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Review Article

Dentistry Section

# Epithelial – Mesenchymal Interactions in Tooth Development and the Significant Role of Growth Factors and Genes with Emphasis on Mesenchyme – A Review

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## ABSTRACT

The recent advancements in medical research field mainly highlights the genetic and molecular aspects of various disease processes and related treatment options, in a specialized "custom-made" approach. The medical and dental field has made tremendous progress in providing even with the smallest insight into pathological entities, thus, making patient management more fruitful. But, short comings have occurred in dental treatments involving odontogenic lesions mainly due to poor understanding of the developmental cycle involved during early stages of developmental process. Multiple numbers of interactions take place during embryo formation and further proliferation of tissue. One such important step is the interaction between epithelium and mesenchyme which tantamount to functional requirements of an individual tooth. The role of extra cellular molecules and genes has to be studied in depth to assess the impact and significance attached to it as the synergistic function of various elements underlines the complex process of development.

**Keywords:** Metalloproteases, Neuroectodermal odontogenesis, Organogenesis, Primordia

## INTRODUCTION

Epithelial-mesenchymal interactions are a series of programmed, sequential and reciprocal communications between epithelium and mesenchyme resulting in differentiation of one or both the cell populations involved [1]. Epithelial-mesenchymal interactions were the hallmark of odontogenesis. The embryonic development of ectoderm derived appendages undergoes these interactions to give rise to a large variety of highly specialized organs. For these interactions to occur there should be some or other form of messenger system between epithelium and mesenchyme, further underlining the importance of cell signaling networks and intricacies of physiological growth of an individual. In the process of embryonic development the ectoderm is composed of surface ectoderm, neural crest and neural tube. This will give rise to the epidermis or skin and the oral epithelium [2].

## THE ROUTE MAP OF DEVELOPMENT

Growth does not occur in one cycle. Multiple channels of cell network co-exist to promote signal propagation between cells, suggesting a type of cell to exhibit its functional capacities. The interactive systems could be anyone or the combination of molecules and ions [Table/Fig-1].

The majority of epithelial-mesenchymal interactions were associated with signaling pathways transmitting interactions between epithelial and mesenchymal cells. Defect in any of these results in arrested tooth and skeletal development and also defects in many organs.

**Epithelial-mesenchymal interactions in development of different organs:** Many organs like salivary glands, lungs, kidney, mammary glands, hair follicles and limb bud depend upon such interactions for their development and differentiation. During early development, these organs exhibit many morphological and molecular similarities. This interaction has a role, not only during embryogenesis but also during adult life. The epithelial components usually originate as thickenings which subsequently form buds and the further development leads to underlying mesenchymal cells to condense around it. The development involves complex processes, such as branching and/or folding of epithelia which denotes advancing morphogenesis. Organ development was characterized by coordinated growth and differentiations of cells in epithelial and mesenchymal cell lineages. The interactions between tissues were crucial for organogenesis. The epithelial mesenchymal interactions were sequential and the advancing development front results due to a series of interactive events. The interactions were also known to be reciprocal occurring in both directions between epithelial and mesenchymal tissues. The non-dental, neural-crest derived mesenchyme forms a tooth after the early dental epithelium was shown the potential to induce such a process. During the early bud stage odontogenic mesenchyme was shown to acquire the ability to instruct non-dental epithelium to synthesize enamel proteins. Thus, these interactions are now regarded to constitute the unique mechanism in vertebrates regulating organ development [3]. Initial experiments designed to determine the role of epithelium and mesenchyme in initiation of tooth development and cell differentiation made use of epithelial-mesenchymal recombination. In these experiments, the epithelium and mesenchyme of developing teeth were experimentally separated. When the epithelium and mesenchyme of a bud, cap or later stage tooth were separated from one another and grown independently, both would proliferate, but no recognizable tooth structures were formed [4,5]. Electron microscopic studies in the differentiation stage of amelogenesis showed that close cell to cell contact, without formation of specialized junctions, occurred between pre-ameloblasts and pre-odontoblasts [6]. During this period, the basal lamina, between pre-ameloblasts and pre-odontoblasts was penetrated by epithelial process.

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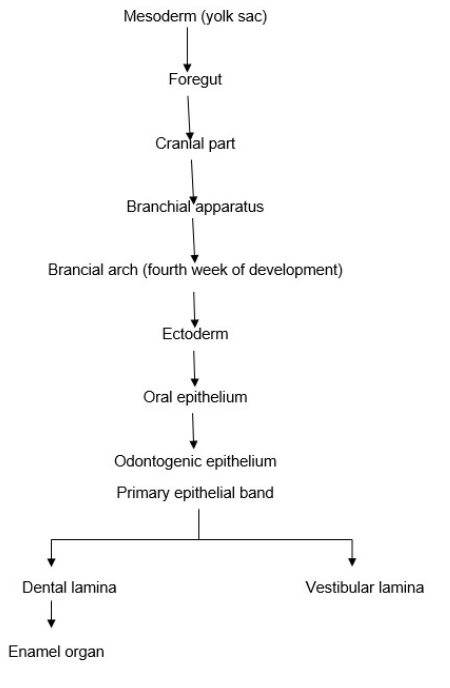
| 1. Direct cell-cell communication involving cytoplasmic process and gap junction. |
| 2. Matrix vesicles between two cell populations. |
| 3. Ions like $K^+$ and $Ca^{2+}$. |
| 4. Extracellular matrix component like collagen IV, I, III, fibronectin, tenascin, E-cadherin, laminin. |
| 5. Molecular diffusion and transfer of information by substances like bone morphogenetic protein (BMP-2, 4, 6, 7) FGF, EGF, EDGF, TGF. |
| 6. Autocrine and paracrine regulators. |
| 7. Messenger RNA. |

**[Table/Fig-1]:** Various factors involved in growth and interaction [2].

**Branchial arch formation [7,8]:** The facial primordium was constituted by a series of swellings produced after the accumulation and proliferation of cranial neural crest cells and ectoderm cells. Mammalian teeth develop on primordias namely frontonasal process and first branchial (pharyngeal) arch which forms mandible and proximal maxilla [Table/Fig-2]. The cranial neural crest cells were derived from these primordial structures. They accumulate beneath ectoderm covering and further develop into face and oral cavity. In addition more caudal swellings were also created which were derived into second, third and forth branchial arches. It was shown that cells behave according to their donor genetic programme and not as the host cells when transplantation of cells between the early mandibular and maxillary primordia was done [9,10].

Another review on role of neural crest in development of tooth emphasizes on the unique significance on these population of cells mainly involving the epithelial component and the molecular pathway leading to their expression [11]. The present review is to stipulate the role played by various molecules and genes in expanding the interactive potential of cells after differentiation from the neural crest. The epithelial mesenchymal interaction further enhances the synergistic effect on developmental procedures before formation of tissues and organs. Further, the mesenchymal component attains chief architect role in development. Pivotal role enacted by rendezvous of various molecules and factors were considered to be defining when the zenith of development and maturation is attained. Thus, it has become highly essential to investigate the process in a different point of view in order to understand the deeper essence of growth.




**[Table/Fig-2]:** Branchial arch formation and tooth development.

## GROWTH FACTORS

These were primarily important for signaling of various developmental steps. The behaviour of another cell in its vicinity or an autocrine affect would be initiated by one cell through signaling of these growth factors molecules per se. Thus, these signaling molecules were vital in development. The well regarded signals belong to the families of Fibroblast Growth Factor (FGF), Epidermal Growth Factor (EGF) and Transforming Growth Factor (TGF) [12,13] [Table/Fig–3].

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| Fibroblast Growth Factor (FGF) |
| Epidermal Growth Factor (EGF) |
| Transforming Growth Factor (TGF) |
| Bone Morphogenetic Protein (BMP) – Member of TGF-β |
| Platelet Derived Growth Factor (PDGF) |

**[Table/Fig-3]:** Major growth factor present in tooth development.

**Fibroblast Growth Factor (FGF):** FGF belongs to a large family of heparin binding proteins that were known to mediate the growth and differentiation of cells from a wide variety of developmental origins. At the time of odontogenic initiation this expression becomes restricted to the area of the presumptive dental epithelium and persists until the beginning of bud stage. An important role by this factor was found in the differentiation of ameloblasts as FGF4 and FGF9 were revealed in the inner enamel epithelium [14]. Various evidences relevant to role of FGF have greater significance in understanding the value of its presence in tooth development [15-19] [Table/Fig-4].

**Epidermal Growth Factor (EGF):** EGF is very important for signaling and synergistic effect of different factors. It has got a vivid role in development of an embryo and highly essential for interaction between key players of development [20]. EGF signaling would be responsible for activation of major tissues like submandibular glands and further studies in this direction could hold better results [21]. Another suggestion was that EGF and EGFR has specific values in development. Evidences pointed to the fact that EGF would be co-relating and important factor in development [21-23] [Table/Fig-4].

**Transforming Growth factor (TGF)**: TGF and its receptor Edar were involved in multiple signaling systems during developmental regulative mechanisms [24]. Another idea was that TGF-β and Shh signaling from Hertwig's epithelial root sheath induces the differentiation of root progenitor cells and thereby has a direct control in modulating and transforming the formation of odontoblasts. Several studies had evidences for contribution of this factor in development [25-28]. It was also established that during tooth morphogenesis, TGF-β signaling controls odontoblast maturation and dentin formation [29].

**Bone Morphogenetic Proteins (BMP):** Large family of dimeric proteins within the TGF beta super family of cytokines consist of BMPs. Wide range of signaling functions that mediate tissue

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| **I.** Bloomquist RF et al., 2015 [15] | **FGF:** FGF10 in condensed dental mesenchyme, FGF7 in forming velum lingual to teeth. |
| Liu et al., 2013 [16] | It regulates fate of craniofacial neural crest during tooth formation. |
| Han D et al., 2012 [17] | Suggested that TGFβ mediated FGF6 signaling cascade needed for tooth development. |
| Jernvall J et al., 2012 [18] | Role of FGF 3 signaling function loss. |
| Caminaga RMS., 2003 [19] | FGF3, FGF4, and FGF10 expressed in odontogenesis. |
| **II.** Mizukoshi K et al., 2016 [21] | **EGF:** Shh and EGF signaling in development. |
| Mohan BC et al., 2015 [22] | EGF-R expression determined in human odontogenesis. |
| Yang J et al., 2008 [23] | EGFR helps in morphogenesis of dental tissues. |

**[Table/Fig-4]:** Supporting evidence for FGF and EGF in tooth development.

interactions during development were mediated through this factor. For example, the expression pattern of BMP-4 shifts from the epithelium to condensing dental mesenchyme at the same time when the inductive potential for odontogenesis shifts from epithelium to mesenchyme [30]. It has a vital significance in modulating TGF signaling between tissues that lead to differentiation of odontoblasts. Evidences revealed that BMP had enormous significance in governing future teeth characteristics [31-35] [Table/Fig-5].

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| **I.** Higa et al., 2016 [25] | **TGF:** Key factor in cell proliferation and differentiation. |
| Chang et al., 2015 [26] | Important for matrix formation and odontogenesis. |
| Zhang H et al., 2015 [27] | TGF-β and Shh signaling in HERS induction. |
| Huang XF., 2012 [28] | Role in differentiation of dental papilla cells into odontoblasts. |
| Oka S et al., 2007 [29] | Significance in odontoblasts maturation |
| **II.** Wang Y et al., 2012 [31] | **BMP:** Vital from dental lamina to bud stage. |
| Li L et al., 2011 [32] | Expression occurring during tooth and palate formation. |
| Gluhak-Heinrich J et al., 2010 [33] | In maturation and coupling of amelogenesis. |
| Yao S et al., 2010 [34] | TNF-α upregulates BMP-2 & 3. |
| Plikus MV et al., 2005 [35] | Tooth characteristics activated by BMP tuning. |

**[Table/Fig-5]:** Supporting evidence for TGF & BMP in tooth development.

## GENETIC FACTORS

The size, shape and structure of teeth and also position of teeth were determined by genes present in the region. Majority of the genes were central regulations of development that are associated with interactions between cells. The pathway includes genes encoding the actual signals, their receptors and mediators of signaling pathways and transcription factors. These genes primarily were associated with major interactions and process involved in development and maturation of teeth namely Msx gene, Pax gene, Shh gene, Wnt/ beta – Catenin signaling, Cbfa-1 gene [36-39] [Table/Fig-6].

**Muscle Segment Homeobox (Msx) gene:** This homeobox gene was the first gene demonstrated which was essential for development of tooth in mice. The significance of the gene was recognized in the fact that Msx1 creates modulation to cap stage through various stages of ectomesenchyme proliferation and condensation [37]. Mice defects for Msx 1 and 2 results in failure of epithelial mesenchymal interactions and defects like anodontia or hypodontia and cleft palate occur. In humans, the cap stage of primary tooth in development has expression of Msx-1 restricted to the dental papilla mesenchyme [40]. It was suggested that they regulate dental mesenchyme proliferation. Msx-1 has not got a major play in root morphogenesis; however they were expressed at morphogenic cap stage. Also, before the actual recognition of ameloblasts and odontoblasts, their activity seizes to exist. The anomalous expression of Msx-2 was reserved to mesenchyme of tooth forming sites as stipulated in various evidence based works and proposals [41-44].

| Gene | Role in tooth development |
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| **Msx:** Suryadeva et al., 2015 [36] | Msx-1 gene – located on short arm of chromosome 4 (4p16.1.). Msx 1 & 2 found in tooth germs. Msx 2 seen in enamel knot, enamel septum. (Transient structures). Expression requires presence of epithelium. |
| **Pax:** Surya deva et al., 2015 [36]; Lin D et al., 2007[37] | Located on chromosome 14(14q12-q13). Contains transcription factor. Role in organogenesis. Pax-9 is mesenchymal responding gene. Loss of Pax-9 causes arrest of tooth development at bud stage. |
| **Shh:** Romero et al., 2016 [38] | In epithelial thickening of future tooth forming regions. Present in enamel knot. |
| **Wnt/β-catenin:** Liu F et al., 2008 [39] | Essential at the lamina-early bud stage. Important for molar cusps development. Large, shapeless tooth buds and ectopic teeth are formed as a result of mutation of β-catenin. |

**[Table/Fig-6]:** Genes present in tooth development.

**Pax Gene (Paired homeobox gene):** This paired homeobox gene is a nine member family and plays a key role during embryogenesis and the significant contribution of this multifaceted gene was unveiled during its expression in some stem cells and mature cells of adult. It also functions as transcription factor present in mesenchyme. Zhao M et al., investigated the presence of Pax in dental mesenchyme and during arrest of tooth development [45]. Bhatt S et al., has studied upon the anchor laid by this special gene in governing the signals needed for neural crest differentiation and further maturation [46]. Paixao-Cortes VR et al., extensively examined the potential and presence in various processes and its structure [47]. Several studies by authors investigated the pivotal axis laid down by this gene in tooth formation and thus agenesis was given supreme importance [48-50] [Table/Fig-7].

**Sonic Hedgehog (Shh) gene:** It was expressed in molar tooth germ and in enamel knot. It spreads along inner enamel epithelium and implies expression of gene in enamel knot, a signaling centre. Shh pathway was one of the vital cog in embryonic

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| **I.** Mimura S et al., 2016 [41] | **Msx:** Association between BMP in neural crest development. |
| Feng X et al., 2013 [42] | Cell cycle regulation of dental mesenchymal cells. Inhibition of BMP-2 and BMP-4 expression during cap stage. |
| Lin D et al., 2007 [37] | Expressed in mesenchyme, including the dental papilla; also in inner enamel epithelium. |
| Tucker et al.,1998 [43] | Emphasis on relation between BMP-4 and Msx-1 in odontogenic mesenchyme. |
| Thesleff I et al.,1996 [44] | Msx-1 and Msx-2 in the dental mesenchyme induced by BMP. |
| **II.** Paixao-Cortes VR et al., 2015 [47] | **Pax:** Present in embryogenesis as well as in adult organogenesis.<br>Pax-9 important for odontogenesis. |
| Hlouskova A et al., 2015 [48] | Pax-9 – transcription factor regulates mesenchymal odontogenic molecule expression. Mutation may cause tooth agenesis. |
| Abu-Hussein M et al., 2015 [49] | Pax-9 mutation may lead to oligodontia or hypodontia |
| Walton VT et al., 2014 [50] | Examined the co-existence between Msx and Pax gene in tooth agenesis. Assessed the importance of other genes in agenesis. |

**[Table/Fig-7]:** Supporting evidence for the role of Msx and Pax gene.

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| **I.** Nguyen A et al., 2015 [51] | **Shh:** Key for embryonic development. Depend on epithelial mesenchymal interactions. |
| Yu JC et al., 2015 [52] | Regulate dental papilla cells and tooth size. |
| Li Z et al., 2013 [53] | Reiterate that Shh has a global control on tooth formation. Associated with enamel formation. Molecular marker for preameloblasts. |
| Galluccio G et al., 2012 [54] | Expressed in first phase of morphogenesis. Follow expression of FGF 8 & 9. Shh regulation controlled may be controlled by FGF. |
| **II.** Tamura M et al., 2016 [55] | **Wnt/ β-Catenin:** Elaborated in epithelium & mesenchyme during development. Present in odontoblasts and dental pulp. |
| Aurrekoetxea M et al., 2016 [56] | Along with BMP determine dental cusps patterning. Differentiation of odontoblasts and ameloblasts. |
| Romero LS et al., 2016[38] | Wnt-10 related to cell matrix interaction. Critical in molar cusps development. |
| Yuan G et al., 2015 [57] | First molecule to start up tooth development. BMP- Wnt/β-catenin signaling required for early development. |
| Fujimori S et al., 2010 [58] | Co-existence and synergic action between Bmp-4 & Wnt/β-catenin vital. |

**[Table/Fig-8]:** Supporting evidence for Shh and Wnt/ β-Catenin pathway.

development. Evaluative evidences clinched that Shh signaling and variants supplement the nuances of the development process by implicating that they predominantly determines the growth of facial structures especially palate which was further depending upon epithelial mesenchymal interactions [51]. Relation between FGF and Shh signaling was studied for better realization of the pathway [52]. Further, this was substantiated by Yu JC et al., and Li Z et al., attributing to the nature and presence of the gene in various steps of development [52,53]. The signaling was found to be a sequential process mediated by epithelial-mesenchymal interactions [54].

**Wnt/ beta – Catenin Signaling Pathway:** In a recent study, the data suggested that the Wnt signaling was present throughout dental epithelium and mesenchyme during tooth development, confirming its role in overall process [55]. They were strongly indicated in odontoblast differentiation. Another view point was that this pathway was the front runner in tooth initiation and this was highly essential for later processes [56,57] and regulates other factors during development [58] [Table/Fig–8].

**Core Binding Factor Subunit Alpha-1 gene (Cbfa-1 gene):** Master gene for tooth development and also required for odontoblasts differentiation. It is now called Runt-related transcription factor 2 (Runx-2). The gene encodes a transcription factor for osteoblast and odontoblast differentiation, including cementoblasts' differentiation and proliferation. Much significance has been attached to their presence expressed during tooth root development [59]. The expression might be different in dental follicle from which cementum was derived to the level in dental papilla [60].

**Role of Extracellular Molecules (Ecm) and Matrix:** ECM was present in interactions in the morphogenesis and differentiation of developing tooth including budding of oral epithelium and condensation of neural crest cells around the bud. In the developing tooth, the epithelial basement membrane contains several types of collagen and also laminin and fibronectin [16]. It was also imperative to understand that ECM may give rise to signaling events with the help of growth-factor-like receptors that were present in laminin, tenascin and others [61]. The interactions mediated by the basement membrane were regulated by the differentiation of mesenchymal cells into odontoblasts and these molecules were elaborated at that time. The structural components of ECM and components affect cellular structure. Also, they were involved in regulation of interactions. The first extra cellular matrix molecule to appear during embryonic development is basement membrane. Their function includes mediation of signals for sustained and proper development. By binding to specific matrix receptors on the cell surface, the extracellular matrix molecules exert their effects on the cells and structural components, thereby completing the circle of organized events that finalizes the nature in which these events turn out [62]. The present review was an attempt to communicate about the multifactorial origin of development of teeth and its dynamic capacity to determine the maturation potential of growth. Though the differentiation of neural crest cells has been discussed in the past, the innate pathways has to be understood to further enhance and nurture the knowledge about the sophisticated and myriad mechanisms involved in development process. The relation between factor like BMP and Msx gene has come of the fore in research scenarios and this will surely help in elaborating the sequence of their pathways. Moreover, Shh and EGF, FGF signaling proves to be the tell-tale route in establishing the continuity of development. Several genes are to be considered as molecular marker in future, which has a tremendous review prospects. Of late, the role of Pax gene in agenesis of tooth is being investigated in depth and this point to future proposals of research. Another significant research analysis has to be set in motion with Wnt/ β-Catenin signaling pathway system which has vital role in assisting and maneuvering various molecules and factors in maturation steps. The present research scenes have presented with great opportunities in detailing every aspect of tooth morphogenesis but significant downfalls have occurred when dealing with queries regarding malformation of teeth and developmental disturbances. Certainly, future studies have to be concentrated more on this field so that consequences of various molecules, growth factors and genes attached to growth and development are dealt extensively in order to envisage that our short comings are well addressed and further details may be elaborated giving us substantial evidences in countering the nuances of adaptations required for proper maturative potential of these processes.

## CONCLUSION

The completion of epithelial mesenchymal interactions and transitions brings about varied changes in the developing embryo and tooth development, thereby increasing the potential of individual cell to grow and substantiate the necessary development required for tooth formation. The complex mechanism involved are to be studied exhaustively in order to overcome the difficulties arising due to the improper knowledge of pathogenesis of a specific odontogenic lesion; thus, jeopardizing treatment options. The expansive field of dentistry requires genetic research and molecular level of contemplation to highlight the significance of biological processes, thus reflecting on the overall management protocols. A paradigm shift is needed in this regard to appropriately digress the meshwork of intricacies associated with any developmental scenarios. The "end of the tunnel" should surely be reached once sufficient knowledge and expertise is gained in further increasing our knowledge on several new pathways and factors attached to developmental scenarios.

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