Role of Morphogens Signaling in Tooth Development

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Abstract:
Morphogens/Growth factors are proteins that bind to receptors on the cell and induce cellular proliferation and/or differentiation. Signals from members of bone morphogenetic protein (BMPs) family, are important in cellular signaling for odontoblast differentiation and stimulation of dentin matrix secretion and are involved in the epithelial-mesenchymal interactions required for regulating tooth development. In the present review, the roles of bone morphogenetic proteins (BMPs) in tooth development are discussed, with focus on recent advances.

Key words: Morphogens, Tooth, Development, Growth factors.

Introduction:
Organ regeneration in which fully functional bioengineered organs can be developed to replace lost or damaged one is a promising and challenging goal. Tooth germ has been bioengineered in vitro, and it has also survived and developed into a mature tooth by transplantation in vivo[1]. One of the earliest step in developing tooth organ is the reciprocal interaction between the dental epithelium and cranial neural crest (CNC)-derived mesenchyme, resulting in the induction of previously quiescent genes that determine the fate of undifferentiated cells[2,3]. Morphogens are extracellularly secreted signals governing morphogenesis during epithelial-mesenchymal interactions. The morphogenetic signaling networks include the five major classes of evolutionarily conserved genes: bone morphogenetic proteins (BMPs), fibroblast growth factors (FGFs), wingless and inter-related proteins (Wnts), Hedgehog proteins (Hhs), and tumor necrotic factor (TNF) superfamilies. These families exhibit redundant and reiterative signaling, each with distinct temporal and spatial expression during initiation, patterning formation and morphogenesis, and cytodifferentiation[4]. How these conserved signals regulate the development of the mammalian tooth remains an interesting and challenging issue.

In the present review, the role of BMPs in tooth development is discussed.

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Morphogenesis and cell differentiation during tooth development:

Teeth form as epithelial appendages and their morphogenesis is regulated by interactions between the epithelium and the underlying neural crest derived mesenchyme. The earliest morphological sign of tooth formation is the appearance of the primary dental laminae (odontogenic bands), which are stripes of thickened epithelium marking the future tooth rows. Within the primary dental lamina placodes, that consist of thickened epithelium and underlying neural crest derived mesenchyme, and they function as the first signaling centers of the tooth.

Cells of the epithelial thickening proliferate and invaginate further into the CNC-derived mesenchyme to form a tooth bud. Next, the epithelium expands deeper to form a tooth germ at the cap and the bell stage. At the cap stage, a cluster of epithelial cells in the center of the tooth bud, named the primary enamel knot, acts as a signaling center that controls the process of tooth morphogenesis. The enamel knot produces signaling molecules essential for the formation of the tooth organ and then undergoes programmed cell death at the late cap stage.

In multicuspid teeth, secondary enamel knots occur at the sites of future cusps after the disappearance of the primary enamel knot. The function of the secondary enamel knots, which differ from the primary enamel knot, is to trigger the folding of the inner enamel epithelium and the formation of the cusps. After deposition of predentine, the adjacent layer of epithelial cells differentiate into ameloblasts and secrete enamel matrix for the organization of enamel and the formation of the hard tissue of the crown[1].

The tooth organ is comprised of dental epithelium, dental papilla and dental follicle. The latter two structures are derived from the CNC. The dental epithelium contains the outer enamel epithelium (OEE), inner enamel epithelium (IEE), stellate reticulum and stratum intermedium. Following crown development, the IEE and OEE form a bilayer epithelial structure, named the Hertwig’s epithelial root sheath (HERS). The HERS migrates apically, and then participates in root formation and the completion of tooth organ development.

Both dental follicle cells and HERS cells can differentiate into cementoblasts and lay cementum on the root, which is required for root maturation. Cells of the outer layer of the dental follicle differentiate into fibroblasts and osteoblasts that, together with cementum, contribute to the periodontium. The interplay of dental follicle cells, osteoblasts and osteoclasts is necessary for mineralised teeth to erupt and later to reach a position for functional occlusion (Fig 1).

![Fig 1 The sequential and reciprocal regulatory signaling between epithelium (red) and mesenchyme (blue) regulates the expression of specific transcription factors (boxes in side boxes).](image)

BMP:

Bmps regulate most aspects of embryonic development and they are used repeatedly during the morphogenesis of various organs. The identification of signaling centres, i.e. enamel knots, in the developing tooth has greatly advanced the understanding of the interactions involved in tooth development. During the initiation of tooth development, epithelial signals induce mesenchymal factors that then reciprocally act on the dental epithelium to form the signaling center, also called dental placode. Bmp4 and Activin A have been proposed to be the key
signals from the mesenchyme to induce the epithelial signaling center and subsequent budding of the tooth.\(^3\)

BMP family members are sequentially and repeatedly involved in embryonic tooth development. Six different Bmps (Bmp2 to Bmp7) are co-expressed temporally and spatially\(^7\). Ten BMP members [Bmp2, Bmp4, Bmp6, Bmp7, Bmp8, Growth/differentiation factor (Gdf) 1, Gdf5, Gdf6, Gdf7, Gdf11, and glial cell line-derived neurotrophic factor (GDNF)] were cloned from rat incisor pulp\(^8\). The interactions between epithelium and mesenchyme are important in tooth development.

BMP signaling has multiple roles in the initiation of tooth development, including regulating the distance between adjacent secondary enamel knots to control the positioning of cusps, and in root development\(^9\). Bmp2, Bmp4, and Bmp7 signals expressed in the enamel knot influence both epithelial and mesenchymal cells and are responsible for the maintenance of the enamel knot and the subsequent morphogenesis of epithelium\(^4\). Repression of BMP signaling by Noggin, which is a wide-range inhibitor of BMP, results in the transformation of tooth shape from incisor to molar. Moreover, tooth development is arrested at the bud stage in Bmprlodeficient mice, indicating that BMP signaling is essential for tooth development\(^10\).

BMP4 functions to regulate tooth organ shape by controlling cell cycle progression and apoptosis. Mild inhibition of BMP signaling in K14-Noggin mice results in severe crown and root defects, suggesting that BMP signaling is essential for tooth hard tissue formation and root development\(^11\).

The BMP signaling networks are complex and regulated at three levels at least. They are extracellular sites, cell membrane site, and intracellular domains. BMP antagonists such as noggin, chordin, and follistatin modulate the bioavailability of the morphogens. Two transmembrane receptors, type I and type II with serine-threonine kinase activity are expressed in dental pulp\(^12\). BMP signals are transduced from the plasma membrane to the nucleus through a limited number of Smad proteins, receptor-activated Smads (R-Smads), common mediator Smads (co-Smads), and inhibitory Smads (I-Smads). Many Smad-interacting proteins have been detected and determine the outcome of the signaling\(^13\).

Conclusion:

TGF-β, BMP signaling is essential for tooth development and in regulating early tooth morphogenesis, subsequent odontoblast differentiation and root development. Members of the TGF-β superfamily, such as TGF-β, BMP play critical roles in odontogenesis.

References:


