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Modulation of Tooth Eruption - An Understanding at the Molecular and Biochemical Level

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Tooth eruption is a localised event whereby the signals for eruption for a given tooth are synthesised in the dental follicle of that tooth with a possible cross talk of signals coming from the adjacent stellate reticulum. The eruption process requires alveolar bone resorption that is primarily regulated by the dental follicle. This is reflected by the fact that failures of eruption often can be traced to either osteoclast deficiencies or to dental follicle abnormalities. Recent advances in application of molecular techniques to animal models allowed for better understanding of gene regulatory events involved in the physiology of tooth eruption. This article attempts to consolidate and organise the facts that offshoot from animal studies.

Key Words: *Tooth Eruption, Dental Follicle, Molecular Biology, Eruption Mechanism*

Introduction

The process of normal tooth eruption and the source of eruptive forces are still controversial topics. Resorption of the roots of deciduous teeth is a synchronised event that accompanies the eruptive movement of their permanent successors. Both processes occur due to the activities of various cell types, and investigations on these functions and their effects, are gradually expanding our knowledge, understanding, and clinical control potential.[1] However, recent advances in application of molecular techniques to animal models allowed for better understanding of gene regulatory events involved in the physiology of tooth eruption.

Significant deviations from the accepted norms of eruption time are often observed in clinical practice. But complete failure of permanent teeth to erupt without any known cause is an infrequent phenomenon. The affected individuals may have no associated systemic illness, endocrine dysfunction, or genetic abnormality. Thus, no etiology or implicated mechanisms are elaborated. Henceforth, establishing the molecular basis of tooth eruption is critical for ultimately understanding the multitude of tooth eruption disorders ranging from impacted third molars to primary failure of eruption. Eruption failure of multiple teeth has been found to be feature in many genetic disorders and syndromes. Various mechanisms have been suggested to explain eruption failure in these conditions.[2,3] There is a considerable amount of work remaining before the genetic etiology of the eruption defects can be completely determined.

For a tooth to erupt from its bony crypt requires initiation by molecular signal(s) such that mononuclear cells (monocytes) are recruited into the dental follicle, the loose connective tissue sac that is required for eruption. In turn, these monocytes form osteoclasts for resorption of the alveolar bone to form an eruption pathway, the culmination of these molecular and cellular events. Eruption is a localised event whereby the signals for eruption for a given tooth are synthesised in the dental follicle of that tooth with a possible cross talk of signals coming from the adjacent stellate reticulum. The possible pathways of molecular signaling suggest that there is redundancy in the function of the tooth eruption genes, ie, in many instances more than one gene product can enhance

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the expression of a given gene. This redundancy also is seen at the cellular level whereby more than one gene product may act to recruit mononuclear cells into the follicle.[1] Consequently, determining which are the preferred pathways of molecular signaling to initiate eruption constitutes a major challenge in future tooth eruption studies.

The findings confirming the role of gene expression in the physiology of tooth eruption are largely based on animal models, predominantly rats, whose teeth are continuously growing and are anatomically different to the teeth of mammals. The fact that growth is continuous and rapid in these teeth makes them useful for eruption studies, as well as the ease of availability and housing of these small animals. Human teeth undergo an eruption process during development and exhibit minor positional adjustments throughout life, supported by investing tissues. Whether the basic mechanisms of tooth eruption in these categories are analogous remains observed. There are marked physiological and morphological contrasts between human teeth and rodent incisors, yet these latter form the predominant experimental model for the investigation of tooth eruption. Care must, therefore, be taken in extrapolating the results from laboratory rodents to the human situation.

Although techniques are available for studying the molecular biology of tooth eruption, especially the role of various cytokines (Laser Capture Micro-dissection), regulation of osteoclastogenesis (Targeted gene studies, enzyme-linked immunosorbent assays and immunoblotting), establishment of dental follicle cell lines (flow cytometry, reverse transcription PCR), most clinical programmes do not train students in these subjects, other than reviews of gross anatomy and the occasional journal article. Molecular and genetic developments in the field have generally been ignored as not relevant to clinical practice. Consequently, the trained specialists remain unfamiliar and uncomfortable with these topics, discouraged by the technical challenges of functional evaluations, and daunted by the complexity of the subject. Nevertheless, few oral biologists have made significant recent progress in understanding normal tooth eruption and their disorders, and the time is ripe to re-introduce these topics to clinicians. In particular, there are new studies addressing the intricate role of dental follicle cells and stellate reticulum and the expression of osteoprotegerin gene in the animal models. It is now high time to carry out new studies on the norms of human performance as related to tooth eruption and their mutability. These could provide a guide map to elucidate the most intriguing aspect of the multitude of eruption disorders in humans, including multiple unerupted permanent teeth.

Eruption Speed and Eruption Pathway Formation

The speed of tooth eruption has several characteristics. First, eruption itself has to proceed at a certain speed to move a tooth into its functional position on schedule. Prolonged delays can prevent eruption and sometimes result in ankylosis of tooth to bone. Second, the eruption speed is not uniform. Erupting teeth tend to move at different speeds and different rates. This implies that bone resorption and formation, like root growth, must occur at a variety of speeds depending on the stage of eruption. During intraosseous eruption, the rate of bone resorption (and root resorption) determines the rate of eruption. While it is not clear what specifically causes eruption to begin, rates to

change, and eruption to slow dramatically at the occlusal plane, considerable information about parts of these processes has been provided by studies in a number of species.

The intraosseous stage of tooth eruption involves bone resorption to form an eruption pathway and interradicular bone formation, root growth and fundic bone apposition, which move the erupting tooth into the eruption pathway. These events are regulated by dental follicle proper, which develops regions to initiate and control bone formation and areas which remain neutral. Where these regions develop in a particular follicle will determine the direction of tooth eruption, when they develop will determine the time of eruption, and how they are synchronised will determine whether there will be complications.

Root begins to form early in eruption and, as Carlson[4] has demonstrated for human premolars, their initial projection from the crown can cause resorption of bone at the base of the crypt. According to Andreasen[5] root growth and the high rate of periodontal turnover during incisor and molar eruption are related more to providing support for and accommodating root growth and a rapidly erupting functional tooth, in the case of incisor, and to occlusal pressures on the molar ridge prior to eruption, than to the mechanism of eruption per se.

When root growth equals the rate of formation of the eruption pathway (EP), no bone is formed in the fundus of the crypt. When root growth exceeds EP formation, basal bone is resorbed accordingly. When root growth is less than EP formation, bone is formed in the fundus. These scenarios can occur episodically during eruption of a tooth or they can characterise the interplay of root growth and basal bone changes during eruption. These reciprocal variables of bone resorption, bone formation and root growth produce different rates of eruption for a single tooth.

Formation of the eruption pathway is the rate limiting step as revealed by rapid catch-up eruption of temporarily impacted teeth, accelerated eruption with early formation of a pathway following colony stimulating factor-1 (CSF-1) administration and failure of eruption when an eruption pathway is not formed. CSF-1 treatment of the osteopetrotic rat mutation toothless (tl) improves tooth eruption[6] and its effect on eruption of a particular tooth depends on when CSF-1 administration begins.[7] CSF-1 treatment begun at birth results in incisor eruption 15 days later. Delaying treatment for 36-48 hours severely restricts incisor eruption. Similarly, the first molar erupts when treatment begins on the third day but they do not erupt when treatment is delayed beyond the eleventh day. This data indicates that each tooth has a characteristic window during which eruption is possible. If an eruption pathway cannot be provided during this time, eruption is compromised because ankylosis develops.[7]

Apoptosis is a physiological process of great importance during organ morphogenesis and development which might be involved in the intense follicular remodeling occurring at the prefunctional stage of eruption. It is possible that the differential spatial and temporal expression of Epidermal Growth Factor (EGF) in the Dental Follicle (DF) induces the initiation of apoptosis in this tissue. Shroff *et al*, strongly support the hypothesis that follicular cells present in the coronal and lateral aspects of the DF become apoptotic during the prefunctional stage of tooth eruption. This major

change in the cell phenotype most probably plays a central role in the creation of an eruption pathway of least resistance.[8] The determinants of tooth eruption at the cellular and molecular level govern the unique aspect of bone remodeling associated with eruption. Failure of eruption teeth, especially when the roots are fully formed could result from the lack of coordination between these physiologic events and poor signal transduction. Further studies are required to extrapolate the nature of candidate genes and their inhibitory role in the occurrence of this uncommon condition. Recent progress in the Human Genome Project offers an optimistic outlook for the identification of the genes and underlying mutations associated with failure of eruption.

Blood Pressure Hypothesis and Eruption

According to Constant (1896), "the blood pressure excited in the vascular tissue which lies between a developing tooth and its bony surroundings is the active mechanical factor in the process known as the eruption of the teeth".[9] Since then, the blood pressure theory of tooth eruption has been supported and has been further developed by several investigators. The pushing force of the rat incisor originates primarily from localised blood pressure within the incisor socket and, in part, from tissue growth. Precise measurement of the eruptive force lends convincing support to the vascular theory of tooth eruption. It is plausible that disturbances of any factor in the pressure system may cause short or long term and minor or major changes in the position of teeth.[10]

It has been suggested that the vasculature in the dental pulp and periodontal tissue plays an important role in producing the eruptive force in continually erupting incisors. The injections of various doses of adrenaline decreased the mean regional blood flow and erupting rate dose-dependently, while those of acetylcholine increased the regional blood flow and erupting rate. These results support the hypothesis that the eruptive zone of the rate incisor is closely related to the vasculature within the socket.[11]

Angiotensin II causes constriction of the peripheral vascular smooth muscles resulting in an increase of arterial blood pressure and a decrease of regional blood flow, followed by a decrease of fluid volume and then a reduction of either the pressure within the socket or of the eruptive force. Shimada *et al*, assume that the regional vascular pressure within the socket plays an important role in determining the position of the rat incisor.[12]

Influence of Pharmacological Agents

A requirement for tooth eruption is the resorption of alveolar bone. Because bone resorption is stimulated by dexamethasone both in vivo and in vitro, dexamethasone 21-phosphate, a soluble form of dexamethasone, was injected into rats to determine its effect in tooth eruption.[13] Such dexamethasone injections accelerate the time of intra-osseous eruption in rat incisors but do not accelerate the eruption time of rat molars. These suggest that the molecular signal for the initiation of tooth eruption (ie, onset of bone resorption) differs between rat incisors and molar. Given that rat incisors are teeth of continuous eruption whereas rat molars are teeth of limited eruption, as are human teeth, care must be taken in extrapolating results derived from rat incisors to human dentition. In vitro, dexamethasone has no effect on the gene expression of either osteoprotegerin

(OPG) or epidermal growth factor (EGF) in dental follicle cells derived from molar. Because OPG expression during normal tooth eruption is transitorily inhibited early postnatally in the molar dental follicle to allow osteoclast formation, the absence of inhibition of its expression by dexamethasone could explain why dexamethasone does not accelerate eruption in molars.[13]

Pamidronate, a bisphosphonate when injected into postnatal rats inhibits the time of tooth eruption of both rat molars and incisors. Pamidronate does not inhibit the gene expression of the putative tooth eruption molecules, CSF-1 and C-fos. Pamidronate does increase the size of the osteoclasts, including an increase in the number of nuclei, suggesting that the precursor mononuclear cells can still fuse to form osteoclaststs despite the reduced ability of the osteoclasts to resorb bone.[14]

Bafilomycin A1 is a reversible blocker of bone resorption. When administered to the crypt of erupting dog premolars for two weeks, bafilomycin A1 blocks bone resorption and eruption during this period without effect on adjacent teeth or on bone formation. Blocking resorption in two weeks causes a fourfold delay in tooth eruption.[15]

All-trans-retinoic acid (ATRA) induces bone resorption, but the molecular mechanisms were unknown. Jacobson *et al*, studied the effects of ATRA on OPG and RANKL expression in human MG-63 osteosarcoma cells and primary osteoblast-like cultures. ATRA dose-dependently down-regulated protein levels of OPG in MG-63 cells, with a maximum (-56%) observed at a dose of 10(-6) M. In primary cultures, the authors found a 3-fold induction of RANKL mRNA expression. Thus, the RANKL /OPG ratio was markedly increased, suggesting a potential mechanism of ATRA- induced bone resorption.[16]

Molecular Regulation

Tooth eruption requires alveolar bone resorption that is regulated by the dental follicle. This is reflected by the fact that failures of eruption often can be traced to either osteoclast deficiencies or to DF abnormalities. Osteoclastogenesis needed for bone resorption appears to occur as a result of a reduction in the expression of the osteoprotegerin (OPG) gene in the dental follicle at a specific time. This reduction in expression is mediated in-vitro in the follicle cells by CSF-1 and PTHrP. The importance of CSF-1 mediated osteoclastogenesis in tooth eruption has been shown in osteopetrotic op/op mice. CSF-1 deficiency in these mice decreased osteoclasts and leads to failure of tooth eruption. Injection of recombinant CSF-1 into op/op mice restores tooth eruption and, in normal rats, accelerates eruption of the first molar.[17,18] CSF-1 is highly expressed in the dental follicle and, to a lesser extent, in alveolar bone and ameloblasts. Peak expression in the follicle occurred at day-3 and correlated with peak influx of monocytes into the follicle and osteoclast activity along the occlusal bone.[19] In contrast to the occlusal region, osteoclast activity in basal bone is only transiently increased during early eruption. However, it is unclear if these cytokines exhibit an expression pattern that correlates with sites of osteoclastogenesis in vivo. A recent study showed that the osteoclast activity in the basal bone (at day-3) decreased despite persistent CSF-1 expression and was associated with increased expression of OPG compared to RANKL. By day-8, osteoclastogenesis declined and correlated with upregulation of OPG at the occlusal and basal regions,

with this effect continuing throughout eruption. These findings suggest that the spatiotemporal pattern and relative abundance of CSF-1, RANKL and OPG during eruption are key determinants of site-specific osteoclast activity in bone surrounding the tooth. Targeting these cytokines to specific regions in alveolar bone may provide a mechanism for regulating osteoclastogenesis in dental disorders associated with altered tooth eruption.[20] Either injecting OPG or enhancing its expression in the follicle at day-3 by injecting PMA (Phorbolmyristate acetate) an activator of protein kinase C, delays the time of tooth eruption. Consequently, the regulation of OPG production by the DF likely affects the alveolar bone resorption needed for tooth eruption.[21]

Osteoclastogenesis is primarily regulated by receptor activator of nuclear factor – Kappa B ligand (RANKL), CSF-1 and OPG. Whether or not RANKL is expressed in vivo in the follicle is controversial, however. It is critical to determine this because some have shown that in partially rescued mice null for RANKL, teeth do not erupt. This suggests that RANKL should be expressed in the follicle for eruption to occur and it is probable that interaction between it, CSF-1 and OPG regulate locally the osteoclastogenesis needed for tooth eruption.[22] BMP-2 acts to down regulate RANKL expression in vitro and in vivo, may promote alveolar bone growth in the basal region of the tooth.[23]

EGF is involved in the activity of cells associated with growth and development of the dentoalveolar complex in kittens. The age-related fluctuations of this growth factor in cells of the apical periodontal, the dental follicle, and bone cells in the eruption path of developing premolars, suggests that at specific times or developmental stages, cells in these regions are engaged in proliferative and / or matrix remodeling activities affiliated with the process of tooth eruption.[24] Cielinski *et al*, compared the effects of neonatal injection of Epidermal growth factor (EGF) (1 microg/g body wt) and CSF-1 (10^6 units) alone or together on the eruption of incisors and first molars. EGF accelerated the eruption of incisors with no significant effect on first molar. CSF-1, in contrast, accelerated molars eruption more than incisor eruption. CSF-1, but not EGF, increased the number of mononuclear cells in the DF and osteoclasts on adjacent alveolar bone surfaces around the first molar and produced enhanced resorption of crypt surfaces as revealed by scanning electron microscope. These data suggest that during eruption, rodent incisors and molars may preferentially respond to different molecular regulators.[25]

Parathyroid hormone related protein (PTHrP) appears to be responsible for triggering tooth eruption by activating osteoclasts on the eruptive surface of the dental crypt. This effect seems to correspond to a true "PTH-like" PTHrP function in vivo and is clearly the only PTHrP function identified that is even remotely reminiscent of the effects of PTH itself.[26]

Bone formation is enhanced by OPG secretion, and incubation of the follicle cells with BMP-2 enhances OPG secretion. Thus, a reduction in secretion of the OPG protein at defined times may promote the osteoclastogenesis and alveolar bone resorption needed for eruption, and enhancement of OPG secretion at other times may promote alveolar bone formation.[27]

Vascular endothelial growth factor (VEGF) may be involved in promoting the secondary bust of

osteoclastogenesis and activator of protein kinase C may upregulate its expression.[28]

Osteoclast Diseases

Much of the current knowledge about tooth eruption has come from careful analysis of dentition in spontaneous osteopetrotic animals. In the last five years or so, many of the genes responsible for "osteoclast diseases", ie, diseases in which the primary defect lies with the osteoclast itself, have been identified. In diseases associated with lack of osteoclast function, problems with tooth eruption are well recognised.[29] Currently, four genes have been identified which are responsible for recessive osteopetrosis in man and three of these are directly involved in the protein generation and secretion pathways, essential for osteoclastic bone resorption. A 4th gene has as yet unknown function and there is at least one more gene to be found for the rare cases of human osteopetrosis where osteoclast formation is affected.[30] A clinically more severe form of osteopetrosis also referred to as malignant juvenile osteopetrosis, is caused by loss of function mutations in a number of genes. In approximately 50% of cases, the gene coding for an osteoclast – specific subunit of the proton pump, which is responsible for proton secretion into the resorption compartment is mutated. This gene, ATP 6i, or TCIRG 1, was knocked out in the mouse and produces a very severe osteopetrosis with normal osteoclast formation, but complete absence of ruffled borders, and is associated with complete lack of tooth eruption.[31] In order to improve understanding and treatment of dental anomalies in osteoclast diseases, it will be important to include detailed observations of the development and eruption of teeth in the phenotypic analysis of the many transgenic models for skeletal disorders that are currently being developed.

Other Bio-chemical Mediators

Growth hormone (GH) is an important regulator of postnatal growth and development, with bone being a major target tissue for its actions. GH may directly influence cells via its receptor (GHR) or through the local production of insulin – like growth factor – 1 (IGF – 1). The dental follicle was found to be positive for all factors, as were the multinucleated, osteoclast-like cells lining the alveolar bone occlusal to the unerupted molar. The co-localisation of all factors in the DF of both normal and osteopetrotic animal genotypes suggests that the regulatory role of the dental follicle in tooth eruption may be related to both tooth development and bone resorption. Osteoclast-like cells located in the eruption pathway region in normal and osteopetrotic animals co-localised all factors, suggesting these factors play a role in the bone resorption and tooth eruption. However, as resorption is defective in the ia rat, the defect is likely downstream from the sites of activity of these factors in tooth eruption.[32]

The dental follicle appears to be a site of intense phosphatase activity during the eruption and resorption of teeth. Acid phosphatase has been shown to be affiliated with resorption of mineralised tissue, while the Alkaline phosphatase is found in cells capable of producing mineralisable matrices. Examinations of the sections by light microscopy revealed that in kittens the outer surface of the dental follicle is located near sites of resorption of the overlying deciduous tooth and alveolar bone, and that

the external, apical resorption is accompanied by a process of internal resorption inside the pulp chamber of the deciduous tooth. These sites of root resorption were typified by intense cellular staining for tartrate resistant acid phosphatase (TRAP). In contrast, the inner enamel epithelium and the periodontium of the erupting tooth presented intense staining for acid phosphatase, particularly in cells located in sites of formation of tooth and alveolar bone. In the complex process of jaw growth and tooth eruption, the DF appeared to be located strategically, in close proximity to sites of resorption of teeth and bone.[33]

Conclusion

The key to the successful clinical management of tooth eruption is understanding that this process consists largely of the local regulation of alveolar bone metabolism to produce resorption in the direction of eruption and formation of bone behind an erupting tooth. The ability to affect these processes selectively and discretely is limited at present. More comprehensive analyses of the molecular mediators of eruption will certainly increase clinical options in the future.

While the exact mechanism of eruption is not clearly understood, numerous experiments of nature, including many of the inborn errors of metabolism, should prove useful in their study. Nutritional studies may also prove useful but will always be problematic. Studies on endocrinologic changes such as puberty, pregnancy, menopause, and diseases such as diabetes, have already shown that the periodontium may not be able to accommodate changes in the body's equilibrium.

REFERENCES

1. Wise G E. Cel and molecular biology of tooth eruption. In: Davidovitch Z, Mah J editors. Biological mechanism of tooth eruption, resorption and replacement by implants, Boston: Harvard society for the advancement of orthodontics, 1998, p.1-8.
2. Wise G E, Frazier-Bowers S, D'Souza R N. Cellular, molecular, and genetic determinants of tooth eruption. Crit Rev Oral Biol Med 2002;13: 323-34.
3. Ritzau M, Gorlin R J, Andreasen J O. Tooth eruption disturbances in genetic disorders and endocrine diseases. In: Andreasen J O, Petersen J K, Laskin D M, editors. Textbook and color atlas of tooth impactions, Munksgaard, Copenhagen, 1997, p.349-368.
4. Carlson H. Studies on the rate and amount of eruption of certain human teeth. Am J Orthod Oral Surg 1944; 30:575-88.
5. Marks S C Jr, Schroeder H E, Andreasen J O. Theories and mechanism of tooth eruption. In : Andreasen J O, Petersen J K, Laskin D M, editors. Textbook and color atlas of tooth impactions, Munksgaard, Copenhagen, 1997, p.40-42.
6. Marks S C Jr, Wojtowicz A, Szperi M, Urbanowska E, Mackay C A, Wiktor-Jedrzejczak W W, Stanley E R, Aukerman S L. Administration of CSF-1 corrects some macrophage, dental and skeletal defects in an osteopetrotic mutation (toothless, tl) in the rat. Bone 1992; 13:89-93.
7. Iizuka T, Cielinski M, Aukerman L, Marks S C. The effects of CSF-1 on tooth eruption in the toothless (osteopetrotic) rat in relation to the critical periods for bone resorption during tooth eruption. Arch Oral Biol 1992; 37:629-36.
8. Shroff B, Rothman J R, Norris K, Herbert C. Follicular apoptosis during tooth eruption. In : Davidovitch Z, Mah J editors. Biological mechanism of tooth eruption, resorption and replacement by implants, Boston: Harvard society for the advancement of orthodontics, 1998, p. 71-77.
9. Constant T E. The mechanical factor in the eruption of the teeth, hitherto unrecognized. J Br Dent Asso 1896; 17 : 723-32.
10. Shimada A, Komatsu K, Chiba M. Effects of local injections of vasoactive drugs on eruption rate of incisor teeth in anaesthetised rats. Arch Oral Biol 2006;51:449-56.
11. Chiba M, Yamaguchi S, Komatsu K. Measurement of the force needed to restrain eruption movement of the rat mandibular incisor. Arch oral Bio 1996; 41: 341-49.
12. Shimada A, Shibata T, Komatsu K. Relationship between the tooth eruption and regional blood flow in angiotensin II induced hypertensive rats. Arch Oral Biol 2004; 49 : 427-33.

13. Wise G E, Grier R L 4th, Lumpkin S J, Zhang Q, Effects of dexamethasone on tooth eruption in rats: Differences in incisor and molar eruption. Chin Anat 2001;14; 204-9.

14. Grier R L 4th, Wise G E. Inhibition of tooth eruption in the rat by a bisphosphonate. J Dent Res 1998; 77: 8-15.

15. Sundquist K, Lasson E K, Marks S C Jr. Altering tooth eruption by blocking bone resorption-the local delivery of bafilomycin A1. Connect tissue Res 1995; 32: 159-63.

16. Jacobson A, Johansson S, Branting M, Melhus H. Vitamin A differentially regulates RANKL and OPG expression in human osteoblasts. Biochem Biophys Res Commun 2004; 322: 162-7.

17. Yoshida H, Hayashi S, Kunisada T, Ogawa M, Nishikawa S, Okamura H, *et al*. The murine mutation osteopetrosis is in the coding region of the macrophage colony-stimulating factor gene. Nature 1990; 345:442-4.

18. Niida S, Abe M, Suemune S, Yoshiko Y, Maeda N, Yamcusaki A. Restoration of disturbed tooth eruption in osteopetrotic (op/op) mice by injection of macrophage CSF. Exp Anim 1997; 46:95-101.

19. Wise G E, Fan W. Changes in the tartrate-resistant acid phosphates cell population in dental follicles and bony crypts of rat molars during tooth eruption. J Dent Res 1989; 68: 150-56.

20. Hesirich J, Bsoul S, Barnes J, Woodruff K, Abboud S. CSF-1, RANKL and OPG regulate osteoclastogenesis during murine tooth eruption. Arch Oral Biol 2005; 50: 897-908.

21. Wise G E, Yao S, Lin D, Injection of OPG and PMA delay tooth eruption. Clin Anat 2005; 19:19-24.

22. Yao S, Ring S, Henk W G, Wise G E. In vivo expression of RANKL in the rat dental follicle as determined by laser capture microdissection. Arch Oral Biol 2004; 49 : 451-56.

23. Liu D, Yao S, Pan F, Wise G E. Chronology and regulation of gene expression of RANKL in the rat dental follicle. Eur J Oral Sci 2005; 113 : 404-9.

24. Guajardo G, Saito S, Shanfeld J L, Davidovitch Z. Localization of epidermal growth factor in dental and paradental cells during tooth eruption in kitten. In : Davidovitch Z, Mah J editors. Biological mechanism of tooth eruption, resorption and replacement by implants, Boston: Harvard society for the advancement of orthodontics, 1998, p 9-15.

25. Cielinski M J, Jolie M, Wise G E, Marks S C Jr. The contrasting effects of CSF-1 and EGF in tooth eruption in the rat. Connect Tissue Res 1995; 32: 165-9.

26. Broadus A E, Philbrick W M. In : Davidovitch Z, Mah J editors. Biological mechanism of tooth eruption, resorption and replacement by implants, Boston: Harvard society for the advancement of orthodontics, 1998, p. 31-37.

27. Wise G E, Ding D, Yao S. Regulation of secretion of osteoprotegerin in rat dental follicle cells. Eur J Oral Sci 2004; 112 : 439-44.

28. Wise G E, Yao S. Expression of vascular endothelial growth factor in the dental follicle. Crit Rev Eukaryot Gene Expr 2003; 13 : 173-80.

29. Helfrich M H. Osteoclast diseases and dental abnormalities. Arch Oral Biol 2005; 50 : 115 – 122.

30. Flanagan A M, Massey H M, Wilson C, Vellodi A, Horton M A, Steward C G. Macrophage colony – Stimulating factor and receptor activator NF – Kappa B ligand fail to rescue osteoclast – poor human malignant infantile osteopetrosis in vitro. Bone 2002; 30 : 85-90.

31. Li Y P, Chen W, Liang Y, Li E, Stashenko P. Atp6i – deficient mice exhibit severe osteopetrosis due to loss of osteoclast mediated extracellular acidification. Nat Genet 1999; 93 : 447-51.

32. Symons A L, Leong K, Waters M J, Marks S C Jr. Growth factor expression associated with odontogenesis and tooth eruption in the incisor absent (osteoeptrotic) rat. In : Davidovitch Z, Mah J editors. Biological mechanism of tooth eruption, resorption and replacement by implants, Boston: Harvard society for the advancement of orthodontics, 1998, p. 55-64.

33. Vitouladitis I, Saito I, Shanfeld J L, Davidovitch Z. Localization of acid and alkalins phosphatases in dental and paradental tissues during tooth eruption in kittens. In : Davidovitch Z, Mah J editors. Biological mechanism of tooth eruption, resorption and replacement by implants, Boston: Harvard society for the advancement of orthodontics, 1998, p.49-53.