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Role Of Apoptosis In Health And Diseased Teeth

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I. Introduction

A precise control of cell proliferation is crucial for human development and survival. Specific cells/cell groups require elimination for proper organogenesis and remodelling of tissues. Their timely removal is also essential for the survival and proliferation of other cells. This is achieved by an all-or-none mechanism of degradation that targets the genetic material and cytoplasmic organelles within a cell. [1]

The term apoptosis means "dropping off" and translates to the falling of leaves from trees. It describes the situation in which a cell actively takes a course toward death on receiving certain stimuli. Since it is a sequential order of cell death, thus, it is referred to as 'programmed cell death'. Apoptosis occurs during development and aging and is also a homeostatic mechanism to maintain tissue cell populations. [2] An imbalance can contribute to abnormal cell growth or proliferation. [3]

The biochemical changes observed in apoptosis include caspase activation, breakdown of DNA (fragmentation and condensation) and protein, membrane changes, and recognition by phagocytic cells. It is a genetically regulated form of cell death that is implicated in biological processes ranging from embryonic development to aging, from normal tissue homeostasis to various human diseases. Apoptosis is characterized by morphological and ultrastructural changes that include chromatin condensation, nuclear fragmentation, cell rounding, and shrinkage, leading to cell breakage into apoptotic (smaller dense) bodies that are rapidly phagocytosed by macrophages [4] or adjacent parenchymal cells.

This programmed cell death differs from pathological cell death (necrosis) in being a faster process that involves individual cells instead of a group of cells. Apoptosis does not involve an inflammatory component, unlike necrosis where pro-inflammatory mediators are generated which chemically attract the inflammatory cells to the necrotic site. [1]

II. Apoptosis In Tooth Development

Tooth offers a great paradigm for interpreting the molecular principles of organogenesis [5**]** Apoptosis has a role in the development and maintenance of normal oral tissues. During embryogenesis, specific cells are destined to die by apoptosis. During the formation of oral epithelium, epithelial-mesenchymal interactions play an essential role in determining which cells are to be shed on and which ones survive. The oral mucosal lining is covered by epithelium that is constantly renewed by proliferating basal cells. Basal keratinocytes differentiate and migrate through epithelial layers to the surface forming keratin squames that are finally shed off. Therefore, keratinocytes undergo division, differentiation, and finally death. So, for maintaining the epithelial structure and function, cell proliferation, terminal differentiation, and spontaneous apoptosis have to be strictly regulated. [6,7]

During tooth development, controlled proliferation, differentiation, and elimination of particular cell populations are considered to determine the final tooth shape, size, and position in the jaw. Apoptosis occurs during all stages of tooth development: early stages of morphogenesis, dentinogenesis, amelogenesis, and eruption. [8]

Multiple roles of apoptosis in odontogenesis have been seen, which include:
- Role in the disruption of dental lamina
- Occur in the central cells of the invaginating epithelium during the early and middle bud stage, which may support the proliferation of underlying basal, mucosal cells
- Role in deciding the final position and size of the tooth in the jaws
- Prevent tooth eruption in edentulous areas by preventing epithelial overgrowth between the teeth and tooth eruption
- Role in deciding the final number of teeth
- Role in morphogenic mechanism in shaping the final crown tooth morphogenesis [7]
-Role in odontogenesis, intimation of tooth bud, and the elimination of the enamel knot (the signalling centre) [9]

At the early bud stage, apoptotic cells are detected at the oral surface and in budding dental epithelium beneath the oral ectoderm, however, at the late bud stage, the streak of apoptotic cells extends to the tip of the epithelial bud, and no apoptosis is detected in the mesenchyme around dental epithelium. [8] Apoptosis in the most superficial layer of the dental epithelium (early and middle bud stages) may support the proliferation of underlying basal mucosal cells. The restricted apoptotic areas in the mucosal layer are a likely factor in determining the position of the tooth germ. [10]

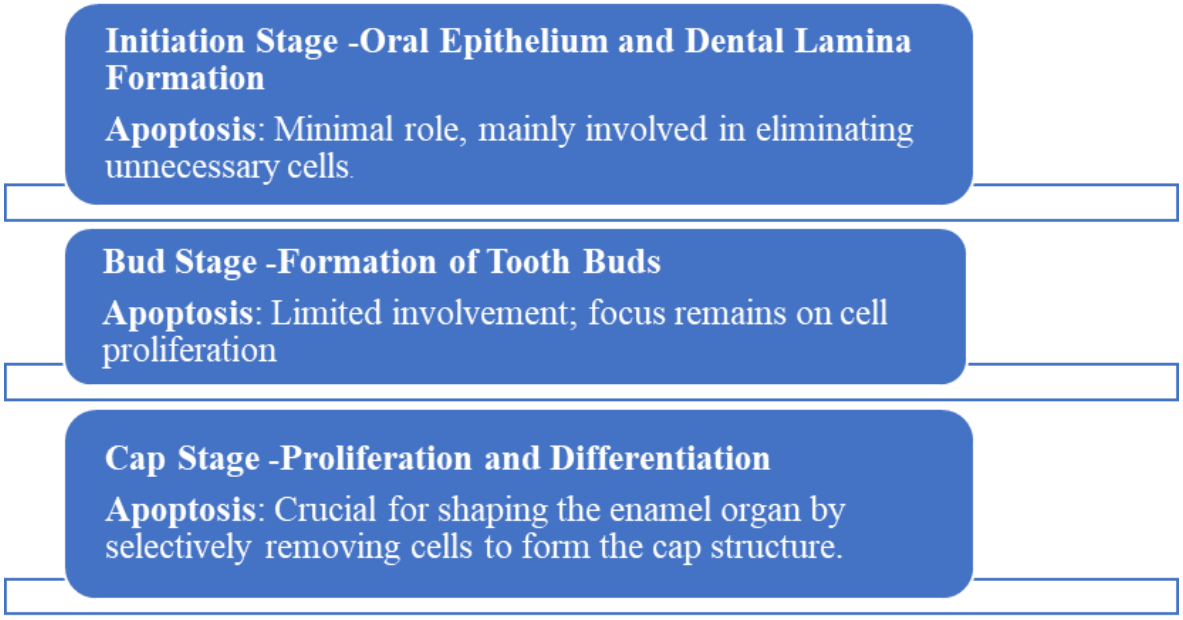
Apoptosis is detected in the bud stage in central cells of the invaginating dental epithelium suggesting its involvement in epithelial budding morphogenesis. During cusp development, apoptotic cells are seen to be located in enamel knots, which are transient clusters of oral epithelial cells proposed to act as signalling centres directing the morphogenesis of tooth cusps. Apoptosis was also detected in other restricted epithelial cell populations including dental lamina, ameloblasts as well as stratum intermedium and stellate reticulum. Apoptosis has a role in the removal of enamel knots which may terminate their task as regulators of patterns of tooth cusps.

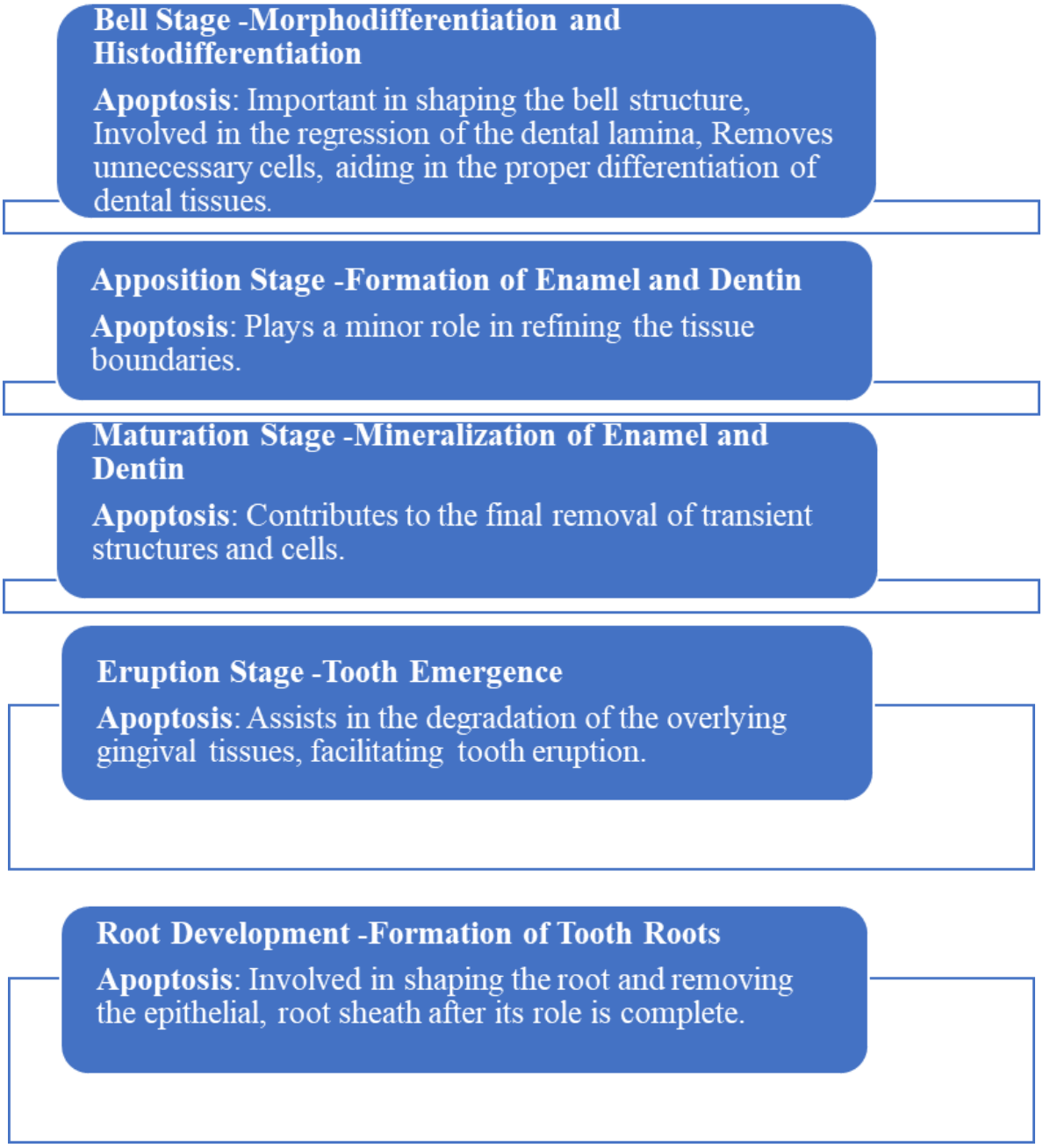
The primary enamel knot appears during the transition from the bud to the cap stage and determines and regulates the cuspal formation. The formation of additional cusps during the bell stage is associated with secondary enamel knots. [8] In the cap stage, when the epithelial bud starts to acquire a cap shape, apoptotic cells are observed within the epithelial enamel knot and the number of apoptotic cells keeps increasing. There is a halt in the cuspal growth with apoptosis of epithelial cells in the enamel knot. Following its apoptosis, the regulation of cell proliferation role is taken up by the cells of stratum intermedium. [1] But at the late cap stage when the enamel knot has largely disappeared, almost no apoptotic cells are detected, though some apoptotic cells can be detected on the periphery of condensed dental mesenchyme throughout the cap stage.[11] Apoptosis is seen in both primary and secondary enamel knots. Thus apoptosis may be the mechanism whereby the enamel knot cells are removed after fulfilling their tasks in initiating cusp formation. [8] To prevent enamel knot cell growth and cause the transitory signalling centre to undergo apoptosis, primary enamel knot cells produce Msx2, Bmp2/4, and the cell cycle inhibitor P21 (CDKN1A). [12]

In the early bell stage, apoptosis is located in epithelial cells of the dental lamina and outer enamel epithelium. The localization of apoptotic cells of the enamel knots significantly shows their role in the regulation of tooth form. The apoptotic cells were also seen in stratum intermedium cells next to the enamel knots. Also in the dental mesenchyme, some scattered apoptotic cells were detected adjacent to the dental follicle.

In the late bell stage, apoptosis continues in the dental lamina and adjacent outer epithelium and there is the presence of apoptotic cells in the dental follicle. Cell death is prominent in stratum intermedium and in the vicinity of these cells, some apoptotic ameloblasts are seen. [8] The disruption of the dental lamina results in a loss of connection between the tooth germ and oral epithelium. The apoptosis in the dental lamina also prevents mesial and vertical overgrowth of the tooth germ and is important in governing the final size and position of the tooth in the jaw. [13]

Flowchart Depicting Apoptosis During Tooth Development:





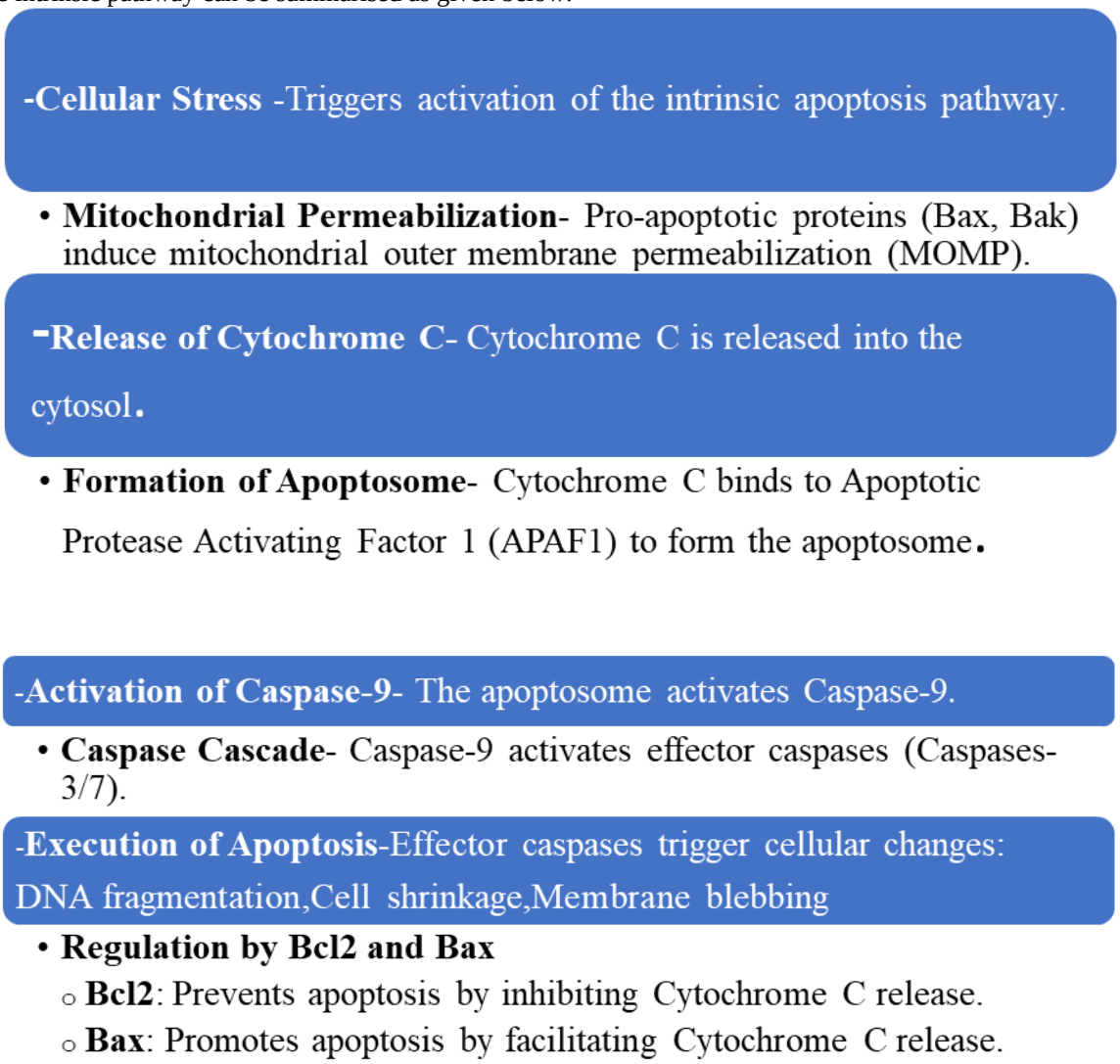
III. Apoptotic Molecular Signaling During Odontogenesis:

Apoptosis may be initiated through two main molecular signalling pathways: intrinsic and extrinsic, both ultimately leading to the activation of caspases and eventual cell death.

Intrinsic Apoptotic Pathway during Odontogenesis - The intrinsic pathway is activated as a response to cellular stress and involves the permeabilization of mitochondria and the release of Cytochrome C. Members of the Bcl2 gene family regulate the intrinsic pathway of apoptosis; acting through several proteins, both anti- (Bcl2, BclXL, Bclw, Mcl1, and A1) and pro- (Bax, Bak, Bok, Bad, Bid, Bik, Blk, Hrk, BNIP3, and BimL) apoptotic proteins, forming dimers to modulate each other's function. It is well known that Bcl2 increases cell lifespan by preventing apoptosis. There is evidence that programmed cell death is hastened and Bcl2's apoptosis-inhibitory action is inhibited when Bax predominates. According to Oltvai et al. (1993), the ratio of Bax to Bcl2 appears to control a cell's susceptibility to programmed death after an apoptotic stimulation. [18] Bax facilitates the release of Cytochrome C by permeabilizing the outer mitochondrial membrane. However, Bcl2 inhibits apoptosis by blocking the release of Cytochrome C from the mitochondria. After release, Cytochrome C subsequently forms a multi-protein complex known as the apoptosome with Apoptotic protease activating factor 1 (APAF1). The apoptosome then activates Caspase-9, which in turn initiates a caspase cascade that leads to the activation of

Caspases-3/7, and finally, apoptosis. Effector caspases are responsible for initiating the hallmarks of the degradation phase of apoptosis, including DNA fragmentation, cell shrinkage, and membrane blebbing. In the early stage of odontogenesis, strong Bcl2 expression in the stellate reticulum and a weaker expression in the inner and outer enamel epithelia are seen. Also, it was seen that the outer enamel epithelium showed a distinct expression of Bax and the dental lamina showed the expression of Bcl2 accurately. Thus, Bcl2 has been proposed to maintain the viability of the enamel organ and preserve stem cells in the dental lamina. [14]

The intrinsic pathway can be summarised as given below:



Extrinsic Apoptotic Pathway During Odontogenesis - Membrane receptors, particularly death receptors [such as the TNF receptor superfamily member 1A (TNFRSF1A, also termed TNFR1) and the Fas cell surface death receptor (FAS, also called CD95)], are responsible for mediating extrinsic apoptosis. [15] The extrinsic pathway involves extracellular signalling and activation of transmembrane death receptors belonging to the TNF receptor superfamily. The Fas ligand is the characterized molecular trigger of apoptosis and is a cell surface glycoprotein that mediates apoptotic signals to the cytoplasm. Upon binding of the corresponding ligand, the Fas receptor undergoes oligomerization, forming a death-inducing signal complex (DISC), through recruitment of the cytosolic adaptor molecules such as TNFR1, Fas-associated death domain (FADD) and TNFR1-associated death domain (TRADD). FADD and TRADD then can further activate other caspases leading to apoptosis. [9,16] The initiator caspases CASP8 (also named caspase 8) and CASP10 (also called caspase 10) drive this process. On the other hand, after their ligands are removed, dependence receptors [such as unc-5 netrin receptor B (UNC5B, also known as UNC5H2) and DCC netrin 1 receptor (DCC)] can trigger extrinsic apoptosis by activating the initiator

caspase CASP9 or dephosphorylating death-associated protein kinase 1 (DAPK1, also known as DAPK). [19] The N-terminal of procaspase-8 binds and activates other downstream caspases, such as Caspase-3, -4, or -7 inducing apoptosis. Therefore, Caspases are the key molecular mediators of apoptosis. [9,16]

The extrinsic pathway can be summarised as given below:

-Extracellular Signaling- Death receptors (e.g., TNF receptor superfamily member 1A (TNFR1) and Fas cell surface death receptor (FAS))are activated by their ligands.

- **Ligand Binding and Receptor Oligomerization**- Ligands (e.g., Fas ligand) bind to the death receptors, causing receptor oligomerization

-Formation of Death-Inducing Signal Complex (DISC)- The oligomerized receptors recruit adaptor molecules such as Fas-associated death domain (FADD) and TNFR1-associated death domain (TRADD).

- **Activation of Initiator Caspases**- DISC activates initiator caspases, mainly Caspase-8 and Caspase-10.

-Caspase Cascade- Initiator caspases activate downstream effector caspases, such as Caspase-3, 4, and 7.

- **Execution of Apoptosis**- Effector caspases trigger cellular changes:
  - DNA fragmentation
  - Cell shrinkage
  - Membrane blebbing

-Regulation by Dependence Receptors- Dependence receptors can activate initiator caspase CASP9 or dephosphorylate DAPK1, promoting apoptosis.

IV. Role Of Apoptosis In Amelogenesis And Dentinogenesis

Apoptosis in amelogenesis - The ameloblasts undergo a remarkable transition from protein secretory cells to cells active in enamel matrix maturation. This transition is accompanied by apoptosis of approximately one-fourth of the ameloblasts. Naturally occurring cell death removes the excess cells and helps in tissue reorganization. An additional one-fourth of ameloblasts undergo apoptosis when the maturation of the enamel matrix takes place with the removal of water and protein from the mineralized matrix [10]. Furthermore, the postmaturation ameloblasts of reduced enamel epithelium undergo apoptosis during the eruption of teeth. Ameloblasts undergo a notable reconfiguration when entering the maturation phase, which is linked to cell death. There is a reduction in the height of ameloblasts, the stratum intermedium disappears, neighboring cells crowd less, and the papillary layer hypertrophy occurs. [17]

Apoptosis in dentinogenesis - Apoptosis intricately contributes to the complex phenomenon of dentinogenesis. Dentinogenesis involves a series of precisely regulated events, including cell proliferation, differentiation, and extracellular matrix deposition, all of which are orchestrated by intricate signalling

pathways.[1,18] Apoptosis, or programmed cell death, emerges as a crucial mechanism in sculpting the dentin matrix and ensuring the proper development of teeth.

One of the key roles of apoptosis in dentinogenesis is in the regulation of odontoblast differentiation and dentin formation. Odontoblasts undergo apoptosis once they have completed secreting the dentin matrix. This regulates the number of cells participating in dentinogenesis, ensuring the proper size and shape of the dentin matrix.

During dentinogenesis, apoptosis occurs in odontoblasts, subodontoblastic regions, central pulp fibroblasts, and perivascular endothelial cells. [19] At the advancing stage of dentinogenesis, odontoblasts become crowded as the pulp space is reduced. It is seen as a pseudostratified layer and an apoptotic elimination of an important percentage of odontoblasts occurs. [10]

Apoptosis also influences the formation of the dentin-pulp complex during tooth development. The pulp tissue, located in the central core of the tooth, consists of various cell types, including odontoblasts, fibroblasts, immune cells, and vascular components. Apoptosis helps to regulate the composition and organization of pulp tissue by eliminating redundant or damaged cells, thereby ensuring the proper function of the dentin-pulp complex. [20]

V. The Role Of Apoptosis In Normal (Functional) And Carious Teeth:

Normal (Functional) Teeth:

Secondary dentin deposition associated with odontoblast reorganization as a single layer results in a decrease in odontoblast number, which seems to result from massive apoptosis. [10] It is seen that odontoblasts are terminally differentiated cells that survive as long as the integrity of the tooth is maintained. [21,22] It is seen that the dental pulp volume decreases gradually on aging due to the continuous production of dentin by odontoblast cells. This age-related reduction in the pulp chamber is associated with eliminating a certain number of odontoblasts by apoptosis. [22,23]

Remodelling of the pulp chamber takes place during successive periods of dentin deposition. [24] The pulp chamber progressively decreases during primary dentin deposition and is reduced to half at the beginning of the secondary dentin deposition and this decrease is accompanied by rearrangements of the odontoblasts within the dental pulp chamber: odontoblasts form a single-layer at the beginning of primary dentin secretion, thereafter they exhibit a multi-layer organization, and at the beginning of secondary dentin deposition they acquire again a single-layer disposal.[25] These changes contribute to the elimination of an important percentage of odontoblasts by apoptosis at the beginning of secondary dentin formation. This shows that aging is accompanied by a general decline in physiological function and a significant increase in apoptosis. [26,27]

Apoptosis is significant in the odontoblastic layer, cells of the sub-odontoblastic layer, and pulp fibroblasts. It is suggested that sub-odontoblastic cells are arrested progenitor cells that can differentiate into odontoblasts. [28,29] Elimination of sub-odontoblastic progenitor cells by apoptosis will restrict the number of cells that can differentiate into odontoblasts, thus reducing the regenerative capacity of the pulp tissue with age. Furthermore, a concomitant elimination of odontoblasts, pulp fibroblasts, and cells of the sub-odontoblastic layer during aging will contribute to a balanced reduction of the pulp chamber volume.

Carious Teeth:

In pathological conditions involving mild carious lesions, odontoblastic activity is stimulated to elaborate ~~a~~ reactionary dentin. [30] But in cases of dental irritations involving violent stresses (i.e. cavity preparations) there is odontoblastic disintegration and newly formed odontoblast-like cells elaborating reparative dentin. Reparative dentinogenesis involves either necrosis or apoptosis of odontoblasts. Reactionary dentinogenesis results from a stimulation of existing odontoblasts and this process takes place in the absence of cell death. However, the deposition of reactionary dentin decreases the pulp chamber volume and could thereafter, favour apoptosis of odontoblasts. [20]

In teeth with carious lesions, the secretory activity of the odontoblasts is stimulated to produce either reparative or reactionary dentin. Apoptosis is seen in odontoblasts facing the carious lesion. In the case of carious teeth, the cavity preparation has the effect of sucking the odontoblasts into the dentinal tubules and this aspiration of odontoblasts in the tubules results in their degeneration. After injury, due to dentin cavity preparation, degenerated odontoblasts are replaced by newly formed odontoblasts, which elaborate the formation of reparative dentin. The newly formed odontoblasts are aligned as a single-cell layer. In mild and medium diffused carious lesions, underlying the carious lesion field odontoblasts, as well as cells of the sub-odontoblastic layer, are eliminated by apoptosis. [27,28]

VI. Dysregulation Of Apoptosis:

Dysregulation of apoptosis in teeth can significantly impact dental development and health. Apoptosis, or programmed cell death, plays a crucial role in shaping the dentin matrix, regulating odontoblast differentiation,

and maintaining tissue homeostasis within the tooth. However, abnormalities in apoptotic pathways can disrupt these processes, leading to developmental defects, pathological conditions, and dental diseases.

One area where dysregulation of apoptosis can occur is in tooth development. During embryogenesis, apoptosis is tightly regulated to sculpt the dental epithelium and mesenchyme, ensuring proper tooth morphogenesis. Aberrant apoptosis during this stage can result in developmental anomalies such as tooth agenesis, where teeth fail to form, or supernumerary teeth, where extra teeth develop beyond the normal complement. Emerging evidence suggests that dysregulation of apoptosis, a tightly regulated process of programmed cell death, plays a critical role in the pathogenesis of ectodermal dysplasias (ED) affecting tooth development. Studies have implicated various signalling pathways and molecular regulators, such as p63, Bcl2 family proteins, and Wnt/β-catenin signalling, in mediating the apoptotic dysregulation observed in ED-associated tooth defects. [31,32,33,34]

There are several ways in which apoptosis dysregulation can occur in amelogenesis. One of the main causes is genetic mutations. Studies have shown that mutations in genes involved in regulating apoptosis can result in tooth enamel defects. For example, mutations in the gene encoding for the protein ameloblastin, which is involved in amelogenesis, have been linked to Amelogenesis Imperfecta, a group of inherited disorders characterized by abnormal enamel structure and density. [35]

In addition to genetic mutations, environmental factors can also lead to the dysregulation of apoptosis in amelogenesis. Exposure to toxins, radiation, or certain drugs during the developmental stages of enamel formation can disrupt the balance of apoptosis and result in developmental defects. The study by Yang et al shows that exposure to high fluoride levels can interfere with the normal process of apoptosis in amelogenesis by targeting the transitional maturation of ameloblasts and inducing greater apoptosis and down-regulating Bcl2 expression. [36]

Moreover, dysregulation of apoptosis in amelogenesis has also been linked to certain diseases and conditions. For instance, in patients with cleft lip and palate (CLP), while the etiology of dental anomalies is multifactorial, emerging evidence suggests that dysregulation of apoptosis may contribute to the disrupted amelogenesis observed in these individuals. The dysregulation of apoptosis in CLP patients can impact multiple aspects of amelogenesis, including enamel matrix secretion, mineralization, and maturation. Studies have implicated apoptotic regulators, such as Bcl2 family proteins, caspases, and p63, in mediating the apoptotic dysregulation observed in CLP-associated dental anomalies. Moreover, altered expression of growth factors and signalling molecules within the cleft microenvironment may further exacerbate apoptotic imbalance and compromise enamel quality and quantity. [37,38,39] Similarly, in individuals with Down syndrome, there is an overexpression of apoptotic genes involved in amelogenesis, potentially influenced by genetic and environmental factors, resulting in delays and defects in enamel formation. The dysregulation of apoptosis in Down syndrome patients can impact multiple aspects of amelogenesis, including enamel matrix secretion, mineralization, and maturation. Studies have suggested aberrant expression of apoptotic regulators, such as Bcl2 family proteins, caspases, and p53, in dental tissues of individuals with Down syndrome. Additionally, altered expression of growth factors and cytokines within the oral microenvironment may further exacerbate apoptotic imbalance and compromise enamel quality and quantity. [40]

The consequences of apoptosis dysregulation in amelogenesis are severe and can have a significant impact on an individual's oral health. Enamel defects resulting from abnormal apoptosis can range from mild discoloration to complete absence of enamel. Enamel defects resulting from abnormal apoptosis can manifest in various ways, ranging from quantitative changes in enamel thickness to qualitative alterations in enamel structure and mineralization. Abnormal apoptosis in the dental epithelium and mesenchyme can disrupt the intricate processes involved in enamel formation, leading to structural abnormalities.

1. Hypoplastic Enamel: Dysregulated apoptosis can decrease cell proliferation or differentiation in the ameloblasts, reducing enamel matrix secretion. This can manifest as hypoplastic enamel, characterized by thin enamel layers with pits, grooves, or localized areas of missing enamel, compromising its function and esthetics.

2. Hypomineralized Enamel: Abnormal apoptosis may affect the mineralization process during enamel formation, resulting in hypomineralized enamel. This type of enamel defect is often associated with decreased mineral content, increased porosity, and susceptibility to dental caries and mechanical wear.

3. Enamel Hypomaturation: Dysregulated apoptosis can disrupt the maturation phase of enamel development, leading to enamel hypomaturation. In this condition, the enamel appears normal in thickness but lacks proper mineralization, resulting in a softer enamel that is prone to post-eruptive breakdown and discoloration.

4. Structural Abnormalities: Abnormal apoptosis can also result in structural abnormalities of the enamel, such as irregularities in enamel prism organization, abnormal crystal orientation, or altered enamel rod patterns. These structural defects can weaken the enamel and increase the risk of fracture and erosion.

Overall, abnormalities in apoptosis can disrupt the delicate balance of cell proliferation, differentiation, and death during enamel development, leading to a spectrum of enamel defects with varying clinical presentations and consequences for oral health. [18,41,42,43]

Furthermore, apoptosis plays a critical role in odontoblast differentiation and dentinogenesis. Odontoblasts, specialized cells responsible for dentin formation, undergo apoptosis once they have completed matrix secretion. This programmed removal of odontoblasts is essential for terminating dentinogenesis and allowing subsequent stages of tooth development to proceed. Disruption of apoptosis in odontoblasts can result in defective dentin formation and structural abnormalities in the teeth. For example, dysregulation of apoptosis has been implicated in conditions such as dentin dysplasia, characterized by defective dentin mineralization and abnormal dentin structure.

Moreover, dysregulated apoptosis can impact the integrity and function of the dentin-pulp complex, the vital tissue within the tooth comprising odontoblasts, pulp cells, nerves, and blood vessels. Excessive apoptosis within the dental pulp can lead to pulp necrosis, a condition characterized by the death of pulp tissue, inflammation, and bacterial infection. Conversely, impaired apoptosis may contribute to pulp tissue overgrowth or hyperplasia, resulting in pulp polyps or other proliferative lesions within the pulp chamber. [27,28]

Moreover, dysregulation of apoptosis can lead to various developmental abnormalities and pathological conditions affecting dentinogenesis. For instance, excessive apoptosis of odontoblasts or pulp cells can impair dentin formation and compromise the structural integrity of teeth, leading to conditions such as dentin dysplasia or dentinogenesis imperfecta. Conversely, inhibition of apoptosis may result in aberrant cell proliferation and tissue overgrowth within the dental pulp, disrupting normal tooth development. [20]

Understanding the mechanisms underlying the dysregulation of apoptosis in teeth is essential for developing targeted therapeutic interventions. Potential approaches may include modulating apoptotic signalling pathways to promote tissue repair and regeneration or targeting specific apoptotic regulators to prevent or treat dental diseases. Additionally, advances in genetic and molecular techniques offer opportunities for personalized interventions tailored to individuals with genetic predispositions to dental abnormalities.

In conclusion, dysregulation of apoptosis in teeth can profoundly affect dental development and health. Abnormalities in apoptotic pathways can lead to developmental defects, structural abnormalities, and pathological conditions affecting the enamel and dentin-pulp complex. Further research into the molecular mechanisms underlying apoptotic dysregulation in teeth is essential for developing effective strategies for preventing, diagnosing, and treating dental diseases.

VII. Conclusion:

Apoptosis plays an active role in odontogenesis and apoptotic cells dynamically influence surrounding cells to trigger tissue remodelling through the regulation of cell division, cell death, cell fate, migration, cell shape, and remodelling of nearby tissues. It has a significant role in odontogenesis and caters to a variety of physiological and pathological manifestations of the oral cavity. Its role in the pathophysiology of normal and carious teeth is also appreciable. Further research in this area will not only enhance our understanding of odontogenesis but also aid in the prevention and treatment of dental defects.

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