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The Role of Autophagy in Regenerative Dentistry

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ABSTRACT

Autophagy plays an important role in the development, differentiation, aging, and tooth morphogenesis. The dental pulp maintains the tooth's homeostasis, and supports dentin formation and regeneration. Autophagy in a pulp cell can either protect or kill the cell, depending on the duration and dose of extrinsic factors. Cell survival and homeostasis are maintained by a balanced synthesis and degradation of cellular proteins and organelles. Failure of autophagy can result in the accumulation of potentially harmful damaged structures. Autophagic activity can help dental pulp stem cells survive under mild stress, whereas it leads to cell death under severe stress. Factors such as aging can promote an increase in autophagy in dental pulp cells, suggesting that autophagy may be important for the differentiation of odontoblasts and pulp mesenchymal cells as well as their survival. A complex cellular activity regulates dental pulp cells' lifespan to guarantee organelle and protein renewal. The detailed mechanisms behind autophagy's participation in the pulpal diseases and healing are still unclear, so more research is needed to better understand the relationship. It is predicted that further research on autophagy will help to the development of innovative and effective targeted therapies in regenerative dentistry.

Key words: Autophagy, Regenerative Dentistry, Dental Pulp Stem Cells, Odontoblasts, Cell Death

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INTRODUCTION

Osteoarthritic Ontogenesis (tooth development) occurs in several complex stages- initiation, morphogenesis, differentiation, root formation, and tooth eruption. Tooth development begins in the first six weeks of intrauterine life and is determined by epithelial-mesenchymal interactions between cells derived from cephalic neural crest and the first pharyngeal arch .Odontogenesis continues with morphogenesis and differentiation into various forms of functional cells to form the enamel and dentin. Ameloblasts epithelially derived cells, form tooth enamel, while the dental mesenchyme forms the pulp dentin complex and cementum.

The permanent and deciduous dentitions both go through the same developmental process. During the embryonic development of a tooth, a large number of interactions take place. The initial signals for tooth development are provided by the oral ectoderm. The initiation, primary, and secondary enamel knots are important signaling centers in the morphogenesis of the dental epithelium. The epithelial and mesenchymal tissues communicate by signaling. When the epithelium sends signals to the mesenchymal cells, the mesenchyme responds with reciprocal signals. A cell triggers the behavior of another cell in its environment by signaling the growth factor molecules.The Fibroblast Growth Factor (FGF), Epidermal Growth Factor (EGF), and Transforming Growth Factor (TGF) are crucial for tooth development. Different tooth types are formed as a result of temporal and spatial control of gene expression.

Genes decide the size, shape, location of teeth, as well as they are key regulators of cell interactions associated with odontogenesis. The Msx gene, Pax gene, Shh gene, Wnt/ beta-catenin signaling, and Cbfa-1 gene are associated with tooth development stages.

Researchers reported that inhibition of one of these signaling pathways can stop odontogenesis at the early stage in the mouse embryo. Various developmental defects and tooth anomalies may be caused by abnormalities in the complex signaling networks that regulate odontogenesis. These dental disorders often occur in conjunction with other birth defects and syndromes.

In several complex stages of tooth development, autophagy preserves cell energy homeostasis by recycling damaged organelles and proteins. Autophagy begins with the formation of double-membrane vesicles, followed by the encapsulation of the cargo and the elongation of the lipid-based membrane to form mature autophagosomes [2,221]. To maintain cytoplasmic homeostasis, autophagosomes combine with lysosomes to remove cellular components.

The master regulator (mTOR) and the autophagy-related gene (ATG) products, both negatively control autophagy. Beclin1 is a component of the PtdIns 3-kinase complex, which is related with the formation of autophagosomes.

Atg5–Atg12 and LC3 are two conjugation systems essential for autophagosome elongation and maturation. LC3 is a yeast Atg8 homolog that is commonly used as an autophagosome marker.

Teeth are susceptible to genetic, intrinsic, and extrinsic influen. Dentin and cementum have a limited regenerative capacity, while enamel is incapable of repairing itself. Enamel is produced by ectoderm-derived ameloblasts. During tooth maturation, the ameloblasts undergo programmed cell death and no longer present in mature enamel.

When enamel is damaged, it cannot be biologically restored. Acellular remineralization is the form of healing that occurs in damaged enamel. Fluoride and calcium phosphate nanocrystals are used in enamel remineralization, they can protect the outer enamel layer, but they do not mimic the similar structure and mechanical properties of natural enamel.

Dentin is made by odontoblasts, which are derived from ectomesenchyme and remain in the pulp throughout one's life. Unspecialized cells identified as clonogenic cells with the ability to self-renew and differentiate into one or more specialized cell types are known as stem cells (SCs). Adult SCs have been found in a variety of body tissues, are thought to play a specific role in tissue repair and regeneration. The dental pulp maintains the tooth's homeostasis, and supports dentin formation and regeneration. Caries, pulpitis, periapical periodontitis, tooth trauma, and other injuries or diseases may cause pulp necrosis, which leads to tooth loss. Vital pulp therapy and regenerative endodontic treatments are therapeutic techniques for endodontic diseases. Vital pulp therapies maintain and save the dental pulp vitality, as well as induce dental pulp stem cells (DPSCs) to differentiate into odontoblasts to form a hard tissue barrier. Regenerative endodontic treatments aim to regenerate the dentin-pulp structure and maintain the normal function of tissues.

Dental pulp stem cells in permanent teeth (DPSCs) and stem cells from human exfoliated deciduous teeth (SHED) are both present in the dental pulp.

In vitro, DPSCs and SHEDs could differentiate into odontoblasts, adipocytes, chondrocytes, and osteoblasts, as well as functionally active neurons. SHEDs have higher proliferation rates and more population doublings than DPSCs.

SCs are non-specialized cells that can differentiate into a variety of adult cells while self-replicating to maintain the SC population. SCs have a long lifespan and go through long periods of quiescence. It is believed that autophagy is required for these unique properties of SCs, including pluripotency and differentiation, self-renewal, and quiescence.

Protein turnover and lysosomal digestion of organelles must be tightly controlled during differentiation and self-renewal processes. By managing protein turnover via mTOR regulation, autophagy plays a critical role in achieving exact shape and function. Autophagy allows for the rapid and efficient elimination of various factors such as enzymes, adhesion molecules, or released products. Furthermore, SCs spend most of their life in the G0 phase of the cell cycle, waiting for signals to return to the cell cycle and differentiation.

Within these quiescent cells, autophagic turnover of proteins and fatty acids are important in removing damaged structures that could induce quiescence loss and cannot be diluted by transfer to daughter cells.

Cellular senescence is characterized by the loss of proliferative ability, as well as a decrease in cell homeostasis and regeneration capability. Autophagy reduces the oxidative burden of damaged mitochondria by the mTOR pathway and other autophagic degradation regulators such as FoxO3, NF-B, p53, and SIRT1.

The pulp–dentin complex undergoes a moderate to extreme inflammatory process when exposed to extrinsic factors. Odontoblasts, fibroblasts, immune cells, Schwann's cells, and vascular/perivascular cells are all present in the healty dental pulp. The repair process starts in viable pulp cells with an inflammatory response, by chemical signaling SCs move to the injured area to start pulp regeneration. Anti-inflammatory cytokines, steroids are released to restrict tissue harm, while proinflammatory cytokines, are released to enhance the immune response. Low levels of inflammatory cytokine signals promote the repair process, while high levels of cytokine signaling may result in other responses in DPSCs.

The wound healing/repair process requires vascularization for cellular proliferation and differentiation [58-60]. The growth factor molecules (VEGF, bFGF and TGF-), which are released by damaged pulp cells, endothelial cells, and extracellular matrix, promote vascularization. The inflammatory, proliferation, and differentiation processes all work together to help the natural healing of pulp–dentin tissue.

Autophagy is triggered in response to stress and is involved in pulp diseases' pathogenesis. It appears to be an important cellular mechanism for protecting dentin-pulp structure and stem cells from damages by extrinsic factors.

Cell survival and homeostasis are maintained by a balanced synthesis and degradation of cellular proteins and organelles. Failure of autophagy can result in the accumulation of potentially harmful damaged structures. Autophagy in a pulp cell can either protect or kill the cell, depending on the duration and dose of extrinsic factors. Autophagic activity can help dental pulp stem cells survive under mild stress, whereas it leads to cell death under severe stress.

Autophagy is increased in a variety of situations, including local anesthetic therapy, fluorosis, periodontal disease, and periapical lesions. Local anesthetics, according to Zhuang et al., can rapidly trigger autophagy in dental pulp cells in both animal models and cultured human cells.

Fluoride has an impact on tooth formation, especially during differentiation. Fluoride causes cell stress in the endoplasmic reticulum and oxidative damage, which causes ameloblasts impairment. Fluoride-induced ROS formation caused oxidative damage to mitochondria and DNA in LS8 cells and/or ameloblasts, according to Suzuki et al.

Factors such as aging can promote an increase in autophagy in dental pulp cells, suggesting that autophagy may be important for the differentiation of odontoblasts and pulp mesenchymal cells as well as their survival. A complex cellular activity regulates dental pulp cells' lifespan to guarantee organelle and protein renewal.

Radicular cysts and periapical granulomas are inflammatory periapical lesions and persistent infection sources. Autophagy interacts with inflammation and immunological responses, and its overexpression or downregulation may be linked to the development of a variety of pathogenic disorders. Hypoxic stimuli have been shown to boost HIF-1a protein synthesis, which is known to promote cell proliferation and is a key mediator of cellular adaptation to hypoxia. The other factor that might activate HIF-1 signaling is inflammation.

The AMPK/ mTOR pathway is another HIF-1a-independent pathway. Under low oxygen conditions, AMPK is also a key cellular response for maintaining energy balance. Activated AMPK phosphate can cause autophagy by inhibiting the mTOR kinase. Autophagy of human dental pulp cells has been shown to protect cells from hypoxia via the AMPK/mTOR pathway.

Autophagy has been found in human inflamed periapical lesions, leading to the conclusion that autophagy in combination with hypoxia could be a factor in the progression and maintenance of inflamed periapical lesions. In radicular cysts and periapical granulomas, Huang et al. reported that pAMPK expression was significantly higher than HIF-1a.

Lipopolysaccharide and lipoteichoic acids, which are significant cell wall components of gram-(-) and gram-(+) bacteria, may induce autophagy in dental pulp cells. Recent research has found that there is significant crosstalk between autophagy and apoptosis in dental pulp cells, suggesting that this could be a promising approach for pulpitis treatment [4].

CONCLUSION

The detailed mechanisms behind autophagy's participation in the pulpal diseases and healing are still unclear, so more research is needed to better understand the relationship. It is predicted that further research on autophagy will help to the development of innovative and effective targeted therapies in regenerative dentistry.

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