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Review Article

Molecular Events of Teeth Development and Role of Dental Stem Cells

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Abstract: Stem cells are immortal cells with the potential to differentiate into various types of cells. These potential stem cells act as an invivo repair and regenerative system for various tissues in the human body, and so physicians are interested in using them to treat various diseases. These stem cells can divide and can either create more groups of stem cells, or they can differentiate into other cells having more specialized functions. Stem cells are truly unique and they are unspecialized cells with a unique capacity of multiplying even after prolonged inactivity. Stem cells are the basic building blocks of life, they have the most amazing abilities and qualities, with the potential to become different types of cell in body tissue, they have the greatest potential to treat degenerative conditions – diabetes, Multiple Sclerosis, Parkinson's disease, Alzheimer's disease, arthritis, blindness, stroke and heart disease. Postnatal stem cells, which are capable of self-renewal, proliferation and differentiation into multiple unique cell lineages have been identified and researched. The ability of stem cells to produce and regenerate pulp-dentine and cementum-periodontal ligament complexes Invivo suggest potential applications of stem cells. Dental stem cells express similar group of proteins which possibly implicates a common origin; however, the dominant cells to repopulate an open apex will be directed by local environmental and growth factors. A greater understanding of anatomical and physiological activity of the stem cells and their environment is necessary to successfully regulate and facilitate differentiation of various cells along a specified developmental path with subsequent tissue regeneration.
Keywords: Stem cells, Teeth, Dentition, Growth Factors, Signaling Pathways.

INTRODUCTION

Cells are the building blocks of life. Cell propagation and differentiation are important for human development. In 1868 Ernst Haeckel used the word Stammzelle. A few decades later August Weismann in 1885 discussed stem cells using the term germplasm [1]. Pappenheim 1905 illustrated diagrammatic representation of stem cell fate in his article "*Cell Stem Cell* "[2]. Russian histologist Alexander Maksimov coined the term stem cells in 1908 [1], Dr. Florence Sabin 1932 supported the existence of hematopoietic stem cells in his article, "The production of osteogenic sarcomata and the effects on lymph nodes and bone marrow of intravenous injections of radium chloride and mesothorium in rabbits"[3,4]. Dr. Thomas in 1950s, research strongly supported the existence of hematopoietic stem cells and stated that there were specific cells in bone marrow that could restore hematopoiesis after lethal irradiation [2]. In 1963, Till and McCulloch published a paper on hematopoietic stem cells, "Cytological demonstration of the clonal nature of spleen colonies derived from transplanted mouse marrow cells,"[5] following these stem cells were discovered in human cord blood in 1978.Three years later ,1981, first in vitro stem cell line developed from mice. In 1996 stem cells biggest success story is written, on July 5th, 1996- Dolly the sheep is cloned from adult stem cells by the Roslin Institute in Scotland and PPL Therapeutics by Ian Wilmut, Keith Campbell, *et al*. [6]. A year later,1997 leukemia origin was found

as hematopoietic stem cell, indicating possible proof of cancer stem cells. In 1998 James Thomson, successfully removed stem cells from spare embryos and cultured them in vitro. He launched stem cell research into the limelight, establishing the world's first human embryonic stem cell line which still exists today [1]. According to the literature, it suggests that these embryonic stem cells have the capacity to become almost any of the specialized cells in the body and replace various tissues of the body.

FORMATION OF TEETH

Interactions between the epithelial component and the underlying mesenchyme lead to morphogenesis of teeth. The human dentition consists of groups of highly specialized teeth; incisors, canines, premolars and molars, which arise from different regions of oral epithelium. While teeth can be formed from both endoderm and ectoderm [8] in human teeth seem to be derived only from the ectoderm. The appearance of the primary dental laminae is the earliest morphological sign of tooth formation where placodes form which consist of epithelial and mesenchymal components. These placodes function as the first signaling centers of the tooth. One hypothesis suggests that each dental placode gives rise to an entire tooth family (incisor, canine, molar). In this scenario only the first tooth of the family buds directly from the placard while the other teeth form successionally from the primed odontogenic epithelium and mesenchyme [8]. Tooth morphogenesis starts from the dental placodes where neural crest derived mesenchymal cells condense under the epithelial placode. During the cap stage, the extension of the bud laterally leads to the formation of epithelial cervical loop. The epithelial component with a stem cell alcove in the cervical loop helps in continuously growing teeth, but disappears in permanent teeth. The enamel knots regulate Tooth crown morphogenesis is regulated by enamel knots and it is characterized by folding of the enamel epithelium.

CELL AND TISSUE INTERACTIONS AND SIGNALING CENTERS

Tooth organogenesis and dental stem cell alcove regulation is a complex dynamic regulatory interactions between epithelial- mesenchymal cells and tissues. Tooth organogenesis is a programmed step-wise process where sequential interactions between compartments regulate cell and tissue morphogenesis and differentiation. The various pathways mediating these programmed interactions include the TGFß, BMP, Wnt, FGF, Hedgehog and Eda pathways and they occur repeatedly during advancing the tooth development. Multiple modulators of the signal pathways such as inhibitors of BMPs like Follistatin and Ectodin/Sostdc1 [9] and of FGFs are required for development of the correct tooth number, exact shape and optimal hard tissue production thus underlining the key role of fine-tuning in regulatory control [10]. The dental plaque initiates the first signaling center of tooth development, and also emits a wide collection of signals that include members of all conserved families regulating epithelial budding and patterning, similar to the placodes of other ectodermal organs such as hairs and glands .The enamel knot expresses twelve different signals which lead to regulation of early growth of the tooth and it also determines the positions of secondary enamel knots to the sites of future cusps [11]. Any tooth shape can be created by altering the parameters that govern the regulatory interactive mechanisms that can modify the position and existence of secondary enamel knots. In short a controlled and programmed modification of the enamel knot patterning can lead to the generation of any desired tooth shape.

REGULATION AND MOLECULAR BASIS OF ODONTOGENIC COMPETENCE

Classic tissue recombination studies between the epithelium and mesenchyme components of different origins and stages have indicated that the epithelium of the first branchial arch can instruct tooth formation when cultured along with the neuronal cells derived from second arch mesenchyme. This type of competence in the epithelium is, however, lost early and the identity information subsequently switches to the mesenchymal compartment. It is unknown about the longevity of the dental mesenchyme component's ability to instruct tooth morphogenesis. Mesenchymal component in adult teeth has, however, has the capacity to regenerate various well differentiated dental tissues, including dentin, cementum and periodontal ligament [12].

More than 200 genes have been identified in developing teeth during morphogenesis and most of theses genes belong to the Hox family, which is unique in possessing an evolutionarily DNA sequence motif found initially in Drosophila genes. The Hox clusters are present today from cephalochordates to mammals, but the orthography of the homeotic genes differs among invertebrates, mice and humans.During the tooth morphogenesis, besides transcription factors, there are many other important molecules that play important roles in the process, like growth factors and extracellular matrix (ECM). These groups of molecules have combined expression in dynamic patterns between epithelial and mesenchymal tissues as a "molecular cascade", which promotes the development of the tooth.

Transcription Factors

Transcription factors are molecules that interact with DNA modulating the expression of a gene. Inactivation of the genes that encode transcription factors can lead to the modification of the phenotype particularly in the early stages of embryogenesis. In case of Homeobox genes, which present domains

conserved phylogenetically, a mutation can attenuate the interaction of this molecule with target DNA [13].

MSX (Muscle Segment Box):

In the mammalian genome, the MSX gene family has three physically unlinked members and the Msx3 is the most primitive gene because its expression resembles the expression pattern of msh gene. The Msx1 and Msx2 genes have formed by successive gene duplications acquiring their expression properties. During the middle of the gestation period, Msx1 and Msx2 expressions can be seen at almost all sites of epithelial- mesenchymal tissue interactions. However, the Msx1 is expressed quite widely in the mesenchyme and the Msx2 expression is limited around the tooth-forming regions of the mesenchymal component. Msx1 is also strongly expressed in the developing molar and incisor tooth germs in a distal-to-proximal gradient in the mesenchyme of the mandibular and maxillary processes. The expression of Msx1 in the dental mesenchymal tissue remains at peak throughout the cap stage and being down regulated for a transient period at the earliest bell stage (E16.5) [14]. The Msx2 gene is only expressed at early cap stage in the enamel knot and in the internal enamel epithelium and the dental papilla of the mesenchyme. In humans, the role of MSX genes in craniofacial development has drawn special attention by recognition of MSX1 and MSX2 mutations. The transverse at the homeobox region of the MSX1 gene results in a substitution of an Arginine to Proline in the conserved domain of the protein. It is the cause of the specific patterns of tooth agenesis; however, the mutation in the MSX1 gene cannot explain all types of tooth agenesis. A mutation in the homeodomain of the MSX2 gene was associated with dominant craniosynostosis [15].

PAX (Paired Box):

The mammalian Pax gene family is organized by nine members that present a conserved DNA-binding motif, named paired domain. Pax proteins have been implicated as regulators of angiogenesis and as key factors in maintaining pleuripotency of stem cell populations during development. Mutations of the Pax genes lead to profound developmental defects in various organisms. The genes of the Parks family can be classified into paralogous relationships: Pax1 and 9, Pax2, 5 and 8, Pax3 and 7, Pax4 and 6 [16]. The Pax1and Pax9 is expressed in developing tooth. The strong expression of the Pax9 is expressed in the mesenchyme from E12.5-E14.5, and it appears to be an early signal of tooth development. Pax9 phenotypically resemble Msx1 gene and exhibit an arrest in molar tooth development at the bud stage. The human AX9 gene is located in chromosome 14q12-q13, mutations in this gene were implicated in tooth agenesis [17].A family with autosomal dominant oligodontia, affecting premolars and molars, presented a frame shift mutation in the paired domain of the PAX9. In one more case, two members of a small family showed deficiency of all molars and premolars both in maxilla and mandible, and also some of the incisors which is probably due to deletion surrounding the PAX9 locus in one chromosome, while the other was normal. These findings suggest that PAX9 is a dosage-sensitive gene in humans, with Haplo insufficiency causing hypodontia [18].

DLX (Distal-Less Box):

In mammals the Dlx gene family consists of six members who are arranged in three closely linked pairs: Dlx1 and 2, Dlx7 and 3, Dlx6. In mouse E12-14, Dlx1 and Dlx2 genes are expressed in dental mesenchyme and epithelium, respectively, coinciding with mesenchymal Msx1 and epithelial Msx2 expression [19]. During the bud stage, Dlx2 and Dlx3 were expressed in the epithelium of the labia, Dlx2 is expressed in the mesenchymal component. During the cap and early bell stages, Dlx1 and Dlx6 are expressed in the dental follicles while Dlx2, Dlx3, Dlx5 and Dlx7 are detected in the dental papilla. During cap and bell stages, total six Dlx genes show complex expression patterns in the developing teeth. The expression of Dlx2 and Dlx3 suggests a role for these genes in ameloblast differentiation. The role of Dlx3 in amelogenesis was supported by mutations of human DLX3 gene that are associated with enamel hypoplasia. Dental enamel expression and maturation are effected by inactivation of Dlx5. In E10.5 murine embryos, none of these Dlx genes were expressed in the lingual side of the medial nasal process. This situation was changed at E16- E17 where all six Dlx members were expressed in the lower incisal region [20].

LEF (Lymphoid Enhancer Factor):

Lef family genes are capable of inducing a sharp bend in the DNA helix and produce proteins characterized as High Mobility Group (HMG). The common properties of HMG domain proteins include interaction with the minor groove of the DNA helix, binding to irregular DNA structures, binding. Studies suggest that, Lef1 plays an important role in the formation of several organs and tissue structures that require tissue interactions. LEF1 is expressed in mature lymphocytes of the adult and during embryogenesis as a cell-specific transcription factor. The human LEF1 is a 54-KDa nuclear protein that potentially binds to a functionally important site in the T- cell receptor alpha and brings enhancer activity. Tooth development is initiated in Lef1 (-/-) embryos; however, it is arrested before the formation of a mesenchymal dental papilla. Likewise, the development of body hair follicles and mammary glands are incomplete or abrogated before morphogenesis. All organs that are affected by the mutation in the Lef1 gene share a requirement for tissue interactions between ectoderm derived epithelium and

mesenchyme. The Lef1 gene expression in E10-E16 mouse embryos can be assessed by fluorescence in situ hybridization (FISH) and immunohistochemistry. At E12, Lef1 is expressed in the condensing mesenchyme around the invaginated epithelial tooth bud. At E13, Lef1 is expressed in the mesenchyme condensed and in the immediately adjacent basal cells of the epithelium. During the subsequent cap and bell stages of tooth development (E14-E16) Lef1 transcripts are continuously detected in both tissues, including the mesenchymal papilla and preodontoblasts, and in the epithelium-derived preameloblasts.The expression of Lef1 in the epithelium seems to be critical for the induction of the mesenchyme between E13 and E14 to form dental papilla, but is dispensable for both the initiation of tooth development and the epithelial and mesenchymal cytodifferentiation. Although Lef1 is expressed at the earliest stages of tooth development, Lef1 (-/-) Mouse embryos initiate the formation of tooth germ. In Lef1 deficient embryos, defects in tooth development can be visualized during the late bud stage around E13 when the dental papilla formation fails. In particular, the mutant dental epithelium does not form the enamel knot and fails to adopt the cap shape at later stages. The epithelial Lef1 expression seems to be necessary for the induction of the mesenchyme, presumably for the formation of the dental papilla, but is dispensable for further Cyto-differentiation.

Growth Factors

Growth factors constitute an important class of signalling molecules. A growth factor produced by one cell may either affect the behavior of another cell in its vicinity (paracrine), or it may have a uterine effect. The effects of growth factors are always mediated through binding to specific cell surface receptors. Signalling interactions, which determine the location, identity, size, and shape of teeth, take place during early stages of tooth development. The most studied signals belong to the families of FGF (Fibroblast Growth Factor), EGF (Epidermal Growth Factor) and TGF (Transforming Growth Factor).

FGF (Fibroblast Growth Factor)

Fibroblast growth factors (FGFs) are a large family of heparin group proteins, which have potent morphogenetic effects in several organs and are potent stimulators of cell proliferation. FGFs induce cell division both in dental mesenchyme and epithelium at several stages of tooth morphogenesis. FGFs also prevent apoptosis in dental mesenchyme, mimicking the effect of epithelium. There is a possible functional redundancy between the co-expressed FGFs. FGF s 2, 4, 8 and 9 genes have same kind of effects on dental mesenchyme in vitro. They all stimulate cell proliferation as well as expression of Msx1 in E11-E15 dental mesenchyme Fgf8 is expressed in the ectoderm covering the tooth-forming region at the initiation stage. At E10.5, expression of Fgf8 in the epithelium of the mandible is accountable for inducing the expression of Pax9 in the mesenchymal component at the prospective sites of odontogenesis. At the initial stages of tooth development Fgf9 is co-expressed along with Fgf8 in the oral ectoderm . It is likely that Fgf8 and Fgf9 act together to control the expression of FGF responsive genes, including Pax9, in the early branchial arch mesenchyme. It was also suggested that FGF signaling and programming was required for development of both molars and incisors. Other members of the FGF family, Fgf3, Fgf4, and Fgf10, are also expressed at different stages of odontogenesis.Fgf4 expression is limited to enamel knot cells while Fgf3 is expressed totally sin the mesenchyme at the late bud stage. Fgf3 and Fgf10 are intensely expressed in the dental papilla during the bell and cap stages. The abundance of FGF receptor expression (FGFR1c, 1b and 2b isoforms) in the cervical loops and in the dental papilla mesenchyme (FGFR1c) suggests that these are target tissues, and this is also in line with the distribution of dividing cells in tooth germ [21].

EGF (Epidermal Growth Factor):

EGF is related to epithelial proliferation and is found in embryonic tissues. In fact, EGF is a mitogen for ectodermal, mesodermal and endodermal cells, stimulating proliferation of embryonic cells during morphogenesis in vivo and in vitro. EGF interacts specifically with its receptor. EGF-R is a transmembrane glycoprotein, which is present in many cell types derived from all three germ layers. EGF and EGF-R (Receptor) appears to be well conserved both structurally and functionally throughout evolution.The initiation of odontogenesis is totally inhibited by blocking the production of EGF in situ. The self-studied the expression pattern of EGF at various stages of tooth development using I-labeled EGF. It was shown that EGF binds especially to embryonic molar epithelium and mesenchyme between gestational days 13 and 17 and the distribution of binding site changes dramatically. Binding to epithelium occurs during bud stage, but the condensing mesenchymal cells around the epithelial bud do not bind EGF. At the cap stage the dental mesenchyme cells bind EGF. This result indicates that EGF helps in proliferation of undifferentiated cells during embryonic development. The detection of EGF MRNA in both epithelium and mesenchyme suggests that the action of EGF in epithelial proliferation could be a result of either autocrine or paracrine mechanisms [22].

TGF-b (Transforming Growth Factor-b):

Members of the Transforming Growth Factor-beta (TGF-b) superfamily regulate cell proliferation, differentiation, and apoptosis, controlling the development and maintenance of most tissues. TGF-b is a growth factor that takes place in the cascade of

signaling events during early tooth development. During the bud stage of molar mouse development, TGF-b is expressed in dental epithelium and mesenchyme. The dental mesenchyme is rapidly proliferating at bud and cap stages while the dental epithelium intensely expresses TGF-b1 MRNA. The mesenchyme itself expresses TGF-b1 although at considerably lower levels. Thus, local expression of Tgf-b1 in dental epithelium may regulate cell proliferation in the underlying dental mesenchyme contributing to the determination of tooth morphology. TGF-b 1 acts as a paracrine and autoinducing factor and participates in the epithelial-mesenchymal interactions. In the cap stage TGF-b is expressed by cells from the inner enamel epithelium, enamel knot, stellate reticulum and dental papilla. During early bell stage TGF-b is expressed by the inner enamel epithelium cells, but at the late bell stage the expression is restricted to preodontoblasts. At E19 TGF-b1 MRNA was detected transiently in stratum intermedium cells before the differentiation of ameloblasts, and by secretory odontoblasts. TGF-b1 is synthesized by stratum intermedium and it regulates the initiation of ameloblast differentiation. The expression of TGF-b1 in ameloblasts is restricted to a short period, only the ameloblasts at the tips of the cusps that remain non-secretory continues to express TGF-b1. Besides the function of the TGF-b in regulation of cell proliferation in the underlying dental mesenchyme, another function of TGF-b during tooth morphogenesis is the regulation of matrix deposition.

BMPs (Bone Morphogenetic Proteins)

Bone Morphogenetic Proteins (BMPs) belong to the superfamily of Transforming Growth Factor-beta (TGF-b). These are originally defined by their ability to induce bone formation in vitro and are a group of homodynamic proteins. Presently, the mammalian BMP superfamily is organized with eight members, which can be grouped into 3 sub-classes based upon similarity of amino acids. The different BMP genes are important for determining of bone shape and organ morphogenesis [23]. The subgroup consisting of the vertebrate Bmp2 and Bmp4 genes is most closely related to the prototypical decapentaplegic (dpp) gene in Drosophila, with 75% amino acid similarity. These genes, have a 95% identity, and are key factors for initiation and morphogenesis of teeth. Bmp2 and Bmp4 are genes which play key roles in morphogenesis. The expression of Bmp4 can be detected very early during tooth development in the form of thickened presumptive dental epithelium. It shifted to the condensed mesenchyme during bud stage. Bmp2 is also expressed in early dental epithelium, where it stays until late cap stage, when expression shifts dental papilla. Bmp2 is expressed in the central mesenchymal cells of the dental papilla during the early bell stage. Bmp2 and Bmp4 are expressed by differentiated odontoblasts and they are therefore, potential inducers in bringing ameloblast differentiation. BMPs act as early signals, which stimulate other "master genes", and their involvement in a cascade of reciprocal signaling events has been cleared up [24].

Extracellular Matrix Molecules

Extracellular matrix (ECM) is involved in the epithelial and mesenchymal interactions in the morphogenesis and differentiation of developing tooth. Morphogenesis and cell differentiation can be disturbed by mutations in collagen and proteoglycan genes. Functional studies [25] in vitro have shown that the integrity of the basement membrane is a prerequisite for tooth epithelial morphogenesis. In the developing tooth, the epithelial basement membrane contains collagen types I, III, and IV, and also laminin, fibronectin and various proteoglycans. These molecules are expressed at a given time when interactions are mediated by the basement membrane which regulates the differentiation of mesenchymal cells into odontoblasts. Tension and Syndecan are most important molecules and their expressions have been extensively analyzed in tooth development, and their correlations with other molecules such as Msx1 and Bmp4 are investigated.

REGENERATION CAPACITY AND STEM CELLS IN MAMMALIAN TEETH

While some of the vertebrates like fish and reptiles can generate new teeth throughout their lifespan, but mammals have largely lost the capacity for tooth regeneration. Mammals replace their teeth at the most, once as a physiological process, which results in humans having a set of deciduous teeth and a subsequent set of permanent teeth. Studies have been started to know and document the cellular and genetic mechanisms involved in the tooth replacement. The analysis and understanding of the tooth replacement phenomenon in ferret embryos gave support for the concept that mammalian replacement teeth originate in the dental lamina which develops as part of the primary tooth. In addition the expression of some regulatory genes, in particular the BMP/Wnt inhibitor Ectodin (Sostdc1) was localized to the site of replacement of tooth initiation. However, the actual stem cells responsible for replacement of tooth formation have not been identified. Although mouse teeth are normally cannot be replaced; denovo tooth formation can be possible in transgenic mice by stimulating the canonical Wnt pathway. The constitutive expression of beta catenin in the ectoderm by using a keratin14 promoter resulted in the excessive formation of extra teeth. These teeth are initiated from signaling centers, which express placodal and enamel knot genes and seem to be iteratively induced in the oral epithelium. When tooth germs from transgenic embryos were cultured in vitro, denovo teeth appeared to develop successionally from previously formed tooth germs. It was learnt and proved

that the novo teeth can be induced even postnatally by Wnt pathway activation. Tiny teeth were induced within the forming roots of molars, in the oral epithelium near the teeth as well as around the incisors. The capacity of the denovo tooth formation was, however, reduced as the age increases and in 10 months old mice teeth were induced mainly from the epithelium of the continuously growing incisors .It is conceivable that there is very little capacity for denovo teeth formation in humans and other adult mammals. With the exception of continuously growing teeth in few mammalian species such as rodent incisors, the most dental epithelium is lost during completion of the mammalian tooth formation. When the tooth erupts to the oral cavity the enamel epithelium which is presently surrounding the tooth crown undergoes apoptosis and sheds. Therefore, the only dental epithelium which remains after the completion of root development is ERM. While ERM cells have been isolated and they can be induced to proliferate under some conditions, it is not known whether they have odontogenic potential or stem cell characteristics.

Mesenchymal stem cells have been identified in the recent studies in adult human teeth in the dental pulp as well as in the dental follicles and these cells have stem cell properties and can be cultured as stem cells in vitro and can be differentiated in vivo into odontoblasts, cementoblasts and periodontal ligament cells but there is a limited evidence that they would maintain capacity either to direct or participate in tooth morphogenesis.

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