cementum, it is more

sensitive to the regulation of Pi/PPi under the control of *Bsp, ANK* and *ALPL*. And *Wnt* signaling may be an important determination of cementum type. El: elongation

area; Fur: Furcation; AC: Acellular cementum; CC: Cellular cementum.

Wnt signaling $OC-Cre; Ctnnb1^{rein}$ No rootKim TH et al. 2013 <sup>10</sup> $2.3b$ $Calla-Dkl1$ Short rootHan XL et al. 2013 <sup>10</sup> $OC-Cre; Canb^{1-barech}$ Short rootBae CH et al. 2013 <sup>10</sup> $Oc-Cre; Wls^{gf}$ Short rootBae CH et al. 2015 <sup>10</sup> $Wnt10a^{}$ Low or no furcationYang J et al. 2013 <sup>10</sup> $Sclerostin^{ch}$ Increased cementumKuchler U et al. 2014 <sup>23</sup> $K14-Cre; Wnt10^{gf}$ Low or no furcationM.Yu et al. 2020 <sup>50</sup> Bmp/Tgf- $\beta$ signaling $K14-Cre; Smad4^{gff}$ No rootHuang X et al. 2010 <sup>11</sup> $Oc-Cre; Smad4^{gff}$ Short rootGao Y et al. 2009 <sup>110</sup> $Oc-Cre; Smad4^{gff}$ Short rootGao Y et al. 2013 <sup>10</sup> $Oc-Cre; Tgfbr2^{gff}$ Short rootHuang X et al. 2019 <sup>10</sup> $Oc-Cre; Tgfbr2^{gff}$ Short rootHuang X et al. 2019 <sup>10</sup> $Oc-Cre; Tgfbr2^{gff}$ Decreased dentin thicknessGluhak-Heinrich J et al. 2010 <sup>50</sup> $Bmpg^{fr}$ Short rootHuang X et al. 2019 <sup>50</sup> $3.6kb Coll-Cre; Egfbr2^{gff}$ Dysplastic dentinAhn YH et al. 2015 <sup>50</sup> $Oc-Cre; Tgfbr2^{gff}$ Short rootSum W et al. 2015 <sup>50</sup> $Oc-Cre; Tgfbr2^{gff}$ Short rootSum W et al. 2016 <sup>50</sup> $Oc-Cre; Tgfbr2^{gff}$ Short rootSum W et al. 2012 <sup>60</sup> $Oc-Cre; Tgfbr2^{gff}$ Short rootLapthanasupkul P et al. 2012 <sup>60</sup> $Oc-Cre; Tgfbr2^{gff}$ Short rootLapthanasupkul P et al. 2012 <sup>60</sup> $Oc-Cre; Cre; SathafShort rootVang X et al. 201260Oc-Cre; Cre; SathafShort ro$	Signaling pathway	Genotype	Root abnormalities	References
2.3kb Colla-DkklShort rootHan XL et al, 2011 <sup>30</sup> OC-Cre: Camb*ismeedbShort root, cementum hyperplasiaBac CH et al, 2015 <sup>30</sup> Oc-Cre: WL <sup>g#</sup> Short rootBac H et al, 2015 <sup>30</sup> Oc-Cre: WL <sup>g#</sup> Low or no furcationKuchler U et al, 2014 <sup>21</sup> Selenostin*Increased cementumKuchler U et al, 2014 <sup>21</sup> K14-Cre: Wn110 <sup>9</sup> Low or no furcationM-Yu et al, 2020 <sup>35</sup> Bmp/Tgf-β signalinK14-Cre: Smad4 <sup>49</sup> No rootGav Y et al, 2010 <sup>10</sup> Oc-Cre: Smad4 <sup>49**</sup> Short rootGav Y et al, 2013 <sup>270</sup> Oc-Cre: Smad4 <sup>49**</sup> Short rootLi J et al, 2015 <sup>30</sup> Oc-Cre: Tgbr2 <sup>49*</sup> Short rootLi J et al, 2015 <sup>30</sup> K14-tr11: tetO-Cre: Bmp1d <sup>49*</sup> Short rootUtang X et al, 2013 <sup>30</sup> Oc-Cre: Tgbr2 <sup>49*</sup> Short rootUtang X et al, 2013 <sup>30</sup> Bmp <sup>6</sup> Short rootUtang X et al, 2013 <sup>30</sup> OthersC-Cre: Tgbr2 <sup>49*</sup> Decreased dentin thicknessGackNo rootAlfaqeb Set al, 2015 <sup>30</sup> CafcShort rootSum Y et al, 2015 <sup>30</sup> Mu1-Cre: Dkx <sup>5*fued</sup> Short rootSum Y et al, 2015 <sup>30</sup> Knf-Cre: Dkx <sup>5*fued</sup> Short rootSum Y et al, 2015 <sup>30</sup> No rootShort rootLaphanasupkul P et al, 2015 <sup>30</sup> Knf-Cre: Oxx <sup>40*fue</sup> Short rootShort rootNo furcationZhag Z et al, 2015 <sup>30</sup> Knf-Cre: Dkx <sup>6*fued</sup> Short rootNo rue al, 2015 <sup>30</sup> Short rootShort rootShort rootNo furcationShort rootShort rootNo furcation	Wnt signaling	OC-Cre; Ctnnb1 <sup>co/co</sup>	No root	Kim TH et al, 2013 <sup>19)</sup>
OC-Cre: Carbb <sup>-instraction</sup> Short root, cementum hyperplasi-Bae CH et al. 2015 <sup>471</sup> Oc-Cre: WL5 <sup>477</sup> Not rootBae CH et al. 2015 <sup>471</sup> Oc-Cre: WL10 <sup>477</sup> Low or no furcationYang Let al. 2014 <sup>571</sup> BrapTgFβ signalingK14-Cre: Smad4 <sup>4771</sup> Low or no furcationM.Yu et al. 2020 <sup>473</sup> BrapTgFβ signalingK14-Cre: Smad4 <sup>4771</sup> No rootHuang X et al. 2010 <sup>471</sup> Oc-Cre: Smad4 <sup>4771</sup> Short rootWang Y et al. 2013 <sup>571</sup> Oxer-Cre: TgBr2 <sup>4761</sup> Short rootHuang X et al. 2015 <sup>571</sup> BrapD <sup>7</sup> Short rootHuang X et al. 2015 <sup>571</sup> BrapD <sup>7</sup> Short rootHuang X et al. 2015 <sup>571</sup> BrapD <sup>6</sup> Short rootHuang X et al. 2015 <sup>571</sup> BrapD <sup>6</sup> Short rootHuang X et al. 2015 <sup>571</sup> BrapD <sup>6</sup> Short rootHuang X et al. 2015 <sup>571</sup> OthersC-Cre: TgBr2 <sup>4761</sup> Dysplastic dentinOthersCaR <sup>-C</sup> No rootNo rootCaR <sup>-C</sup> Short rootDuverger O et al. 2012 <sup>670</sup> MI1-Cre: DK3 <sup>471</sup> Short rootDuverger O et al. 2012 <sup>670</sup> Krig La <sup>-1</sup> /		2.3kb Col1a-Dkk1	Short root	Han XL et al, 2011 <sup>50)</sup>
Dec.Cre; Wis <sup>gff</sup> Short rootBae CH et al, 2015 <sup>30</sup> Wn1/0a <sup></sup> Low or no furcationYang J et al, 2015 <sup>30</sup> Sclerostin <sup></sup> Increased cementumKuchler U et al, 2014 <sup>20</sup> K14-Cre; Smad4 <sup>gfff</sup> No rootHuang X et al, 2009 <sup>41</sup> Dec.Cre; Smad4 <sup>gffff</sup> Short rootGao Y et al, 2009 <sup>41</sup> Oc-Cre; Smad4 <sup>gffffffffffffffffShort rootHuang X et al, 2010<sup>11</sup>Dec.Cre; Smad4<sup>gffffffffffffffffffffffffffffffffffff</sup></sup>		<i>OC-Cre:Catnb</i> <sup>+/lox(ex3)</sup>	Short root, cementum hyperplasiaBae CH et al, 201318)	
Wnt10a <sup>-/-</sup> Low or no furcationYang J et al, 2015 <sup>30</sup> Sclerostin <sup>-/-</sup> K14-Cre; Wnt10 <sup>497</sup> Increased cementum Low or no furcationKuchler U et al, 2014 <sup>37</sup> ) MYu et al, 2020 <sup>53</sup> Bmp/Tgf-β signatinK14-Cre; Smad4 <sup>967</sup> No rootGao Y et al, 2009 <sup>41</sup> )Oc-Cre; Smad4 <sup>9670</sup> Short rootGao Y et al, 2001 <sup>37</sup> )Oc-Cre; Tgfbr2 <sup>697</sup> Short rootWang Y et al, 2013 <sup>57</sup> )K14-rtTA; tetO-Cre; Bmp4 <sup>697</sup> Short rootHuang X et al, 2013 <sup>57</sup> )Bmp9 <sup>-/-</sup> Short rootHuang X et al, 2013 <sup>57</sup> )Sckb Col1-Cre; Bmp4 <sup>697</sup> Decreased dentin thicknessGluhak-Heinrich J et al, 2015 <sup>56</sup> )Orbersc-Fos <sup></sup> No rootHang X et al, 2013 <sup>57</sup> )CaR <sup></sup> No rootSun W et al, 2015 <sup>57</sup> )Mu1-Cre; Dix3 <sup>58az2</sup> Short rootSun W et al, 2012 <sup>69</sup> )Kng1a-ri, Ring1b <sup>-karkan</sup> Short rootSun W et al, 2012 <sup>69</sup> )Kng1a-ri, Ring1b <sup>-karkan</sup> Short rootLapthanasupkul P et al, 2012 <sup>69</sup> )Kng1a-ri, Ring1b <sup>-karkan</sup> Short rootUang X et al, 2012 <sup>69</sup> )Kng1a-ri, Ring1b <sup>-karkan</sup> Short rootZhang H et al, 2015 <sup>69</sup> )Sox2-Cre; Fam20C <sup>68</sup> Short rootZhang H et al, 2015 <sup>69</sup> )Sox2-Cre; Rapt0 <sup>691</sup> Short rootDia et al, 2015 <sup>69</sup> )Askb Col11-Cre Osx <sup>697</sup> Short rootZhang H et al, 2015 <sup>69</sup> )Sox2-Cre; Rapt0 <sup>698</sup> Short rootDia J et al, 2015 <sup>69</sup> )Sox2-Cre; Rapt0 <sup>eff8</sup> Short rootNoi Y et al, 2019 <sup>69</sup> )Kur Cre, izEG-Dix2Short rootNoi Y et al, 2019 <sup>69</sup> )Kur Cre, izEG-Dix2 <td>Oc-Cre; Wls<sup>fl/fl</sup></td> <td>Short root</td> <td>Bae CH et al, 2015<sup>51)</sup></td>		Oc-Cre; Wls <sup>fl/fl</sup>	Short root	Bae CH et al, 2015 <sup>51)</sup>
Sclerostin*Increased cementum Low or no furcationKuchler U et al, 2014 <sup>22</sup> M.Yu et al, 2009 <sup>41</sup> Bmp/Tgf-\$p signaliniK14-Cre: Smad4 <sup>109</sup> No rootHuang X et al, 2010 <sup>11</sup> Oc-Cre: Smad4 <sup>109</sup> Short rootWang Y et al, 2013 <sup>27</sup> Oc-Cre: Tgfbr2 <sup>407</sup> Short rootWang Y et al, 2013 <sup>27</sup> K14-rtTA: tetO-Cre: Bmpr1d <sup>878</sup> Short rootLi J et al, 2015 <sup>43</sup> Bmp9 <sup>4</sup> Short rootHuang X et al, 2013 <sup>40</sup> Bmp9 <sup>4</sup> Decreased dentin thicknessGluhak-Heinrich J et al, 2015 <sup>43</sup> Bmp9 <sup>4</sup> Decreased dentin thicknessGluhak-Heinrich J et al, 2015 <sup>43</sup> OthersC-Cre: Tgfbr2 <sup>69</sup> Dysplastic dentinMn YH et al, 2015 <sup>40</sup> Othersc-Ro <sup>4</sup> Nor rootAlfaqeeh S et al, 2010 <sup>40</sup> Kmf1-Cre: Dix3 <sup>efaat2</sup> Short rootDuverger O et al, 2012 <sup>60</sup> Kmg1a-/: Ring1b <sup>dinctan</sup> Short rootWang X et al, 2012 <sup>60</sup> King1a-/: Ring1b <sup>dinctan</sup> Short rootWang X et al, 2012 <sup>60</sup> King1a-re: Dix3 <sup>efaat2</sup> Short rootWang X et al, 2012 <sup>60</sup> King1a-re: Ring1b <sup>dinctan</sup> Short rootWang X et al, 2012 <sup>60</sup> King1a-re: Ring1b <sup>dinctan</sup> Short rootWang X et al, 2015 <sup>61</sup> Short rootShort rootZhang H et al, 2015 <sup>61</sup> Short rootShort rootShort rootKim TH et al, 2015 <sup>61</sup> Short rootNo fue et al, 2015 <sup>61</sup> Kim TH et al, 2015 <sup>61</sup> Short rootNo W et al, 2016 <sup>61</sup> Kim TH et al, 2015 <sup>61</sup> Short rootNo W et al, 2016 <sup>61</sup> Kim TH et al, 2016 <sup>61</sup> No furcationNakatomi		$Wnt10a^{}$	Low or no furcation	Yang J et al, 2015 <sup>20)</sup>
Bmp/Tgf-β signalingKl 4-Cre; Smad 4 <sup>6%</sup> No rootHuang X et al, 2010 <sup>11)</sup> Oc-Cre; Smd 4 <sup>6%7</sup> Short rootGao Y et al, 2013 <sup>21)</sup> Oxx-Cre; Tgfbr2 <sup>8/ff</sup> Short rootLi J et al, 2015 <sup>43</sup> Bmp9 <sup>-/-</sup> Short rootHuang X et al, 2019 <sup>50)</sup> 3.6kb Coll-Cre; Bmp4 <sup>6/ff</sup> Decreased dentin thicknessGluhak-Heinrich J et al, 2010 <sup>50)</sup> 3.6kb Coll-Cre; Bmp4 <sup>6/ff</sup> Decreased dentin thicknessYang Z et al, 2013 <sup>40)</sup> O'C-Cre; Tgfbr2 <sup>8/ff</sup> Dysplastic dentinAhn YH et al, 2015 <sup>57)</sup> Othersc-Fos <sup>-6</sup> No rootAlfaqech S et al, 2015 <sup>50)</sup> Othersc-Fos <sup>-6</sup> Short rootSun W et al, 2010 <sup>59)</sup> Min1-Cre; Dk3 <sup>6/mez</sup> Short rootSun W et al, 2012 <sup>50)</sup> Nort-Cre; Fam20Cro <sup>60</sup> Short rootLapthanasupkul P et al, 2012 <sup>61)</sup> Sox2-Cre; Fam20Cro <sup>60</sup> Short rootZhang X et al, 2013 <sup>61)</sup> DC-Cre; Osx <sup>60</sup> Short rootZhang X et al, 2015 <sup>63)</sup> CoC-Cre; Cosx <sup>60</sup> Short rootZhang H et al, 2015 <sup>50)</sup> CoC-Cre; Cosx <sup>60</sup> Short rootZhang H et al, 2015 <sup>60)</sup> Dosx-Cre; PPR <sup>4an</sup> Short rootShart rootOc-Cre; Cosx <sup>60</sup> Short rootZhang H et al, 2015 <sup>60)</sup> CoC-Cre; StffShort rootZhang H et al, 2015 <sup>60)</sup> CoC-Cre; Cosx <sup>60</sup> Short rootDai J et al, 2017 <sup>60)</sup> Coc-Cre; Cosx <sup>60</sup> Short rootDai J et al, 2017 <sup>60)</sup> Coc-Cre; ShartShort rootSie F et al, 2019 <sup>60)</sup> Coc-Cre; ShartShort rootSie F et al, 2016 <sup>60)</sup> Fix-Cre: Lfgf <sup>60</sup> No		Sclerostin <sup>-/-</sup> K14-Cre; Wnt10 <sup>fl/fl</sup>	Increased cementum Low or no furcation	Kuchler U et al, $2014^{52}$ M.Yu et al, $2020^{53}$
Oc-Cre: Smalf <sup>oveo</sup> Short rootGao Y et al, 2009 <sup>41</sup> )Ox-Cre:, Tgfbr2 <sup>8ff</sup> Short rootWang Y et al, 2013 <sup>27)</sup> K14-rtTA; tetO-Cre:, Bmp7la <sup>8ff</sup> Short rootHuang X et al, 2019 <sup>45</sup> )Bmp9 <sup>-6</sup> Short rootGluhak-Heinrich J et al, 2010 <sup>45</sup> )3.6kb Coll-Cre:, Bmp4 <sup>8ff</sup> Decreased dentin thicknessGluhak-Heinrich J et al, 2010 <sup>45</sup> ) <i>Krt5-rtTAlietO-Cre!Alk3(Bmp7la)<sup>fff</sup></i> Ectopic cementogenesisYang Z et al, 2013 <sup>40</sup> Oc-Cre:, Tgfbr2 <sup>8ff</sup> No rootAlfaqeeh S et al, 2015 <sup>470</sup> <i>CaCre</i> No rootAlfaqeeh S et al, 2015 <sup>470</sup> <i>CaR<sup>-</sup></i> Short rootSun W et al, 2010 <sup>470</sup> <i>Knt1-Cre: Dk3<sup>5*lacZ</sup></i> Short rootDuvegre O et al, 2012 <sup>40</sup> ) <i>Knt6<sup>-1</sup></i> Short rootVang X et al, 2012 <sup>40</sup> ) <i>Knt6<sup>-1</sup></i> Short root, No furcationZhang Z et al, 2013 <sup>40</sup> <i>Lix6<sup>-1</sup></i> Short root, No furcationZhang Z et al, 2013 <sup>40</sup> <i>Lix6<sup>-1</sup></i> Short root, No furcationZhang Z et al, 2013 <sup>40</sup> <i>Sox2-Cre:, Fam20C<sup>weice</sup></i> Short rootWang X et al, 2015 <sup>40</sup> <i>Sox4</i> Short rootVang X et al, 2015 <sup>40</sup> <i>Coc-Cre:, Osx<sup>40ff</sup></i> Short rootDai J et al, 2015 <sup>40</sup> <i>Sox5</i> Short rootDai J et al, 2017 <sup>40</sup> <i>Sox4</i> No furcationNakatomi M et al, 2017 <sup>40</sup> <i>Coc-Cre:, Raptop<sup>20fff</sup></i> Short rootDai J et al, 2017 <sup>40</sup> <i>Sox-Cre:, Paptop<sup>20fff</sup></i> No furcationNakatomi M et al, 2017 <sup>40</sup> <i>Kitf -tTL-Cre:, Dixf</i> <sup>40fff</sup> No furcationChu EY et al, 2016 <sup>40</sup> <i>Kitf -tTL-Cre:, Raptof<sup>20ff</sup></i>	Bmp/Tgf-β signaling	K14-Cre; Smad4 <sup>fl/fl</sup>	No root	Huang X et al, 2010 <sup>11)</sup>
$Oxx-Cre; Tgfbr2^{& gff}$ Short rootWang Y et al. 2013 <sup>27)</sup> $K14-rtTA; tetO-Cre; Bmpr1a^{& gff}$ Short rootLi J et al. 2015 <sup>54)</sup> $Bmp9^{c^{-}}$ Short rootHuang X et al.2019 <sup>55)</sup> $3.6kb Coll-Cre; Bmp4^{gff}$ Decreased dentin thicknessGluhak-Heinrich J et al. 2010 <sup>56)</sup> $Krt5-rtTA/1etO-Cre/Alk3(Bmpr1a)^{gff}$ Ectopic cementogenesisYang Z et al. 2013 <sup>10</sup> $OC-Cre; Tgfbr2^{& gff}$ Dysplastic dentinAhn YH et al.2015 <sup>57)</sup> Others $c-Fos^{-c}$ No rootAlfaqeeh S et al. 2015 <sup>460</sup> $CaR^{c^{-}}$ Short rootSun W et al. 2010 <sup>59)</sup> $Mr1-Cre; Dk3^{FilacZ}$ Short rootUayna supkul P et al. 2012 <sup>610</sup> $Sox2-Cre; Fan20C^{wcw}$ Short rootWang X et al. 2013 <sup>40</sup> $5x2-Cre; Fan20C^{wcw}$ Short rootMang Z et al. 2013 <sup>40</sup> $3.6kb Coll - Cre; Osx^{& fff}$ short rootMang X et al. 2012 <sup>400</sup> $3.6kb Coll al - Cre Osx^{& fff}$ short rootMang Z et al. 2013 <sup>40</sup> $3.6kb Coll al - Cre Osx^{& fff}$ short rootMang X et al. 2015 <sup>400</sup> $3.6kb Coll al - Cre Osx^{& fff}$ Short rootMang X et al. 2015 <sup>400</sup> $0C-Cre; Cre; Sx^{& fff}$ Short rootDai J et al. 2015 <sup>400</sup> $0C-Cre; Cre; Sx^{& fff}$ Short rootMatomi M et al. 2015 <sup>400</sup> $0c-Cre; Righot - MingShort rootMaid et al. 20154000c-Cre; Cre; Sx^{& fff}Short rootMaid et al. 20154000c-Cre; Cre; Sx^{& fff}Short rootMaid et al. 20154000c-Cre; Righot - MingNo furcationNakatomi M et al. 2017400$		Oc-Cre; Smad4 <sup>co/co</sup>	Short root	Gao Y et al, 2009 <sup>41)</sup>
K14-rtTA: tetO-Cre: Bmp1a <sup>d#ff</sup> Short rootLi J et al, 2015 <sup>45</sup> )Bmp9 <sup>-/-</sup> Short rootHuang X et al, 2019 <sup>55</sup> )3.6kb Col1-Cre: Bmp4 <sup>#ff</sup> Decreased dentin thicknessGluhak-Heinrich J et al, 2010 <sup>56</sup> )Krt5-rtTA/tetO-Cre/Alk3(Bmp1a) <sup>#ff</sup> Ectopic cementogenesisYang Z et al, 2013 <sup>10</sup> )OC-Cre: Tgfb2 <sup>#ff</sup> Dysplastic dentinAhn YH et al, 2015 <sup>57</sup> )CaR <sup>-/-</sup> No rootAlfaqeeh S et al, 2015 <sup>86</sup> )CaR <sup>-/-</sup> Short rootSun W et al, 2010 <sup>60</sup> )Wnt1-Cre: Dk3 <sup>FfacZ</sup> Short rootUuverger O et al, 2012 <sup>60</sup> )Krigla-/-: Ring1b <sup>-backan</sup> Short rootUagt at al, 2013 <sup>61</sup> )Sox2-Cre: Fam20C <sup>caren</sup> Short root, No furcationZhang Z et al, 2013 <sup>61</sup> )J.5kb Col1-Cre: Osx <sup>#ff</sup> Short root, No furcationZhang Z et al, 2015 <sup>61</sup> )J.6kb Coll1-Cre: Osx <sup>#ff</sup> Short rootCong X et al, 2015 <sup>61</sup> )J.6kb Coll1-Cre: Osx <sup>#ff</sup> Short rootDon W et al, 2016 <sup>61</sup> )Oc-Cre: osx <sup>#ff</sup> Short rootDon W et al, 2016 <sup>61</sup> )Urt1-Cre: iZEG-Dbx2Short rootDon W et al, 2016 <sup>61</sup> )Wnt1-Cre: iZEG-Dbx2Short rootDon W et al, 2016 <sup>61</sup> )Virt2-Cre: ift/6 <sup>fff</sup> No furcationNakatomi M et al, 2013 <sup>15</sup> )Fixe2-Cre: ift/6 <sup>fff</sup> No furcationChu E'Y et al, 2015 <sup>61</sup> )Edar <sup>-/-</sup> No furcationChu E'Y et al, 2015 <sup>61</sup> )Bag <sup>-/-</sup> Decreased accllular cementumCao, Z et al, 2012 <sup>66</sup> )Fixe2-Cre: ift/6 <sup>ffff</sup> No furcationCao, Z et al, 2012 <sup>66</sup> )Fixe2-Cre: ift/6 <sup>fffff</sup> Decreased accllular cementum <td>Osx-Cre; Tgfbr2<sup>#/ft</sup></td> <td>Short root</td> <td>Wang Y et al, 2013<sup>27)</sup></td>		Osx-Cre; Tgfbr2 <sup>#/ft</sup>	Short root	Wang Y et al, 2013 <sup>27)</sup>
Bmp9 <sup>-/-</sup> Short rootHuang X et al_2019 <sup>53</sup> )3.6kb Col1-Cre; Bmp4 <sup>feff</sup> Decreased dentin thicknessGluhak-Heinrich J et al_2010 <sup>50</sup> )Krt5-rtTA/ItetO-Cre/Alk3(Bmp1a) <sup>feff</sup> Ectopic cementogenesisYang Z et al_2013 <sup>10</sup> )OchersDysplastic dentinAhn YH et al_2015 <sup>57</sup> )c-Fosc <sup>-/-</sup> No rootAlfaqeeh S et al_2015 <sup>80</sup> CaR <sup>-/-</sup> Short rootSun W et al_2010 <sup>90</sup> )Wnt1-Cre; Dk3 <sup>FlacZ</sup> Short rootLapthanasupkul P et al_2012 <sup>60</sup> )Kingla-/-; Ringlb <sup>-lacton</sup> Short rootLapthanasupkul P et al_2012 <sup>61</sup> )Sox2-Cre; Fam20C <sup>coren</sup> Short root, No furcationZhang Z et al_2013 <sup>61</sup> )J.skb Col1-Cre; Osc <sup>467</sup> Short root, No furcationZhang Z et al_2015 <sup>60</sup> )Oc-Cre; osc <sup>467</sup> Short rootChang T et al_2016 <sup>60</sup> )Cre; re, regotor <sup>467</sup> Short rootDoi W et al_2016 <sup>60</sup> )Oc-Cre; Osc <sup>467</sup> Short rootOno W et al_2016 <sup>60</sup> )Virl-Cre; iZEG-Dk2Short rootDoi W et al_2013 <sup>10</sup> )Fixe2-Cre; Irf6 <sup>678</sup> Short rootNait et al_2013 <sup>10</sup> )Fixe2-Cre; irf6 <sup>678</sup> No furcationNakatomi M et al_2013 <sup>10</sup> )Fixe2-Cre; irf6 <sup>678</sup> No furcationChu E y et al_2013 <sup>10</sup> )Fixe2-Cre; irf6 <sup>678</sup> Reduced cellular cementumCao, Z et al, 2012 <sup>68</sup> )Alf-Cre; Osc <sup>4677</sup> Reduced cellular cementumCao, Z et al, 2012 <sup>68</sup> )Fixe2-Cre; irf6 <sup>678</sup> No furcationChu E y et al, 2015 <sup>69</sup> )Fixe2-Cre; irf6 <sup>678</sup> Reduced cellular cementumCao, Z et al, 2012 <sup>68</sup> )Fixe2-Cre; irf6 <sup>678</sup> No furcation		K14-rtTA; tetO-Cre; Bmpr1a <sup>#/ft</sup>	Short root	Li J et al, 2015 <sup>54)</sup>
$3.6kb$ Coll-Cre; $Bnp4^{gft}$ Decreased dentin thicknessGluhak-Heinrich J et al, 2010 <sup>56</sup> ) $Krt5-rtTAltetO-Cre/Alk3(Bmprla)^{gft}$ Ectopic cementogenesisYang Z et al, 2013 <sup>10</sup> ) $OC-Cre; Tgfbr2^{gft}$ Dysplastic dentinAhn YH et al, 2015 <sup>57</sup> )Others $c-Fos^{-/}$ No rootAlfaqeeh S et al, 2015 <sup>88</sup> ) $CaR^{-'}$ Short rootSun W et al, 2010 <sup>69</sup> ) $Wntl-Cre; Dk3^{Flacz}$ Short rootDuverger O et al, 2012 <sup>60</sup> ) $Ring1a-/-; Ring1b^{fac/cha}$ Short rootLapthanasupkul P et al, 2012 <sup>61</sup> ) $Sox2-Cre; Fan20C^{cacco}$ Short root, No furcationZhang Z et al, 2013 <sup>53</sup> ) $2.3-kb$ Coll-Cre; Osx <sup>6ff</sup> Short rootZhang Z et al, 2015 <sup>40</sup> ) $3.6kb$ Colla1-Cre Osx <sup>6ff</sup> ,Short rootZhang H et al, 2015 <sup>40</sup> ) $OC-Cre; re; iZEG-Dk2$ Short rootDia et al, 2016 <sup>40</sup> ) $Wntl-Cre; iZEG-Dk2$ Short rootDai J et al, 2019 <sup>40</sup> ) $Oxs-Cre; Raptorl0ff$ Short rootNi et al, 2015 <sup>40</sup> ) $Oxs-Cre; Inf6fff$ No furcationNakatomi M et al, 2013 <sup>40</sup> ) $Pitx2-Cre; Inf6fff$ No furcationNakatomi M et al, 2013 <sup>40</sup> ) $Pitx2-Cre; Inf6ffff$ No furcationChu EY et al, 2016 <sup>67</sup> ) $Pitx2-Cre; Inf6ffff$ No furcationChu EY et al, 2016 <sup>67</sup> ) $Pitx2-Cre; Inf6ffff$ No furcationChu EY et al, 2016 <sup>67</sup> ) $Pitx2-Cre; Inf6ffff$ No furcationChu EY et al, 2016 <sup>67</sup> ) $Pitx2-Cre; Inf6ffffNo furcationChu EY et al, 201569)Pitx2-Cre; Inf6ffffNo furcationChu EY et al, 201667)<$		Bmp9 <sup>-/-</sup>	Short root	Huang X et al,201955)
Krt5-rtTAltetO-CrelAlk3(Bmprla)Ectopic cementogenesisYang Z et al, 2013 <sup>(in)</sup> OC-Cre; Tgfbr2 <sup>6ff</sup> Dysplastic dentinAhn YH et al, 2015 <sup>(57)</sup> Others $c$ -Fox <sup>(-/-</sup> No rootAlfaqeeh S et al, 2015 <sup>(58)</sup> $CaR^{-/-}$ Short rootSun W et al, 2010 <sup>(59)</sup> $Wnt1-Cre; Dk3^{F/lacZ}$ Short rootDuverger O et al, 2012 <sup>(60)</sup> $Ring 1a^{-/-; Ring 1b^{chor/cho}}$ Short rootLapthanasupkul P et al, 2012 <sup>(61)</sup> $Sox2-Cre; Fam20Crol/coShort rootWang X et al, 2013(61)Sox2-Cre; Fam20Crol/coShort root, No furcationZhang Z et al, 2013(61)2.3-kb Coll-Cre; Osx^{6ff}short rootZhang H et al, 2015(50)3.6kb Colla1-Cre Osx^{6ff}Short rootMin H et al, 2015(64)OC-Cre; csx^{6ff}Short rootDoi W et al, 2016(64)Nrt1-Cre; iZEG-Dlx2Short rootDai J et al, 2017(65)Osx-Cre; Raptor1/(2ff)Short rootXie F et al, 2019(66)Fvec^{-1}No furcationNakatomi M et al, 2013(16)Pitx2-Cre; Irf6(6ff)No furcationChu EY et al, 2019(67)Edar^{-1}No furcationCon, Z et al, 2011(61)2.3kb Coll-Cre; Osx^{6ff}Reduced cellular cementumFost er BL, 2015(60)Bsp^{-1}Decreased acellular cementumFost er BL, 2015(60)Phosphol^{-/-}Increased cellular cementumScel et al, 2017(61)Phosphol^{-/-}No furcationBac CH et al, 2017(61)Phosphol^{-/-}No furcationBac CH et al, 2017(61)$		3.6kb Coll-Cre; Bmp4 <sup>#/fl</sup>	Decreased dentin thickness	Gluhak-Heinrich J et al, 201056)
$OC$ - $Cre; Tgfbr2^{diff}$ Dysplastic dentinAhn YH et al,2015 <sup>57)</sup> Others $c$ - $Fos^{c'}$ No rootAlfaqeeh S et al, 2015 <sup>58)</sup> $CaR^{c'}$ Short rootSun W et al, 2010 <sup>60)</sup> $Wntl$ - $Cre; Dlx3^{FlacZ}$ Short rootDuverger O et al, 2012 <sup>60)</sup> $Ring1a$ - $I$ -; $Ring1b^{chacka}$ Short rootLapthanasupkul P et al, 2012 <sup>61)</sup> $Sox2$ - $Cre; Fam20C^{cacico}$ Short rootWang X et al, 2012 <sup>62)</sup> $Lhx6^{c'}$ Short root, No furcationZhang Z et al, 2013 <sup>61)</sup> $2.3$ - $kb$ Coll 1- $Cre; Osx^{diff}$ short rootZhang H et al, 2015 <sup>59)</sup> $3.6kb$ Coll 1- $Cre osx^{diff}$ Short rootDia J et al, 2016 <sup>64)</sup> $Oc$ - $Cre; Osx^{diff}$ Short rootDai J et al, 2016 <sup>64)</sup> $Vmt1$ - $Cre; iZEG$ - $Dkz2$ Short rootDai J et al, 2017 <sup>65)</sup> $Osx$ - $Cre; PapR^{diff}$ Short rootXie F et al, 2019 <sup>660)</sup> $Evc^{-c}$ No furcationNakatomi M et al, 2013 <sup>16)</sup> $Pitx2$ - $Cre; Irf6^{flyff}$ No furcationChu EY et al, 2016 <sup>67)</sup> $Edar^{-c}$ No furcationCon, Z et al, 2012 <sup>68)</sup> $Bsp^{-c}$ Decreased acellular cementumGao, Z et al, 2012 <sup>68)</sup> $Bsp^{-c}$ Decreased acellular cementumSweifter LE. 2016 <sup>70)</sup> $Phospho1^{-c'}$ Increased cellular cementumBae CH et al, 2017 <sup>48)</sup> $Npp1^{atignf}$ Ectopic acellular cementumBae CH et al, 2017 <sup>48)</sup>		Krt5-rtTA/tetO-Cre/Alk3(Bmpr1a) <sup>fl/fl</sup>	Ectopic cementogenesis	Yang Z et al, 2013 <sup>10)</sup>
Others $c$ - $Fos^{-'}$ No rootAlfaqeeh S et al, 2015 <sup>58</sup> ) $CaR^{-'}$ Short rootSun W et al, 2010 <sup>59</sup> ) $Wnt1$ - $Cre; Dtx3^{FlacZ}$ Short rootLapthanasupkul P et al, 2012 <sup>60</sup> ) $Ring1a$ - $/-; Ring1b^{chockn}$ Short rootWang X et al, 2012 <sup>61</sup> ) $Sox2$ - $Cre; Fam20C^{cocco}$ Short root, No furcationZhang Z et al, 2013 <sup>63</sup> ) $Lhx6^{-'}$ Short root, No furcationZhang Z et al, 2013 <sup>63</sup> ) $2.3$ - $kb$ Coll- $Cre; Osx^{difl}$ short rootZhang H et al, 2015 <sup>59</sup> ) $3.6kb$ Coll- $Cre; Osx^{difl}$ Short rootMin H et al, 2015 <sup>69</sup> ) $Oc$ -Cre; Osx <sup>difl</sup> Short rootDai J et al, 2017 <sup>65</sup> ) $Osx$ -Cre; PPR <sup>#n</sup> Short rootDai J et al, 2017 <sup>65</sup> ) $Osx$ -Cre; Raptor <sup>figl</sup> Short rootXie F et al, 2019 <sup>66</sup> ) $Fvc^{-'}$ No furcationNakatomi M et al, 2013 <sup>16</sup> ) $Pitx2$ -Cre; $Irf6^{figl}$ No furcationChu EY et al, 2016 <sup>67</sup> ) $Edar^{-'}$ No furcationCau, Z et al, 2012 <sup>68</sup> ) $Bsp^{-''}$ Decreased acellular cementumCao, Z et al, 2012 <sup>68</sup> ) $Bsp^{-''}$ Decreased acellular cementumSweifter LE, 2016 <sup>67</sup> ) $Phosphol^{-'_{-'}}$ Increased cellular cementumBae CH et al, 2017 <sup>48</sup> ) $Npp1^{ationj}$ Ko furcationBae CH et al, 2017 <sup>48</sup> )		OC-Cre; Tgfbr2 <sup>fl/fl</sup>	Dysplastic dentin	Ahn YH et al,2015 <sup>57)</sup>
$CaR^{-}$ Short rootSun W et al, 2010 <sup>99</sup> $Wnt1-Cre; Dk3^{FlacZ}$ Short rootDuverger O et al, 2012 <sup>60</sup> $Ring1a-/-; Ring1b^{dacCov}$ Short rootLapthanasupkul P et al, 2012 <sup>61</sup> $Sox2-Cre; Fam20C^{colcov}$ Short rootWang X et al, 2012 <sup>62</sup> $Lhx6^{-/-}$ Short root, No furcationZhang Z et al, 2013 <sup>63</sup> $2.3-kb \ Coll-Cre; Osx^{fl/fl}$ short rootZhang H et al, 2015 <sup>40</sup> $3.6kb \ Coll1al$ -Cre $Osx^{fl/fl}$ Short rootKim TH et al, 2015 <sup>40</sup> $3.6kb \ Coll1al$ -Cre $Osx^{fl/fl}$ Short rootNo fur et al, 2016 <sup>64</sup> $OC$ -Cre; $Osx^{fl/fl}$ Short rootOno W et al, 2016 <sup>64</sup> $OC$ -Cre; $Osx^{fl/fl}$ Short rootDai J et al, 2017 <sup>65</sup> $Osx$ -Cre; Raptor <sup>fl/fl</sup> Short rootDai J et al, 2017 <sup>65</sup> $Osx$ -Cre; $Irf6^{fl/fl}$ No furcationNakatomi M et al, 2013 <sup>10</sup> $Fix2-Cre; Irf6^{fl/fl}$ No furcationShort root $Raptical et al e$	Others	<i>c-Fos-</i>	No root	Alfaqeeh S et al, 201558)
$Wnt1-Cre; Dls3^{F/lac2}$ Short rootDuverger O et al, 2012 <sup>60</sup> ) $Ring1a-/-; Ring1b^{cha/cho}$ Short rootLapthanasupkul P et al, 2012 <sup>61</sup> ) $Sox2-Cre; Fam20C^{ox/co}$ Short rootWang X et al, 2012 <sup>62</sup> ) $Lhx6^{-/-}$ Short root, No furcationZhang Z et al, 2013 <sup>63</sup> ) $2.3-kb \ Coll-Cre; Osx^{fl/f}$ short rootZhang H et al, 2015 <sup>30</sup> ) $3.6kb \ Colla1-Cre; Osx^{fl/f}$ Short rootKim TH et al, 2015 <sup>40</sup> )OC-Cre; Osx <sup>fl/fl</sup> Short rootOno W et al, 2016 <sup>40</sup> )OC-Cre; Osx <sup>fl/fl</sup> Short rootDai J et al, 2017 <sup>65</sup> )Osx-Cre; PPR <sup>fl/fl</sup> Short rootDai J et al, 2019 <sup>66</sup> ) $Vnt1-Cre; iZEG-Dlx2$ Short rootXie F et al, 2019 <sup>66</sup> ) $Osx-Cre; Raptor^{fl/fl}$ Short rootNie F et al, 2019 <sup>66</sup> ) $Evc^{-/-}$ No furcationNakatomi M et al, 2013 <sup>16</sup> ) $Pits2-Cre; Irf6^{fl/fl}$ No furcationChu EY et al, 2016 <sup>67</sup> )Edar <sup>-/-</sup> No furcationFons Romero JM et al, 2017 <sup>15</sup> ) $2.3kb \ Coll-Cre; Osx^{fl/fl}$ Reduced cellular cementumFoster BL, 2016 <sup>60</sup> ) $Bsp^{-/-}$ Decreased acellular cementumFoster BL, 2016 <sup>60</sup> ) $Phospho1^{-/-}$ Increased cellular cementumBac CH et al, 2017 <sup>48</sup> ) $Npp1^{us/us/j}$ Ectopic acellular cementumBac CH et al, 2017 <sup>48</sup> ) $No furcationJing J et al, 201917)$		$CaR^{-/-}$	Short root	Sun W et al, 2010 <sup>59)</sup>
Ring la-/-; Ring lb^choichoShort rootLapthanasupkul P et al, 2012Sox2-Cre; Fam20CcoichoShort rootWang X et al, 2012Lhx6 <sup>-/-</sup> Short root, No furcationZhang Z et al, 20132.3-kb Coll-Cre; Osx4 <sup>BIJ</sup> short rootZhang H et al, 20153.6kb Collal-Cre Osx4 <sup>BIJ</sup> Short rootKim TH et al, 2015OC-Cre; OsxShort rootOno W et al, 2016OC-Cre; OsxShort rootDai J et al, 2016Wnt1-Cre; iZEG-Dlx2Short rootDai J et al, 2019Osx-Cre; RaptorShort rootXie F et al, 2019Pitx2-Cre; irf6No furcationNakatomi M et al, 2013Pitx2-Cre; Irf6No furcationChu EY et al, 2016Edar <sup>-/-</sup> No furcationCao, Z et al, 20122.3kb Coll-Cre; Osx <sup>BIJ</sup> Reduced cellular cementumFoster BL, 2015Bsp <sup>-/-</sup> Decreased acellular cementumStorer BL, 2015Phospho I <sup>-/-</sup> Increased cellular cementumBae CH et al, 2017Np I <sup>ast/anj</sup> Ko furcationJing J et al, 2017		Wnt1-Cre; $Dlx3^{F/lacZ}$	Short root	Duverger O et al, 2012 <sup>60)</sup>
Sox2-Cre; Fam20C <sup>caico</sup> Short rootWang X et al, 2012 $^{62}$ Lhx6 <sup>-/-</sup> Short root, No furcationZhang Z et al, 2013 $^{63}$ 2.3-kb Coll-Cre; Osx <sup>#0#</sup> short rootZhang H et al, 2015 $^{39}$ 3.6kb Colla1-Cre Osx <sup>#0#</sup> Short rootKim TH et al, 2015 $^{40}$ OC-Cre; Osx <sup>#0#</sup> Short rootOno W et al, 2016 $^{64}$ Osx-Cre; PPR <sup>##</sup> Short rootDai J et al, 2017 $^{65}$ Osx-Cre; Raptor <sup>#0#</sup> Short rootDai J et al, 2019 $^{66}$ $Vnt1$ -Cre; iZEG-Dlx2Short rootXie F et al, 2019 $^{66}$ $Vxc'^-$ No furcationNakatomi M et al, 2013 $^{16}$ $Pitx2$ -Cre; $Irf6^{#0#}$ No furcationChu EY et al, 2016 $^{67}$ Edar <sup>-/-</sup> No furcationCox, Z et al, 2012 $^{68}$ $Rsp^{-/-}$ Decreased acellular cementumCao, Z et al, 2012 $^{69}$ $Phospho1^{-/-}$ Increased cellular cementumZweifler LE, 2016 $^{70}$ $Npf1^{asi/asi}$ Ectopic acellular cementumBae CH et al, 2017 $^{48}$ $No furcationNo furcationJing J et al, 2017 ^{48}$		Ring1a-/-; Ring1b <sup>cko/cko</sup>	Short root	Lapthanasupkul P et al, 2012 <sup>61)</sup>
Lhx644Short root, No furcationZhang Z et al, 2013 $^{433}$ 2.3-kb Coll-Cre; Osx <sup>#/#</sup> short rootZhang H et al, 2015 $^{490}$ 3.6kb Collal-Cre Osx <sup>#/#</sup> Short rootKim TH et al, 2015 $^{400}$ OC-Cre; Osx <sup>#/#</sup> Short rootOn W et al, 2016 $^{640}$ Osx-Cre;PPR <sup>#/#</sup> Short rootDai J et al, 2017 $^{650}$ <i>Wntl-Cre; iZEG-Dlx2</i> Short rootDai J et al, 2019 $^{660}$ <i>Osx-Cre; Raptor<sup>#/#</sup></i> Short rootNakatomi M et al, 2013 $^{160}$ <i>Pitx2-Cre; Irf6<sup>#/#</sup></i> No furcationNakatomi M et al, 2013 $^{160}$ <i>Edar</i> <sup>-/-</sup> No furcationChu EY et al, 2016 $^{670}$ <i>Bap</i> <sup>-/-</sup> Decreased acellular cementumCao, Z et al, 2012 $^{680}$ <i>Phospho1</i> <sup>-/-</sup> Increased cellular cementumZweifler LE. 2016 $^{670}$ <i>Np1</i> <sup>-suj/suj</sup> Ectopic acellular cementumBae CH et al, 2017 $^{480}$ <i>No furcation</i> Jing J et al. 2017 $^{480}$		Sox2-Cre; Fam20C <sup>co/co</sup>	Short root	Wang X et al, 2012 62)
$2.3 \cdot kb \ Coll - Cre; Osx^{#lfl}$ short root $Zhang \ H et al, 2015^{39}$ $3.6 kb \ Collal-Cre \ Osx^{#lfl}$ Short rootKim TH et al, 2015 <sup>40</sup> $OC$ -Cre; Osx <sup>#lfl</sup> Short rootOno W et al, 2016 <sup>64</sup> $Osx$ -Cre; PPR <sup>#fl</sup> Short rootDai J et al, 2017 <sup>65</sup> $Vntl$ -Cre; iZEG-Dlx2Short rootDai J et al, 2019 <sup>66</sup> $Vsx$ -Cre; Raptor <sup>#flfl</sup> Short rootXie F et al, 2019 <sup>66</sup> $Evc^{-/-}$ No furcationNakatomi M et al, 2013 <sup>16</sup> $Pitx2$ -Cre; $Irfo^{#flf}$ No furcationChu EY et al, 2016 <sup>67</sup> Edar <sup>-/-</sup> No furcationFons Romero JM et al, 2017 <sup>15</sup> $2.3kb \ Coll$ -Cre; $Osx^{#flf}$ Reduced cellular cementumFoster BL, 2012 <sup>68</sup> $Bsp^{-/-}$ Decreased acellular cementumFoster BL, 2015 <sup>69</sup> $Npp 1^{asj/asj}$ Ectopic acellular cementumBae CH et al, 2017 <sup>48</sup> $Osr2$ -Cre; $Ezh2^{#fl}$ No furcationJing J et al. 2017 <sup>15</sup>		Lhx6-/-	Short root, No furcation	Zhang Z et al, 2013 <sup>63)</sup>
$3.6kb$ Collal-Cre Osx $0C$ -Cre; Osx $4^{0/1}$ Short rootKim TH et al, 2015 $4^{00}$ OSx-Cre; Osx $4^{0/1}$ Osx-Cre; Osx $4^{0/1}$ Short rootOno W et al, 2016 $6^{4/1}$ Wntl-Cre; iZEG-Dlx2Short rootDai J et al, 2017 $6^{5/1}$ Osx-Cre; Raptor $f^{0/1}$ Short rootXie F et al, 2019 $6^{60}$ $Vxtl-Cre; iZEG-Dlx2$ No fur cotionNakatomi M et al, 2013 		2.3-kb Coll-Cre; Osx <sup>fl/fl</sup>	short root	Zhang H et al, 2015 <sup>39)</sup>
Osx-Cre;PPR $^{dr/l}$ Short rootOno W et al, 2016 $Wnt1-Cre; iZEG-Dlx2$ Short rootDai J et al, 2017 $Osx-Cre; Raptor^{lt/l}$ Short rootXie F et al, 2019 $Osx-Cre; Raptor^{lt/l}$ No furcationNakatomi M et al, 2013 $Evc^{-/-}$ No furcationChu EY et al, 2016 $Pitx2-Cre; Irf6^{lt/l}$ No furcationChu EY et al, 2016Edar <sup>-/-</sup> No furcationFons Romero JM et al, 2017 $2.3kb Coll-Cre; Osx^{lt/l}$ Reduced cellular cementumCao, Z et al, 2012 $Bsp^{-/-}$ Decreased acellular cementumFoster BL, 2016 $Phosphol^{-/-}$ Increased cellular cementumBae CH et al, 2017 $Npp1^{ass/asj}$ Ectopic acellular cementumBae CH et al, 2017 $Osr2-Cre; Ezh2^{lt/l}$ No furcationJing J et al. 2019		3.6kb Collal-Cre Osx <sup>fl/fl</sup> ; OC-Cre; Osx <sup>fl/fl</sup>	Short root	Kim TH et al, 2015 <sup>40)</sup>
$Wnt1-Cre; iZEG-Dk2$ Short rootDai J et al, $2017^{65}$ $Osx-Cre; Raptor^{Ryl}$ Short rootXie F et al, $2019^{66}$ $Evc^{-/-}$ No furcationNakatomi M et al, $2013^{16}$ $Pitx2-Cre; Irf6^{Ryl}$ No furcationChu EY et al, $2016^{67}$ Edar <sup>-/-</sup> No furcationFons Romero JM et al, $2017^{15}$ $2.3kb$ Coll-Cre; $Osx^{Ryl}$ Reduced cellular cementumCao, Z et al, $2012^{68}$ $Bsp^{-/-}$ Decreased acellular cementumFoster BL, $2015^{69}$ $Phospho1^{-/-}$ Increased cellular cementumZweifler LE. $2016^{70}$ $Npp1^{asylasyl}$ Ectopic acellular cementumBae CH et al, $2017^{48}$ $Osr2-Cre; Ezh2^{Ryl}$ No furcationJing J et al. $2019^{17}$		Osx-Cre;PPR <sup>fl/fl</sup>	Short root	Ono W et al, 2016 <sup>64)</sup>
Osx-Cre; RaptorShort rootXie F et al, 2019 $Evc^{-/-}$ No furcationNakatomi M et al,2013 $Pitx2-Cre; Irf6^{#/f}$ No furcationChu EY et al, 2016 $Edar^{-/-}$ No furcationFons Romero JM et al, 2017 $2.3kb Coll-Cre; Osx^{#/f}$ Reduced cellular cementumCao, Z et al, 2012 $Bsp^{-/-}$ Decreased acellular cementumFoster BL, 2015 $Phosphol^{-/-}$ Increased cellular cementumZweifler LE. 2016 $Npp1^{as/asj}$ Ectopic acellular cementumBae CH et al, 2017 $Osr2-Cre; Ezh2^{#/f}$ No furcationJing J et al. 2019		Wnt1-Cre; iZEG-Dlx2	Short root	Dai J et al, 2017 <sup>65)</sup>
$Evc^{-/-}$ No furcationNakatomi M et al,2013 <sup>16</sup> ) $Pitx2-Cre; Irf6^{#jt}$ No furcationChu EY et al, 2016 <sup>67</sup> )Edar <sup>-/-</sup> No furcationFons Romero JM et al, 2017 <sup>15</sup> ) $2.3kb Coll-Cre; Osx^{#jt}$ Reduced cellular cementumCao, Z et al, 2012 <sup>68</sup> ) $Bsp^{-/-}$ Decreased acellular cementumFoster BL, 2015 <sup>69</sup> ) $Phospho1^{-/-}$ Increased cellular cementumZweifler LE. 2016 <sup>70</sup> ) $Npp1^{asj/asj}$ Ectopic acellular cementumBae CH et al, 2017 <sup>48</sup> ) $Osr2-Cre; Ezh2^{#jt}$ No furcationJing J et al. 2019 <sup>17</sup> )		Osx-Cre; Raptor <sup>fl/fl</sup>	Short root	Xie F et al, 201966)
Pitx2-Cre; Irf6 <sup>0/fl</sup> No furcationChu EY et al, 2016 <sup>67)</sup> Edar <sup>1/-</sup> No furcationFons Romero JM et al, 2017 <sup>15)</sup> 2.3kb Coll-Cre; Osx <sup>fl/fl</sup> Reduced cellular cementumCao, Z et al, 2012 <sup>68)</sup> $Bsp^{-/-}$ Decreased acellular cementumFoster BL, 2015 <sup>69)</sup> Phospho1 <sup>-/-</sup> Increased cellular cementumZweifler LE. 2016 <sup>70)</sup> Npp1 <sup>ass/asy</sup> Ectopic acellular cementumBae CH et al, 2017 <sup>48)</sup> Osr2-Cre; Ezh2 <sup>n/fl</sup> No furcationJing J et al. 2019 <sup>17)</sup>		<i>Evc</i> <sup>-/-</sup>	No furcation	Nakatomi M et al,201316)
EdarNo furcationFons Romero JM et al, 2017 $2.3kb Coll-Cre; Osx^{#/fl}$ Reduced cellular cementumCao, Z et al, 2012 $Bsp^{-/-}$ Decreased acellular cementumFoster BL, 2015 $Phospho1^{-/-}$ Increased cellular cementumZweifler LE. 2016 $Npp1^{asi/asj}$ Ectopic acellular cementumBae CH et al, 2017 $Osr2-Cre; Ezh2^{#/fl}$ No furcationJing J et al. 2019		Pitx2-Cre; Irf6 <sup>#/#</sup>	No furcation	Chu EY et al, 2016 <sup>67)</sup>
2.3kb Coll-Cre; $Osx^{h/l}$ Reduced cellular cementumCao, Z et al, $2012^{68}$ $Bsp^{-/-}$ Decreased acellular cementumFoster BL, $2015^{69}$ Phospho1^{-/-}Increased cellular cementumZweifler LE. $2016^{70}$ $Npp1^{asj/asj}$ Ectopic acellular cementumBae CH et al, $2017^{48}$ Osr2-Cre; $Ezh2^{n/l}$ No furcationJing J et al. $2019^{17}$		Edar-/-	No furcation	Fons Romero JM et al, 2017 <sup>15)</sup>
$Bsp^{-/-}$ Decreased acellular cementumFoster BL, 2015^{69} $Phospho1^{-/-}$ Increased cellular cementumZweifler LE. 2016^{70} $Npp1^{asi/asj}$ Ectopic acellular cementumBae CH et al, 2017^{48} $Osr2-Cre; Ezh2^{n/t}$ No furcationJing J et al. 2019^{17}		2.3kb Col1-Cre; Osx <sup>#/ft</sup>	Reduced cellular cementum	Cao, Z et al, 2012 <sup>68)</sup>
Phospho1-2Increased cellular cementumZweifler LE. $2016^{70}$ Npp1^{asj/asj}Ectopic acellular cementumBae CH et al, $2017^{48}$ Osr2-Cre; Ezh2 <sup>fl/fl</sup> No furcationJing J et al. $2019^{17}$		$Bsp^{-/-}$	Decreased acellular cementum	Foster BL, 2015 <sup>69)</sup>
Npp1^{as/asj}Ectopic acellular cementumBae CH et al, $2017^{48}$ Osr2-Cre; Ezh2 <sup>n/fl</sup> No furcationJing J et al. $2019^{17}$		Phospho1	Increased cellular cementum	Zweifler LE. 2016 <sup>70)</sup>
<i>Osr2-Cre; Ezh2<sup>tl/fl</sup></i> No furcation Jing J et al. $2019^{17}$		$Npp1^{asj/asj}$	Ectopic acellular cementum	Bae CH et al, 2017 <sup>48)</sup>
		Osr2-Cre; Ezh2 <sup>#/fl</sup>	No furcation	Jing J et al. 2019 <sup>17)</sup>

#### Table 1. Current mouse models of root abnormalities

# Acknowledgements

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (No. 2018R1A2A3074639).

## References

- Thesleff I, Sharpe P: Signalling networks regulating dental development. Mech Dev 67: 111-123, 1997. DOI: 10.1016/S0925-4773(97)00115-9.
- Huang X, Bringas P Jr, Slavkin HC, Chai Y: Fate of HERS during tooth root development. Dev Biol 334(1): 22-30, 2009. DOI: 10.1016/j.ydbio.2009.06.034.
- Pispa J, Thesleff I: Mechanisms of ectodermal organogenesis. Dev Biol 262(2): 195-205, 2003. DOI: 10.1016/s0012-1606(03)00325-7.
- Tucker A, Sharpe P: The cutting-edge of mammalian how the embryo makes teeth. Nat Rev Genet 5(7): 499-508, 2004. DOI: 10.1038/nrg1380.
- Fujiwara N, Tabata MJ, Endoh M, Ishizeki K, Nawa T: Insulin-like growth factor-I stimulates cell proliferation in the outer layer of Hertwig's epithelial root sheath and elongation of the tooth root in mouse molars in vitro. Cell Tissue Res 320(1): 69-75, 2005. DOI: 1007/s00441-004-1065-5.
- Sakuraba H, Fujiwara N, Sasaki-Oikawa A, Sakano M, Tabata Y, Otsu K, Ishizeki K, Harada H: Hepatocyte growth factor stimulates root growth during the development of mouse molar teeth. J Periodontal Res 47(1): 81-88, 2012. DOI: 10.1111/j.1600-0765.2011.01407.x.
- Fujiwara N, Akimoto T, Otsu K, Kagiya T, Ishizeki K, Harada H: Reduction of Egf signaling decides transition from crown to root in the development of mouse molars. J Exp Zool B Mol Dev Evol 312B(5): 486-494, 2009. DOI: 10.1002/jez.b.21268.
- Yokohama-Tamaki T, Ohshima H, Fujiwara N, Takada Y, Ichimori Y, Wakisaka S,Ohuchi H, Harada H: Cessation of Fgf10 signaling, resulting in a defective

.

dental epithelial stem cell compartment, leads to the transition from crown to root formation. Development 33(7): 1359-1366, 2006. DOI: 10.1242/dev.02307.

- Hosoya A, Kim JY, Cho SW, Jung HS: BMP4 signaling regulates formation of Hertwig's epithelial root sheath during tooth root development. Cell Tissue Res 333(3): 503-509, 2008. DOI: 10.1007/s00441-008-0655-z.
- Yang Z, Hai B, Qin L, Ti X, Shangguan L, Zhao Y, Wiggins L, Liu Y, Feng JQ, Chang JY, Wang F, Liu F: Cessation of epithelial Bmp signaling switches the differentiation of crown epithelia to the root lineage in a β-catenin-dependent manner. Mol Cell Biol 33(23): 4732-4744, 2013. DOI: 10.1128/MCB.00456-13.
- 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* 25(5): 1167-1178, 2010. DOI: 10.1359/jbmr.091103.
- Zhang Y, Zhang Z, Zhao X, Yu X, Hu Y, Geronimo B, Fromm SH, Chen YP: A new function of BMP4: dual role for BMP4 in regulation of Sonic hedgehog expression in the mouse tooth germ. Development 127(7): 1431-1443, 2000. DOI: 10.1007/ s004290050320.
- Khan M, Seppala M, Zoupa M, Cobourne MT: Hedgehog pathway gene expression during early development of the molar tooth root in the mouse. Gene Expr Patterns 7(3): 239-243, 2007. DOI: 10.1016/ j.modgep.2006.10.001.
- Sohn WJ, Choi MA, Yamamoto H, Lee S, Lee Y, Jung JK, Jin MU, An CH, Jung HS, Suh JY, Shin HI, Kim JY: Contribution of mesenchymal proliferation in tooth root morphogenesis. J Dent Res 93(1): 78-83, 2014. DOI: 10.1177/0022034513511247.
- Fons Romero JM, Star H, Lav R, Watkins S, Harrison M, Hovorakova M, Headon D, Tucker AS: The impact of the Eda pathway on tooth root development. J Dent Res 96(11): 1290-1297, 2017. DOI: 10.1177/0022034517725692.
- Nakatomi M, Hovorakova M, Gritli-Linde A, Blair HJ, MacArthur K, Peterka M,Lesot H, Peterkova R,

Ruiz-Perez VL, Goodship JA, Peters H: Evc regulates a symmetrical response to Shh signaling in molar development. J Dent Res 92(3): 222-228, 2013. DOI: 10.1177/0022034512471826.

- Jing J, Feng J, Li J, Han X, He J, Ho TV, Du J, Zhou X, Urata M, Chai Y: Antagonistic interaction between Ezh2 and Arid1a coordinates root patterning and development via Cdkn2a in mouse molars. Elife 8: e46426, 2019. DOI: 10.7554/eLife.46426.
- Bae CH, Lee JY, Kim TH, Baek JA, Lee JC, Yang X, Taketo MM, Jiang R, Cho ES: Excessive Wnt/β-catenin signaling disturbs tooth-root formation. J Periodontal Res 48(4): 405-410, 2013. DOI: 10.1111/jre.12018.
- Kim TH, Bae CH, Lee JC, Ko SO, Yang X, Jiang R, Cho ES: β-catenin is required in odontoblasts for tooth root formation. J Dent Res 92(3): 215-221, 2013. DOI: 10.1177/0022034512470137.
- 20. Yang J, Wang SK, Choi M, Reid BM, Hu Y, Lee YL, Herzog CR, Kim-Berman H, Lee M, Benke PJ, Lloyd KC, Simmer JP, Hu JC: Taurodontism, variations in tooth number, and misshapened crowns in Wnt10a null mice and human kindreds. Mol Genet Genomic Med 3(1): 40-58, 2015. DOI: 10.1002/mgg3.111.
- 21. Ten Cate AR: The role of epithelium in the development, structure and function of the tissues of tooth support. Oral Dis 2(1): 55-62, 1996. DOI:10.1111/j.1601-0825.1996.tb00204.x.
- Begue-Kirn C: Comparativeanalysis of TGF-β, BMPs, IGF1, msxs, fibronectin, osteonectin and bone sialoprotein gene expression during normal and in vitro-induced odontoblast differentiation. Int J Dev Biol 38(3): 405, 1994. DOI: 10.1016/0020-711X (94)90138-4.
- 23. 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 34(1): 16-24, 1999. DOI: 10.1111/ j.1600-0765.1999.tb02217.x.
- Unterbrink A, O'Sullivan M, Chen S, MacDougall M: TGF beta-1 downregulates DMP-1 and DSPP in odontoblasts. Connect Tissue Res 43(2-3): 354-358, 2002. DOI: 10.1080/03008200290000565.

- Oka S, Oka K, Xu X, Sasaki T, Bringas P Jr, Chai Y: Cell autonomous requirement for TGF-beta signaling during odontoblast differentiation and dentin matrix formation. Mech Dev 124(6): 409-415, 2007. DOI: 10.1016/j.mod.2007.02.003.
- Bae CH, Kim TH, Chu JY, Cho ES: New population of odontoblasts responsible for tooth root formation. Gene Expr Patterns 13(5-6): 197-202, 2013. DOI: 10.1016/j.gep.2013.04.001.
- Nakashima M, Nagasawa H, Yamada Y, Reddi AH: Regulatory role of transforming growth factor-beta, bone morphogenetic protein-2, and protein-4 on gene expression of extracellular matrix proteins and differentiation of dental pulp cells. Dev Biol 162(1): 18-28, 1994. DOI: 10.1006/dbio.1994.1063.
- Wang Y, Cox MK, Coricor G, MacDougall M, Serra R: Inactivation of Tgfbr2 in Osterix-Cre expressing dental mesenchyme disrupts molar root formation. Dev Biol 382(1): 27-37, 2013. DOI: 10.1016/j.ydbio.2013.08.003.
- Yun CY, Choi H, You YJ, Yang JY, Baek JA, Cho ES: Requirement of Smad4-mediated signaling in odontoblast differentiation and dentin matrix formation. Anat Cell Biol 49(3): 199-205, 2016. DOI: 0.5115/ acb.2016.49.3.199.
- 30. Lohi M, Tucker AS, Sharpe PT: Expression of Axin2 indicates a role for canonical Wnt signaling in development of the crown and root during pre- and postnatal tooth development. Dev Dyn 239(1): 160-167, 2010. DOI: 10.1002/dvdy.22047.
- Yamashiro T, Zheng L, Shitaku Y, Saito M, Tsubakimoto T, Takada K, Takano-Yamamoto T, Thesleff I: Wnt10a regulates dentin sialophosphoprotein mRNA expression and possibly links odontoblast differentiation and tooth morphogenesis. Differentiation 75(5): 452-462, 2007. DOI: 10.1111/j.1432-0436.2006.00150.x.
- 32. Yokose S, Naka T: Lymphocyte enhancer-binding factor 1: an essential factor in odontoblastic differentiation of dental pulp cells enzymatically isolated from rat incisors. J Bone Miner Metab 28(6): 650-658, 2010. DOI: 10.1007/s00774-010-0185-0.

· 1\

- 33. Lin M, Li L, Liu C, Liu H, He F, Yan F, Zhang Y, Chen Y: Wnt5a regulates growth, patterning, and odontoblast differentiation of developing mouse tooth. Dev Dyn 240(2): 432-440, 2011. DOI: 10.1002/ dvdy.22550.
- 34. Fjeld K, Kettunen P, Furmanek T, Kvinnsland IH, Luukko K: Dynamic expression of Wnt signaling-related Dickkopf1, -2, and -3 mRNAs in the developing mouse tooth. Dev Dyn 233(1): 161-166, 2005. DOI: 10.1002/dvdy.20285.
- Nakashima K, Zhou X, Kunkel G, Zhang Z, Deng JM, Behringer RR, de Crombrugghe B: The novel zinc finger-containing transcription factor osterix is required for osteoblast differentiation and bone formation. Cell 108(1): 17-29, 2002. DOI: 10.1016/s0092-8674(01)00622-5.
- 36. 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 30(4): 742-746, 2015. DOI: 10.1002/jbmr.2391.
- Kim TH, Bae CH, Lee JC, Kim JE, Yang X, de Crombrugghe B, Cho ES. Osterix regulates tooth root formation in a site-specific manner. J Dent Res 94(3): 430-438, 2015. DOI: 10.1177/0022034514565647.
- Park JC, Herr Y, Kim HJ, Gronostajski RM, Cho MI: Nfic gene disruption inhibits differentiation of odontoblasts responsible for root formation and results in formation of short and abnormal roots in mice. J Periodontol 78(9): 1795-1802, 2007. DOI: 10.1902/ jop.2007.060363.
- Lee TY, Lee DS, Kim HM, Ko JS, Gronostajski RM, Cho MI, Son HH, Park JC: Disruption of Nfic causes dissociation of odontoblasts by interfering with the formation of intercellular junctions and aberrant odontoblast differentiation. J Histochem Cytochem 57(5): 469-476, 2009. DOI: 10.1369/jhc.2009.952622.
- Lee DS, Park JT, Kim HM, Ko JS, Son HH, Gronostajski RM, Cho MI, Choung PH, Park JC: Nuclear factor I-C is essential for odontogenic cell proliferation and odontoblast differentiation during tooth root development. J Biol Chem 284(25): 17293-17303, 2009. DOI: 10.1074/jbc.M109.009084.

- Nakatomi M, Morita I, Eto K, Ota MS: Sonic hedgehog signaling is important in tooth root development. J Dent Res 85(5): 427-431, 2006. DOI: 10.1177/154405910608500506.
- 42. Gao Y, Yang G, Weng T, Du J, Wang X, Zhou J, Wang S, Yang X: Disruption of Smad4 in odontoblasts causes multiple keratocystic odontogenic tumors and tooth malformation in mice. Mol Cell Biol 29(21): 5941-5951, 2009. DOI: 10.1128/MCB.00706-09.
- Diekwisch TG: The developmental biology of cementum. Int J Dev Biol 45(5-6): 695-706, 2001. DOI: 10.1177/2051013614565354.
- Slavkin HC: Towards a cellular and molecular understanding of periodontics. Cementogenesis revisited. J Periodontol 47(5): 249-255, 1976. DOI: 10.1902/ jop.1976.47.5.249.
- 45. Slavkin HC, Bringas P Jr, Bessem C, Santos V, Nakamura M, Hsu MY, Snead ML,Zeichner-David M, Fincham AG: Hertwig's epithelial root sheath differentiation and initial cementum and bone formation during long-term organ culture of mouse mandibular first molars using serumless, chemically-defined medium. J Periodontal Res 24(1): 28-40, 1989. DOI: 10.1111/j.1600-0765.1989.tb00854.x.
- 46. 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 94: 1-9, 2018. DOI: 10.1016/j.archoralbio.2018.06.014.
- 47. Itaya S, Oka K, Ogata K, Tamura S, Kira-Tatsuoka M, Fujiwara N, Otsu K, Tsuruga E, Ozaki M, Harada H: Hertwig's epithelial root sheath cells contribute to formation of periodontal ligament through epithelial-mesenchymal transition by TGF-β. Biomed Res 38(1): 61-69, 2017. DOI: 10.2220/biomedres.38.61.
- Bae CH, Choi H, You HK, Cho ES: Wnt activity is associated with cementum-type transition. J Periodontal Res 52(3): 334-341, 2017. DOI: 10.1111/jre.12396.
- 49. Foster BL, Nagatomo KJ, Nociti FH Jr, Fong H, Dunn D, Tran AB, Wang W, Narisawa S, Millán JL, Somerman MJ. Central role of pyrophosphate in acellular cementum formation. PLoS One 7(6): e38393, 2012.

DOI: 10.1371/journal.pone.0038393.

- 50. Han XL, Liu M, Voisey A, Ren YS, Kurimoto P, Gao T, Tefera L, Dechow P, Ke HZ, Feng JQ: Post-natal effect of overexpressed DKK1 on mandibular molar formation. J Dent Res 90(11): 1312-1317, 2011. DOI: 10.1177/0022034511421926.
- Bae CH, Kim TH, Ko SO, Lee JC, Yang X, Cho ES: Wntless regulates dentin apposition and root elongation in the mandibular molar. J Dent Res 94(3): 439-445, 2015. DOI: 10.1177/0022034514567198.
- 52. Yu M, Liu Y, Wang Y, Wong SW, Wu J, Liu H, Feng H, Han D: Epithelial *Wnt10a* is essential for tooth root furcation morphogenesis. J Dent Res 99(3): 311-319, 2020. DOI:10.1177/0022034519897607.
- 53. Kuchler U, Schwarze UY, Dobsak T, Heimel P, Bosshardt DD, Kneissel M, Gruber R: Dental and periodontal phenotype in sclerostin knockout mice. Int J Oral Sci 6(2): 70-76, 2014. DOI: 10.1038/ ijos.2014.12.
- 54. Li J, Feng J, Liu Y, Ho TV, Grimes W, Ho HA, Park S, Wang S, Chai Y: BMP-SHH signaling network controls epithelial stem cell fate via regulation of its niche in the developing tooth. Dev Cell 33(2): 125-135, 2015. DOI: 10.1016/j.devcel.2015.02.021.
- 55. Huang X, Wang F, Zhao C, Yang S, Cheng Q, Tang Y, Zhang F, Zhang Y, Luo W,Wang C, Zhou P, Kim S, Zuo G, Hu N, Li R, He TC, Zhang H: Dentinogenesis and Tooth-Alveolar Bone Complex Defects in BMP9/ GDF2 Knockout Mice. Stem Cells Dev 28(10): 683-694, 2019. DOI: 10.1089/scd.2018.0230.
- 56. Gluhak-Heinrich J, Guo D, Yang W, Harris MA, Lichtler A, Kream B, Zhang J,Feng JQ, Smith LC, Dechow P, Harris SE: New roles and mechanism of action of BMP4 in postnatal tooth cytodifferentiation. Bone 46(6): 1533-1545, 2010. DOI: 10.1016/ j.bone.2010.02.024.
- 57. Ahn YH, Kim TH, Choi H, Bae CH, Yang YM, Baek JA, Lee JC, Cho ES: Disruption of Tgfbr2 in odontoblasts leads to aberrant pulp calcification. J Dent Res 94(6): 828-835, 2015. DOI: 10.1177/0022034515577427.
- 58. Alfaqeeh S, Oralova V, Foxworthy M, Matalova

E, Grigoriadis AE, Tucker AS : Root and Eruption Defects in c-Fos Mice Are Driven by Loss of Osteoclasts. J Dent Res 94(12): 1724-1731, 2015. DOI: 10.1177/0022034515608828.

- Sun W, Sun W, Liu J, Zhou X, Xiao Y, Miao D: Alterations in phosphorus, calcium and PTHrP contribute to defects in dental and dental alveolar bone formation in calcium-sensing receptor-deficient mice. Development 137(6): 985-992, 2010. DOI: 10.1242/dev.045898.
- Duverger O, Zah A, Isaac J, Sun HW, Bartels AK, Lian JB, Berdal A, Hwang J, Morasso MI: Neural crest deletion of Dlx3 leads to major dentin defects through down-regulation of Dspp. J Biol Chem 287(15): 12230-12240, 2012. DOI:10.1074/jbc. M111.326900.
- Lapthanasupkul P, Feng J, Mantesso A, Takada-Horisawa Y, Vidal M, Koseki H, Wang L, An Z, Miletich I, Sharpe PT: Ring1a/b polycomb proteins regulate the mesenchymal stem cell niche in continuously growing incisors. Dev Biol 367(2):140-153, 2012. DOI: 10.1016/j.ydbio.2012.04.029.
- Wang X, Wang S, Lu Y, Gibson MP, Liu Y, Yuan B, Feng JQ, Qin C: FAM20C plays an essential role in the formation of murine teeth. J Biol Chem 287(43): 35934-35942, 2012. DOI: 10.1074/jbc.M112.386862.
- 63. Zhang Z, Gutierrez D, Li X, Bidlack F, Cao H, Wang J, Andrade K, Margolis HC, Amendt BA: The LIM homeodomain transcription factor LHX6: a transcriptional repressor that interacts with pituitary homeobox 2 (PITX2) to regulate odontogenesis. J Biol Chem 288(4): 2485-2500, 2013. DOI: 10.1074/jbc. M112.402933.
- 64. 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 7:11277, 2016. DOI: 10.1038/ncomms11277.
- Dai J, Si J, Ouyang N, Zhang J, Wu D, Wang X, Shen G: Dental and periodontal phenotypes of Dlx2 over-expression in mice. Mol Med Rep 15(5): 2443-2450, 2017. DOI: 10.3892/mmr.2017.6315.
- 66. Xie F, Dai Q, Liu X, Wang J: Conditional Knockout

of Raptor/mTORC1 Results in Dentin Malformation. Front Physiol 10:250, 2019. DOI:10.3389/ fphys.2019.00250.

- 67. Chu EY, Tamasas B, Fong H, Foster BL, LaCourse MR, Tran AB, Martin JF, Schutte BC, Somerman MJ, Cox TC: Full Spectrum of Postnatal Tooth Phenotypes in a Novel Irf6 Cleft Lip Model. J Dent Res 95(11): 1265-1273, 2016. DOI: 10.1177/0022034516656787.
- Cao Z, Zhang H, Zhou X, Han X, Ren Y, Gao T, Xiao Y, de Crombrugghe B, Somerman MJ, Feng JQ: Genetic evidence for the vital function of Osterix in cementogenesis. J Bone Miner Res 27(5): 1080-1092, 2012. DOI: 10.1002/jbmr.1552.
- 69. Foster BL, Ao M, Willoughby C, Soenjaya Y, Holm E, Lukashova L, Tran AB, Wimer HF, Zerfas PM, Nociti FH Jr, Kantovitz KR, Quan BD, Sone ED, Goldberg HA,Somerman MJ: Mineralization defects in cementum and craniofacial bone from loss of bone sialoprotein. Bone 78: 150-164, 2015. DOI: 10.1016/j.bone.2015.05.007.
- Zweifler LE, Ao M, Yadav M, Kuss P, Narisawa S, Kolli TN, Wimer HF, Farquharson C, Somerman MJ, Millán JL, Foster BL: Role of PHOSPHO1 in Periodontal Development and Function. J Dent Res 95(7): 742-751, 2016. DOI: 10.1177/0022034516640246.

# www.kci.go.kr

# 한글초록

# 치아뿌리 형성과정에 대한 이해

양류, 조의식

전북대학교 치과대학 두개안면생물학실험실

최근 바이오치아에 대한 연구는 동물실험을 통해 광범위하게 연구되고 있으나 사람에게 적용할 수 있는 치아를 재생하는 것은 여전히 불가능한 상태이다. 특히 치아뿌리는 치아를 턱뼈에 유지시키는데 있어서 핵 심적인 역할을 수행한다. 치아뿌리의 형성과정에 대한 이해의 증진은 치아재생을 달성하는데 있어서 필수 적인 부분이나 이에 대한 이해는 부족한 실정이다. 본 논문에서는 문헌고찰을 통해 치아뿌리의 발생을 조절 하는 기전에 대한 최근 연구동향에 대해 살펴보았다. 치아뿌리의 형성을 개시하는 Hertwig 상피치근집의 형성과 치아뿌리 상아질의 형성과정 그리고 시멘트질의 형성을 조절하는 기전에 대해 조사하고, 치아뿌리 형성과정에서 상피와 간엽간의 상호작용에 대한 최신 연구 동향을 조사하였다. 또한 치아뿌리 형성이상을 표현형으로 나타내는 다양한 유전자변형 동물모델에 대해 살펴보았다. 치아뿌리 형성과정에 대한 이해는 향후 치아재생을 달성하는데 있어서 필수적인 지식기반을 제공할 것이다.

주제어: 치아뿌리형성, 상피, 간엽, 상아질형성, 시멘트질형성

www.kci.go.kr