Role of Growth Factors in Development of Tooth : A Review

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Abstract

Growth factors are small polypeptides that have various functions in vivo, including regulation of normal cell growth and differentiation during development and tissue repair. Growth factors are involved in the occurrence of various diseases, and in tumor formation. However, their expression in human odontogenesis has not been explored much. The present article review the role of these growth factors in tooth development.

Keywords: Growth Factors, Odontogenesis, Tooth germ

Introduction

Human odontogenesis is a result of complex epithelial- mesenchymal interactions. These processes involve a series of inductive and permissive interactions that result in the determination, differentiation and organization of odontogenic tissue[1].Tooth development can be divided into three overlapping phases- initiation, morphogenesis and histodifferentiation. During initiation, the sites of the future teeth are established with the appearance of tooth germs along an invagination of the oral epithelium called the dental lamina. During morphogenesis the shape of the tooth is determined by a combination of cell proliferation and cell movement. During histogenesis, differentiation of cells proceeds to give rise to fully formed dental tissues.

Growth factors are naturally occurring group of polypeptide molecules of approximately 6-45 K.D. These proteins bind to receptor on the cell surface with a primary result of activating cellular proliferation and/or differentiation. They are also known as biologic modifiers[2]. Many growth factors are quite versatile, stimulating cellular division in cell types, while others are specific to a particular cell type. The commonly known growth factors are platelet derived growth factor, epidermal growth factor, transforming growth factor, fibroblast growth factor, nerve growth factor, transforming growth factor, insulin like growth factor and hepatocyte growth factor. These growth factors have the potential for widespread effects because of their circulation in the blood stream and availability to many different cell types. Growth factors are key regulators of the process of self proliferation via their action at different stages of cell cycle[3]. The present article reviews the role of growth factors in tooth development

Stage of Initiation

Cell determination and differentiation during tooth morphogenesis is accom-panied by several molecular changes. The earliest molecular changes identified in the developing tooth are associated with the initation phase. In situ hybridization first detected homeodomain- containing transcription factor Hox 8 mRNA first in the early mesenchyme corresponding to the area of the future tooth suggesting a role in tooth initiation[4,5]. Other early molecular changes identified include expression of Hox 7.1 syndecan and retinoid acid receptor m-RNAs in the condensing dental mesenchyme[6,7,4]. Immunohistochemical analysis of syndecan core proteins revealed that different isoforms of syndecan (syndecan-1to-4) function differently during amelogenesis[8].

The roles of syndecan, tenascin, choindroitin-4 and chondroitin-6 sulphates have been suggested in early tooth morphogenesis based on their immuno-location in the early dental lamina or mesenchyme[9,10,11]. Fibronectin and laminin are the other ECM protein associated with early morphogenetic and differentiative effects. Fibronectin was weak in cap stage and increases in the bell stage [12,13]. Insulin like growth factor fulfill the important role in growth and development of teeth, mandible, maxilla and tongue. Members of the transforming growth factor-β (TGF-β) super family are critical regulators that control cell proliferation, differentiation and apoptosis. In the bud stage transcripts for TGF-β1 and β2 have been detected in the dental epithelium and TGF-β1 Peptide both in the epithelium and mesenchyme. Cranial neural crest derived ectomesenchymal cells were capable of responding to the inductivestimulus of dentin non collagenous protein (DNCP) In addition , a transient expression of early growth response gene(Egr-1) m RNA has been demonstrated in the bud staged dental mesenchyme

Stage of Morphogenesis

In the cap stage, a high expression level of TGF-β1 mRNA has been detected in the inner enamel epithelium of the tooth germ. In the early bell stage, transient expression of MMP-2 mRNA has been detected in the inner enamel epithelium of the tooth germ suggesting that MMP-2 may regulate remodeling of the ECM during early tooth morphogenesis.

The fibroblast growth factor related proto-oncogene int-2mRNA, has been detected in the dental mesenchyme in the bud, cap and bell stage.[14] Differential expression of types I, III and IV collagen genes has been detected during the tooth morphogenesis. In addition, temporospacial expression patterns for TGF-β1, 2,3 mRNA and polpeptide transcripts for DVR/BMP-2 , Vgr-1 and the inhibin / activin βA subunit have been detected during tooth morphogenes, sugesting multiple roles for several TGF-β family members (Heine et al, 1987 ; Lehnert and Akhurt , 1988 ; Cam et al , 1990 ; D'Souza el al, 1990; Lyons et al, 1990; Pelton et al, 1990, 1991; Vaahtokari et al, 1991; Roberts et al , 1991; Jepson et al, 1992.

EGF inhibits early tooth morphogenesis (Rhodes et al 1987; Bigeard and Sommermater, 1991)[15]. EGF-R has also been shown to be an important mediator of dental cell growth and differentiation (Abbott and Pratt, 1998, Hu et al., 1992) Recently organ culture method was used to examine root development and it was shown that EGF maybe one of the regulatory factors involved in the change from cervical loop epithelium to HERS during root development.

Stage of Histodifferentiation

Differentiation of ameloblasts is accompanied by production of enamel-specific ECM proteins, amelogenins and enamelins, and dentin specfic phospho- proteins, dentin sialoprotein (DSP) and Osteocalcin (Slavkin, 1991; Butler et al 1992.)[16] Tenascin and Fibronectin have been associated with odontoblast differentiation and dentin formation[17]. Moreover various marked changes in the expression of various structural and regulatory genes have been detected in terminally differentiated odontoblast. The in vitro application of recombinant GEP up-regulated molecular markers showed that GEP is important for odontogenesis (DMP1, DSPP, and ALP) and amelogenesis (ameloblastin, amelogenin and enamelin).

Production of ECM is enhanced by dental follicle cells, suggesting that it may act as a signaling factor for developing periodontal ligament cells (Wise et al, 1992)[18]. The combined effects of TGF β1 and DVR /BMP2 initiate odontoblast diffentiation in vitro. Retinoids have been shown to alter murine tooth morphogenesis and cytodiffertiation in vitro 2. Exogenous retinoids induce formation of supernumerary epithelial buds, increase epithelial proliferateion and upregulate EGF mRNA expression (Kronmiller et al, 1992).

Retinoid acid is a potential negative regulator for differention of human periodontal ligament cell. The insulin like growth factor family may act as an autocrine or paracrine system that influences not only cell differentiation but also the physiological activity of the ameloblasts[19] IGF family also increases the enamel formation by inducing expression of the enamel mineralizing specific gene.

Other growth factors and their receptors implicated in tooth morphologenesis and cytodifferntiation include EGF and its receptor (EGF-R), nerve growth factor (NGF) and its receptor (NGF-R), insulin growth factor 1 (IGF -1), and acidic and basic fibroblast growth factor. NGF was characterized as a potent promoter of mineralization during dentin formation. For the first time, TM14 was included in odontoblast genotype analysis and proved that NGF also promotes in vitro odontoblast differentiation.[20].

Discussion

Epithelial mesenchymal interactions form the basis for the tooth morphogenesis and cytodifferentiation. Tissue recombi- nation experiments have shown that tooth development is initiated by the oral epithelium and that the early dental epithelium can also induce teeth in non odontogenic ectomesenchyme. The inductive role shifts from the epithelium to the dental papilla mesenchyme in the bud stage where the dental papilla mesenchyme can induce teeth in epithelium of the non-dental origin[21].

Various studies since then have focused on identification of regulatory molecules mediating epβithelial mesenchymal interactions during the tooth development . Diffusible growth factors and their receptors retinoids and hormones have been shown to affect dental cell growth and differntiation in vivo and in vitro. Other molecules implicated in tooth development include ECM molecules and Homeobox genes.

Platelet - derived growth factor (PDGF) and IGF I have been shown to stimulate proliferation of human and bovine pulp cells in culture (Nakashima, 1992b; Rutherford et al., 1992)[22]. It has been suggested that TGF β, PDGF, aFGF and bFGF regulate differentiation of pulp cells into odonto-blasts. Production of Extracellular matrix protein is enhanced by FGF and IGF-1 and IGF-2. TGF β1 also stimulate production of ECM Protein in cultured dental follicle cell, suggesting that it may act as a signaling factor for developing periodontal ligament cells. The combined effect of TGF-β1 and DVR/ BMP2 initiate odontoblast differentiation in vitro. It has been suggested that DVR/BMP2 initiate odontoblast differentiation in vitro.

Retinoids have been shown to alter murine morphogenesis and cytodifferen- tiation in vitro. Insulin may be associated with differentiation of odontoblast[23].

Conclusion

Tooth development is largely dependent on sequential and reciprocal epithelial mesenchymal interactions. Multiple growth factors signaling molecules have been implicated in mediating these tissue interactions via linking and signaling loops between tissue layers by responding to inductive signals and regulating the expression of other signaling molecules. The current article fulfills the aim of summarizing the data that have been accumulating in the recent years linking the various growth factors to a number of physiological processes related to the development of teeth. The recent progress in the understanding and the studies of the role of growth factors in the development of teeth can be integrated into a developmental pathway controlling cell differentiation and will provide fundamental knowledge for the realization of human tooth regeneration in the near future.

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