

Review article

The role of autophagy in oral cancer

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ABSTRACT

Autophagy is a universally preserved process in which cells break down their own intracellular organelles to control their regular renewal and eliminate dysfunctional organelles to maintain a balance inside the cell. Autophagy is a biological mechanism that helps cells adapt and protect themselves against stressors such as hypoxia, nutrient deficiency, and energy deprivation. Disruption of autophagy has been linked to a range of diseases, such as neurological disorders, infectious diseases, and cancer.

Oral cancer is a highly destructive illness that results in the loss of numerous lives worldwide annually. The existing array of therapy modalities fails to adequately address the requirements of patients. Personalized medicine or targeted medicines are necessary due to the heterogeneity of the disease. Hence, it is imperative to promptly identify possible targets for oral cancer therapy. Autophagy has been discovered to potentially play a function in both the inhibition and advancement of oral cancer. Cancer cells employ the autophagy mechanism to enhance their survival in response to the stress induced by chemotherapy. Hence, it is of utmost importance to comprehend the processes underlying the suppression of cytoprotective catabolism and the exploitation of autophagic cell death to enhance the susceptibility of malignant tumor cells to certain therapeutic drugs and devise efficacious treatment strategies.

KEYWORDS: ATG; Cell; Macroautophagy; Microautophagy; Squamous cell carcinoma.

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INTRODUCTION

Autophagy is a tightly controlled biological mechanism in which proteins and damaged organelles are enclosed within autophagosomes, vesicles with double membranes. Once formed, autophagosomes combine with lysosomes, resulting in the breakdown of the substances contained within the autophagosomes.¹ Autophagy is categorized into three basic types based on how cellular components are transported to the lysosome: macroautophagy, chaperone-mediated autophagy (CMA), and microautophagy.² Microautophagy is a biological process in which cytoplasmic material is broken down inside the lysosome by the folding or deformation of the lysosomal membrane.² CMA entails the identification of soluble intracellular proteins containing a KFERQ pattern by heat shock protein 70 (HSP 70). The proteins are subsequently targeted to lysosomes for degradation by the action of lysosome-associated membrane protein 2A (LAMP2A).³ The process of macroautophagy encompasses the generation of autophagosomes, which are vesicles characterized by a double-membrane structure. These autophagosomes serve the purpose of eliminating organelles or proteins that have incurred damage. Subsequently, the autophagosome undergoes fusion with the lysosome, leading to the degradation of damaged organelles or proteins through the action of lysosomal hydrolases. Macroautophagy, which is extensively investigated, is the predominant type of autophagy⁴ and will be denoted as autophagy throughout this article.

Oral cancer (OC) is the sixth most prevalent form of cancer around the world, exhibiting a five-year survival rate of around 50%. This relatively low survival rate can be attributed to delayed detection, the aggressive nature of the disease, and the emergence of resistance to therapeutic interventions.⁵ According to existing literature, it has been observed that around 90% of oral malignancies can be classified as squamous cell carcinomas.⁵ Malignant neoplasms arising from connective tissue, lymphoid tissue, minor salivary glands, or melanocytes account for around 10% of oral malignancies.⁶

In instances of adverse physiological circumstances, the maintenance of cellular homeostasis, development, and metabolic balance heavily relies on the basal levels of autophagy.⁷ Additionally, it is regarded as a cellular

adaptive response to many cellular stressors, including hypoxia, nutrition, and energy deprivation. This response has a cytoprotective function.⁷ The dysregulation of autophagy is implicated in the etiology of numerous diseases, including neurological disorders, infectious diseases, and cancer.⁷ Autophagy has been observed to potentially have a role in both the suppression and advancement of OC. Autophagy exhibits noteworthy correlations with clinicopathologic characteristics and prognostic outcomes in oral squamous cell carcinoma (OSCC).^{8,9}

This article focuses on the impact of autophagy on OC, followed by a concise overview of the autophagy mechanism and the regulatory processes managing autophagy.

Mechanism and Regulation of Autophagy

Autophagy is a cellular mechanism that allows cells to efficiently deal with many external and internal stressors, such as lack of food and the presence or absence of insulin and other growth hormones.¹⁰ The control of autophagy is dictated by a diverse array of proteins that are produced by autophagy-related genes (ATG).² The autophagosome undergoes a series of four distinct stages, including induction, phagophore elongation, autophagosome development, and finally, lysosomal fusion and disintegration.¹¹

Autophagy is initiated in response to heightened cellular stress caused by the buildup of damaged organelles and proteins.¹² The ULK1 serine threonine kinase complex, comprising ULK1, FIP200, ATG13, and ATG101, has a vital function in initiating autophagy by phosphorylating numerous downstream components.¹² The mechanistic target of rapamycin complex 1 (MTORC1), the primary serine/threonine kinase involved in food sensing pathways, serves as a significant suppressor of autophagy.¹³ When there are plenty of nutrients available, the MTORC1 complex (MTORC1) becomes active due to the actions of phosphoinositide 3-kinase (PI3K) and AKT/PKB. As a result, MTORC1 phosphorylates ULK1 and ATG13, which somewhat hinders the process of autophagy.¹³ When cells receive signals indicating food deprivation, the activity of MTORC1 is suppressed by AMP-activated protein kinase (AMPK), which can be directly triggered via the low ratio of ATP to ADP. AMPK modulation can result in the suppression of MTORC1 and the activation of the ULK complex, which in turn stimulates the autophagy cascade.¹⁴ Signals that trigger the initiation of macroautophagy include hypoxia and the lack of growth hormones. Despite the existence of enough nutrition, the lack of growth hormones triggers the initiation of macroautophagy. Both growth factors and hypoxia exert control over macroautophagy, partially via MTORC1. Furthermore, hypoxia has the ability to suppress MTORC1, even when there are plenty of nutrients and growth hormones present.¹⁵ The class III phosphatidylinositol 3-kinase (PI3K) complex, consisting of VPS34, VPS15, Beclin 1, and

ATG14, plays a vital role in the start of phagophore production.¹² This complex is accountable for the synthesis of phosphatidylinositol-3-phosphate (PI3P), which is necessary to attract PI3K-binding proteins to the phagophore attachment site.¹² The elongation of the phagophore is regulated by two ubiquitin-like conjugation systems, specifically ATG12-ATG5-ATG16 and microtubule-associated protein 1 light chain 3 (LC3).¹⁶ The ATG12-ATG5-ATG16 complex promotes the extension of the phagophore, resulting in the generation of the autophagosome. Subsequently, it dissociates from the autophagosome membrane.¹⁶ In the LC3 conjugation system, the precursor LC3 is cleaved by ATG4, leading to the creation of LC3-I. LC3-I is then attached to phosphatidylethanolamine (PE) to produce LC3-II, which promotes the extension of the membrane.¹⁶ Unlike the ATG12-ATG5-ATG16 complex, LC3-II persists on the autophagosome membrane even once the autophagosome is fully closed. This characteristic makes LC3-II the most often used biomarker for autophagosomes.¹⁶ Additionally, the cargo receptors sequestosome-1/ubiquitin-binding protein p62 (SQSTM1/P62) and NBR1 have significant functions in attracting cytoplasmic cargo to LC3-II in autophagosomes.¹⁷ Subsequently, the autophagosome merges with the endolysosomal compartment, resulting in the formation of autolysosomes. Acidic lysosomal hydrolases break down the cytoplasmic cargo, releasing biomolecules that can be reused in the cytoplasm.¹⁶

Oral Cancer

Head and neck cancers are quite widespread, and among them, OC is the sixth most prevalent form of cancer worldwide.⁵ According to the latest data from the International Agency for Research on Cancer (IARC), the yearly occurrence of OC exceeds 300,000 cases, resulting in an annual fatality rate above 145,000 deaths.¹⁸ Men have a higher incidence of OC compared to women, with an average age of diagnosis of 62 years.⁶ The median 5-year survival rate is 50%, and in the presence of metastases, the median 5-year survival rate is 39%. Nevertheless, if the diagnosis is established in the first phase, the 5-year survival rate is 84%. Hence, timely identification of OC plays a crucial role in enhancing patients' chances of survival.⁶

OSCC, often known as OC, arises from the nonkeratinized epithelium of the oral mucosa, accounting for around 90% of cases. OC can arise in any region of the oral cavity, although it most frequently occurs in the tongue and floor of the mouth, with the lips or alveolar process being the next most commonly afflicted sites.¹⁹ The elevated prevalence of OC in low-resource nations can be attributed to various customary practices, including alcohol drinking, smoking, tobacco chewing, and areca nut chewing. OC can also arise from human papillomavirus (HPV) infection, inadequate dental care, substandard hygiene, and the consumption of an unhealthy diet.¹⁹ The presence of these risk factors contributes to the emergence of different genetic imbalances and molecular changes, such as

the reduction of tumor suppressor genes like TP53, RB, and CDKN2A and the increase of oncogenes like cyclin D1.²⁰ The clinical manifestation of OSCC exhibits significant variability. It is typically observed as a non-healing ulcerated lesion in the oral cavity, characterized by palpable, hard edges. Additional symptoms may encompass tooth movement, bleeding, discomfort, or numbness in the mouth or face.⁶

Possible treatment choices encompass surgical excision, radiation, and postoperative adjuvant radiotherapy. Chemotherapy is primarily employed as an adjuvant treatment following surgery.²¹ Typically, surgery, radiotherapy, and chemotherapy adversely affect the patient's quality of life, resulting in speech and swallowing difficulties, alterations in physical appearance, sensory impairments, and persistent discomfort.²¹ Hence, it is imperative to acquire a more comprehensive comprehension of the molecular and cellular mechanisms implicated in the genesis and advancement of OSCC in order to enhance pharmacological interventions and mitigate the adverse repercussions associated with these treatments.

Oral Cancer and Autophagy

Several of the proteins that induce autophagy are classified as oncoproteins and tumor suppressor proteins.²² Oncoproteins such as class I PI3K, RAS, RHEB, and AKT have the ability to activate MTORC1, which in turn hinders the process of autophagy. On the other hand, certain proteins known as tumor suppressors, including PTEN, AMPK, STK11/LKB1, and TSC1/2, have the ability to inhibit MTOR and promote autophagy.²²

Autophagy can promote the development of many types of cancer, such as OSCC, by safeguarding tumor cells against the scarcity of nutrients and oxygen in their surroundings. A recent investigation using 7 samples of normal tissue, 41 samples of leukoplakias, and 120 samples of OSCC has revealed a correlation between higher levels of LC3II, the severity of leukoplakia, and the stage of OSCC. The observed elevation in LC3II levels as leukoplakia advances is associated with the lesions' inclination towards malignant conversion.²³ Experimental investigations have demonstrated a robust correlation between the autophagy indicators LC3B and P62 and worse outcomes in individuals with OSCC.²⁴ ATG9A is a transmembrane protein that controls the transportation of membranes in the early stages of autophagy.¹⁴ The excessive expression of ATG9A is clearly linked to the recurrence of the disease and shows a strong negative relationship with the ultimate survival of individuals with OSCC. These findings suggest that the existence of ATG9A in the cytoplasm of cancerous cells may be a reliable biomarker for forecasting the likelihood of OSCC recurrence and the patient's overall survival.²⁵ ATG16L1 is crucial for the production of autophagosomes and is associated with a poor outcome in patients with OSCC.²⁶ Increased expression of ATG16L1 levels was observed in 33

cases of typical keratinizing-type OSCCs and in 27 out of 90 OSCC tissues.²⁶ There is a suggestion that when there is a high level of ATG16L1 expression in the stroma, this is linked to an elevated presence of invasive tumor cells in the lymphovascular system and a positive status of lymph nodes.²⁶ ATG5 forms a covalent bond with ATG12, and together with ATG16L1, it mostly participates in the elongation of the phagophore.¹⁴ The simultaneous presence of ATG5 and Beclin1 is a negative predictor of the prognosis for OSCC.²⁷ SQSTM1, a receptor protein that orchestrates certain autophagy and ubiquitination processes, functions as a central signaling center for various activities in cells.²⁸ An investigation showed that elevated levels of LC3-II expression, heightened cytoplasmic SQSTM1, and reduced nuclear SQSTM1 were linked to aggressive clinicopathologic characteristics and a malignant prognosis.⁹ Furthermore, there have been reports of an excessive amount of SQSTM1 in OSCC, which is associated with a worse prognosis. This abundant SQSTM1 could potentially lead to the induction of glutathione and resistance to cytotoxic radiation.²⁹ Collectively, these findings indicate that the aberrant expression of ATG genes may have varying effects on the unintentional stimulation or suppression of autophagy and could potentially be used as different prognostic markers for OC.

The induction of autophagy in tongue SCC cell lines and tissues is hindered by the decreased expression of two crucial components, Beclin1 and LC3.³⁰ Decreased expression of Beclin1 leads to decreased levels of LC3-II, ATG4, and ATG5, while also causing higher growth, emigration, and invasion of tongue SCC cells. Conversely, an elevated level of Beclin1 has the opposite impact.³¹ Therefore, autophagy may control the progression of cancer in advanced stages and exhibit a correlation with the malignant characteristics of OC.^{30, 31}

In the early phases of tumor development, inadequate vascularization can restrict the delivery of oxygen and nutrients to the cancer cells. At this phase of tumor development, the activation of AMPK and HIF-1 can trigger autophagy, which enhances the survival of these oxygen-deprived cells. The protein ATG16L1, which plays a vital role in the autophagy process, is found in both malignant cells and stroma but is absent in healthy tissues. This suggests that there is an elevation in autophagy levels in malignant tissues.²⁶ Autophagy in this scenario is likely to function as a defensive mechanism for tumor cells, enabling their survival in this challenging setting.

HPV/HPV16 infection is the main cause of oesophageal cancer, as well as a substantial fraction of OCs. These OCs are mainly found in the tonsillar and tonsillar crypt regions, as well as beneath the lingual region. It is important to recognize the impact of this virus on autophagy, which not only helps maintain the amount of virus in the body but also promotes the development

of cancer by suppressing autophagy.³² According to reports, the autophagic process is regulated by the activation of E7 and the suppression of E6, which are essential carcinogenic proteins generated by HPV. Suppression of the autophagic process enhances viral survival and, consequently, tumor survival.³³

Autophagy has the potential to affect the ability of cells to provoke an immunological response. Recent studies have indicated that autophagy can help cells evade the immune system by breaking down MHC-1 molecules. Additionally, autophagy may also play a role in the control of immune defense against tumors by regulating the activity of YKT6, a protein that is implicated in the assembly of autophagosomes and lysosomes.³⁴ Further evidence of control in this way in squamous cell carcinoma is the inhibition of the immune response in HNSCC through the mediation of SOX2. This phenomenon is achieved through an indirect mechanism in which SOX2 facilitates the degradation of STING through an autophagic process. Consequently, this leads to the suppression of IFN-1 signaling and the reduction of any immunological response.³⁵

Autophagy-Specific Therapeutic Strategy

Manipulating the autophagy process by chemical means has effectively inhibited tumor activity in head and neck squamous cell carcinoma (HNSCC). Deguelin, an AKT inhibitor, significantly enhanced cell death in HNSCC cells by inducing autophagy and apoptosis simultaneously.³⁶ The use of a mTOR kinase inhibitor effectively suppressed proliferation in HNSCC by inhibiting the mTOR pathway, thus demonstrating the tumor-suppressing effects of autophagy.³⁷ Death-Associated Protein Kinase (DAPK) is a dynamic controller of autophagy and can be suppressed by methylation of the DAPK gene. The activation of autophagy through DAPK is recognized as a tumor-suppressing role of this enzyme. However, the function of DAPK as a tumor suppressor can be compromised by methylation or hypermethylation, which promotes tumor growth. Pathological samples of HNSCC showed hypermethylation of DAP-kinase in areas where tumor growth was extensive and uncontrolled.³⁸ The methylation of this gene is considered to have substantial potential as a marker of epigenetic changes in OSCC.³⁹

A significant determinant in patients with OSCC is the delayed detection, necessitating the management of advanced, end-stage tumors. Chemotherapy is less successful for these types of tumors because considerable changes have happened in the DNA of the tumor cells, making them less sensitive to substances that induce cell death. As a consequence of the positioning of OSCCs, excising the tumor frequently leads to the extraction of a substantial quantity of facial tissue, significantly impacting the patients' quality of life. Tumors rely on autophagy to endure hypoxic and nutrient-depleted environments. Consequently, tumor cells often experience an upregulation of autophagy,

which grants them a competitive edge in their ability to survive when confronted with DNA-damaging agents such as chemotherapy treatments.⁴⁰ Research has demonstrated that the effectiveness of cisplatin treatment can be improved by suppressing autophagy in OSCC cell lines.⁴¹ Additionally, inhibiting autophagy has been found to reduce resistance in tongue SCC.⁴² Chloroquine, a medicine that inhibits autophagy and is effective against a wide range of diseases, including malaria, has been studied in clinical studies to assess its potential when used alongside chemotherapy. The results have demonstrated the capacity to augment the efficacy of the treatment.⁴³

CONCLUSION

Autophagy levels are high in malignant tissues, suggesting that it functions as a defense mechanism for tumor cells. Autophagy may promote OSCC development by protecting tumor cells against nutrient and oxygen scarcity. Autophagy may help cells escape the immune system by controlling the immune response against tumors. Autophagy provides them with a survival benefit when they are exposed to compounds that cause damage to DNA, such as chemotherapy medicines. Suppressing autophagy may improve treatment effectiveness in OC. It is expected that further exploration of the autophagy landscape in the future may result in the discovery of new targets, which are essential for developing innovative and effective therapeutic approaches.

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Otofajinin Oral Kanserdeki Rolü

ÖZET

Otofaji, hücrelerin düzenli yenilenmelerini kontrol etmek için hücre içi organellerini parçaladıkları ve hücre içindeki dengeyi korumak için işlevsiz organelleri ortadan kaldırdıkları evrensel olarak korunmuş bir süreçtir. Otofaji, hücrelerin hipoksi, besin eksikliği ve enerji yoksunluğu gibi stres faktörlerine karşı uyum sağlamalarına ve kendilerini korumalarına yardımcı olan biyolojik bir mekanizmadır. Otofajinin bozulması nörolojik bozukluklar, bulaşıcı hastalıklar ve kanser gibi bir dizi hastalıkla ilişkilendirilmiştir.

Oral kanser, dünya genelinde her yıl çok sayıda kişinin hayatını kaybetmesine neden olan son derece yıkıcı bir hastalıktır. Mevcut tedavi yöntemleri, hastaların gereksinimlerini yeterince karşılayamamaktadır. Hastalığın heterojenliği nedeniyle kişiselleştirilmiş tıp veya hedefe yönelik ilaçlar gereklidir. Bu nedenle, oral kanser tedavisi için olası hedeflerin derhal belirlenmesi gerekmektedir. Otofajinin, oral kanserin hem inhibisyonunda hem de ilerlemesinde potansiyel olarak bir işlev oynadığı keşfedilmiştir. Kanser hücreleri, kemoterapinin neden olduğu strese yanıt olarak hayatta kalmalarını artırmak için otofaji mekanizmasını kullanır. Bu nedenle, malign tümör hücrelerinin belirli terapötik ilaçlara duyarlılığını artırmak ve etkili tedavi stratejileri geliştirmek için sitoprotektif katabolizmanın baskılanmasının ve otofajik hücre ölümünün kullanılmasının altında yatan süreçleri anlamak büyük önem taşımaktadır.

ANAHTAR KELİMELE: ATG; Hücre; Makrotofaji; Mikrotofaji; Skuamöz hücreli karsinom