REVIEW ARTICLE

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Autophagy in dentistry: A review article

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SUMMARY

The word Autophagy is derived from the Greek which means eating of self. It is a catabolic process involving the degradation of aberrant cellular components through lysosomal hydrolysis. It has also been regarded as a pivotal cellular event for stem cell protection from damages caused by extrinsic factors. The three types of autophagy are macro-autophagy, micro-autophagy and chaperone-mediated autophagy. This review attempts to highlight the association of autophagy with various oral conditions.

Key Words: *Autophagy, lysosomes, odontoblasts, autophagosomes, mitochondria.*

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Introduction

Autophagy is a catabolic process which involves the degradation of unimportant or aberrant cellular components through lysosomal hydrolysis.1It is a major cellular process which has been involved in an array of cellular and tissue events, including cell stress, endogenous and exogenous cellular component clearance, development, aging and cancer.1 The word 'autophagy' is derived from the Greek which means 'eating of self'. It was coined by Christian de Duve over 40 years ago. It was mostly based on the observed degradation of mitochondria and other intra-cellular structures within the lysosomes of rat liver perfused with glucagon, the pancreatic hormone.2

Based on the systems, autophagy has been frequently linked with mitochondrial dysfunctions and autophagosomes are constantly localized within the mitochondria.1 Recently, autophagy has been regarded as an important cellular event for protection of stem cells from damages caused by extrinsic factors.3 Macro-autophagy, micro-autophagy, and chaperone-mediated autophagy are the three types of autophagy. At the lysosome, they promote proteolytic degradation of cytosolic components. Macro-autophagy involves delivery of cytoplasmic cargo to the lysosome via double membrane-bound vesicle, called as an autophagosome. This fuses with the lysosome forming an autolysosome. In case of microautophagy, the cytosolic components are directly engulfed by the lysosomes through invagination of the lysosomal membrane. Chaperone mediated autophagy involves translocation of the lysosomal proteins in a complex with chaperone proteins. These proteins are recognized by the lysosomal membrane receptor lysosomal-associated membrane protein 2A (LAMP-2A) which results in their unfolding and degradation.4 While many normal types of cells need a certain well-controlled level of autophagy, any condition above the capacity of a cell to control can provoke a specific killing machinery: autophagic cell death.1

Tooth

Autophagy persists at a lower level in odontoblasts and pulpal cells. 5,6 Despite a high prevalence of tooth diseases, the association of key cellular protection and autophagy with regard to tooth development and various dental diseases have not been researched adequately till date.7 In a human tooth, conditions such as fluorosis, periodontal diseases (through lipopolysaccharide) and during local anesthetic treatment have been shown to elevate autophagy. The affected tooth cells could be of epithelial or mesenchymal origin based on the specific condition and location where one factor acts.7

An epidemiological study conducted by Swee J et al

showed that local anesthetics could induce tooth agenesis.8 Zhuang et al, in their study using detailed dynamic cellular energetic analysis suggested that local anaesthetics have the ability to rapidly induce autophagy in the tooth pulp cells, both in animal models and in cultured human cells.6 The induction of autophagy is secondary to an increase in mitochondrial respiration, which is believed to counteract the drug toxicity which is a protection mechanism.6

Factors such as aging can cause an elevation in autophagy in the tooth pulp cells which suggests that potentially autophagy is also vital for maintainence of functional actions or survival of the differentiated odontoblasts and pulp mesenchymal cells.5

Fluoride

Fluoride can also affect tooth development primarily during differentiation. Fluoride causes induction of cell stress, including endoplasmic reticulum stress and oxidative stress. This leads to impairment of ameloblasts, which are responsible for dental enamel formation.9 Suzuki et al concluded that fluoride-induced ROS generation caused oxidative damage to mitochondria and DNA in LS8 cells and/or ameloblasts. Fluoride causes activation of SIRT1/autophagy via ROS-mediated JNK signaling to protect cells from fluoride-induced cytotoxicity, thus imparting a protective action.9

Periodontal diseases

Periodontitis is generally a chronic disorder which is characterized by the breakdown of tooth-supporting tissues thus producing a loss of dentition. It is the most prevalent chronic inflammatory human disease affecting 30% to 40% of the population over 35 years of age. 10

Bullon et al conducted a study which showed that increased levels of autophagy gene expression and high levels of production of mitochondrial reactive oxygen species in peripheral blood mononuclear cells in patients with periodontitis in comparison to controls.11 An increase in the expression of autophagy-related mRNA and proteins were observed, demonstrating the activation of autophagy after enhancement of reactive oxygen species(ROS) which occurred after mitochondrial dysfunction induced by P. gingivalis lipopolysaccharide. It has been stated that ROS production and oxidative stress are a common outcome of dysfunctional mitochondria and play a chief role in the development of autophagy.12

Periapical lesions

Inflammatory periapical lesions which include radicular cysts (RCs) and periapical granulomas (PGs), are part of the body's defence reaction to the threat of microbial infestation in root canals. Due to persistent infection sources through the root canals, inflammatory periapical lesions cannot undergo healing and hence continue to persist.13

The hypoxia and inflammatory surroundings can promote angiogenic processes, cell proliferation or cell protection via various mechanisms such as autophagy in order to help cells overcome this challenging position.14,15 Huang Y et al, in their study concluded that autophagy in association with hypoxia can be a probably cause in the advancement and maintenance of inflamed periapical lesions.16

Oral squamous cell carcinoma

Oral Squamous Cell Carcinoma (OSCC), the malignant neoplasm of the oral cavity, has the propensity to aggressively develop, if early diagnosis does not take place. Worldwide, miscellaneous ethnic communities have customarily used herbal products for prevention and treatment of various chronic diseases.17,18 Several natural chemicals have been stated to display anticancer action by triggering both autophagy and apoptosis.19,20 Polyphyllin G has been demonstrated to have powerful anticancer action in a broad array of human cancer cell lines.21 Autophagy has lately emerged as a promising objective of research for drugs to treat several diseases. It has also been involved in the pathogenesis of cancers and diseases.22 Hsieh MJ et al, in their study concluded that Polyphyllin G induced apoptosis in oral cancer cells via activation of AKT, ERK1/2, p38 and JNK1/2. Also, the activation of ERK1/2 and JNK1/2 were accountable for Polyphyllin G-induced autophagy.23

Conclusion

The literature pertaining to autophagy and oral health is scarce. But it is understood that it has a protective role in various oral conditions. Several mechanisms of autophagy are not yet clearly understood. Although the shortcomings, it has been the objective for drug research. Hence more research is vital in this aspect in order to have a better understanding of the mechanism of autophagy, and its promising role in drug research.

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