Recent perspectives *vis-à-vis* the biological basis of tooth eruption

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ABSTRACT

A thorough understanding of recent advancements regarding the molecular interactions responsible for tooth eruption is indispensable to all dental specialties and may provide insight for treating clinical eruption disorders. The biological processes responsible for tooth eruption have long been a matter of debate. Several types of cells of dental origin and numerous molecular factors that were believed to be responsible for this process have repeatedly been considered and investigated. Most existing eruption theories have concentrated on selective cells or processes as the sole generating forces of tooth eruption. This article reviews previously proposed eruption theories, in the light of significant advances in the understanding that the sequential interactions between dental epithelium and ectomesenchymal cells pattern the initiating cascade of the eruption process. These findings are presented in the context of tooth development within the milieu of a changing bony socket. Understanding the process of tooth eruption in this framework points to the fact that tooth eruption is essentially a stage of tooth development which, through selective resorption and deposition of bone, allows the developing tooth to be displaced through the alveolar bone to its position of function in the oral cavity.

Key words: tooth eruption, dental follicle, paracrine signaling, bone remodeling

ACRONYMS

BMP-2: Bone Morphogenetic Protein-2
CSF-1: Colony-stimulating Factor-1
DF: Dental Follicle
EGF: Epidermal Growth Factor
ERS: Epithelial Root Sheath
IL-1α : Interleukin-1α
MCP-1: Monocyte Chemotactic Protein-1
MMPs: Matrixmetalloproteinases
RANKL: Receptor Activator of Nuclear factor Kappa B Ligand
REE: Reduced Enamel Epithelium
TNF- α: Tumour Necrosis Factor–α

INTRODUCTION

Tooth movements during the lifetime of an individual can generally be divided into pre-eruptive, eruptive and post-eruptive phases. For the purpose of this overview we will focus on the eruptive phase only. Tooth movements during this phase are subdivided into intra-osseous and supra-osseous stages referring to the movement of the tooth from a position within the bone to its functional position in occlusion.[1] Tooth eruption is a complex process in which the interplay of several tissues and mechanisms have been proposed. All the tissues within the vicinity of the tooth, and thought to be capable of generating some kind of force, have been implicated as contributing to the process of tooth eruption.[2] Common theories of dental eruption include hydrostatic pressure, the periodontal ligament, root formation and elongation, selective bone resorption and formation, and the role of the dental follicle surrounding the developing tooth.

The purpose of this article is to review the previously proposed mechanisms of tooth eruption as a platform for presenting the newest significant findings regarding the intricate interplay of inductive signals between the dental follicle, reduced enamel epithelium, stellate reticulum and alveolar bone in the process of tooth eruption.

HISTORICAL THEORIES

The **hydrostatic pressure** theory is one of the oldest tooth eruption theories known.[3-5] According to this theory, blood pressure exerted in the vascular tissue between a developing tooth and its bony surroundings creates a mechanical force causing tooth eruption.[5] Although a pressure gradient from apical to occlusal was revealed in the teeth of dogs,[6] this theory was contradicted by studies which proved hypotensive drugs[3] and hemodynamic influences such as changes in pulse rate and blood pressure[7] to not have any effect on tooth eruption. Other studies on human and rat

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teeth respectively propose contradictory mechanisms and therefore this theory remains inconclusive.[8, 9,10,11]

Fibroblasts and **collagen** fibers of the periodontal ligament have long been implicated as generating the eruptive force for tooth eruption.[12-18] The proliferation and subsequent occlusal migration of these periodontal ligament fibroblasts have been proposed as main factors responsible for tooth eruption.[15,18] Periodontal fibroblasts in an *in vivo* situation of eruption exhibit characteristics of cells actively synthesizing and secreting protein rather than those of motile or contractile cells as described by these studies. The role of collagen has also been investigated,[19] but the use of sodium morrhuate, known to reduce production and maturation of collagen, had no effect on the process of eruption.[20] Collagen remodeling has been proposed to be a crucial factor in tooth eruption[21] and the lack of matrixmetalloproteinases (MMPs) seems to be related to abnormal tooth eruption in humans.[22] Collagen, its synthesis, remodeling and the cells implicated in these processes can however not be accepted as the sole mediators of tooth eruption as a tooth without a periodontal ligament can still erupt.[23] It is however possible that the periodontal ligament could play a role in the supra-osseous phase of the eruptive process in lifting the tooth into the occlusal plane.[24]

The theory that **root formation** results in tooth eruption seems plausible as both processes take place simultaneously.[23, 25] It seems logical that root formation and subsequent elongation would result in extrusion of the tooth from the bony socket. It has however been proven by studies in dogs and mice that rootless teeth do erupt and that teeth may also sometimes erupt a greater distance than the length of the roots.[1,26-29] Pressure applied to bone generally results in bone resorption.[30] Therefore, if root elongation was indeed responsible for "pushing" the tooth into occlusion as the root elongates, it would mean that pressure would have to be applied to the bone by the elongating root. The force generated by this kind of pressure would definitely result in bone resorption at the apical base. Therefore root formation is accommodated during tooth eruption and can be regarded as a consequence, rather than a cause, of the process.[31, 32]

The **dental follicle** (DF) refers to the condensed ectomesenchyme encapsulating the unerupted, developing tooth. (Figure 1) It was demonstrated, as early as 1980, that once the DF of unerupted teeth were surgically removed,

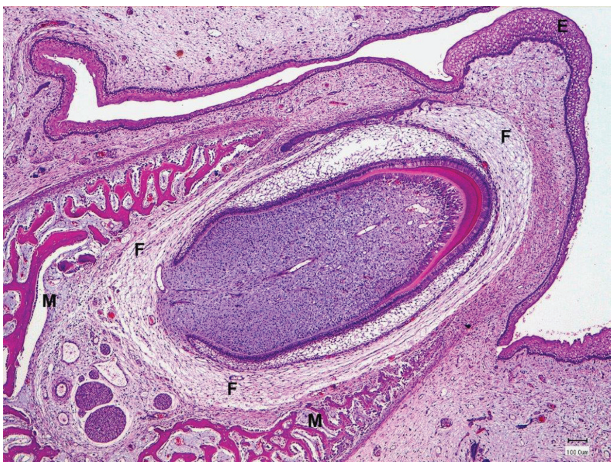

Figure 1: Photomicrograph of a developing dog tooth indicating the position of the dental follicle **(F)** around the developing tooth, developing mandibular alveolar bone **(M)** and overlying oral epithelium **(E).**

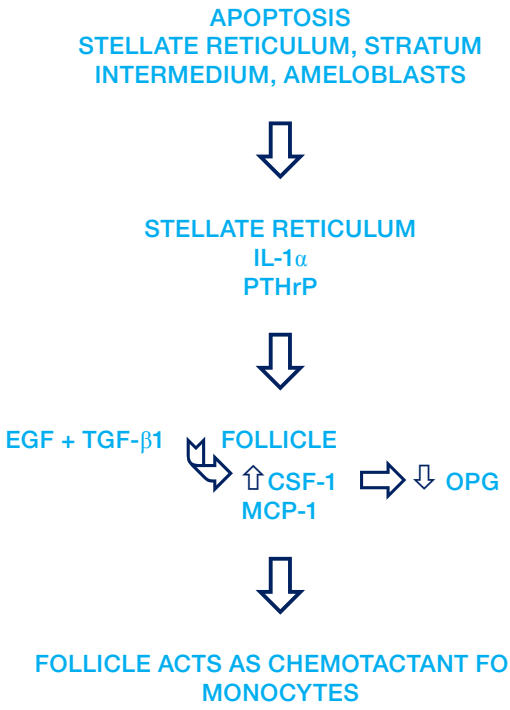

Figure 2: Schematic representation of paracrine signalling at the coronal aspect of the developing tooth**.**

those teeth failed to erupt.[29] When a developing unerupted premolar tooth was surgically removed and replaced with a metal replica, the replica erupted, provided that the DF was retained.[27] These studies clearly demonstrate the essential role of the DF in the process of tooth eruption, while simultaneously eliminating the role of other tissues such as the dental pulp, periodontal ligament and root formation.

Regional differences in the DF were described following further studies on dog premolars.[33] If the basal (apical) half of the DF was left intact and the coronal half was removed, alveolar bone resorption did not occur, an eruption path did not form and the tooth eruption was impeded.[33] Conversely, if the coronal half was left intact and the basal half removed, bone resorption did occur at the coronal aspect, but the tooth did not erupt as no bone was formed at the base of the tooth socket.[33] Therefore this study suggested that the coronal aspect of the DF regulates osteoclastogenesis (bone resorption) and the basal aspect of the DF is responsible for osteogenesis (bone formation); both processes essential for tooth eruption.[33] Regional differences in gene expression of the DF were assessed using laser capture microdissection.[34] The coronal and basal halves of the DFs of rat first mandibular molars were isolated and RNA extracted from both halves respectively.[34] Real time reverse transcription-polymerase chain reaction (RT-PCR) was used to measure the expression of marker genes for bone resorption (osteoclastogenesis) and bone formation (osteogenesis).[34] The receptor activator of nuclear factor kappa B ligand (RANKL) gene was utilised as a marker gene for osteoclastogenesis, therefore for bone resorption. Bone morphogenetic protein-2 (BMP-2) gene served as a marker for osteogenesis or bone formation. The results showed a higher expression of bone-resorption genes (RANKL) in the coronal half of the DF,[34] but higher expression of bone-formation genes (BMP-2) in the basal half of the follicle.[34] Therefore, clearly, the DF regulates bone formation and resorption via spatial expression of different genes at different levels and times.

Current concepts regarding the paracrine signaling role of the dental follicle in tooth eruption

Tooth development is initiated and crown and root development regulated by a cascade of reciprocal interactions between the dental epithelium and the dental mesenchyme.[35,36]

Correspondingly, the process of tooth eruption is represented by a cascade of cellular events leading to the recruitment of monocytes to the dental follicle followed by osteoclastogenesis and bone resorption, a prerequisite for tooth eruption.[37] This cascade of molecular events is initiated by epithelial-ectomesenchymal interactions between the dental follicle, the reduced enamel epithelium (REE) and the stellate reticulum (Figure 2).[36] The REE consists of the layer of ameloblasts fused with the stratum intermedium, stellate reticulum and the outer enamel epithelium upon completion of crown formation.[1]

Apoptosis of epithelial cells of the stellate reticulum, stratum intermedium and ameloblast layer during the advanced stages of enamel secretion have been reported.[38] This apoptotic process is believed to have a direct influence on osteoclastogenesis through the release of interleukin-1α (IL-1α) by the cells of the stellate reticulum, the receptors for which are located on the cells of the dental follicle.[37] IL-1α subsequently stimulates the expression of colony-stimulating factor-1 (CSF-1) and monocyte chemotactic protein-1 (MCP-1) within the cells of the dental follicle, thereby allowing the dental follicle to act as a chemoatractant for monocytes.[37, 39] The stellate reticulum cells also participate in osteoclastogenesis by releasing parathyroid hormone-related protein (PTHrP) which further increases the expression of both MCP-1 and CSF-1.[40] Concurrently with osteoclastogenesis, CSF-1 down-regulates the expression of osteoprotegerin (OPG), a well-known decoy receptor for RANKL which would normally inhibit osteoclast differentiation.[41] The cells of the REE and stellate reticulum therefore jointly exert a paracrine effect on the cells of the dental follicle, enhancing the expression of chemoattractant molecules.[42] Additionally, the REE also secretes proteases that aid in creating an eruption pathway for the tooth through enzymatic digestion of collagens.[43, 44] Other molecules such as epidermal growth factor (EGF) and transforming growth factor β 1 (TGF-β1) released by the cells of the dental follicle further enhance the expression of CSF-1 within the dental follicle.[45-47] Paracrine signalling involving both the ectomesenchyme derived dental follicle and epithelial cells of the REE and stellate reticulum are therefore the key role players in the process of tooth eruption. In the study, conducted in 1984, where tooth crowns were removed and replaced with metal or silicone replicas which “erupted” into the oral cavities, the authors did not specifically mention whether the REE of the 15 week old beagle dogs was retained or removed with the tooth crowns during the study.[27] If we assume that the REE was removed during the procedure, we propose that the dental follicles associated with the metal replicas had already received signalling from the epithelial cells at the stage of surgical intervention. Signalling for monocyte attraction to the area of resorption had therefore already been accomplished at that stage, which apparently allowed eruption of the object.

Bone resorption with the creation of an eruption pathway is however not sufficient for the displacement of the tooth from its bony crypt into occlusion. Coronal bone resorption is therefore coupled with apical bone formation resulting in the physical displacement of the erupting tooth. The dental follicle cells located in the basal aspect express bone morphogenic proteins 2 and 3 (BMP 2 and BMP 3) responsible for the promotion of bone formation.[48] The expression of these BMP’s is greatly enhanced by tumour necrosis factor–α (TNF-α) expression in the dental follicle cells.[48] TNF-α expression is maximally upregulated in the rat dental follicle when rapid bone deposition occurs at the base of the tooth crypt.[48] The cascade of signalling events associated with tooth eruption at the apical aspect of the developing tooth, have not been completely elucidated.[49] Further studies are required to shed some light on the reciprocal signalling between the epithelial root sheath cells and the associated dental follicle during the eruptive process.

CONCLUSION

Tooth eruption represents a series of precisely regulated cascades of paracrine signaling events between epithelial cells of the enamel organ and ectomesenchymal cells of the dental follicle. These tightly regulated processes which bring about selective alveolar bone resorption in the coronal aspects of the erupting tooth and bone formation in the apical aspects of the tooth, are considered central to the process of tooth eruption.

The authors thus propose that tooth eruption should be regarded as a stage of tooth development which, through epithelial-ectomesenchymal interactions, represents the very mechanism that allows the dental follicle to assume its fundamental role in the process of selective bone remodeling required for the movement of a tooth from its developmental position in bone to its functional position in the oral cavity.

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