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Original Research

Histophysiologically, Morphogenesis and Molecular Mechanism of Tooth Development

Bhavya Joshi

BDS Student, Dasmesh Institute of Research and Dental Sciences, Faridkot, Punjab, India

ABSTRACT:
Tooth development is a well-coordinated event called odontogenesis, which is complex. Thus, teeth will be formed as a result of many actions that take place in an interrelated manner. The process comprises different steps, such as initiation, morphogenesis and differentiation that begin at the embryonic stage to postnatal period. Growth factors, transcription factors, signalling pathways like BMP, FGF SHH WNT are part of the complex genetic and molecular network that caters for teeth development. Developmental abnormalities resulting from any interruption in these signaling networks can affect teeth size shape number structure. This knowledge supports the understanding of dental diseases as well as normal dental development.

Keywords: Anomalies; Dental lamina; Odontogenesis; Genetic control

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Corresponding author: Bhavya Joshi, BDS Student, Dasmesh Institute of Research and Dental Sciences, Faridkot, Punjab, India

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INTRODUCTION

Tooth development, also known as odontogenesis, is the process by which teeth form and mature. It is a complex and highly regulated process that occurs in multiple stages during embryonic and postnatal development.

Stage1: Approximately six weeks into foetal development is when the tooth's basic structure forms. The oral epithelium thickens in this process, eventually forming the dental lamina. While the neural crest ectomesenchyme gives rise to other tooth components, the ectoderm of the oral cavity also produces the cells that makeenamel.

Stage2: The hard tissue that surrounds the teeth forms between three and four months of pregnancy.

Stage3:nThetooth erupts from the gums after birth.

Stage 4: Deciduous teeth are exfoliateand replaced are by permanent teeth, which undergo the same developmental process.

Tooth development involves developmental stages, histophysiology and most important molecular mechanism that can affect the tooth structure if any gene mutation occurs and causes anomalies.

The primitive oral cavity or stomodeum is lined by stratified squamous epithelium called oral ectoderm or primitive oral epithelium. The oral ectoderm contacts the endoderm of the foregut to form buccopharyngeal membrane. At about the 27th day of gestation period, this membrane ruptures and the oral cavity is establishes a connection with the foregut. Most of the connective tissue cells underlying the oral ectoderm are the neural crest or ectomesenchyme in origin. These cells are thought to instruct or induce the overlying ectoderm to start tooth development, which begins in the anterior portion of what will be the future maxilla and mandible and proceeds posteriorly.

What is dental lamina?

The dental lamina is a crucial structure in embryonic tooth development. It's a band of epithelial cells that forms from the oral epithelium during the early stages of embryogenesis. The dental lamina serves as the foundation for the initiation of tooth formation and gives rise to tooth buds, which eventually develop into primary teeth. At about the 7th week, the primary epithelial band divides into an inner (lingual) process

called dental lamina and an outer (buccal) process called vestibular lamina.

Here's a breakdown of the dental lamina and its significance in tooth development:

1. **Formation:** The dental lamina begins to develop around the sixth week of embryonic development in humans. It arises from localized thickening of the oral epithelium along the dental ridge, which is a region in the developing jaw where teeth will form.
2. **Location:** The dental lamina extends along the oral epithelium in a continuous band-like structure. It runs parallel to the future arch of the dental arcade, where teeth will eventually erupt.
3. **Initiation of Tooth Development:** The formation of the dental lamina marks the initial step in tooth development. It serves as the site where signalling interactions between the epithelium and underlying mesenchyme occur, leading to the induction of tooth buds.
4. **Precursor to Tooth Buds:** The dental lamina gives rise to tooth buds, which are the early stages of tooth formation. These buds emerge from localized outgrowths of the dental lamina into the underlying mesenchyme, initiating the process of tooth morphogenesis.
5. **Regional Specification:** Different regions of the dental lamina correspond to specific tooth types (e.g., incisors, canines, molars). Regional specification is controlled by spatial gradients of signalling molecules and transcription factors, which determine the fate of tooth development in each region of the dental arch.
6. **Continued Development:** As tooth development progresses, the dental lamina undergoes further morphological changes and eventually degenerates as tooth buds mature into fully formed teeth. However, remnants of the dental lamina may persist in the oral mucosa as epithelial remnants known as the gubernaculum dentis anatomical structure connecting the dental follicle of the permanent tooth to the overlying gingiva.

Fate of Dental Lamina

During the bell stage of tooth development, the dental lamina breaks down into tiny epithelial clusters and is resorbed, paving the way for the development of dental hard tissue. On the other hand, if the clusters don't resorb, they may create eruption cysts, which postpone the eruption of the tooth into the mouth. The glands of Serres are another name for these dental lamina remains.

It is evident that the total activity of the dental lamina extends over a period of at least 5 years.During embryonic development, at the locations of future tooth rows, the oral epithelium and ectomesenchyme thicken to create the dental lamina. It forms the basis of the ectodermal section of deciduous teeth, and with the development of the jaw, the dental lamina also extends to give rise to the permanent molars.

Vestibular Lamina

Vestibular lamina is labial and buccal to the dental lamina in each dental arch, another epithelial thickening develops independently and somewhat later. It is the vestibular lamina, also termed the lip furrow band. It subsequently hollows and forms the oral vestibule between the alveolar portion of the jaws and the lips and cheeks. Vestibule lamina band is created at about 37 days of development in utero.The primitive ectoderm that lines the primitive oral cavity proliferates, leading to the development of the vestibular lamina during the sixth week of intrauterine life. The lips and cheeks on one side and the developing jaws and teeth on the other side are divided by a fissure formed by the cells' enlargement and subsequent degeneration known as cleft. This cleft is the oral vestibule.

TOOTH DEVELOPMENT

Morphogenesis

Tooth development morphologically is basically divided into three stages:

Bud stage

Cap stage

Bell stage

Initiation Stage: Teeth initiation starts at the sixth week of pregnancy, when the oral epithelium is immediately beneath an accumulation of ectomesenchymal cells. It is believed that the neural crestcell population is the origin of these cells.

A primary epithelial ring is subsequently formed as the oral epithelium multiplies downward into the ectomesenchyme.

The major epithelial band separates into the vestibular and oral laminae at the seventh week of pregnancy: The vestibule, or external entrance to the oral cavity, is formed by the vestibular lamina.

Teeth are formed by the dental lamina.

There are ten dental buds in each jaw, which are epithelial swellings that develop within the dental lamina. They give rise to the enamel organs, which are the precursors to tooth enamel and indicate the earliest phases of the creation of distinct tooth types.

Below the enamel organs, the ectomesenchymal tissue compress to form the dental papilla harbinger to dentin and pulp.

Bud Stage: The proliferation stage of tooth development is another name for the bud stage. It's the initial phase of tooth development, starting in the eighth week of foetal development.

The dental lamina, a dense ring of cells that develops in the upper and lower jaws, gives rise to dental epithelium cells. At the bottom end, these cells grow into a knob-like structure that mimics a flower bud. The developing tooth germ is the knob, and the vertical stalk that connects it to the layer is a portion of the dental lamina. Soft tissues required for tooth

growth make up the tooth germ. The enamelorgan looks like a small bud.

The enamel organ is made up of centrally positioned polygonal cells and peripherally located low columnar cells.

The surrounding mesenchymal cells multiply and condense into two regions as a result.

The dental papilla is the region of condensation directly beneath the enamel organ.

The tooth sac is the ectomesenchymal condensation that encircles the dental papilla and tooth bud.

The late bud stage of tooth development, also known as the crown stage that is the second half of the bell stage which is discussed further. The enamel epithelium folds and starts to form the tooth's crown at this point. Molecules secreted by ameloblasts and odontoblasts build the crowns of teeth. Additionally, the tooth starts to mineralize and harden.

Cap Stage: This stage is characterized by the enamel organ's growth and expansion, which causes an inner aspect concavity to form. The growth continues, and from the inner cuboidal cells of the enamel organ, inner enamel epithelium forms at around 12 weeks of intrauterine life, or during the late cap stage. In contrast to the cuboidal enamel organ cells, the inner enamel epithelium cells are columnar in shape. This layer establishes the contours of the crown and subsequently gives rise to the ameloblasts that produce enamel. The outer enamel epithelium is made up of cuboidal cells from the enamel organ's outer layer. They preserve the form of the enamel organ.

Beneath the inner enamel epithelium, the condensed mesenchymal cells form the dental papilla, which afterwards forms the pulp. Fibrous capsule surrounding the enamel organ is known as the dental follicle, which forms the periodontal ligament afterwards.

In addition to the inner and outer enamel epithelium, two further layers—the stratum intermedium and stellate reticulum—form at 14 weeks of intrauterine life.The inner enamel epithelium is covered by the two or three cell layers that make up the stratum intermedium. Among its duties is the movement of nutrients to and from the ameloblasts, the cells that produce enamel. Between the outer enamel epithelium and the stratum intermedium is the stellate reticulum layer. Stellate is the form and safeguard the underlying dental tissues.

Hertwig's root is ultimately formed by the cervical loop formed by the continued expansion of the inner and outer enamel epithelial cells and hence determines the shape of future root.

Bell Stage: Bell stage is divided into mainly two stages that are early bell stage and advance bell stage.At this point, two significant events happen: the enamel organ begins to expand into the shape of a bell. The enamel organ's cells first differentiate, or alter in function. They will belong to one of four cell groups based on their newrole:

Inner Enamel Epithelium, Enamel's Outer Epithelium
Stratum Intermedium
Reticulum Stellate

These cell types cooperate to form the tooth's enamel layer. The enamel epithelium folds into the eventual shape of the tooth crown during the second event in this stage, and the dental lamina begins to degrade.

Early Bell Stage: In the early bell stage, a high degree of histodifferentiation is attained.Theenamel organ exhibits four unique layers:

1. The inner enamel epithelium, or IEE: It is made up of a single layer of cells called ameloblasts that develop into columnar cells before amelogenesis. These elongated cells are joined laterally by junctional complexes, and to the stratum intermedium by desmosomes. The RNA-rich IEE cells. The cell-free zone, measuring approximately 1-2 µm in width, and the basement membrane divide the IEE from the oral papilla's peripheral cells.

The cells in this layer have two functions: they first organize the underlying ectomesenchymal cells of the dental papilla so that they can differentiate into odontoblasts, which make enamel, and then they differentiate into ameloblasts. Additionally, once the crown's enamel formed, the IEE and OEE combined to form the cervical loop's structure, which is known as the Hertwig's epithelial root sheath and produced the root.

2. Stratum intermedium (SI):Layers of flattened cells located between the stellate reticulum and IEE initially emerge during the early bell stage. This layer's cells are made up of several layer of squamous cells joined together tightly by gap junctions and desmosomes.

Because stratum intermedium cells have a high level of the enzyme alkaline phosphatase, they play a significant role in the mineralization of enamel during amelogenesis. Additionally, the cells in this layer are involved in the movement of substances to and from the IEE, where they eventually mature into ameloblasts.

3. The stellate reticulum (SR):The high concentration of glycos-aminoglycans causes the intercellular gaps to fill with fluid, which is likely related to osmotic effects.

Furthermore, alkaline phosphatase is present in the cells yet possess very little glycogen and RNA. The bodies of the star-shaped cells have numerous branching processes and conspicuous nuclei. This layer's cells have a lot of tonofilaments and not a lot of endoplasmic reticulumor mitochondria, which are found in the cytoplasm. There are gap junctions and desmosomes in between the cells.

Stellate reticulum's primary purpose is mechanical in nature. This has to do with keeping the tooth's form and shielding the underlying IEE from external disruption. Within the stellate reticulum, the hydrostatic pressure produced is in balance with that of the dental papilla, allowing the proliferative pattern of the IEE cells to determine the crown morphogenesis, however a change in either of these

pressures might lead to change in the outline of the IEE and this is important for crown morphogenesis.
4. The epithelium of outer enamel (OEE) :This produces the outer layer of cuboidal cells that encircles the enamel organ, as its name implies. A 1-2µm thick basement membrane, which corresponds to the basal lamina and hemidesmosomes at the ultrastructural level (under an electron microscope), separates it from the surrounding ectomesenchymal tissue of the dental sac or follicle.
The nuclei of the OEE cells are big and positioned in the center. From an ultrastructural perspective, they have modest amounts of the intracellular organelles involved in protein synthesis, such as the Golgi complex, mitochondria, and endoplasmic reticulum, and they interact with one another through desmosomes and gap junctions.
It is believed that OEE has a role in both the substance exchange between the enamel organ and its surroundings as well as the preservation of the enamel organ's shape.When dentin is laid down during the advance bell stage, the outer enamel epithelium's previously smooth surface is deposited in folds. The surrounding dental sac mesenchyme creates papillae between the folds, which are containing capillary loops and supplying nutrients for the high metabolic activity of the avascular enamel organ during enamel production.
Dental papilla:The invaginated part of the enamel organ encloses the dental papilla.
Under the organizing influence of the epithelium, the peripheral cells of the mesenchymal dental papilla develop into odontoblasts prior to the inner enamel epithelium starting to produce enamel. When dentin production starts at the cuspal tip of the bell stage tooth germ, the dental papilla eventually gives rise to dental pulp.
The membrana preformativa is the basement membrane that divides the enamel organ from the dental papilla right before dentin forms.
Dental sac:Resembling a capsular structure, the dental sac has a circular fiber arrangement prior to the onset of dental hard tissue production. The dental sac's fibers undergo differentiation into periodontal ligament fibers during root formation, and these fibers get implanted in the cementum and alveolar bone.
Crown Stage or Advance (late) Bell Stage:Enamel and dentin are the hard tissues that grow atthe advanced bell stage
.Some researchers refer to this stage as the "crown" or "apposition stage."
form, all of the IEE cells were dividing rapidly to increase the size of the tooth bud overall. This process is known as mitosis. Dentin is the first mineralized hard tissue to form at this site. Simultaneously, the IEE cells transform into pre-ameloblasts by changing from cuboidal to columnar in shape. In this phase, the future D.E.J. (dentino- enamel junction) is defined by the line separating odontoblasts from inner E. epithelium. Furthermore, the basal margin of the enamel organ (cervical loop) gives rise to the epithelial root sheath.

Enamel Knot, Enamel Cord and Enamel Niche
The enamel knot is a localized condensation of cells in the inner enamel epithelium of the tooth. The enamel knot often continues as a pillar of cells towards the outer enamel epithelium. This column of cells that divides the enamel organ into two is called the enamel cord or septum.
The enamel knot and enamel chord are believed to be involved in determining the initial position of the first cusp of the tooth during crown formation.
The enamel niche is an apparent structure created by the plane of section during histologic sectioning. It is seen as mesenchymal structures surrounded by the dental epithelium at the site of attachment of the enamel organ to the dental lamina.

Root Formation
Once the enamel and dentin formation reaches the future cemento-enamel junction, the formation of the root begins. The outer and the inner enamel epithelium proliferate from the cervical loop of the enamel organ to form a double layered cell sheath called epithelial Root Sheath. This sheath of epithelial cells grow around the dental papilla to enclose the major portion of the dental papilla. The inner enamel epithelial cells initiate differentiation of odontoblasts from cells of the dental papilla. Thesedifferentiation of odontoblasts form the root dentin or radicular dentin. As soon as tooth dentin formation starts, the epithelial root sheath loses its structural continuity and forms a strand of cells called as rests of Malassez.
The root sheath prior to elongation in ana apical direction, forms an epithelial diaphragm which is a horizontal extension of the epithelial cells at the future cemento- enamel junction. As the root sheath elongates linearly, differentiation of odontoblasts and formation of dentin occurs. Subsequently the epithelial cells disintegrate and move away from the surface of dentin there by exposing it to the connective tissue cells of the dental sac which differentiation into cementoblastsand deposit layer of cementum over the dentin. The wide open apical foramen is gradually reduced by apposition of dentin and cementum at the root apex.
In case of multirooted teeth the epithelial diaphragm develops tongue like extensions which grow inwards and divides the root trunk into two or three hollow tubes which forms as many roots.

Histophysiologically
Tooth development histophysiology is divided into three stages:
Growth
Mineralisation
Eruption
Growth: The embryonic period, pseudograndular stage, bell stage.

The embryonic period: Beginning around the sixth week of pregnancy, during the embryonic stage, tooth development starts. The dental lamina is formed when the oral epithelium invaginates into the underlying mesenchyme.

Both primary and permanent teeth will emerge from tooth buds, which are formed by the proliferation of the dental lamina.

The pseudograndular stage (7 to 16 weeks): Over the tooth bud, the enamel organ, which is produced from the dental lamina, takes the form of a cap. The stratum intermedium, stellate reticulum, inner enamel epithelium, and outer enamel epithelium are the several cell layers that make up the structure.

Around the enamel organ, the mesenchymal cells condense to produce the dental sac and papilla. The dental sac forms the cementum, periodontal ligament, and alveolar bone, whereas the dental papilla gives rise to the dentin and pulp.

Bell Stage (Weeks 14–20):Histodifferentiation: The enamel organ's cells differentiate into distinct cell types that are in charge of the production of enamel, dentin, and dental pulp.

Appositional Growth: Enamel-forming ameloblasts and dentin-forming odontoblasts release enamel and dentin matrix proteins, respectively, which triggers the mineralization of the enamel and dentin matrices.

Mineralisation: Mineralization is a crucial process in tooth development that involves the deposition of minerals, primarily calcium and phosphate ions, to form the hard tissues of the tooth, namely enamel, dentin, and cementum. Here's an overview of mineralization during tooth development:

Enamel Mineralization: Enamel is the hardest tissue in the human body and forms the outer layer of the tooth crown. It primarily consists of hydroxyapatite crystals, which are crystalline structures made of calcium and phosphate ions.Enamel mineralization occurs predominantly during the late bell stage and continues into the maturation phase. During this process, ameloblasts, specialized epithelial cells, secrete enamel matrix proteins, mainly amelogenin, enamelin, and ameloblastin. The proteins organize into a matrix that serves as a scaffold for the deposition of calcium and phosphate ions. Ameloblasts actively transport these ions from the blood plasma into the enamel matrix, where they crystallize to form hydroxyapatite crystals.The crystallization process begins at multiple sites within the enamel matrix and gradually extends throughout the tissue, resulting in the hardening of enamel.

Dentin Mineralization: Dentin is the hard tissue that forms the bulk of the tooth structure, underlying the enamel in the crown and surrounding the pulp chamber in the root.Dentinogenesis, the process of dentin formation, involves the secretion of dentin matrix proteins, primarily collagen type I, by odontoblasts, specialized cells located at the periphery of the dental pulp.Similar to enamel mineralization, dentin mineralization involves the deposition of calcium and phosphate ions within the dentin matrix. Odontoblasts regulate this process by secreting dentin sialoprotein and dentin phosphoprotein, which aid in nucleation and crystal growth. The mineralization of dentin occurs continuously throughout the lifespan of the tooth, allowing it to undergo repair and secondary dentin formation in response to external stimuli or injury.

Cementum Mineralization: Cementum is a mineralized tissue that covers the roots of teeth and serves as an attachment surface for the periodontal ligament fibers. Cementogenesis, the process of cementum formation, involves cementoblasts, specialized cells derived from the dental sac, which secrete cementum matrix proteins, such as cementum attachment protein (CAP) and cementum-derived growth factor (CDGF). Similar to enamel and dentin, cementum mineralization occurs through the deposition of calcium and phosphate ions within the cementum matrix. This process helps cementum achieve its mineralized and hard structure, facilitating its role in tooth anchorage and support.

Mineralization is a dynamic process essential for the formation of the hard tissues that comprise the tooth structure, ensuring its strength, durability, and functionality. Disruptions in mineralization can lead to developmental defects, such as enamel hypoplasia, dentin dysplasia, or cementum abnormalities, affecting the integrity and function of the tooth.

Eruption: Teeth erupt into the oral cavity through a combination of bone resorption and epithelial cell proliferation. Primary teeth typically erupt between 6 months and 3 years of age, while permanent teeth erupt from around age 6 to early adulthood.

Maturation: After eruption, the tooth continues to mature and undergo functional adaptation to the oral environment. This involves changes in the structure and composition of the tooth tissues.

Molecular Mechanism

Tooth development molecular mechanism:

The molecular mechanisms underlying tooth development involve a complex interplay of signaling pathways, transcription factors, and morphogens that orchestrate the differentiation, proliferation, and patterning of dental tissues. Here's an overview of some key molecular players and processes involved in tooth development:

Epithelial-Mesenchymal Interactions: Tooth development begins with reciprocal interactions between the oral epithelium and the underlying cranial neural crest-derived mesenchyme.Signaling molecules such as fibroblast growth factors (FGFs), bone morphogenetic proteins (BMPs), and sonichedgehog (SHH) secreted by the epithelium induce the condensation and differentiation of mesenchymal cells into odontogenic cells.In turn, mesenchymal-derived signals, including Wnt and Eda/Edar/NF-κBsignaling, regulate epithelial cell proliferation and differentiation.

Initiation and Bud Stage: The expression of transcription factors such as Pax9, Msx1, and Lef1 in the dental epithelium and mesenchyme marks the initiation of tooth development and the formation of tooth buds.BMP and Wntsignaling pathways are crucial for maintaining the epithelial-mesenchymal interactions necessary for tooth bud formation and patterning.

Cap Stage and Bell Stage: During the cap stage, the enamel organ undergoes morphogenesis to form a cap-like structure over the dental papilla. This process involves the proliferation, differentiation, and spatial organization of epithelial cells. Signaling molecules such as FGFs, BMPs, and SHH play critical roles in regulating the morphogenesis and differentiation of the enamel organ.Transcription factors such as Pitx2, Dlx2, and Runx2 are involved in specifying the fate of dental epithelial and mesenchymal cells and promoting their differentiation into enamel-secreting ameloblasts and dentin-secreting odontoblasts.

Matrix Formation and Mineralization: Ameloblasts and odontoblasts secrete enamel matrix proteins (e.g., amelogenin, enamelin) and dentin matrix proteins (e.g., collagen type I, dentin sialoprotein), respectively, which form the organic matrix of enamel and dentin. Calcium and phosphate ions are transported into the matrix by specialized transporters, where they mineralize to form hydroxyapatite crystals, giving enamel and dentin their hardness and structural integrity.

Eruption and Maturation: Eruption involves the movement of the tooth from its developmental position within the jaw to its functional position in the oral cavity. Molecular mechanisms underlying eruption include bone resorption by osteoclasts and epithelial cell proliferation.After eruption, teeth undergo maturation, during which the enamel and dentin undergo further mineralization and structural refinement.

Signaling Pathways:

FGF (Fibroblast Growth Factor) Signaling:FGFs, such as FGF8 and FGF10, play essential roles in tooth development by regulating epithelial-mesenchymal interactions, epithelial proliferation, and tooth bud formation.

BMP (Bone Morphogenetic Protein) Signaling: BMPs are critical for tooth development, with BMP4 and BMP7 playing prominent roles in mesenchymal cell condensation, tooth bud initiation, and differentiation of odontogenic cells into odontoblasts

WntSignaling: Wntsignaling is involved in multiple stages of tooth development, including tooth bud initiation, enamel knot formation, and regulation of epithelial and mesenchymal cell differentiation. Key components of this pathway include β-catenin and Lef1.

Transcription Factors:

Pax9 and Msx1: These transcription factors are expressed in the dental epithelium and mesenchyme and are essential for tooth initiation and early morphogenesis. They regulate the expression of genes involved in epithelial-mesenchymal interactions and tooth bud formation.

Runx2 and Dlx2: Runx2 is critical for odontoblast differentiation and dentin formation, while Dlx2 plays a role in specifying the fate of dental epithelial cells and promoting ameloblast differentiation.

Pitx2: Pitx2 is involved in regulating tooth morphogenesis, particularly in the development of molars and incisors. It contributes to the patterning and differentiation of dental epithelial and mesenchymal cells.

Epithelial-Mesenchymal Interactions:

Eda/Edar/NF-κBSignaling: Mutations in genes encoding components of the ectodysplasin (Eda) signaling pathway, including Eda, Edar, and Edaradd, lead to ectodermal dysplasia syndromes characterized by abnormal tooth development. This pathway regulates the morphogenesis and differentiation of dental epithelial cells via NF-κBsignaling.

Shh (Sonic Hedgehog) Signaling: Shh is expressed in the epithelial signalingcenters known as enamel knots, which regulate tooth morphogenesis and cusp patterning. Shh signaling is essential for the proliferation and differentiation of dental epithelial cells during tooth development.

Matrix Formation and Mineralization:

Enamel Matrix Proteins: Ameloblasts secrete enamel matrix proteins such as amelogenin, enamelin, and ameloblastin, which form the organic matrix of enamel. These proteins regulate enamel crystal growth and organization during mineralization.

Dentin Matrix Proteins: Odontoblasts secrete dentin matrix proteins, including collagen type I, dentin sialoprotein, and dentin phosphoprotein, which form the organic matrix of dentin. These proteins play crucial roles in dentin mineralization and dentinogenesis.

Signaling molecules play critical roles in orchestrating the complex processes of tooth development. They regulate cell proliferation, differentiation, and tissue patterning, ensuring the proper formation of teeth. Here are some of the keysignaling molecules involved:

1. **Fibroblast Growth Factors (FGFs):** FGFs are essential signaling molecules involved in the initiation and early stages of tooth development. They play a crucial role in inducing the thickening of the oral epithelium to form the dental lamina and promoting epithelial-mesenchymal interactions. FGFs are also involved in regulating cell proliferation and survival during tooth morphogenesis.
2. **Bone Morphogenetic Proteins (BMPs):** BMPs are members of the transforming growth factor-

beta (TGF-β) superfamily and are critical regulators of tooth development. They play multiple roles, including inducing the expression of key transcription factors in dental mesenchyme, regulating odontogenic differentiation, and controlling tooth morphogenesis and patterning. BMP signaling is essential for the formation of both enamel and dentin.

3. **WntSignaling Pathway:** The Wntsignaling pathway is involved in various aspects of tooth development, including tooth initiation, patterning, and differentiation. Wnt ligands interact with Frizzled receptors and co-receptors, leading to the activation of intracellular signaling cascades. Wntsignaling regulates the expression of key transcription factors such as Lef1 and promotes epithelial-mesenchymal interactions critical for tooth morphogenesis.
4. **Sonic Hedgehog (Shh):** Shh is a secreted signaling molecule that plays essential roles in tooth development, particularly in regulating epithelial-mesenchymal interactions and tooth patterning. Shh is expressed in the epithelium and acts on the underlying mesenchyme to control the proliferation and differentiation of dental mesenchymal cells. It also plays a role in regulating the growth of tooth cusps and shaping tooth morphology.
5. **Notch Signaling Pathway:** The Notch signaling pathway is involved in cell-cell communication and regulates various aspects of tooth development, including epithelial cell differentiation, enamel knot formation, and dental epithelial stem cell maintenance. Notch signaling mediates interactions between adjacent epithelial and mesenchymal cells and is crucial for the proper patterning and morphogenesis of teeth.
6. **Epidermal Growth Factor (EGF):** EGF signaling is involved in regulating cell proliferation, survival, and differentiation during tooth development. EGF and its receptor, EGFR, are expressed in dental epithelium and mesenchyme and play roles in epithelial-mesenchymal interactions, tooth bud formation, and enamel matrix production.

These signaling molecules, along with their receptors and downstream effectors, form intricate networks that control the spatiotemporal dynamics of tooth development. Dysregulation of these signaling pathways can lead to developmental abnormalities and congenital dental disorders.

Genetic mutations affecting key signaling pathways, transcription factors, or matrix proteins can lead to developmental disorders like ectodermal dysplasias, amelogenesis imperfecta, dentinogenesis imperfecta, and tooth malformations.

Molecular insights into tooth development hold promise for regenerative dentistry and tissue engineering approaches aimed at repairing or replacing damaged or missing dental tissues.

Targeting specific molecular pathways involved in tooth development may offer therapeutic strategies for promoting tooth regeneration, enhancing dental tissue repair, or even preventing dental diseases.

ANOMALIES

Anomalies in the development of tooth

The term anomaly implies abnormal variation of teeth and tooth form. The cause of most dental anomalies can be ascribed to hereditary, congenital factors, or to developmental and metabolic disturbances. The permanent dentitions is much prone to abnormalities than the deciduous teeth. The dental anomaly can manifest at a specific physiologic stage of tooth development. The tooth development can be classified into the following stages based on the physiological process that occur at that time period.

Initiation: The earliest stage is the initiation process which includes the dental lamina and bud stages. Any factor that presents itself during this phase can result in absence or additional tooth buds.

Proliferation: The next stage is proliferation and occurs during the bud, cap, and bell stages of tooth development. This stage influences the size and proportions of the tooth.

Histodifferentiation: This process of histodifferentiation occurs from the advanced cap stage and the bell stage of the tooth development. This phase comprises of formation of potential enamel and dentin forming cells.

Morphodifferentiation: Morphodifferentiation occurs during the bud, cap, and bell stages. The shape and size of the tooth is determined during this process. Thus, a disturbance during morphodifferentiation may influence the size and shape of a tooth with no effect on the enamel and dentin formation.

Apposition: This process comprises of laying down of enamel and dentin and occurs from the bell stage through to the completion of the root.

Anomalies in Number of Teeth

Supernumerary teeth: Teeth that are extra to the normal complement are termed as the supernumerary teeth. These teeth have abnormal morphology and do not resemble normal teeth. Extra teeth that resemble the normal teeth are called supplemental teeth. Over 75% of supernumerary teeth remain impacted in the bone and are only diagnosed radiographically. Males are more frequently affected than females (2:1). A frequently seen supernumerary tooth is mesiodens that occurs in the maxillary midline. They can occur singly or as pair and are usually conical in shape. Unerupted mesiodens is one of the causes of midline spacing. Supernumerary teeth cam also occur in the premolar or third molar regions. Supernumerary teeth that occur beyond the third molar are called distmolars and those that occur in the molar area are called paramolars. Supplemental teeth are most often seen in the

premolar and lateral incisor region. It is uncommon to find and extra lower incisor.

Missing teeth: Congenital absence of teeth is referred to as hypodontia if some teeth are missing from the arch or anodontia if all of teeth are absent. If six or more permanent are missing, the term 'oligodontia' is used. Hypodontia usually affects the last teeth in each series, i.e. third molars, upper laterals, second premolars. Frequency in permanent dentition is 3.0-7.5% and in primary dentiton is 0.1-0.7%. The following are some of the commonly missing teeth in decreasing order of the frequency: third molar, maxillary lateral incisors, mandibular second premolars, mandibular incisors, maxillary second premolars. Absence of teeth can be unilateral or sometimes bilateral. They may occur along with other anomalies such as presences of extra teeth.

Anomalies of Tooth Size

Microdontia: Microdontia refers to teeth that appear smaller in size compared to normal. It is important to note that the teeth affected are usually the ones that are also most often congenitally hypopituitarism or exposure to radiation or chemotherapy during dental development. Microdontia is frequently seen in association with Down syndrome and various types of ectodermal dysplasia. Frequency in permanent dentition is 0.5% while in primary dentition it is less than 1%. Smaller sized teeth or microdontia predispose to spacing. A commonly seen anomaly is the presence of smaller sized maxillary lateral incisors. Microdontia can be classified as true microdontia which is seen in pituitary dwarfs who exhibit generalised microdontia and false microdontia involving individual teeth.

Macrodontia: Macrodontia refers to teeth that appear larger in size compared to normal. It may result in crowding. Fusion between two adjacent teeth or between a supernumerary tooth may predispose to large teeth. Macrodontia can be classified as true macrodontia which is rare case of pituitary gigantism where all the teeth are large in size and false macrodontia which involves certain individual teeth. Variations in size of teeth can occur along with variations of shape.

Anomalies of Tooth Shape

Anomalies of tooth size and shape are very often interrelated. The presence of abnormal crown and root shapes most often signifies disturbances during the morphodifferentiation and appositional stages of tooth development. The following are some of the examples of frequently seen tooth shape anomalies:

The presence of peg shaped maxillary lateral incisors is often accompanied by spacing and migration of teeth.

Another anomaly of tooth shape is the presence of an abnormally large cingulum on a maxillary incisor.

Dilaceration is described as a condition characterized by an abnormal angulation between the crown and root of a tooth or angulation within the root.

Taurodontism is a condition characterised by a crown which occupies a much greater proportion of the total tooth bulk than is normal. The CEJ exhibits no constriction, the furcation is found in the apical half of the tooth, and the floor of the pulp chamber is likewise displaced apically.

Germination is a condition resulting in incomplete splitting of a single tooth germ. The tooth is wide mesiodistally, and has an incisal notch representing the split. It normally has a single root with a common pulp cavity.

Twinning is termed used to identify a situation where germination has been complete, resulting in two identical teeth.

Fusion of teeth is a result of union of two adjacent tooth buds. The two portions are always united through the enamel and dentin, and occasionally even the pulp. Unlike germination, there are normally two identifiable pulp cavities.

Concrescence involves the union of the root structure of two or more teeth through the deposition of cementum only.

Accessory cusps or additional cusps on teeth can be seen in molars and premolars. The mandibular second premolar can exhibit two cusps. Incisors can exhibit an over- developed cingulum. In the maxillary incisors, this is called talon cusp.

Dens in dente is a condition where the enamel organ becomes invaginated and the normally external structures of enamel and dentin become invaginated inside the pulp cavity. This creates an x-ray appearance of a small tooth within a tooth and is most commonly found in the permanent maxillary lateral incisor.

Hypercementosis is a condition that results in excessive cementum formation around the root of a tooth, and is most often associated with the roots of permanent molars.

GENETIC CONTROL OF EARLY TOOTH DEVELOPMENT DISORDERS

Disorders related to the genetic control of early tooth development can manifest in various ways, leading to a range of dental abnormalities and congenital conditions. Here are some examples:

1. **Tooth Agenesis:** Tooth agenesis refers to the absence of one or more teeth due to failure of tooth development. This condition can be caused by mutations in genes involved in tooth initiation, such as MSX1 and MSX2, or genes involved in later stages of tooth development. Tooth agenesis can affect both primary (baby) and permanent teeth and can occur as isolated cases or as part of syndromes.
2. **Ectodermal Dysplasia:** Ectodermal dysplasia is a group of genetic disorders characterized by abnormalities in the development of ectodermal

structures, including teeth, hair, nails, and sweat glands. Individuals with ectodermal dysplasia may have missing teeth (hypodontia), abnormal tooth shape, and defects in enamel formation. Mutations in genes such as EDA, EDAR, and EDARADD have been associated with ectodermal dysplasia.

3. **Amelogenesis Imperfecta (AI):** Amelogenesis imperfecta is a genetic disorder characterized by defects in enamel formation, resulting in teeth that are discolored, malformed, or prone to decay. AI can be caused by mutations in genes encoding enamel matrix proteins such as AMELX, ENAM, and MMP20, which are involved in enamel formation and mineralization.
4. **Dentinogenesis Imperfecta (DI):**Dentinogenesis imperfecta is a genetic disorder characterized by defects in dentin formation, resulting in teeth that are discolored, translucent, and prone to fracture. DI can be caused by mutations in genes encoding dentin matrix proteins such as DSPP and DMP1, which are involved in dentin formation and mineralization.
5. **Cleidocranial Dysplasia (CCD):** Cleidocranial dysplasia is a genetic disorder characterized by skeletal abnormalities, including delayed eruption of permanent teeth, supernumerary teeth (extra teeth), and abnormalities in tooth shape and size. CCD is caused by mutations in the RUNX2 gene, which is involved in skeletal development and osteoblast differentiation.
6. **Gorlin Syndrome:** Gorlin syndrome, also known as nevoid basal cell carcinoma syndrome, is a genetic disorder characterized by multiple basal cell carcinomas, skeletal abnormalities, and developmental defects such as jaw cysts and missing teeth. Gorlin syndrome is caused by mutations in the PTCH1 gene, which is involved in the Hedgehog signaling pathway.
7. **Hypophosphatasia:** Hypophosphatasia is a genetic disorder characterized by defects in bone and tooth mineralization due to deficiency of the enzyme alkaline phosphatase. Individuals with hypophosphatasia may have premature loss of primary teeth, delayed eruption of permanent teeth, and defects in tooth structure.
8. Tumourstreatment for disorders related to the genetic control of early tooth development varies depending on the specific condition and its severity. Examples like odontogenic tumours and odontogenic cysts.

Examples of odontogenic tumours are ameloblastoma, odontoma, adenomatoid odontogenic tumour (AOT).
Examples of odontogenic cysts are dentigerous cysts, odontogenic keratocyst.

TREATMENT OF GENETIC CONTROL OF EARLY TOOTH DEVELOPMENT DISORDERS

Treatment for disorders related to the genetic control of early tooth development varies depending on the specific condition and its severity. Here are some general approaches to treatment:

1. **Orthodontic Treatment:** Orthodontic interventions may be necessary to correct dental alignment and occlusion abnormalities caused by missing teeth, supernumerary teeth, or abnormal tooth shape and size. Orthodontic appliances such as braces, retainers, and space maintainers may be used to optimize dental alignment and support proper jaw development.
2. **Prosthodontic Treatment:** Prosthodontic interventions may be needed to restore missing teeth or improve the appearance and function of malformed or damaged teeth. This can include the placement of dental implants, bridges, crowns, or dentures to replace missing teeth and restore proper chewing and speech function.
3. **Enamel and Dentin Restoration:** For individuals with enamel or dentin defects such as amelogenesis imperfecta or dentinogenesis imperfecta, dental restorations may be performed to strengthen and protect the affected teeth. This can involve the application of dental bondingmaterials, composite resins, or porcelain veneers to improve the appearance and durability of the teeth.
4. **Endodontic Treatment:** Endodontic procedures such as root canal therapy may be necessary to treat teeth with defects in dentin or enamel that have become infected or decayed. Root canal therapy can help preserve the affected tooth and prevent further damage or loss.
5. **Surgical Interventions:** In some cases, surgical interventions may be required to address skeletal abnormalities or other complications associated with genetic disorders affecting tooth development. This can include procedures such as orthognathic surgery to correct jaw alignment, extraction of supernumerary teeth or impacted teeth, or surgical removal of jaw cysts or tumors.
6. **Genetic Counseling:** Genetic counseling may be beneficial for individuals and families affected by genetic disorders related to tooth development. Genetic counselors can provide information about the underlying genetic cause of the condition, recurrence risks, and available genetic testing options. They can also offer support and guidance in making informed decisions about family planning and medical management.
7. **Preventive Dental Care:** Regular dental visits and preventive care are essential for individuals with genetic disorders affecting tooth development. This includes professional cleanings, fluoride treatments, and sealants to prevent tooth decay and gum disease. Additionally, maintaining good oral hygiene practices at home, such as brushing and flossing regularly, can help minimize the risk of dental problems and preserve oral health.

Overall, treatment for disorders related to the genetic control of early tooth development aims to address functional and aesthetic concerns, prevent complications, and optimize dental health and quality of life for affected individuals. Treatment plans should be tailored to the specific needs and circumstances of each patient and may involve a combination of dental, orthodontic, surgical, and genetic interventions. Close collaboration between dental professionals, medical specialists, and genetic counselors is important for providing comprehensive care and support for individuals with these conditions.
These are just a few examples of disorders related to the genetic control of early tooth development. Each disorder has its own characteristic features and may require multidisciplinary management involving dentists, orthodontists, geneticists, and other healthcare providers. Early diagnosis and intervention are important for optimizing dental health and improving quality of life for affected individuals.
Treatment for disorders related to the genetic control of early tooth development varies depending on the specific condition and its sand speech function.

SUMMARY

Tooth development, also known as odontogenesis, is a multi-stage process that forms teeth from embryonic cells. It begins with the initiation stage, where interactions between the oral epithelium and mesenchyme create the dental lamina. This is followed by the bud stage, where cell proliferation forms the early tooth shape.Next is the cap stage, where the tooth's structure becomes more defined, and the dental papilla and enamel organ start to form. During the bell stage, the shape of the future tooth becomes recognizable, and cells begin to differentiate into specific types like ameloblasts, which will produce enamel, and odontoblasts, which will form dentin.Mineralization then occurs, where enamel and dentin harden. The final stage is eruption, where the fully formed tooth emerges into the mouth.Throughout these stages, various genetic and molecular signals regulate the process. Disruptions in these signals can lead to developmental issues, affecting tooth number, size, shape, and structure. Understanding tooth development is crucial for diagnosing and treating dental anomalies.

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