



Mechanism of tooth eruption & its clinical significance - A systematic review of literature

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ABSTRACT

Tooth eruption is an important, complex and highly regulated process. It involves signaling from a large number of genes and molecules. This review outlines the possible mechanism of tooth eruption right from its development in the bony crypt to its eruption till the occlusal level. Active tooth eruption starts from intra-osseous stage when there is formation of eruption pathway. Colony stimulating factor (CSF-I) and monocyte chemotactic protein (MCP) plays an important role in osteo- clastogenesis. Inhibition of osteoprotegrin (OPG) transcription and enhancement of receptor activator of nuclear factor kappa B ligand (RANKL) is important. Paracrine signaling by parathyroid hormone-related protein (PTHrP) and Interleukin-1 α produced in stellate reticulum may also play a role in regulating eruption. Wnt/ β -catenin signaling plays a critical role in bone formation and regeneration and thus tooth eruption. Correct understanding of this important event is needed to diagnose and treat disorders of tooth eruption.

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Introduction

Tooth eruption is defined as the movement of the tooth from its site of development in alveolar bone to the occlusal plane in the oral cavity. For the tooth to erupt, there has to be resorption of alveolar bone overlying the crown of the tooth such that an eruption pathway is formed & there has to be a biological process that will result in the tooth moving through this eruption pathway. Disturbance in tooth eruption time could be a symptom of general condition or indication of altered physiology and craniofacial development.

Review of Literature

The tooth eruption is a complex and tightly regulated process which is divided into five stages: pre-eruptive movements, intra-osseous stage, mucosal penetration, pre-occlusal and post-occlusal stages.¹ All the movements from early initiation and formation of tooth germ to the time of crown completion are known as pre eruptive movements. It involves remodeling of bony wall of the crypt in response to positional changes of the neighboring crowns, changes in maxilla and mandible and to place teeth in position for eruption.

These small movements of the developing crown are local and not in the direction of eruption. Whether these movements are mediated by the follicular events accompanying eruption or reflect regional differences in the growth and maturation of the jaws is not known.² A study done on mandibular third molars showed that the developing third molar continuously changes its angular position relative to the mandibular plane and adjacent teeth. Disturbances in these preeruptive movements could lead to their impaction.³ As all teeth develop within the alveolar bone of the jaws, major challenge is to escape from the bone surrounding the crown and to redirect the growth of the alveolar bone proper to surround and support the developing root.² For tooth to erupt there has to be bone resorption and formation of

eruption pathway. Once the tooth erupts through the alveolar bone and approaches the surface epithelium, there is thickening and transformation of the enamel epithelium and fusion with the oral epithelium. These processes are accomplished by proliferation of the outer enamel epithelium and via local proteolytic activity.⁴ A major accomplishment of mucosal penetration is formation of the junctional epithelium on the tooth surface. Preocclusal eruption from gingival emergence to the occlusal plane is accomplished by root growth and formation of bone at the base of the crypt and/or the interradicular septa.²

Bone resorption and formation of eruption pathway:

It is important to understand the biology of bone resorption due to which eruption pathway is formed & through this pathway tooth erupts.

Studies done in osteopetrotic rodents showed that osteopetrosis, a congenital bone disease marked by reduced bone resorption but not reduced bone formation⁵ is often characterized by failure of teeth to erupt. Pamidronate, a bisphosphonate that reduces bone resorption by osteoclasts, was injected into rats. In these animals, the eruption of the first mandibular molars and mandibular and maxillary incisors was delayed by 8, 1.6, and 2.5 days, respectively.⁶ Thus bone resorption and formation of eruption pathway is an important step in the process of tooth eruption. Cahill showed that pressure from the tooth does not result in eruption pathway formation. He placed trans-mandibular wires over dog premolars prior to the onset of eruption. An eruption pathway formed in the alveolar bone above the temporarily impacted premolars even though there was no tooth movement. When the wires were removed, the tooth rapidly erupted.⁷ In succedaneous dentition, this pathway follows the Gubernacular Canal above each tooth; i.e., bone resorption widens this canal to allow the crown to move through it and exit the alveolar bone.⁸

Role of dental follicle

Originating from cranial neural crest mesenchyme, the dental follicle (DF) is a loose connective tissue sac surrounding the enamel organ of each tooth. Removal of the DF from premolars prior to the onset of eruption prevented the unerupted tooth from erupting.⁹ Leaving the DF intact, but removing the tooth and inserting an artificial replica such as dental amalgam, resulted in eruption of the artificial tooth.¹⁰ The expression of a marker gene for osteoclastogenesis, receptor activator of nuclear factor kappa B (RANKL), and the expression of a marker gene for osteogenesis, bone morphogenetic protein-2 (BMP-2), were measured by real-time RTPCR. The expression of RANKL was greater in the coronal half whereas the expression of BMP-2 was greater in the basal half.¹¹

If the coronal one-half of the follicle were removed but the basal (apical) half was left intact, alveolar bone resorption & formation of eruption pathway did not occur and the tooth did not erupt. If the basal half of the DF were removed and the coronal half left intact, alveolar bone resorption occurred but the tooth did not erupt because of the absence of alveolar bone formation at the base of the crypt.¹²

A rare disease of multiple calcifying hyperplastic dental follicles (MCHDF) is characterized by unerupted teeth with atypical follicles containing hyperplastic dense connective tissue and numerous deposits of calcified tissue.¹³⁻¹⁵ Unerupted teeth are seen in another genetic disorder, Mucopolysaccharidosis VI (Maroteaux-Lamy syndrome), in which eruption of permanent molar teeth is retarded, & the dental follicles of such teeth are abnormal in that they have excessive accumulations of dermatan sulfate.¹⁶

Cellular and molecular basis for eruption

Chronological expression of various genes in dental follicle is critical for initiating and promoting the osteoclastogenesis needed for eruption.

Chronology of the localization of the potential eruption molecules parallels the timing of the cellular events of eruption.¹⁷ Epidermal growth factor (EGF) was the first molecule which was shown to accelerate incisor eruption in rodents.¹⁸ Later incisor eruption in mice was also shown to be accelerated by Transforming growth factor (TGF).¹⁹ Studies in rat mandibular first molar showed that TRAP- positive mononuclear cells are recruited into the DF at day 3 postnatally^{20,21} and are fused to form osteoclasts, as seen by electron microscopy.²² Two molecules known to promote osteoclastogenesis, CSF-1 and RANKL, are required for this major burst.²³

Studies showing that in RANKL knockout mice rescued with a RANKL transgene expressed in both B and T lymphocytes, there still is no tooth eruption just as is the case with RANKL knockouts^{24,25}. In the RANKL rescued transgenics, osteoclasts and bone resorption occur in the endosteum of long bones but not in alveolar bone.²⁵ Thus, the RANKL needed for alveolar bone resorption (and hence tooth eruption) has to come from another source; i.e., the DF.²⁶ Also down regulation of osteoprotegerin (OPG), an inhibitor of osteoclastogenesis is seen at day 3.²⁷ It is CSF-1, maximally expressed at day 3, that down-regulates the expression of OPG to enable osteoclastogenesis to occur.²⁸ Microarray studies show that one other molecule that inhibits osteoclastogenesis, secreted frizzled-related protein-1 (SFRP-1) also has its gene expression down-regulated in the DF at day 3 (time of major burst of osteoclastogenesis) and at day 10 (time of minor burst of osteoclastogenesis).²⁹ Targeted RT-PCR studies showed that

colony-stimulating factor-one (CSF-1) and monocyte chemotactic protein-1 (MCP-1) were maximally expressed in the DF of rat at day 3.³⁰ In vitro, both MCP-1 and CSF-1 are secreted by the DF cells and are chemotactic for monocytes.³¹ Endothelial monocyte-activating polypeptide (EMAP-II), a cytokine with a chemokine domain expressed in the DF,²⁸ has been shown to have a chemotactic effect on mononuclear cells.^{32,33}

In-vitro study was done in which EMAP-II expression was knocked down, which lead to decreased recruitment of mononuclear cells into the dental follicle as EMAP-II up regulates the gene expression of both CSF-1 and MCP-1 & this indirectly promoted mononuclear cell recruitment.³⁴

Null mice devoid of either the transcription factor gene *c-fos*³⁵ or the transcription factor genes NFkB1 and NFkB2^{36,37}, which are needed for osteoclast differentiation, lack osteoclasts, and their teeth do not erupt. It has been shown that knockout mice devoid of the osteoclast differentiation factor (ODF) gene, a gene that is required for osteoclast formation and activation, have unerupted teeth.³⁸ In knockout mice lacking a functional type I receptor for interleukin-1α (IL-1R), tooth eruption is delayed for 2 days in molars and 1 day in incisors.³⁹ The receptor for IL-1α (IL-1R) is localized in the DF, and its gene expression is enhanced either by a ligand present in the stellate reticulum- TGF-β1, or by a molecule present in the DF-EGF.⁴⁰ IL-1α acts on the receptor present in DF to increase the gene expression of CSF-1,⁴¹ MCP-1,⁴² MCP-1 synthesis and secretion,⁴³ and gene expression of NFkB.⁴⁴

Two new genes are shown to be expressed at day 10 prior to the eruption. CSF-1 expression is reduced and appears to be replaced by vascular endothelial growth factor (VEGF) which is maximally expressed in the DF at days 9–11.⁴⁵ Similar to CSF-1, VEGF up regulates the expression of RANK on osteoclast precursors.⁴⁶ Tumor necrosis factor alpha (TNF-α) which promotes osteoclastogenesis, is maximally expressed in the DF at day 9 and it enhances the gene expression of VEGF in the DF cells.⁴⁷ OPG levels are high at day 10²⁷, but still a favorable RANKL/OPG ratio to promote osteoclast formation is present due to maximal expression of RANKL at day 10.⁴⁸ Thus, dental follicle produces the majority of the potential eruption molecules. The remainder of the molecules resides in the stellate reticulum adjacent to the DF.¹⁷ Paracrine signaling from the molecules in the SR (IL-1α, PTHrP, TGF-β) affects gene expression of the molecules in the DF.⁴⁹

Bone formation

Alveolar bone formation is required for tooth eruption. Although alveolar bone resorption occurs in knockout mice deficient in membrane-type 1 matrix metalloproteinase (MT1-MMP), it was observed that alveolar bone growth did not occur and eruption was delayed.^{50,51} Basal half of dental follicle is required for bone formation during tooth eruption. Bone morphogenetic protein (BMP-2) is expressed more in the basal half¹¹, and chronologically gene expression of BMP-2 in rat DF cells begins to increase at day 3 with maximal expression at day 9 postnatally.⁵² BMP regulate the expression of Cbfa1 (core binding factor α1, also known as Osf2-osteoblast-specific transcription factor 2, or Runx2), which binds to and regulates the expression of multiple extracellular matrix genes in osteoblasts, and its overexpression can induce osteoblast-specific gene expression in fibroblasts and myoblasts.⁵³ These results firmly establish the role of Cbfa1 as a key transcriptional regulator of osteoblast differentiation during bone formation.

Biochemical aspect

Dental follicle is a highly hydrated structure which reaches its maximal weight at the time eruption begins. Collagen content increases upto 250% and proteoglycans upto 45% during eruption.⁵⁴ At the onset of eruption, the most prominent sialoprotein of 95,000 relative molecular weight (DF-95), is reduced by exactly the amount of three new sialoproteins of MW 20-25,000 which appear at this time. This has been interpreted to mean that fragmentation of DF-95 is a biochemical marker of the beginning of tooth eruption.² Immunolocalization of DF-95 in the reduced enamel epithelium⁵⁵ is a biochemical evidence that this epithelium is involved in and may initiate eruption. Proteases have been identified in the enamel organ during tooth development.⁵⁶ Activation of these proteases at the completion of crown formation could cause fragmentation of DF-95 and initiate eruption by release of metalloproteinase from the dental follicle.² Additional studies have shown that dental follicles contain collagenolytic activity,⁵⁷ and that the follicular content of the metalloproteinases (collagenase and stromelysin) is reduced during eruption,⁵⁸ suggesting a role for these enzymes in tissue turnover and thus tooth eruption.

Role of Wnt/ β -catenin signaling in tooth eruption

Wnt/ β -catenin signaling plays a critical role in bone formation and regeneration. In a study done on mice, conditional β -catenin activation mice were generated through intercross of *Catnb*^{+/lox(ex3)} mice with *Col1a1-cre* mice. In mutant mice there was inhibition of Wnt/ β -catenin signaling that led to local activation of β -catenin in the osteoblasts and odontoblasts. In these mutant mice, there was aberrant dento-alveolar complex formation, increased bone formation in mandible and disrupted tooth formation and eruption. Lower incisors and molars did not erupt. Therefore, appropriate inhibition of Wnt/ β -catenin signaling is important for the dento-alveolar complex formation and undisturbed tooth formation and its eruption.⁵⁹

Role of stem cells in tooth eruption

The presence of stem cells in the dental follicle⁶⁰ raises the question as to their potential role in tooth eruption. Given that these stem cells exhibit pluripotency in being able to differentiate under appropriate conditions into adipocytes, osteoblasts/cementoblasts or neurons⁶⁰, perhaps they also contribute to formation of some of the osteoclasts and osteoblasts needed for tooth eruption.²⁶ In a study done on rodent incisors, it was shown that unerupted incisors have more cells expressing markers of mesenchymal stem cell like population compared to that of erupted incisors. Identification of role of stem cells during tooth eruption still needs further research.⁶¹

Clinical significance

To understand and correct eruption disorders, an understanding of the cellular and molecular basis for normal eruption is necessary. Errors or deficits in gene expression results in many tooth eruption disorders. One of the most intriguing among conditions affecting tooth eruption is Primary Failure of Eruption (PFE), where localized failure of eruption of permanent teeth distal to the most mesially affected tooth exists with no other systemic involvement. This condition affects mainly permanent posterior teeth that are fully formed but are unable to reach the occlusal plane due to a primary defect in the eruption mechanism itself.⁶² Teeth affected by PFE are not impacted by any structures and are non-ankylosed, thus making this condition one of the most difficult to diagnose and treat among the human anomalies of tooth eruption. Since PFE exclusively affects posterior teeth without the involvement of any systemic disorder, we can deduce that genes for PFE would

be molecules that function solely in the pre-eruptive phase and that are expressed in cells of the dental follicle and surrounding structures. Hence, it is likely that genes like CSF-1, NFkB, and c-fos are prime and equally likely candidate genes responsible for the eruption defect in human PFE.¹⁷

Discussion:

Tooth eruption is a complex process that involves the timely action and interaction of cells of the dental (enamel) organ, follicle, and alveolus (osteoclasts and osteoblasts). Active tooth eruption begins in an intraosseous environment. It requires formation of an eruption pathway by osteoclasts, and the direction in which this pathway is formed will determine the direction of crown eruption initially. Eruption pathway formation requires bone resorption which is regulated mainly by the dental follicle and also by stellate reticulum. Various molecules like TGF, EGF, IL-1 α , VEGF, PTHrP, EMAP-II up regulates the expression of CSF-I & MCP-I which recruits mononuclear cells into the dental follicle. Down regulation of OPG & SFRP-1, which inhibits osteoclastogenesis is also important. For osteoclastic differentiation, transcription factor gene c-fos, NFkB1 and NFkB2 are required. As tooth erupts bone formation takes place at the apical end which requires the expression of Cbfa1 gene, membrane-type 1 matrix metalloproteinase (MT1-MMP) and Bone morphogenic protein (BMP).

Inhibition of β -catenin by Wnt/ β -catenin signaling pathway is also important for undisturbed dento-alveolar complex formation, tooth formation and tooth eruption. Presence of stem cells in dental follicle might play a role in tooth eruption. Knowledge of genes and molecules that are required for tooth eruption and their chronological order is important so as to treat various disorders of tooth eruption mainly the permanent failure of eruption. When "molecular orthodontic" procedures are available for delivering the appropriate molecules or factors necessary to "erupt" individual teeth, the clinician can select the appropriate treatment for the patient based on the underlying cause of the eruption problem.¹⁷

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