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Growth Factors in Odontogenesis- A Review

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ABSTRACT
E-M interactions are hallmark of odontogenesis. Development of teeth and many other organs such as Lungs, hair, kidneys, salivary glands, mammary glands, oral mucosa etc. are characterized by such interactions. Development of tooth in mammals has served as a useful model for the study of E-M interactions. Growth factors and other paracrine signal molecules regulate communication between cells in all developing organs. The current review aims to delineate role of various growth factors in the mechanism of tooth development.

Keywords: Growth Factors; Epithelial-Mesenchymal Interactions; Odontogenesis; FGF; EGFR

INTRODUCTION

Epithelial mesenchymal (E-M) interactions are series of programmed, sequential and reciprocal (complex and multiphasic) communications between the epithelium and mesenchyme (two heterotypic cell populations) resulting in the differentiation of one or both the cell populations involved.1 Odontogenesis is the phenomena by which tooth development takes place. Interaction between the epithelium and underlying mesenchymal components is necessary as it regulates tooth morphogenesis. 2 Many signal molecules like extra cellular matrix molecules, growth factors and genes are implicated in the medication of such interactions.

Tissue interactions are central mechanisms of regulation of development, also called 'embryonic induction'. Signaling functions for growth factors were first demonstrated in the primary embryonic inductive events involving formation of mesoderm and neural tissue. Same growth factors act as signals during organogenesis including teeth.3

GROWTH FACTORS:

Growth factors are an important group of signaling molecules, which exert this effect locally, and are either paracrine or autocrine in nature. The effects of these molecules are always mediated through binding of the factors to specific surface receptors. There is evidence that growth factors act as diffusible signals mediating E-M interactions that regulate tooth development at all stages.3

Growth factors are grouped into many families on the basis of similarities in structure and new factors that were discovered constantly. Growth factors bind to this characteristic cell surface receptor.3

Many growth factor and their receptors have been implicated in the formation of mesenchymal condensation and in epithelial morphogenesis of tooth. The main growth factors involved are TGFβ, IGF, FGF and EGF, which also regulate morphogenesis in other organs. These occur in transient, tissue specific pattern in many organs including teeth.4, 5

It is also shown that the above-mentioned factors are responsible for congenital malformations of many syndromes in several organs affected either due to defect in these factors / factor receptors.5

Epidermal Growth Factors and Insulin like Growth Factors (EGF & IGF): A study on growth factors in human tooth development by using monoclonal antibodies against Epidermal Growth Factors (EGF) and Insulin-like Growth Factors-1 (IGF-1) receptors showed that these factors act as signaling molecules in the modulation of cell proliferation and differentiation.6 They also showed that these factors play a role in E-M interactions in odontogenesis and also found associations between Transforming Growth Factorsβ1 (TGFβ1) RNA expression and E-M interactions during mouse odontogenesis, using In-situ hybridization (ISH) and tissue recombinations. Their results clearly indicated such interactions occurring when the tooth mesenchyme was combined with dental and non-dental epithelium. The expression was negative, when the tooth epithelium was combined with a nondental mesenchyme. However, TGFβ1 did not express in the oral epithelium during normal tooth development, but was seen when cultured with the dental mesenchyme.7

ISH method was applied for localization of two growth factors, TGFβ1 and Int-2 (a proto-oncogene, coding for FGF related protein) during mouse tooth morphogenesis. The findings suggested that the expression of TGFβ1 and Int-2 were associated with phenotypic properties of the odontoblastic cell lineage and also suggested a role for TGFβ1 and Int-2 in signaling between the epithelial and mesenchymal tissues that lead to differentiation of odontoblasts. But the expression was lost from odontoblasts and from pulpal mesenchyme for int-2 during the progression stages of tooth development. 8

TGFβ2 may also play an important role in E-M interaction in human tooth morphogenesis. The study showed both paracrine and / or autocrine mode of action for TGFβ2 in early (cap / early bell stage) human tooth germs 9

Bone Morphogenic Protein: The BMPs are homeodimeric proteins originally defined by their ability to induce bone formation in vitro. The mammalian BMP family consists of eight members and grouped into three subclasses.3

BMPs and FGF family growth factors are expressed in dental epithelium during the initiation of tooth development and subsequently have inductive effects on underlying mesenchyme. 10

BMP-4, a member of TGFβ super family was shown to mediate E-M interactions during early tooth development. It was the first signaling molecule in developing mammalian tooth germ.10

BMP-4 is a crucial signaling molecule during E-M interactions. BMP-4 expressed in dental epithelium during initiation of tooth development and the expression shifts to the dental mesenchyme. This shift of BMP-4 expression pattern is consistent with the known pattern of sequential and reciprocal E-M interactions. Analysis of the data suggested that BMP-4 is actively involved in entire process of tooth morphogenesis, first in the epithelium, then in the mesenchyme, and later in all matured tooth tissues including ameloblasts, odontoblasts and pulp cells.11, 12

BMP2 and BMP4 regulate the expression of transcription factor such as Msx-1, Msx-2 and Erg-1.4, 5, and 10 these homeobox genes are required for tooth formation. All these findings supported the hypothesis that BMPs mediate E-M interaction during early tooth development.3

BMP-4 does also induce P21, an epithelial cyclin dependent kinase inhibitor and subsequently is associated with apoptosis of the differentiated cells of enamel knot, a transient epithelial structure, which acts as an embryonic signaling centre for the initiation of tooth shape (morphogenesis). Hence BMP-4 is involved both in induction of epithelial structure (enamel knot) and later in the termination of the enamel knot by apoptosis regulation. But BMP4 is expressed only in the dental mesenchyme after the onset of enamel knot formation and in turn induces P21, which acts as a differentiation factor in E-M interactions.13, 14

BMPs are secretory signaling molecules, known for a variety of regulatory functions during morphogenesis and cell differentiation. An ISH expression of different BMPs (BMP-2 to BMP-7) starting from initiation to completion of crown, when dentin and enamel matrices were deposited was done.BMPs -2, -4 and -7 were frequently co-distributed and showed marked associations with E-M interactions. The expression of these molecules was shifted between the epithelium and mesenchyme from tooth initiation stage and subsequently seen in enamel knot, a signaling centre for regulation of tooth shape. BMP-6

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was also implicated in E-M interactions controlling cytodifferentiation.13

The expression of BMP-3 was confined to mesenchymal cells, mainly dental follicle cells that gave rise to cementoblasts. BMP-5 was seen only in the ameloblasts and was intense in the secretory stage of ameloblasts. BMP6 was weakly expressed in dental mesenchyme during bud and cap stages. The results were in line with the earlier studies of BMP-2, -4 and -7, in regulating tooth initiation and development. BMP-5 may be involved in the induction and formation of dentin and enamel as well.15

Fibroblast Growth Factors (FGF): The expression patterns of different Fibroblast growth factors (FGFs) in developing mouse tooth germs from initiation to completion of morphogenesis by ISH were analyzed. The expression of three FGFs -4, -8 and -9 was seen in dental epithelium during E-M interactions, which regulates tooth morphogenesis. The effect of FGFs on the expression of homeobox containing transcription factors Msx-1 and Msx-2 was also analysed. The three FGFs stimulated the expression of Msx-1 intensely but not Msx-2, in the dental mesenchyme.16

The expression of Msx-1 is associated with tissue interactions and regulated by dental epithelium. Hence the three FGFs act as epithelial signals mediating inductive interactions between dental epithelium and mesenchyme during several successive stages of tooth formation. The co-expression of FGFs with other signaling molecules including Shh and several BMPs suggests that these participate in signaling of E-M interactions during odontogenesis.3

Later, the role of other FGFs like FGF3, FGF-7 and FGF10 was studied. The results suggested that FGF-3 and FGF-10 function as mesenchymal signals regulating epithelial morphogenesis of the tooth. FGF-7 was restricted to the developing bone surrounding the tooth germ. They also showed that Shh, BMP2 and TGFβ1 have no role on either FGF3 or FGF10. The expression patterns of different FGFs in dental epithelium and mesenchyme and their interactions are suggestive of regulatory signaling cascades between epithelial and mesenchymal tissue during tooth development.17

FGF4 mimics the effect of FGF8 and FGF9, expressed by early dental epithelium and these act as signals stimulating tenascin expression in underlying mesenchymal cells.18

Glial cell line derived neurotrophic factor (GDNF): It is a recently identified, distant member of the TGFβ super family and was originally identified on the basis of its neurotrophic activity of several populations of neurons in central & peripheral nervous system and also regulates kidney development. It is strictly confined in mesenchymal tissues and not found in epithelia. 18, 19

ISH expression patterns of GDNF and its receptors Ret, GFRα1 (GDNF family receptor alpha 1) and GFRα2 from initiation to the completion of crown showed positive, when E-M signaling regulates tooth morphogenesis. The expression of GDNF was seen in the mesenchyme around the tooth germ and receptors were expressed both in epithelial and mesenchymal cells. So GDNF and its receptors may have a non-neuronal organogenesis function during tooth formation.19

Hepatocyte growth factors (HGF): Dental expression of HGF (Hepatocyte growth factor), which interacts with a receptor, is specifically confined to dental papilla. Culture of molar tooth germs in mice against HGF will result in inversion of normal tooth morphology, and the cytodifferentiation of ameloblasts. Odontoblasts were unaffected. 20

Platelet derived growth factor (PDGF) and its receptors play a role in signal transduction between or within the dental epithelium and mesenchyme.3

Neurotrophins are a group of growth factors that support and sustain peripheral sensory neurons during development and also in non-neuronal tissue development. All four neurotrophins, nerve growth factor (NGF), brain derived neurotrophic factor (BDNF) and neurotrophin (NT) 3 and 4 were seen during tooth development with specific patterns.21

NGF and BDNF were mainly seen in dental papilla and pulp postnatally and were correlated with the onset of dental innervation. NT3 and NT4 were predominantly expressed in epithelium and expression was intense during early developmental stages when teeth are not yet innervated.21

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NGF was first seen in both epithelium and mesenchyme and later shifted to the odontoblastic and subodontoblastic zone. BDNF was present in low levels in dental organ, but increased in pulp and odontoblast cell layer of developing teeth. Both NT3 and NT4 were observed in oral epithelium and in inner enamel epithelium (IEE). NT4 was more evenly distributed in the dental epithelium.21

Based on the results, it is suggested that neurotrophins participate in E-M interactions in early tooth morphogenesis and result in proliferation and differentiation of epithelial and mesenchymal cells into ameloblasts and odontoblasts respectively. It is also suggested that NGF and BDNF participate in establishing and maintaining the innervation of the teeth.21

Growth hormone dependent molecules such as decorin and biglycan, chondroitin sulfate rich proteoglycans were seen in the cells of outer enamel epithelium (OEE), at the interface between the enamel organ and mesenchyme of the dental follicle separated by a basement membrane. Decorin and biglycan have been identified as having a high affinity for TGFβ. Since decorin and biglycan accumulate during the stages of dental tissue differentiation and development, they may have roles in cell-cell and cell-matrix interactions. The decreased expression of these molecules in dental tissues and matrices in deficient mice gave rise to disordered cell differentiation & dental tissue matrix formation, tooth morphogenesis and even tooth eruption.22

CONCLUSION:

The tooth development is under genetic control, and multitude of genetic and growth factors have been identified which regulate embryonic development. The majority of genes are associated with signaling pathways transmitting interactions between cells and tissues. To conclude, better understanding of molecular mechanisms in regulating embryonic developments will aid in prevention, early diagnosis, and advanced treatment of congenital defects.

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