PERSPECTIVE

Tooth Eruption without Roots

X.-P. Wang

Department of Developmental Biology, Harvard School of Dental Medicine, Boston, MA 02115, USA; xiuping_wang@hsdm.harvard.edu

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ABSTRACT

Root development and tooth eruption are very important topics in dentistry. However, they remain among the less-studied and -understood subjects. Root development accompanies rapid tooth eruption, but roots are required for the movement of teeth into the oral cavity. It has been shown that the dental follicle and bone remodeling are essential for tooth eruption. So far, only limited genes have been associated with root formation and tooth eruption. This may be due to the difficulties in studying late stages of tooth development and tooth movement and the lack of good model systems. Transgenic mice with eruption problems and short or no roots can be used as a powerful model for further deciphering of the cellular, molecular, and genetic mechanisms underlying root formation and tooth eruption. Better understanding of these processes can provide hints on delivering more efficient dental therapies in the future.

KEY WORDS: root formation, dental follicle, Hertwig's epithelial root sheath, odontogenesis, Wnt.

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In this issue of the *Journal of Dental Research*, Kim *et al.* analyze the tooth phenotypes in conditional knockout mice with deletion of β-catenin in odontoblasts under the *Osteocalcin* promoter (*OC-Cre;Ctnnb1*$^{co/co}$). The most striking result of their study was that the roots did not form in the molar teeth, but nevertheless they erupted into the oral cavity (Kim *et al*., 2013). β-catenin is a critical intracellular signal transducer of canonical Wnt signaling, and plays critical roles in regulating cell proliferation, differentiation, and cell fate decision (Logan and Nusse, 2004; He and Chen, 2012; Wang *et al.*, 2012). Curiously, in the *OC-Cre;Ctnnb1*$^{co/co}$ mice, Hertwig's epithelial root sheath formed, but root odontoblasts did not differentiate, nor did they secrete root dentin. This phenotype is similar to *Nfic*-deficient mice, which also exhibited erupted rootless molars (Steele-Perkins *et al*., 2003; Park *et al.*, 2007). The study by Kim *et al.* adds more evidence to the growing realization that root formation is a consequence, rather than a cause, of tooth eruption (Wise and King, 2008; Wise, 2009).

Tooth eruption, the movement of a tooth from its site of development to its functional position in the mouth through bone and overlying soft tissues, is a local but fascinatingly programmed event. The process of eruption can be divided into 5 stages: pre-eruptive movement (movement of the developing tooth germ prior to the completion of the crown), intra-osseous eruption, mucosal penetration, pre-occlusal eruption, and post-occlusal eruption. Each step involves intense reciprocal interactions between the tooth and its surrounding tissues and is temporally and spatially controlled to coordinate the growth of the jaw and the position of other teeth. The cellular, molecular, and genetic mechanisms governing tooth eruption, however, remain less-studied and -understood.

A number of theories have been postulated to explain various aspects of tooth eruption. Currently, the most accepted theory is that asymmetric bone remodeling around the tooth is responsible for teeth moving into the oral cavity. There is resorption on the coronal side and bone formation on the apical (basal) side of the tooth (Marks and Schroeder, 1996; Wise and King, 2008). During this process, the dental follicle, a loose connective tissue sac surrounding the enamel organ of each tooth, is thought to play a pivotal role in recruiting osteoclasts and osteoblasts in a polarized pattern. In the 1980s, Cahill and Marks conducted a series of elegant experiments that helped to decipher the role of the dental follicle during tooth eruption. They showed that removal of the dental follicle from developing premolars of dogs prevented tooth eruption (Cahill and Marks, 1980). More dramatically, if the dental follicle was left intact, but the tooth germ was removed and replaced with a metal or silicone replica, the artificial tooth still erupted on schedule, with formation of a normal eruption pathway in the overlying bone and trabecular bone at the base of the bony crypt (Marks and Cahill, 1984). Furthermore, removal of either the coronal or basal halves of the dental follicle prevented tooth eruption. Removal of the coronal part of the follicle eliminated bone resorption and the eruption pathway, whereas removal of the basal part caused no bone apposition (Marks and Cahill, 1987), suggesting that polarized resorption and formation of bone around the erupting tooth might be regulated by differentially expressed genes in the

adjacent parts of the dental follicle and that both processes are required for tooth eruption (Wise *et al*., 2007; Wise and King, 2008). Recently, some of the signaling molecules that are differentially expressed in the follicle have been identified in the rat, including RANKL and BMP2 (Wise and Yao, 2006; Liu *et al*., 2012). These studies provided convincing evidence that the dental follicle is essential for tooth eruption and also challenged the previously supposed requirement of dental pulp, periodontal ligaments, and roots in the process of tooth eruption.

Because tooth eruption is accompanied with the development of roots, which causes an overall increase in tooth length, root formation has long been considered the force responsible for eruption. However, rootless teeth have been observed to erupt into the mouths of humans, monkeys, dogs, and rodents (Gowgiel, 1961, 1967; Carl and Wood, 1980; Marks and Cahill, 1984; Brin *et al*., 1985). In patients with dentin dysplasia Type I and in children treated with irradiation, root formation was disrupted, but rootless tooth crowns did erupt into the mouth (Carl and Wood, 1980; Kalk *et al*., 1998; Nirmala *et al*., 2009). Experiments by Cahill and Marks also showed that, after one or even all of the roots in developing premolars were cut off in dogs, teeth still erupted into the oral cavity at normal speed (Cahill and Marks, 1980). Even after removal of the Hertwig's epithelial root sheath, apical papilla, and periapical tissues, teeth still erupted, and the void created by the absence of roots during eruption was filled with alveolar bone. Analysis of these data indicated that root formation is not required for tooth eruption.

Interestingly, the authors of the current article reported earlier that constitutive activation of ß-catenin under the same OC-Cre promoter leads to excessive dentin formation, indicating that Wnt/ß-catenin signaling plays a critical role in promoting odontoblast differentiation and dentin formation (Kim *et al*., 2011; Bae *et al*., 2012). It is important to note that, in the current study by Kim *et al*., the deletion of ß-catenin affected odontogenesis only in the roots, not the crowns. The most likely explanation is that the OC-Cre transgenic mouse used by the authors had only weak and sparse LacZ expression in odontoblasts in the developing crown in newborns, but showed an intense expression at 10 post-natal days, when the crown formation had finished and roots started to form (Gao *et al*., 2009). Further studies are needed to test whether the unaffected odontogenesis in the crown was due to timing of the expression of Cre recombinase relative to active crown formation, or whether there is differential regulation of dentin formation in the crown and root regions. Nevertheless, these rootless teeth extend the models available for studying the molecular and genetic mechanisms underlying root formation and tooth eruption.

In addition to the molar phenotypes, in the *OC-Cre;Ctnnb1$^{co/co}$* mice, the mutant incisors did not erupt. Previous studies suggested that periodontal ligaments play an important role in the eruption of continuously growing rodent and rabbit incisors (Berkovitz and Thomas, 1969; Moxham and Berkovitz, 1974). In those teeth, when the proximal parts were surgically removed or the incisors were transected and inserted with an impermeable barrier between the 2 parts, the distal (incisal) portion still erupted at the same rate as that in the control animal. These surgical procedures effectively eliminated dental pulpal pressure, dentin formation, and the cervical loop from contributing to incisor eruption, and the periodontal ligaments seemed to be the only attached tissue responsible for eruption of this tooth (Berkovitz and Thomas, 1969; Moxham and Berkovitz, 1974). These results, however, may apply only to the supra-osseous phase of tooth eruption and do not address the factors involved in its intra-osseous phase. Furthermore, it has been reported that, in teeth with limited or finite eruption, such as dog premolars and rat molars, there are no organized periodontal ligaments attaching to the adjacent alveolar bone until the tooth pierces the gingiva, suggesting that the periodontal ligament may not be the primary moving force in tooth eruption (Cahill and Marks, 1982; Wise *et al*., 2007). The ability of rootless teeth to erupt on schedule also implies that the periodontal ligament is not essential for the eruption of these teeth (Gowgiel, 1961, 1967; Carl and Wood, 1980; Marks and Cahill, 1984; Brin *et al*., 1985). Further studies should attempt to identify the factors causing impaction of *OC-Cre;Ctnnb1$^{co/co}$* mutant incisors, although care should be taken when the information from continuously growing incisors is applied to teeth with limited eruption, including human teeth.

In sum, unraveling the mechanisms of root formation and tooth eruption is essential for the understanding of clinical eruption disorders and congenital syndromes with abnormal tooth eruption and bone remodeling. Such knowledge will help in the design of more effective therapies by delivering appropriate molecules or factors for "erupting" impacted teeth or reducing unwanted bone resorption, thus paving a way for the molecular dentistry of the future.

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