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Implications of tooth development and evolution for tooth regeneration

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Introduction

Teeth are special organ in vertebrates and have been developed in its present form over the long period. The molecular basis and morphogenetic processes involved in tooth development have been investigated intensively over the last three decades, and the tooth is an important research model system for many scientific areas including developmental biology, paleontology, anthropology, and evolutionary biology. From the late of 19th century, many studies of tooth development had focused on the morphological aspects of tooth formation in a range of animals including human. Most of these studies provided the histological results using various embryonic teeth. Then after understanding of the DNA and genes, from early 1990's, these signaling pathways was intensively examined to find the principle mechanisms in tooth development. Recently, the molecular mechanisms underlying tooth morphogenesis have been elucidated with the impor-

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tant signaling pathways and have been integrated the signaling communications between cells and tissues. Tooth formation is originated from two principal sources including the oral epithelium and the neural crest derived ectomesenchymal cells, and regulated by interactions between them, called epithelial-mesenchymal interactions. These interactions would lead these tissues and cells into the various components of craniofacial region such as the skeletal structures, and teeth, including enamel, dentin, cementum, dental pulp, alveolar bone, and periodontal ligament.

Tooth morphogenesis

In mice, tooth development is initiated between embryonic day (E) 8.5 and 10, with the first morphological sign of odontogenesis, a thickening of the oral epithelium at E11 in the mouse (week 7 of gestation in humans)[1]. After the molecular interactions between epithelial and mesenchymal compartments, developing tooth shows specific morphological changes; bud, cap and bell shapes in molar. At E12.5 and E13.5 in mice, the bud stage, the dental epithelium invaginate into the underlying mesenchyme to form the columnar shape of epithelial bud, surrounded by condensed mesenchymal cells[2]. At cap stage, E14.5 in mice, the epithelial tissues proliferate and invaginate into the underlying mesenchymal tissues to from the cap shape of epithelium with the formation of the specific structure, primary enamel knot, an important signaling center in tooth formation[3]. At this stage, outer enamel epithelium, inner enamel epithelium and dental lamina structures are clearly observed. The end of this stage, primary enamel knot structure is apoptotically disappeared and secondary enamel knots are formed at the future cusps forming regions, in the teeth with multiple cusps (mouse molar)[4]. The epithelial cells become the enamel organ and remain attached to the lamina. The mesenchyme forms the dental papilla, which becomes the dental pulp. The cells of the enamel organ have differentiated into the outer

enamel epithelial cells, which cover the enamel organ, and inner enamel epithelial cells, which become the ameloblasts that form the enamel of the tooth crown[5]. At cap and bell stages, a group of star-shaped cells are formed between the outer and inner enamel epithelium, called stellate reticulum[6]. At bell stage, E16 in mice, the tooth germ increases further in size, and the final shape of the tooth crown becomes increasingly apparent. From the bell stage, cells in the most outer part of the dental papilla are differentiated into odontoblasts, which elongate and become columnar to form a matrix of collagen fibers identified as predentin, which eventually forms dentin[5]. After completion of tooth crown development, at postnatal (PN) 5 day in mice, the epithelial bilayer of Hertwig's epithelial root sheath (HERS) develops from the fusion of inner and outer enamel epithelia below the level of cervical margin of crown to form the structure of the tooth roots. At these root development stages, the dental follicle cells are differentiated into fibroblast, osteoblast, and cementoblast to form the periodontal ligament, alveolar bone and cementum, respectively[5,7].

Signaling regulations in tooth development

During last three decades, many of signaling regulations, involved in tooth development, have been experimentally examined and established intensively. There are many literatures on the genetic signaling pathways and here we will summarize some of the important and conserved major signaling pathways in tooth development. Tooth development is mainly controlled by epithelial-mesenchymal interactions, mediated by multiple growth and transcription factors[3]. Paracrine signaling molecules including Bmps, Fgfs, Wnts and Hh are expressed in the presumptive dental epithelium during the initiation of tooth development and these molecules affect on the adjacent mesenchymal cells through receptor binding, cascade relay to the transcriptional regulations. When blocking of these signaling,

including Bmps, Fgfs, Msx1 and Msx2, in in-vivo or in-vitro cause the tooth agenesis or developmental arrest at dental lamina or bud stage2,[8,9]. Also, mesenchymal signaling, such as Bmp4, regulates epithelial expression of signaling molecules such as Shh[10] and plays important roles in developmental processes from tooth bud to cap stage with induction of the enamel knot in the epithelium. During the development of tooth, three transient signaling centers appear which regulate the important stages of tooth development. Initiation of an individual tooth starts with the formation of dental placode. During the bud to cap transition, another signaling center called primary enamel knot (PEK) appear at the tip of the tooth bud which is non-proliferative and regulate the development of tooth crown formation. The PEK subsequently induces the formation of the third set of signaling centres, the secondary enamel knots (SEK) determining the sites of tooth cusps in molars. These transient signaling centers produce critical signaling molecules such as BMPs, FGFs, SHH and Wnt signal families. In addition, the secondary enamel knots, also non-proliferative and removed apoptotically[11], determine the development of cusp patterns by expressing Fgf4 exclusively on the future cusp tips with the epithelial rearrangement (Fig. 1)[4]. In vitro slice cultivation at E13 for 1 day showed that there was non-migrated pattern of primary enamel knot, microinjected with Di.I., a fluorescent lipophilic cationic indocarbocyanine dye (Fig. 1).

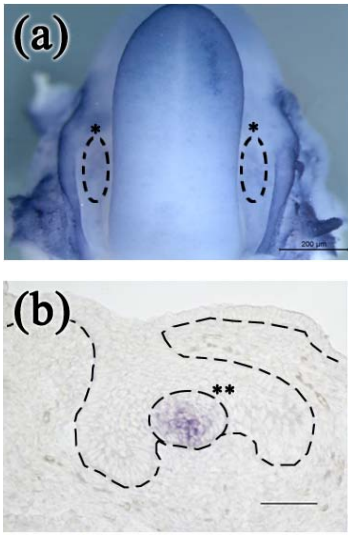

Figure 1. Expression pattern of Fgf4 in developing mandible. (a) at E14, Fgf is expressed in molar forming region. (b) Section *in situ* hybridization shows enamel knot restricted expression of Fgf4 at E14.

Table 1. A range of experimental animal models for tooth development based on altered morphogenesis of tooth.

Altered tooth morphogenesis	Gene	Description	Experimental model	References
Tooth agenesis or missing cusps	**Eda**	① Eda(-/-) mice appeared to have small or missing teeth, lack of certain types of hair, and absence of sweat glands ② The Eda(-/-) dogs also have a very severe tooth phenotype, characterized by absence of most permanent premolars and incisors	① Eda(-/-) mice [13] ② EDA(-/-) dogs [14]	① Tucker et al., 2000[13] ② Casal et al., 2007[14]
	Fgf20	Fgf20 KO mice had smaller teeth and several cusps were missing	Fgf20 KO mice[15]	Haara et al., 2012[15]
	Msx1	Tooth agenesis in KO mice. No BMP4 was found in the dental mesenchyme	Msx KO mice[16]	Satokata et al., 1994[16]
Supernumerary tooth or cusps	**Shh**	KO mice resulted in fusion of molars and formation of numerous cups	K14-Cre;Shh conditional KO mice [17]	Dassule et al., 2000[17]
	Sostdc1	Inhibitor of Wnt, BMP. KO mice appeared to have fused 1st and 2nd molars and extra cusps	Sostdc1 KO mice[18]	Kassai et al., 2005[18]
	Wnt	① Inhibition of Wnt signaling prevents the formation of tooth placodes at the initiation stage ② The over-expression of Wnt signaling induces extensive formation of new teeth	① Inhibition of Wnt signaling by over-expressing the Dkk1[19] ② Forced activation of Wnt signaling in oral epithelium[20]	① Andl et al., 2002[19] ② Jarvinen et al., 2006 [20]

These reciprocal interactions modulate the tooth morphogenesis until its eruption. The roles and significance of these genes in tooth development have been reviewed in the previous studies (Table 1)[8,12]. With the advantage of sophisticated genetic techniques to manipulate odontogenic genes, a range of knock-out (KO) and transgenic (TG) mice were generated and the roles of several genes have been elucidated which has been tabulated in table 1[13-20].

Various types of tooth development in comparative anatomy and evolution

Tooth development from lower

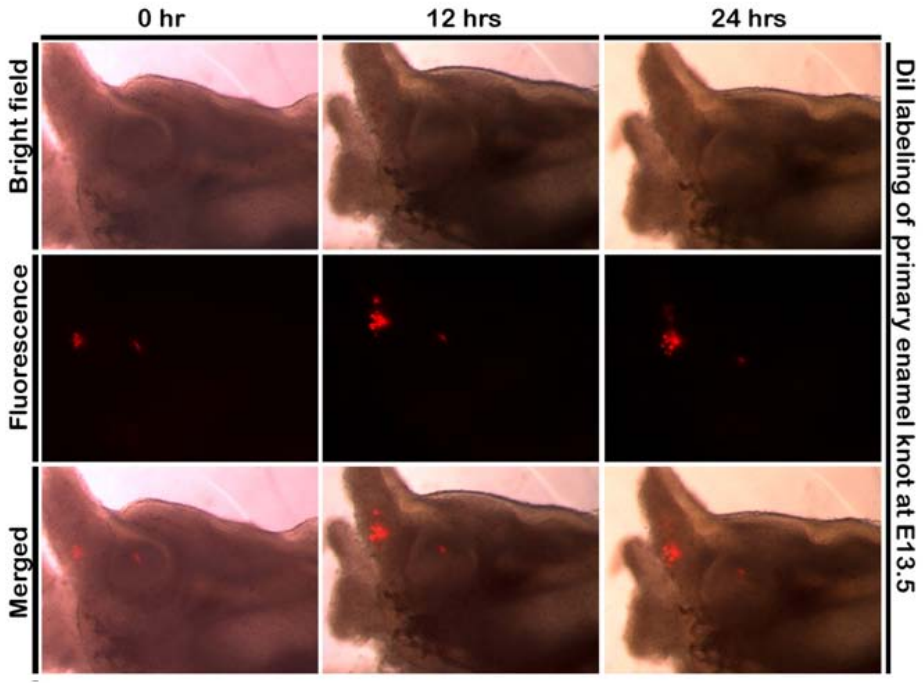

Figure 2. *In vitro* slice cultivation of tooth germ at E13.5 for 1 day. Di.I. microinjection is applied into enamel knot at E13.5. For 24 hours, Di.I. injected cells are not migrate or proliferate, while mesenchymal cells are dispersed.

vertebrates to human shows distinctive features in structure and replacement, but shared the similar signaling regulations, which would be conserved during evolution, across species[21]. It is suggested that modulations in enamel knot signaling and environmental adaptation may account for the variation of morphogenesis of teeth including cusp patterns during the process of evolution[22]. In addition, there are a range of mode for tooth replacement and regeneration in vertebrates such as monophyodont, diphyodont, polyphyodont, and Hypselodonts. In diphyodont, after primary teeth develop from the buds, the leading edge of the lamina continues to develop and grow the permanent teeth, called the succession dental lamina. In this study, we studied and summarized the conserved signalings and specific features of teeth replacement using recent litera-

tures. Accurate and detailed information of expression database and morphogenesis of teeth were well accumulated. In this study, we classified the tooth development as shape formation and modification, and tooth renewal as successional replacement and continuous growth.

Except wear and damage, teeth are not modified after the eruption, and their structures were only formed during the developmental stages through signaling regulations, which would explain the modification of tooth including complex shape and cusp numbers. In fish, it is not elucidated properly yet that teeth have enamel knots or signaling center, but Astyanax shows enamel knot-like regulation to form the multi-cusped teeth, resulted from the differential growth of inner enamel epithelium (IEE)[4]. In reptile, leopard gecko has a small bicusped teeth, which would be resulted from the no mammal-like folding of IEE[23]. Some reptiles have multicusped teeth including iguana. The secondary enamel knots would determine the specific morphogenesis of vertebrae tooth, which share the similar pattern of regulating cusp development. Recently there are reported cusp patterning gene in the mouse including Bmps, Eda, Fgf3, Fgf4, Sostdc1, Spry2, Spry4, Wnt and so on. For example, FGF signaling would regulate the folding of IEE around the enamel knots. Interestingly, there are most of vertebrates have multiple cusps through evolution. Against these morphological features of diverse cusps patterning, the signaling regulations, responsible for the tooth development, appear to be highly conserved throughout the vertebrates. The similar or same signaling pathways are examined to be involve during tooth formation in fish, reptiles and mammals.

The developmental pattern of the different groups, which showed the specific characteristics in tooth development is prepared as a table 2. During the evolution, many specimens have evolved the specific strategy to prevent from losing tooth in their life span. Some monophyodonts, which only develop tooth once in their life time, display hypselodontic or

Table 2. Types of tooth development and renewal

Dentition	Tooth development and ability of tooth renewal	Animals	Remark
Monophyodont	Single generation of functional teeth . Some monophyodont display hypselodonty (continuously growing teeth)	Shrews, Tooth whales, some bats, somemoles and bony fishes	In cow, very high crowns protecting the tooth (Hypsodont)
Diphyodont	Two sets of teeth. Dental lamina connects the developing functional tooth to its replacement tooth on the lingual side of the jaw	Most of mammals	
Polyphyodont	Replace their teeth continuously .	Chondrichthyans, Amphibians, Reptiles (crocodilia)	
Hypselodonts	Most of mammals have one replacement but molars of rabbit and guinea pig and incisors of rodents continue to grow for their lifespan (apical bud)	Rabbits, Guinea pigs, Rats, Mice, Fish	

hypsodontic features. Hypselodonts teeth retains stem cells at its base and continues to grow throughout their life. For example, the incisors of mice show this characteristics. Hypsodonts teeth have become tall by delaying root formation and hence, the teeth can withstand abrasion more effectively. Teeth of cow are in this manner and this is where the name of taurodontia came from. The diphyodonts and polyphyodonts would be classified by number of renewal of tooth development. In human, example for dihyodonts, two generation of teeth, deciduous teeth are replaced to the permanent teeth. While, polyphyodonts can continuously replace their teeth in their life time. It has been elucidated that several factors including these signaling molecules are responsible for these differences in the dentition. In fish, teeth can be replaced at oral epithelium, outer enamel epithelium, and successional dental lamina; in trout, tooth replacement would be detected with the specific expressions of Pitx2 and Bmp4[24] In reptile, such as lizards and alligators, tooth replacement is regulated by the successional dental lamina regardless tooth wear or loss. Like a crocodilian, they have teeth which attached to the bone by fibrous tissues and the capacity to replace the teeth. For development, activities of both Wnt and BMP

signaling were detected during the initiation of successional lamina, whereas Shh expression was absent[25,26]. Some of mammals show the continuous growing tooth such as mice incisor, which has stem cell niche at cervical loop of apical bud[27]. In mice incisor, FGF protein is important and interactions between Bmp4 and activin modulate the FGFs for continuous growing of incisor.

Tooth development in many vertebrates have shown that the similar or same molecular pathways that modulate both tooth shape and renewal throughout the evolution. The detailed process of tooth development and renewal is still necessary to be elucidated. Defining the molecular and cellular signaling regulations involved in tooth development and evolution would be helpful to understand and treat the congenital anomaly and disease of tooth including regeneration and restoration of tooth. Overall, these findings would contribute as a blueprint for regeneration and restoration of tooth and related tissues in near future.

Stem cell as a candidate source for regeneration of tooth

Undifferentiated cells that have ability to differentiate into specialized cells are termed as "Stem cell". Stem cells have two important features; self-renewal and potency which explain that maintenance of the undifferentiated state during cell cycle and the ability to differentiate into specified condition, respectively. These two features made stem cells as distinctive source of cell engineering. In field of dentistry, many researchers already got interests in using stem cells for regenerating teeth. Clinically stem cells can be easily obtained from the dental tissues including teeth and surrounding tissues; dental pulp stem cells (DPSC), stem cells from human exfoliated deciduous teeth (SHED), periodontal ligament stem cells (PDLSC), tooth root apical papilla stem cells (stem cells from apical papillae, SCAP), dental follicle stem cells (DFSC), oral soft tissue derived MSC (mesenchymal stem cells) (Table

Table 3. Dental related stem cell sources and their use

Name	Source	Description	Experiment
DPSC (Dental Pulp Stem Cells)	Permanent tooth pulp	These cells are characterized for high proliferation properties when compared to bone marrow stem cells (BMSC)	Transplantation experiment: generation of functional dental tissue in the form of dentine/pulp-like complexes[28]. Differentiation experiment: adipoctyes, osteoblasts and endotheliocytes[29].
SHED (Stem cells from Human Exfoliated Deciduous teeth)	Exfoliated deciduous tooth pulp	Isolated from the pulp of human exfoliated deciduous teeth.	Transplantation experiment: bone and dentin formation[30,31,32]
PDLSC (Periodontal Ligament Stem cells)	Periodontal ligament	Located between alveolar bone and cementum	Differentiation experiment: multilineages to produce cementoblast-like cells and adipocytes[33]
SCAP (Stem Cells from Apical Papilla)	Apical papilla of developing root	Located near the apical papilla(near to root foramen)	SCAP appear to be a source of primary odontoblasts responsible for the formation of root dentine[34]
DFSC (Dental Follicle Stem cells)	Dental follicle of developing tooth	Appeared during developmental stage of tooth formation which surrounds crown	Transplantation experiment: differentiate into cementoblasts[35]
Oral soft tissue derived MSC (mesenchymal stem cells)	Surrounding soft tissue	Such as gingival fibroblasts (play crucial role in wound healing)	Isolation and establishment of stem cells: from gingival fibroblasts[36,37,38,39].

3)[28-39].

There have been a range of reports using difference stem cell sources such as, developing mouse tooth germ cells, E10 dental epithelium or E14.5 dental mesenchyme, have odontogenic potential to make tooth[40]. In chick, when chick oral epithelium was recombined with mouse E14.5 dental mesenchyme, tooth organ was formed[41]. After combining the E14.5 mouse dental mesenchyme with epithelial cell sheets with iPS-like cells from urine produced tooth-like structures[42]. Recently, copious studies have been reported that embryonic developing potential to make teeth were applied to make regenerated teeth[43,44,45].

Conclusion

As described above, using stem cells for teeth regeneration seems very prospective. However, our knowledge of tooth forming mechanism is too restricted to control

the precise histological structure, size, and shape of tooth yet. To facilitate the these approaches in tooth regeneration, we have to understand the precise mechanisms of conserved signaling pathway in development and evolution of tooth. Overall, Differentiation of stem cells, especially derived from dental organs, based on the evo-devo signaling regulation would be important for tissue engineering.

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ABSTRACT

치아재생을 위한 발생학과 진화학 측면의 고찰

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치아는 수백만 년 전부터 현재까지 많은 척추동물에서 진화한 독특한 구강 내 구조물이다. 지난 약 사십 여 년 동안의 연구에 의해 치아발생의 시작에서 맹출 까지 자세한 형태형성 과정과 분자생물학적 신호전달 과정에 관한 지식이 심도 있게 밝혀졌다. 다양한 종에서 발생단계 및 진화과정 동안 보존된 신호전달 조절 규칙은 한정된 조직과 시공간에서 일어나는 치아 형태형성과정을 조절하며, 이 조절 규칙과 관련된 유전자의 돌연변이는 결과적으로 치아와 주위조직의 치명적인 구조와 기능의 결함을 초래하여, 이와 관련된 다양한 치과질환을 야기할 수 있다. 또한 치아는 오랜 시간을 화석으로 견딜 수 있는 경조직의 특징을 갖고 있으며 발생단계의 독특하고 분명한 형태형성과정을 확인할 수 있는 장점을 갖고 있어 치아를 이용하여 진화의 원리를 연구하고, 다양한 종간의 형태학적인 차이를 연구하여, 발생진화학과 재생의학으로 연구범위를 넓힐 수 있을 것으로 기대된다. 그리고 치아조직에서 유래된 다양한 줄기세포들은 현재까지 다양한 연구를 거쳐 줄기세포의 정립과 작용을 위한 연구 모델시스템으로 이용되고 있다. 이 논문에서는 치아발생 과정에 나타나는 유전자의 발현과 치아형성에 관여하는 세포들의 재배열 경향에 대해 확인하고, 치아의 발생과 재생을 진화의 과정과 비교하여 정리하였다. 또한 치아 대체 및 재생 치료에서의 치아유래 줄기세포의 조작이 갖는 향후 연구 및 발전 가능성에 대한 내용들을 제시하고자 하였다.

주제어 : 치아재생, 치아발생, 형태형성, 진화, 신호전달체계, 줄기세포