Short Communication

Unravelling the role of autophagy in human dental pulp

Tulika Wakhloo[1], Sanjeev Kishore[2], Prashant Durgapal[2]

Departments of [1]Dentistry, [2]Pathology, All India Institute of Medical Sciences (AIIMS), Rishikesh, Uttarakhand, India

Abstract

Autophagy is an evolutionarily conserved intracellular catabolic process that recycles and degrades proteins, organelles and pathogens. It is an endogenous defence mechanism regulating multiple cellular pathways like apoptosis, inflammation, immune response and pathogen clearance and acts as a modulator of pathogenesis. This article highlights the emerging role of autophagy in inflammation and regeneration of human dental pulp. It emphasizes exploring autophagy and autophagy agonists as potential targets for the development of novel therapeutic interventions.

Keywords: Autophagy, platelet-rich plasma, pulpitis, rapamycin, regenerative dentistry, therapeutic targets

Address for correspondence: Dr. Tulika Wakhloo, Department of Dentistry, All India Institute of Medical Sciences (AIIMS), Rishikesh - 249 202, Uttarakhand, India.
E-mail: tulikawakhloo@gmail.com

Submitted: 29-Apr-2023, **Revised:** 25-Sep-2023, **Accepted:** 27-Oct-2023, **Published:** 15-Apr-2024

INTRODUCTION

Autophagy is a basic physiological intracellular catabolic process scavenging damaged organelles, toxic protein aggregates and pathogens. The cellular components are sequestered in phagophores which undergo expansion through acquisition of lipids and subsequently close to form double membrane autophagosomes. The mature autophagosomes then fuse with the lysosomes leading to the degradation of the vesicular contents via lysosomal hydrolysis and the resulting macromolecules go back into the cytosol for reuse. This highly conserved lysosomal degradation process acts as an endogenous defence mechanism and is crucial for maintaining cellular homeostasis.[1] It is primarily dependent on proteins belonging to the ATG family that also help in molecularly analysing the autophagy process, for example, Microtubule Associated Protein 1 Light Chain 3 (MAP1LC3/LC3) which is a key ubiquitin-like protein mediating autophagosome formation. Studies have revealed the dual role of autophagy in several diseases like oral cancer where it allows the cells to survive during harsh conditions such as hypoxia, oxidative damage and starvation and on the other hand participates in a pro-death mechanism known as autophagic or type II programmed cell death. This dual role depends on the specific disease and its level of progression.[1] Furthermore, recent research provides new insights into the role of autophagy in the initiation and progression of oral diseases; however, the precise mechanisms still remain unknown. Considering that autophagy regulates multiple cellular pathways like apoptosis, inflammation, immune response and pathogen clearance; it acts as a modulator of pathogenesis and hence is a potential therapeutic target.[1]

Pulpitis is the inflammation of the dental pulp which occurs as a sequela to dental caries since demineralization of enamel and dentin led by caries causes microorganisms, subsequently leading to the deterioration of pulp tissue.[2,3] The reported high failure rate of clinical treatment of

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Quick Response Code:

Website: https://journals.lww.com/JPAT/

DOI: 10.4103/jomfp.jomfp_197_23

How to cite this article: Wakhloo T, Kishore S, Durgapal P. Unravelling the role of autophagy in human dental pulp. J Oral Maxillofac Pathol 2024;28:106-8.

pulpitis is estimated to be 60% after 5 years making it imperative to find effective methods that inhibit its development.[2] It has been reported that the innate immunity of host dental pulp is provided via the pattern recognition receptors (PRRs) which recognize pathogen-associated molecular patterns (PAMPs). The two PRRs associated with pulpitis are toll-like receptor 4 (TLR4) and nucleotide-binding oligomerization domain-containing protein 2 (NOD2) which are found in various cell types, namely neutrophils, macrophages, dendritic cells, epithelial cells and endothelial cells.[2]

A study by He Q *et al*.[2] analysed the presence, distribution and localization of TLR4, NOD2, interleukin-1 (IL-1) beta and autophagy marker (LC3) using immunohistochemistry in the human pulp tissue of 47 human third molars divided into three groups, namely normal teeth, teeth with caries but no spontaneous pain and teeth with pulpitis. High expression of TLR4, NOD2 and LC3 in the caries and the pulpitis group was found with distinct localization in the odontoblastic layer as these are the first cells to encounter bacterial infection. Increased inflammation was also found in these groups which were attributed to the synergism between TLR4 and NOD2 for cytokine production and upregulation of IL-1B, IL-6, IL-8, IL-10 and tumour necrosis factor-alpha in primary monocytes. The simultaneous activation of TLR4 and NOD2 occurred as a response to toxins produced by microorganisms and due to the fact that the same bacteria can cause the activation of multiple PRRs. TLR4 was found to play a crucial role in sensing cariogenic bacteria, producing inflammatory cytokines and activating autophagy as a defence mechanism to protect the host against bacterial infection. Furthermore, the microflora in deep caries is dominant with gram-negative anaerobic bacteria and LPS is the main component of their cell walls triggering an inflammatory response that leads to cell death by pyroptosis. It has been found that LPS caused low-level activation of autophagy which occurred as a self-help strategy in dental pulp cells. However, rapamycin, an autophagy agonist, resulted in the inhibition of LPS-induced pyroptosis in cultured dental pulp cells via inhibition of IL-1 beta expression and regulating the nuclear factor kappa B signalling pathway. Hence, targeting autophagy and exploring the potential of rapamycin can be an effective therapy for pulpitis.[3]

The dental pulp is a vascular-rich tissue crucial for maintaining tooth vitality. Its limited self-repair capacity and restricted blood supply through a narrow apical foramen make it vulnerable to necrosis by trauma and infections and make its regeneration difficult. It has been recently reported that transplantation of aggregated human deciduous pulp stem cells (hDPSC) can lead to morphological and functional regeneration of full-length dental pulp. In addition, apoptosis has been reported to play an important role in tissue homeostasis and regeneration since specific metabolites released by apoptotic cells act as goodbye signals which further modulate the biologic functions of neighbouring cells.[4] Apoptotic vesicles (apoVs) are a type of extracellular vesicle released by apoptotic cells that can transfer multiple substances like micro-RNAs, proteins and lipids and initiate signal transduction. An *in vitro* study by Li Z *et al*.[4] revealed that exogenous hDPSCs underwent apoptosis and released apoVs that specifically activated autophagy in endogenous endothelial cells. Activated autophagy in otherwise inactive host endothelial cells promoted their angiogenic abilities along with their proliferation, migration, differentiation and secretion. This led the host blood vessels to grow in an ischemic-hypoxic environment and subsequently resulted in pulp revascularization and tissue regeneration. Another *in vitro* study reported that platelet-rich plasma (PRP) when cultured with hDPSCs increased their regenerative potential. It was found that PRP-induced autophagy was evident by the significant increase in the autophagy marker LC3 in PRP-treated hDPSC. It was further reported that cell migration, proliferation and osteogenic differentiation of hDPSC were upregulated in the presence of an autophagy activator and downregulated in the presence of an autophagy inhibitor. Therefore, autophagy can restore the lost pulp tissue based on hDPSC-apoVs-mediated early revascularization and tissue regeneration.[5]

CONCLUSION

Autophagy has a promising role to play in the inflammation and regeneration of human dental pulp tissue. Further research is required to better elucidate and understand the interaction of autophagy with other processes in human dental pulp. This can lead to the development of novel therapeutic interventions with significant clinical impact.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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