Review Articles: A Focus on Gene-Related Tooth Development

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Abstract

Human teeth are vertebrate-specific structures involving many genes interacting in their development, which can lead to anomalies occurring in the disturbance of these genes expression. There is little summarized knowledge of gene related tooth development, therefore, this article reviewed these genes during tooth development. Tooth development stages can be classified as initiation, proliferation and morphogenesis, cell differentiation, hard tissue genesis, and root formation. In the initiation stage of tooth development, there are LIM homobox genes such as Lhx6 and Lhx7 of activated mesenchymal cells at the oral region and Dlx1-7 develop at the inter-arch within the brachial region. Also, in this stage, Fgf8, Barx1, and Dlx2 are expressed proximally overlying the presumptive molar field. BMP4 regulates the expression of MSX1 and MSX 2 which are expressed distally overlying the presumptive incisor filed. The Lymphoid Enhancer-binding factor (Lef1) from dental mesenchyme activates cell proliferation, morphogenesis, and cytodifferentiation until dental papilla and Sonic hedgehog (Shh) form. All of the proposed genes above cause tooth development in the oral cavity.

Keywords: Tooth development, Gene, Dental mesenchyme, Morphogenesis, Teeth

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Introduction

The tooth is a special organ in humans. The special organ of the tooth includes the crown and root formation. Enamel, dentin, and cementum are all hard tissues. All hard tissues of all living animals in this world must compose of a substance called “hydroxy apatite” (HA) (1). HA is a complex hexagonal crystal. Ameloblasts, odontoblasts, and cementoblasts can synthesize HA, but they are all under the control of “Genes” (2).

The fundamental processes of genes are to control and generate all organs. In the early stages, genes play a role in the morphology and transfer of offspring. The characteristic of the DNA is a double helix. Deoxyribose is two strands in this DNA structure. The group of bases includes Cytocine (C), Glysine (G), Adenine (A), and Thyamine (T) that adhere to the deoxyribose (3). The arrangement of those bases is the key to controlling genetic codes. One genetic code contains three bases; therefore, the possible genetic code of an equal 64 code (4).

Genes or DNA transfer the duplicated genetic code to the messenger RNA which then transfers it to the cytoplasm, which is called transcription. Ribosome plays a role in amino acid synthesis, which is called translation (5). The polypeptides can be compared to stimulants, which can activate the reactions in their own or surrounding cells. The activated process is caused by binding receptors, leading to cellular responses (6). The cellular response contributes to cell migration, proliferation, and differentiation which can generate enamel and dentine, respectively (7).

Stage of tooth development

Teeth are vertebrate-specific structures that, like other organs, develop through a series of sequential and reciprocal interactions between the epithelium and mesenchyme (8). Mammalian teeth are initiated from the oral ectoderm covering the maxillary, frontonasal and mandibular processes (9).

The tooth development is caused by two different cells including ectoderm and ectomesenchyme. The ectoderm can differentiate into ameloblasts, causing enamel growth. Ectomesenchyme is a central core consisting of mesenchyme derived from lateral plate mesoderm invaded by neural crest cells (10). The ectomesenchyme can differentiate into odontoblasts, and cementoblasts, causing dentin and cementum, respectively. These ectodermal and ectomesenchymal cells have interacted with each other to induce gene expression for initiating the tooth development (11)

The first branchial arch is populated by neural crest cells from the caudal part of the midbrain and rostral part of the hindbrain (12). The first branchial arch is the origin of the odontoblasts, dentin, pulp tissue, cementum, and periodontal ligaments of teeth (13). Therefore, tooth development is classified into 5 processes: initiation, proliferation and morphogenesis, cell differentiation, hard tissue genesis, and root formation (14).

1. Initiation

The initiation phase is controlled by the ectoderm. The odontogenic or dental epithelium of the ectoderm has the potential to initiate tooth buds (15). Disturbances in the initiation phase will cause missing teeth or hypodontia.

Moreover, several transcription factors (TFs), growth factors (GFs), and extracellular matrices (ECM) are expressed in the epithelium and mesenchyme of the first brachial arch in spatially and temporally regulated patterns (16). TFs bind to specific sequences on DNA and help to attract RNA polymerase to the start point of transcription. GFs promote the growth, survival, proliferation, or differentiation of cells. ECM causes cell movement and cell proliferation (17).

High levels of fibroblast growth factor 8 (Fgf8) signaling activate the mesenchymal expression of the LIM homeobox genes, Lhx6 and Lhx7, in the oral (rostral) region (18,19). Fgf8 and endothelin (ET1) from the mandibular arch ectoderm activate Goosecoid (GSC) expression in the caudal mesenchymal region (20-22).

The jaw is therefore divided into a tooth-forming Lhx-positive domain and a non-tooth-forming Gsc-positive domain (23). Distal-less genes might be involved in establishing inter-arch identity within the branchial region (24). There are 6 members of this family: Dlx-1, -2, -3, -4, -5, and -6. These genes are arranged in pairs, with each pair having a similar domain of expression including Dlx-1/2, Dlx-3/4, and Dlx-5/6 (25). Fgf8 and Fgf9 are expressed proximally overlying the presumptive molar field (26,27). Bmp4 is expressed distally overlying the presumptive incisor field (28). However, these initial domains, which are set up in the epithelium, remain unclear. Fgf8 induces Barx1 expression. As well as, Barx1 induces Dlx2 expression in the underlying proximal mesenchyme (29). BMP4 positively regulates the expression of Msx1 and Msx2 in the underlying distal mesenchyme (30), and at the same time negatively regulates Barx1 expression. Moreover, the restriction of Barx1 and Dlx2 occurs in the presumptive molar region whilst the restriction of Msx1/2 occurs in the presumptive incisor region (31). We summarized in Fig 1.

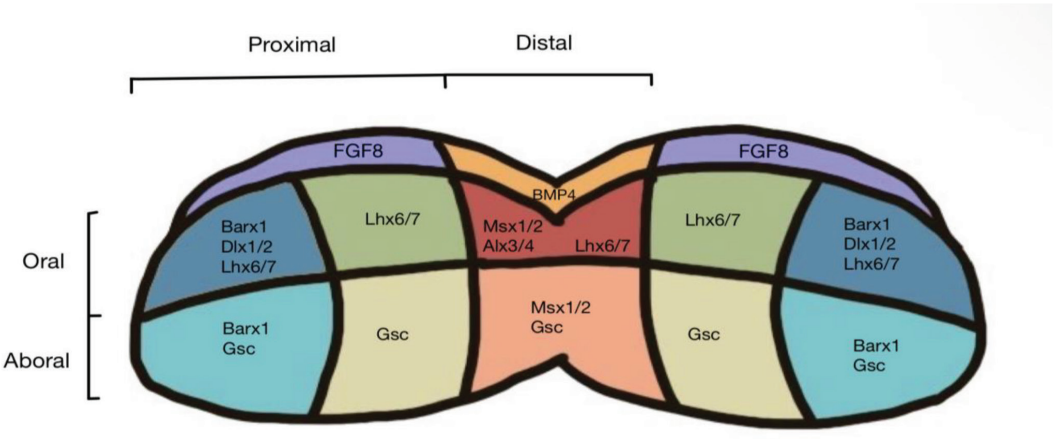

Fig. 1 Pattern of gene expression in the developing tooth (modified from Rhrich, F., & amp; Aghoutan, H. Embryological development of human molars. Human Teeth - Key Skills and Clinical Illustrations. 2020:1-16)

2. Proliferation

The proliferation phase is where the epithelium of the ectoderm divides and penetrates the ectomesenchyme, causing the enamel organ to grow. When the mesenchyme is divided and aggregated under the enamel organ, it causes dental papilla, odontogenic mesenchyme, and genes related to the initiation phase. The enamel organ and dental papilla can promote the proliferation together. The enamel organ is responsible for controlling the penetration of the cell itself, whereas the dental papilla is responsible for the direction of proliferation (32,33).

3. Morphogenesis

Tooth morphogenesis is a complex multi-factorial process where differential mitotic activities, apoptosis as well as cell migration, and cell adhesion may play an important role (34). The interaction of the dental papilla and enamel organ causes cap formation, followed by the differentiation of the Internal Enamel Epithelium (IEE) and Stratum Intermedium (SI). Cap formation is achieved through folding along the mesiodistal axis of the enamel organ and is orchestrated by the enamel knot (35). An enamel knot is a transient signaling center intimately involved with the regulation of tooth shape or outline (36). The morphogenesis of the epithelium during the cap and bell stages involves rapid proliferation and folding of the cells at the site of the tips of future tooth cusps (7,37). Thus, FGFs are the key regulators for the growth and folding of the epithelium (38). FGF signaling combined with areas of non-dividing epithelial cells (the enamel knot) surrounded by areas of strongly proliferative epithelia may play a central role in the folding of dental epithelia (39). BMPs have been suggested to play a role in the formation of periodic patterning by inhibiting the spreading of FGF signaling. FGFs and BMPs regulate the distance between forming cusps (40,41).

In addition, in a wild-type mouse, Osr2 was expressed in a lingual-to-buccal gradient across the jaw axis and restricted Bmp4–Msx1 pathway activity in the lingual region (42). In Osr2 -/-, Bmp4–Msx1 activity is unrestricted and propagates mesenchymal activation for tooth induction in the lingual region, causing supernumerary teeth (43). Therefore, Osr2 is an important determinant for patterning the mammalian dentition into a single row across the jaw (44,45).

4. Cell Differentiation

After a tooth germ's shape is determined, IEE and dental papilla can differentiate into ameloblasts and odontoblasts, respectively (46). An ameloblast can generate enamel, and an odontoblast can generate dentin-pulp complex. Differentiating IEE cells secrete some proteins, together with GFs (eg. BMP-2, TGF-b1), to induce the terminal differentiation of odontoblasts (47,48). As odontoblasts differentiate, they secrete organic matrices of dentin which is ultimately mineralized (49). IDE cells continue their differentiation into ameloblasts producing an enamel matrix (50). Root formation is initiated through further apical growth of the cervical loop (51).

5. Hard Tissue Genesis

Hard tissue genesis is the last stage of tooth development. This process is not correlated with any odontogenic tissue (52). The ameloblast and odontoblast can play a role themselves.

Ameloblasts can synthesize the HA in the hexagonal structure, causing the enamel structure of the teeth to form (53,54). Odontoblasts can generate a dentine-pulp complex (55). However, some genes are related to hard tissue genesis.

The tooth buds do not undergo branching morphogenesis like many other organs such as glands and lungs but instead start to invaginate at their tip, which leads to folding along the anteroposterior (mesiodistal) axis of the bud (31,56). The site at the tip of the tooth bud where the folding of epithelium starts marks the formation of the enamel knot (2,39).

Moreover, the Lymphoid Enhancer-binding factor (Lef1) from dental mesenchyme activates cell proliferation, morphogenesis, and cytodifferentiation until it forms dental papilla and Sonic hedgehogs (Shh) (57,58).

Known genes that are involved in and are responsible for the regulation of the "Tooth shape" can include Msx-1 and -2 and Alx-3 together for an incisor (31,39,59). For molars, we can see many gene expressions of Dlx-1 and -2 together with Barx-1 (60). If we knock Msx-1 or -2 (genes for incisor) out of the dental papilla of an incisor tooth and overexpress by the Barx-1 gene (a gene for molar), it will result in the production of a molar (9,61).

For root development, epithelial cells of the IEE and OEE proliferate from the cervical loop of the enamel organ to form a double layer of cells known as Hertwig's epithelial root sheath (HERS) (62). HERS extends around the dental pulp until it encloses all but the basal portion of the pulp (63). The rim of the root sheath, the epithelial diaphragm, encloses the apical foramen. The root sheath of multirooted teeth is formed as a collar hanging from the enamel organ. HERS extends around each apical foramen forming many epithelial tubes (64). Once the HERS forms, it rapidly initiates root dentinogenesis and then becomes fragmented, forming discrete clusters of epithelial cells known as the epithelial cell rests of Malassez (ERM) (65,66). As the HERS fragmented, ectomesenchymal cells of the dental follicle penetrate opposing newly formed root dentin. Root dentin induces the follicular mesenchyme to form cementoblasts (67). Some epithelial cells of HERS might undergo an epithelial-mesenchymal transformation and subsequently secrete a cementum matrix forming acellular cementum. During root formation, HERS acts as a barrier that establishes the root shape and may mediate cementum formation (68,69).

Finally, the tooth germs that give rise to the permanent incisors, canines, and premolars form as a result of further proliferative activity within the deciduous dental lamina (70). The molars of the permanent dentition have no deciduous predecessors, so their tooth germs develop from the dental lamina that burrows posteriorly beneath the lining epithelium of the oral mucosa into the ectomesenchyme (11,59,71). We summarized genes related to the tooth development in figure 2.

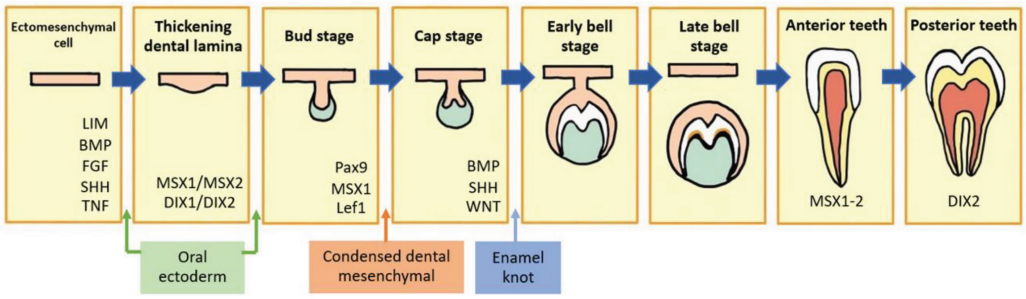

Fig 2. Summary of genes related to the tooth development (modified from Thesleff I. Current understanding of the process of Tooth Formation: Transfer from the Laboratory to the clinic. Australian Dental Journal. 2013;59:48–54.)

Conclusion

Human teeth are vertebrate-specific structures involving many genes interacting in their development, which could lead to anomalies occurring, which may disturb these genes' expression. The tooth development stages can be classified into initiation, proliferation and morphogenesis, cell differentiation, hard tissue genesis, and root formation. Subsequently, this article may provide the knowledge for further study and forecasting the diseases in each stage of tooth development. Nevertheless, the gene-related tooth development still requires more research studies.

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