

Autophagy in oral cancer: Promises and challenges (Review)

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Abstract. Autophagy captures damaged or dysfunctional proteins and organelles through the lysosomal pathway to achieve proper cellular homeostasis. Autophagy possesses distinct characteristics and is given recognized functions in numerous physiological and pathological conditions, such as cancer. Early stage cancer development can be stopped by autophagy. After tumor cells have successfully undergone transformation and progressed to a late stage, the autophagy-mediated system of dynamic degradation and recycling will support cancer cell growth and adaptation to various cellular stress responses while preserving energy homeostasis. In the present study, the dual function that autophagy plays in various oral cancer development contexts and stages, the existing arguments for and against autophagy, and the ways in which autophagy contributes to oral cancer modifications, such as carcinogenesis, drug resistance, invasion, metastasis and self-proliferation, are reviewed. Special attention is paid to the mechanisms and functions of autophagy in oral cancer processes, and the most recent findings on the application of certain conventional drugs or natural compounds as novel agents that modulate autophagy in oral cancer are discussed. Overall, further research is needed to determine the validity and reliability of autophagy promotion and inhibition while maximizing the difficult challenge of increasing cancer suppression to improve clinical outcomes.

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1. Introduction

Autophagy was first discovered in mammals in 1963 and proposed as a process in the study by de Duve and Wattiaux (1). There are three defined types of autophagy: Macroautophagy (hereinafter referred to as autophagy), microautophagy and chaperone-mediated autophagy, of which macroautophagy is considered to be the main type (2-4). Lysosomes, the digestive organelles of the cell, mediate all of these internal degradation mechanisms. Through the employment of double membrane-bound vesicles known as autophagosomes, which interact with lysosomes and fuse to form autolysosomes, autophagy transports cytoplasmic cargo to lysosomes (5). By contrast, lysosomes directly absorb and degrade membrane components during autophagy by invaginating the lysosomal membrane (6). The highly selective process known as chaperone-mediated autophagy involves the translocation of certain proteins into a chaperone complex that is identified by the lysosomal membrane receptor and described as lysosome-associated membrane protein 70A (7,8) (Fig. 1).

Although autophagy was discovered >60 years ago, substantial progress has been made in the last decade, with numerous studies elucidating the function and role of this ubiquitous process. Autophagy is essential to human health and is involved in the turnover of proteins and organelles (9). The process plays a range of physiological and pathological roles in development, physiology, lifespan and various types of disease, including neurodegeneration, cancer and microbial infections (10,11). Numerous research investigations have demonstrated that the dysregulation of autophagy leads to a disturbance of homeostasis, which in turn plays a significant role in the pathophysiology of multiple human illnesses, such as neurodegeneration, cancer, autoimmune diseases, aging, cell death, atherosclerosis and infection. Autophagy helps cells clear damaged proteins, organelles, pathogens, or aggregates, and it has been proposed as a cell death mechanism, programmed cell death (PCD) type II, while apoptosis is a unique PCD type I (12). Autophagy can affect cancer cell survival in both positive and negative ways. While it may initially prevent cancer, once tumors develop, cancers use autophagy to defend their own cells (13). The role of

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autophagy in oral cancer has always been of particular note, with substantial evidence demonstrating the importance of autophagy in the regulation of oral cancer, and research in this area has expanded considerably over the past few decades, showing promise for the application of autophagy in cancer therapy (14). Removal of damaged or dysfunctional cellular usually prevents tumor development, but also contributes to proliferation or drug resistance in established tumors (15).

Nonetheless, autophagy can be broadly characterized as an anti-stress mechanism whose function is contingent upon the type of stress, when it occurs, the cell's genetic composition and the characteristics of the surrounding microenvironment (16). In general, autophagy serves as an anti-apoptotic mechanism when it is triggered in normal cells; however, when it is activated in abnormal cells, it may also trigger apoptosis or cause cell death. Autophagy may function as a potent barrier and successfully stop the transformation of normal cells into malignant cells (17). Since tumors rely on autophagy more than healthy cells do, altering autophagy may be a useful intervention method in the fight against cancer. Comprehensive insights into how autophagy acts upon oral cancer are desperately needed. Recent studies have helped to more accurately identify the contributions of autophagy and how these contribute to the pro/suppressive tumor activities of this complicated process. In the present study the most recently published studies on autophagy control are reviewed, including autophagic regulation of oral cancer development, invasion and metastasis, and drug resistance. A comprehensive analysis is conducted on the molecular underpinnings of autophagy in tumor biology and its function in cancer, with a focus on the biological implications of the findings. Finally, several key questions and challenges for future research are explored, which may drive the pace of clinical application of autophagy in cancer therapy.

2. Autophagy mechanism

Autophagy is considered to be an essential metabolic regulation system and quality control pathway in cells (18). In theory, autophagy functions as a non-selective volumetric degradation system in cells, and it is considered to contribute just as much as the ubiquitin-proteasome system to the intracellular degradation of proteins (19). Essentially, autophagy continues when selected portions of the cytoplasm are engulfed by the double membrane, forming so-called autophagosomes. These subsequently fuse with lysosomes, where a variety of catabolic enzymes aid in the cargo's degradation, allowing the possibility of recovering the metabolites produced (18,20,21). Autophagy, as a highly conserved adaptive catabolic process, is activated in response to different forms of stress, including non-specific metabolic stimuli or highly specific signals, driving to promote the removal of damaged or redundant proteins or organelles, thereby maintaining normal cellular homeostasis (22). The process occurs at basal levels in almost all cells and is further increased under stress circumstances such as nutrient deprivation, hypoxia, growth factor depletion, organelle damage and abnormal protein accumulation (23).

Double-membrane vesicles newly formed during autophagy can enclose specific cargo (2), including damaged mitochondria, protein aggregates, lipids (liposomes as

well as membrane lipids), nucleic acids, carbohydrates, and pathogenic or defective organelles, and transport them to lysosomes to regulate cellular homeostasis and defend cellular integrity, thereby achieving a self-protection mechanism (19). Autophagy is complex and contradictory. Too little autophagy cannot protect cells, and too much autophagy, that is, uncontrolled autophagy, can lead to cell death (24,25). Therefore, autophagy must be tightly regulated so that it is induced when needed but otherwise maintained at basal levels (24). Whether autophagy can promote survival or death depends on different factors, including the type and stage of cancer cells, the stress environment and the microenvironment. Dysregulation of autophagy can disrupt the balance in the body and lead to the development of numerous human diseases, including infection, metabolic disorders, neurodegenerative diseases, aging, cancer, inflammation and infectious diseases, which can resist stimulation and result in death (24). Among these diseases, cancers, especially oral squamous cell carcinoma (OSCC), involve autophagy in a main role. In a paradoxical autophagy can contribute to cell death even though it mostly serves as a defense mechanism for cells (26). Apart from elucidating the role of autophagy in maintaining metabolic equilibrium, studies conducted in the past couple of decades have associated autophagy with a range of physiological activities, such as immunity and organ development, indicating the multiplicity of roles autophagy plays at the cellular level (24,26).

The identification of autophagy-related (ATG) genes in yeast is a real turning point in modern autophagy biology. At present, >40 genes encoding ATG proteins have been identified in yeast (27,28). There is evidence that autophagy is an evolutionarily conserved mechanism, as the majority of ATG genes are conserved in both yeast and humans (29). Atg1/unc-51-like kinase (ULK) complex, two ubiquitin-like protein (Atg12 and Atg8/LC3) coupling systems, class III phosphatidylinositol 3-kinase (PtdIns3K) and the ATG9A circulatory system are the key components for autophagy-induced autophagy (30). In particular, the PtdIns3K complex produces phosphatidylinositol-3-phosphate on the phagocytic membrane, which is necessary to promote the binding of other ATG factors, such as complex 1 composed of Vps34, Vps15, Atg6 and Atg14, and complex I composed of Vps34, Vps15, Atg6 and Vps38 (31). The main regulator of autophagy is a conserved serine/threonine kinase known as mechanistic target of rapamycin (mTOR), which acts by responding to changes in intracellular microenvironment and extracellular stress (26). Under normal and nutrient-rich growth conditions, ULK1 causes autophosphorylation and hyperphosphorylation of ATG13 subunit and FAK family kinase-interacting protein of 200 kD (FIP200; also known as Atg11 and Atg17 in yeast), thus blocking their interaction (31).

In addition to this steady-state function, autophagy is also a process in which cells adapt metabolism to cope with a state of nutrient depletion, which is caused by the decrease of intracellular metabolites caused by the decrease of extracellular nutrients or the loss of growth factor signal transduction. Under this condition of nutrient depletion, autophagosomes absorb different cellular debris to recover key nutrients such as amino acids or lipids, but autophagy is highly selective to a large extent (32,33). These external and intracellular stimulators cause cells to starve, which causes mTOR

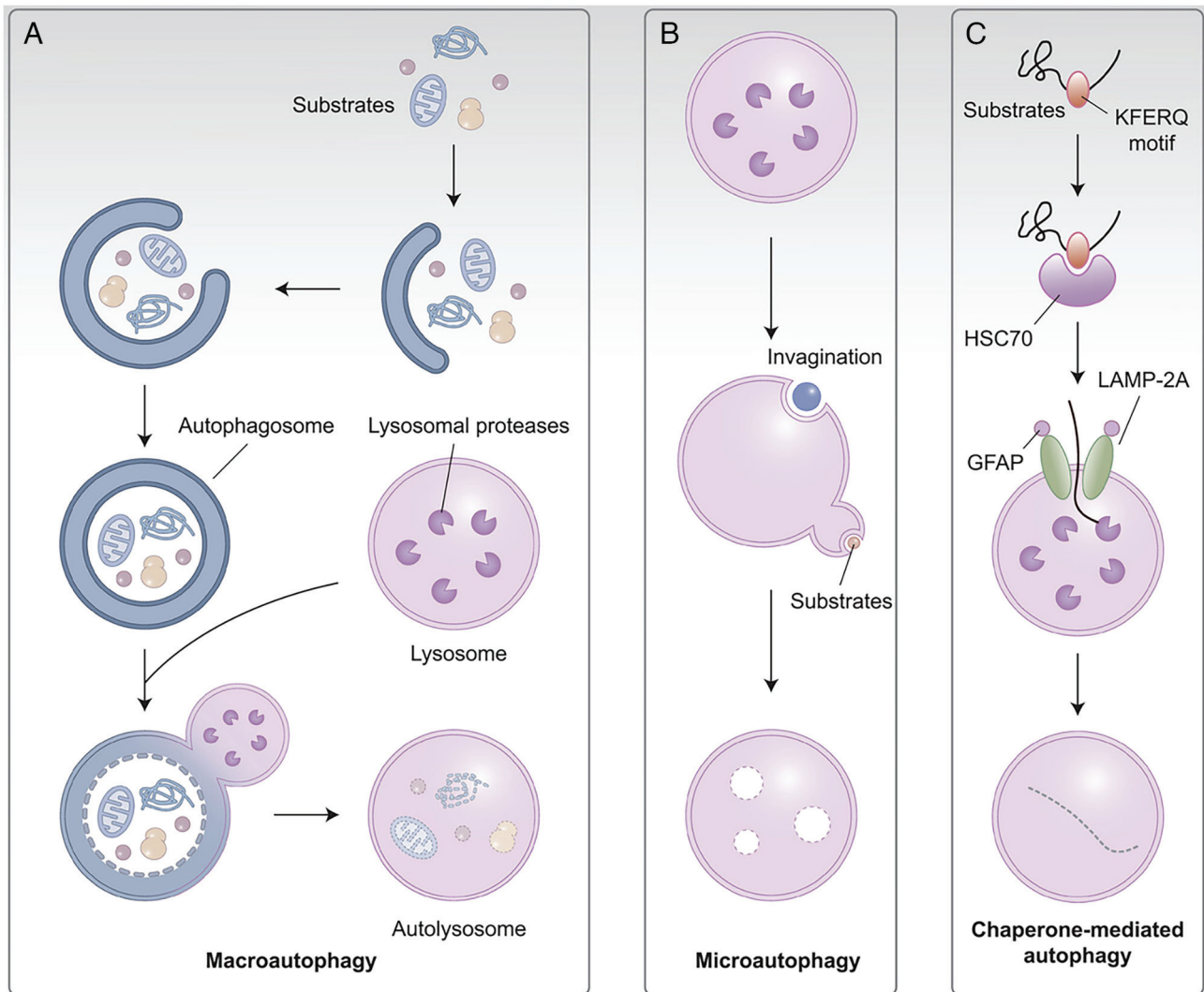


Figure 1. Classification of autophagy in mammals. (A) Macroautophagy: Envelopment of the cargo in an autophagic separating membrane, which, via intricate multistep interaction between certain proteins and lipids, forms the bilamellar structure of the autophagosome. The autophagic lysosomal complex is then formed to degrade the cargo. (B) Microautophagy and endosomal microautophagy: Capture of the cytoplasmic cargo in small vesicles that are formed by lysosomal membrane invagination, selectively through the recognition and targeting of the HSC70 and yet-to-be-identified co-chaperone proteins (7). (C) Chaperone-mediated autophagy: Involves the cochaperones and chaperone HSC70 delivering KFERQ-like motif proteins to the lysosome. KFERQ-like motif proteins are selectively degraded and then internalized into lysosomes through the receptor known as LAMP2A (7) (Copyright 2023, reproduced with permission from Wiley). LAMP2A, lysosome-associated membrane protein type 2A; HSC70, heat-shock homologous protein 70.

complex 1 to dissociate due to signals from the energy sensor AMP-activated protein kinase (AMPK) and amino acid signal transduction deactivation (34). ULK1, ULK2 and mAtg13 are partially dephosphorylated, and activation of ULK1 and ULK2 promotes the phosphorylation of FIP200 (35). ATG13 anchors ULK1 to the autophagy prestructure phagophore assembly site (PAS), and most of the key Atg proteins gather on PAS, while FIP200 forms scaffolds for downstream ATG protein assembly on PAS. Under the condition of autophagy induction, the functional unit ULK1/Atg1 acts as the autophagy initiation complex, in which ATG13 is the key protein in the interaction between FIP200 and ULK1 (35). The subsequent steps of autophagy are membrane nucleation, membrane expansion, membrane forming and pore closure (2). Autophagy involves >20 core autophagy proteins (encoded by the ATG gene) (Fig. 2). The coupling of light chain 3 [LC3; also known as microtubule-associated protein 1 light chain 3 (MAP1LC3)] and GABA type A receptor-associated protein family proteins

to the lipid phosphatidylethanolamine (PE) is a critical phase in the development of autophagy. This coupling is mediated by autophagy coupling mechanisms, which include ATG12, ATG7, ATG5 and ATG3 (15). Additional functional components that target PAS hierarchically, and aid in the assembly and production of autophagosomes, are the ATG9A system, the ULK1 complex, the ATG12 coupling system, the PI3K complex and the MP1LC3 coupling system (15,36). Significantly, these coupling events often serve as a technique to track autophagy levels (the coupling rate of LC3B to PE is the most widely used approach to quantify autophagy) (15,37). Two ubiquitin-like proteins, Atg12 and LC3, control the expansion and closure of autophagosomes simultaneously. The Atg3 and Atg7 proteins facilitate the fusion of autophagosomes and lysosomes to generate autophagy lysosomes, which subsequently degrade their contents (37).

Under stressful circumstances, such as malnourishment and hypoxia, activated autophagy-activating protein 1 regulates the

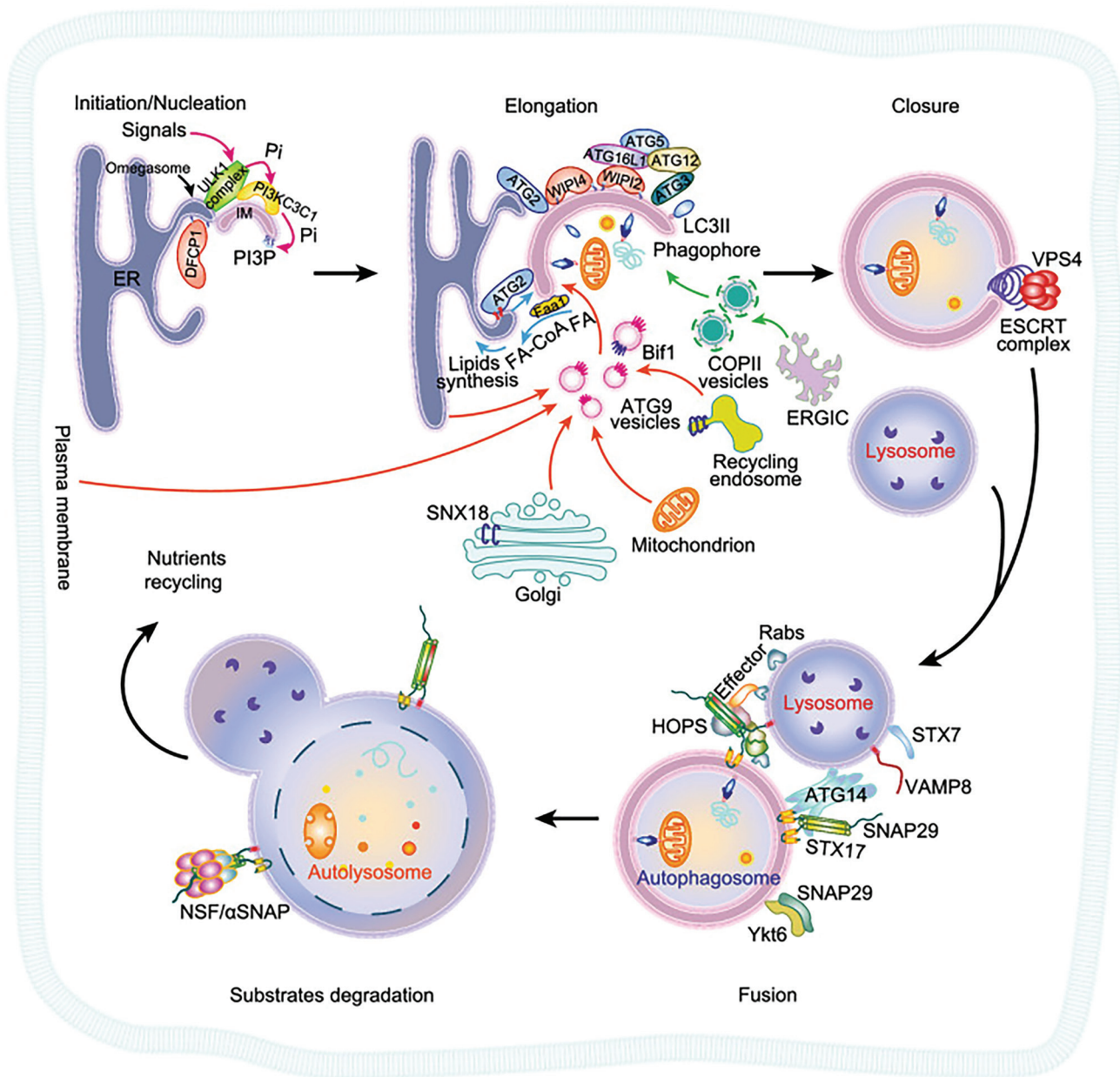


Figure 2. Overview of autophagy of membrane-associated proteins (27). The steps of autophagy are i) autophagy initiation and membrane nucleation; ii) membrane elongation; iii) closure to form autophagosomes; iv) fusion between autophagosomes and lysosomes; and v) degradation of autophagic lysosomal contents. Atg, autophagy-related protein; ER, endoplasmic reticulum; ERGIC, ER-Golgi intermediate compartment; ESCRT, endosomal sorting complexes required for transport; HOPS, homotypic fusion and protein sorting complex; LC3, light chain 3; PI3P, phosphatidylinositol-3-phosphate; PI, phosphatidylinositol; PI3KC3C1 complex, class III phosphatidylinositol-3-kinase complex I; SNX18, sorting nexin-18; SNAP29, synaptosomal-associated protein 29; ULK1, autophagy activating kinase 1; VAMP8, vesicle-associated membrane protein 8; VPS4, vacuolar protein sorting 4; WIPI4, WD repeat domain phosphoinositide-interacting protein 4 (Copyright 2020, reproduced with permission from Oxford University Press).

recruitment of the vacuolar sorter protein 34 (Vps34) complex, which contains the Atg14 antibody (Atg14L) (38). The Vps34 complex is then more active as a result of ULK1 phosphorylating the autophagy effector Beclin-1. Vps34 is an important protein in the autophagy process, as it phosphorylates phosphatidylinositol to produce phospholipid 3-phosphate, which is necessary for autophagy membrane extension (39). After initiation, the autophagosome precursors undergo expansion, elongation and nucleation, and are isolated into double-layer spherical autophagosomes (Fig. 3) (38,40).

The complexity of autophagy is increasing, and previous studies have revealed other roles of ATG proteins in addition

to autophagosome formation, thus expanding their functions and importance in diseases (16). Given the role of autophagy in protein and organelle renewal, intracellular transport and mammalian metabolism, it is not surprising that its disorders are associated with numerous diseases, such as inflammation, metabolic diseases, neurodegenerative diseases, infectious diseases and cancer (41,42).

Autophagy can also be used as a form of non-apoptotic PCD (43). It is now clear that other forms of PCD exist apart from typical apoptosis. Since autophagy is an adaptive response to numerous stresses and typically prevents cell death and inhibits apoptosis, the relationship between autophagy

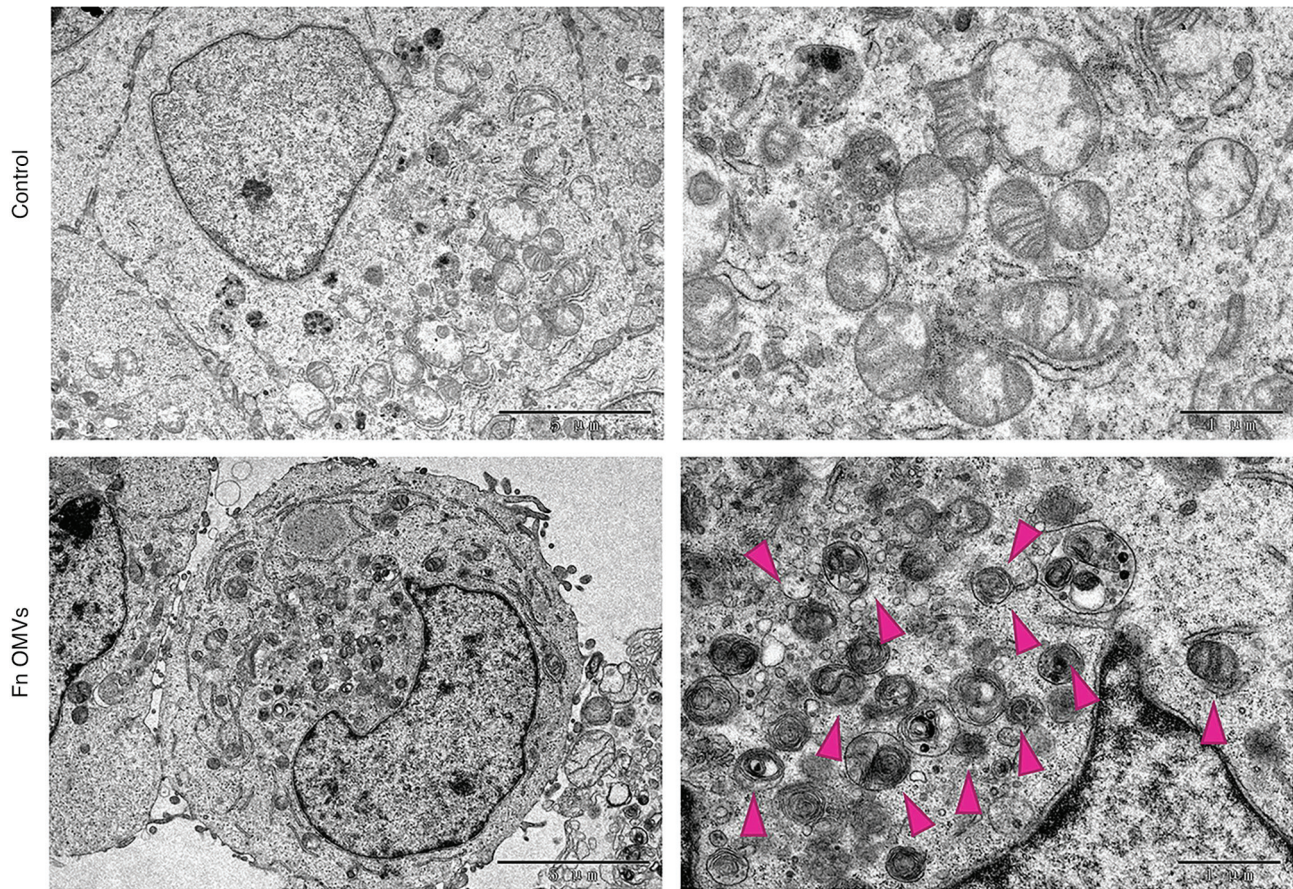


Figure 3. Autophagosome formation. Electron microscopic and confocal microscopic images of oral squamous cell carcinoma cells. Arrowheads indicate autophagosomes. Scale bar, 5 μ m (left). Scale bar, 1 μ m (right) (20) (Copyright 2024, reproduced with permission from Elsevier).

and cell death is complicated. In some cases, however, it may also lead to another pathway of cell death, known as type II cell death. Organelle stress affecting mitochondria and endoplasmic reticulum can induce specific autophagy, leading to the removal of damaged organelles and protecting cells. Beyond the threshold, this stress can lead to apoptosis. Therefore, the final process of autophagic death is carried out by over-activated autophagy flux rather than apoptosis or necrotic apoptosis (43).

Autophagic flux is a measure of the degradation activity of autophagy system; during the whole process of autophagy, goods are included in autophagosomes and transported to lysosomes to promote the fusion of lysosomes and autophagosomes, and then they decompose and release the resulting macromolecules back to the cytoplasmic sol (44). Although there are numerous methods to evaluate autophagy flux, the most popular marker of autophagy formation is LC3, which can also be used to measure the amount of LC3-II (a membrane-bound post-translation product) by western blotting and indirectly estimate the number of autophagosomes based on the abundance of LC3-II proteins (45). Transmission electron microscopy is considered to be the gold standard in numerous autophagy research applications (46); its advantage is that it can directly evaluate the size of autophagosomes in cells and the continuous morphological changes during autophagy. Fluorescence microscopy can be used for living cell imaging, and optical sections of whole cells can measure the

intact autophagy pool in a single cell over time. LC3 coupled to green fluorescent protein (LC3-GFP) specifically marks the autophagosomal membrane, and thus, each LC3-GFP spot represents an individual autophagosome. To determine whether or not autophagosomes accumulated, the subcellular distribution of GFP-LC3 was examined by counting the number of LC3-GFP cells (47). The accumulation of autophagosomes is typically indicated by the punctate rise of LC3-II or GFP-LC3, although this observation alone does not prove that autophagy flux increases correspondingly (45). MCherry-LC3 transgenic mouse model 37 and a photoactivated fluorescent probe can be used to measure autophagy flux *in vivo* (48,49). At the same time, the accumulation of autophagosomes may be the result of autophagy induction, or it may be a defect in the process of autophagosome-lysosome fusion or lysosome degradation (44). In the latter case, autophagy flux can be monitored with lysosomal inhibitors, and several of the most widely used lysosomal inhibitors, such as bafilomycin A1 (H translocation ATP enzyme inhibitor), protease inhibitor mixture and chloroquine (CQ), can be used interchangeably to block autophagy *in vitro*, assuming that they mainly block lysosome degradation (50,51). CQ inhibits autophagy mainly by damaging the fusion of autophagosomes with lysosomes, rather than by affecting the acidity and/or degradation activity of the organelles (51).

LC3 has been used as a specific marker for monitoring autophagy. The LC3 interaction region (LIR) is necessary for

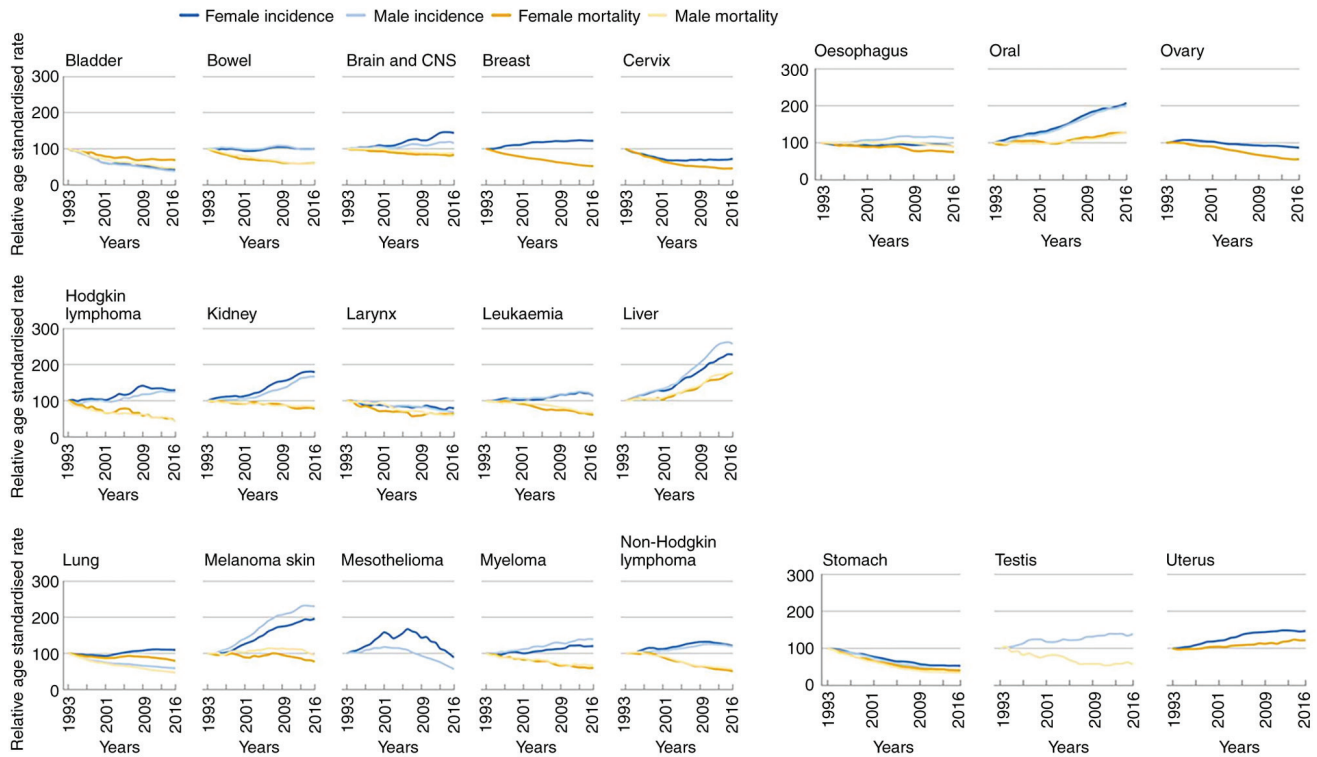


Figure 4. Relative European 2013 age standardized incidence and mortality rates by year, in the UK, for men and women aged 35-69 years from 1993-95 to 2016-18 (the reference year is 1993-95=100), by cancer site. Oral cancer is increasing in incidence and mortality (57). (Copyright 2024, reproduced with permission from BMJ).

mammals to degrade proteins by autophagy (52). Ubiquitin-binding protein p62 (p62) is an autophagy connector; it is a multi-domain protein that can interact with the autophagy mechanism through domains such as Phox1 and Bem1p as key adapters for the target cargo (53). p62 promotes the formation of autophagosomes through the interaction between the LIR domain and LC3 (54). The autophagosome is the main controller of protein degradation through the autophagy-lysosome pathway. As the substrate of autophagy, p62 is widely used to monitor autophagy flux.

3. Basic information about oral cancer and autophagy

Prior to discussing the function of autophagy in oral cancer, the present review discusses the basic information on oral cancer. Oral cancer, encompassing cancers of the lip, various oral tissues and the oropharynx, is the 13th most prevalent type of cancer worldwide (55). There are >450,000 new cases of oral cancer worldwide each year, and only 40% of patients survive 5 years after diagnosis (56). It is estimated that there were 377,713 new cases of oral cancer and 177,757 deaths worldwide in 2020, ranking the disease 16th in the world in terms of morbidity and mortality, and that it is the common cause of male cancer deaths in South Asia, South-East Asia and large regions of the Western Pacific (56). Over the past 20 years in the United Kingdom, age-standardized morbidity and mortality rates have risen in both men and women aged 35-69 years (Fig. 4) (57). A survey conducted in the United States between 2007 and 2016 showed that the incidence of oral and pharyngeal cancer increased at an average annual rate of 0.6%. Increases were recorded in other oral and pharyngeal

cancers (3.4%), root tongue cancer (1.8%), pre-tongue cancer (1.8%), gingival cancer (1.9%), tonsillar cancer (2.4%) and oropharyngeal cancer (1.9%). Decreased incidences were recorded for cancer, soft palate and uvula cancer (-3.7%), hard palate cancer (-0.9%), floor of mouth cancer (-3.1%), lip cancer (-2.7%), hypopharyngeal cancer (-2.4%) and nasopharyngeal cancer (-1.3%) (58). The incidence of cheek cancer and other oral and salivary adenocarcinomas was reported as stable. Oral cancer is more common in men and the elderly, and the mortality rate of men is higher than that of women. Epidemiological studies have shown that smokers are five to nine times more likely to develop oral cancer than non-smokers, and moderate to heavy drinkers have a three- to nine-fold increase in oral cancer risk in smoking control studies (59,60). By contrast, the incidence of OSCC has been increasing in recent decades due to chronic latent infection of the human viruses (especially human papilloma virus 16), and appears to disproportionately affect young individuals (61). Oral cancer and maxillary sinus carcinoma are the most common invasive and malignant oral cancers, accounting for 90-95% of all oral cancers in the world. Therefore, numerous studies use OSCC to refer to oral cancer. OSCC is the most malignant tumor in the oral cavity, tending to become malignant in the absence of an early diagnosis. The prevalence of OSCC varies from location to location, with high rates observed in some areas of Africa, South America and Asia (62).

Chemotherapy, radiation therapy, surgical resection and a combination of these therapies are commonly used to treat oral cancer (63,64). The best treatment depends on the circumstances of the individual case, such as the stage and location of the cancer, as well as the patient's overall health status and

preferences (62,65). Patients with early (stage I and II) and late- (stage III and IV) stage OSCC typically have 5-year survival rates of 83-90% and 50-60%, respectively. However, it has also been reported that the average highest survival rate of patients with oral cancer within 5 years is only 56-68% (66). Thus, the development of more potent treatments for oral cancer is urgently needed. However, surgical resection can lead to cosmetic and functional deformities, and radiotherapy and chemotherapy can lead to serious side effects. Drug resistance, one of the problems in cancer treatment, weakens the efficacy of chemotherapy, which makes tumors more aggressive and recurrent, and makes the prognosis of patients with cancer worse. No screening strategy has been proven to be effective, and careful physical examination remains the main method of early detection. However, most advanced patients do not have a clinical history of precancerous tumors (67).

Despite the continuous improvement and innovation of treatments, they have had little effect on the 5-year survival rate of oral cancer. At the same time, numerous studies have proved that autophagy is involved in cancer development, but the dual effect of autophagy on tumors varies with tumor type, tumor microenvironment, tumor genotype, occurrence stage and treatment. Autophagy can be used as a tumor inhibitory mechanism in the early stage of tumorigenesis in genetically engineered mice by inhibiting DNA damage, and inhibiting reactive oxygen species (ROS), promoting oncogene-induced aging and genomic instability as tumor inducers (42,68,69). Autophagy tends to promote metastasis in the advanced stage of cancer by supporting the distant survival and colonization of metastatic cells separated from the extracellular matrix, which also induces metastatic cells to enter a dormant state when they fail to establish a connection with the extracellular matrix in a new environment (70). In tissues such as the pancreas and liver, chronic tissue injury and inflammation-related lesions cause tumors. When Atg7 or Atg5 are specifically ablated, genetically modified KrasG12D/+ mice develop benign pancreatic intraepithelial neoplasia, and spontaneous hepatic adenomas arise (71). In the late stage of tumorigenesis, Atg7 deficiency leads to defective mitochondrial accumulation, proliferation deficiency, reduced tumor load, transformation of adenomas and adenocarcinomas into cancer tumors, and prolonged life in mice (72). A decrease in autophagic flux may lead to the transformation from a more aggressive adenoma to a less aggressive oncocytoma (73). Over time, autophagy has been shown to assist the metabolic flexibility of cancer cells by breaking down carbohydrates, proteins, lipids and nucleotides, thereby providing nearly all of the essential components of carbon metabolism (15). Correspondingly, autophagy is also an active process of tumor inhibition, which itself can be regulated by the tumor inhibition pathway (74). Numerous investigations have demonstrated that autophagy may directly contribute to tumor control by inhibiting tumor inflammation and normal tissue damage (24,41,74). When the level of p53 increases, it activates genes involved in promoting autophagy, including the regulatory subunit, which encodes damage-regulated autophagy regulatory factor 1 and AMPK (75). In the breast cancer mouse model, the depletion of BCL2 interacting protein 3 reduces mitochondrial autophagy, resulting in an increase in mitochondrial ROS levels. This helps to increase the stability of hypoxia-inducible factor-1 α and

promote tumor progression (76). ATG2B, ATG5, ATG9B and ATG12 have frameshift mutations in gastrointestinal cancer and hepatocellular carcinoma, and ATG5 and ATG7 have also been shown to be downregulated in melanoma (77).

4. Oral cancer and autophagy

The role of autophagy in cancer has been particularly noteworthy, and research in this field has greatly expanded in the past few years. Traditional treatments such as chemotherapy, thermotherapy and ROS stress can induce tumor cell protective autophagy, while upregulation of protective autophagy can be used as a resistance mechanism to weaken antitumor therapy (78). Autophagy plays a very different role in cancer treatment under different circumstances, as the stimulation and inhibition of autophagy can both be used as interventions beneficial to anticancer therapy. Due to this, cancer treatments targeting autophagy are controversial (79,80) (Fig. 5). A large range of drug types target autophagy by regulating the process; the double-edged sword of autophagy can be considered to play an important role in the therapeutic supplements of anticancer drugs or natural substances, which lead to their survival or promote their death. Autophagy identifies the specific targets in oral cancer in different ways. As a delicate process, autophagy may play a role in promoting or fighting cancer, depending on the situation. The present review, to the best of our knowledge, is the first to comprehensively analyze the interaction between autophagy and carcinogenesis, and its synergism in the manipulation of SCC. These findings suggest that both the induction and inhibition of autophagy may produce enhanced anti-SCC activity.

Regulating the development of cancer. Numerous studies conducted in the last few years have revealed a strong correlation between the formation and occurrence of cancers and aberrant autophagy regulation (81-83). The regulatory relationship between autophagy and tumors is bi-directional and complex, which often has different effects due to the stage of the tumor cells, the differences in intracellular signal regulation pathways, and even the changes in the microenvironment around the cells. The expression of LC3B and p62 in the normal oral mucosa is limited and low in the cytoplasm, and the expression levels of LC3B and p62 in the cytoplasm and nucleus are positively correlated. In OSCC, p62 and LC3B are highly expressed through the changes in nuclear and cytoplasmic shuttling. The activity of autophagy changes during carcinogenesis, and the promoted functional autophagy may be related to the invasive clinicopathological features and adverse clinical outcomes of OSCC (81).

After exposure to photobiological regulation, Cal27 cells upregulate autophagy markers Beclin-1, LC3B and p62 at the levels of mRNA and protein expression, and inhibit the colony formation of malignant cells (82). MAP3K11 is a potential kinase of autophagy regulatory protein molecules, which is highly expressed in patients with OSCC. In one study, *in vitro* experiments revealed that inhibition of MAP3K11 decreased the activity of autophagy-related proteases, resulting in slower growth of oral cancer cells and reduced cell viability in cooperation with starvation. Specifically, MAP1LC3 could increase the autophagic flux of autophagosome staining and

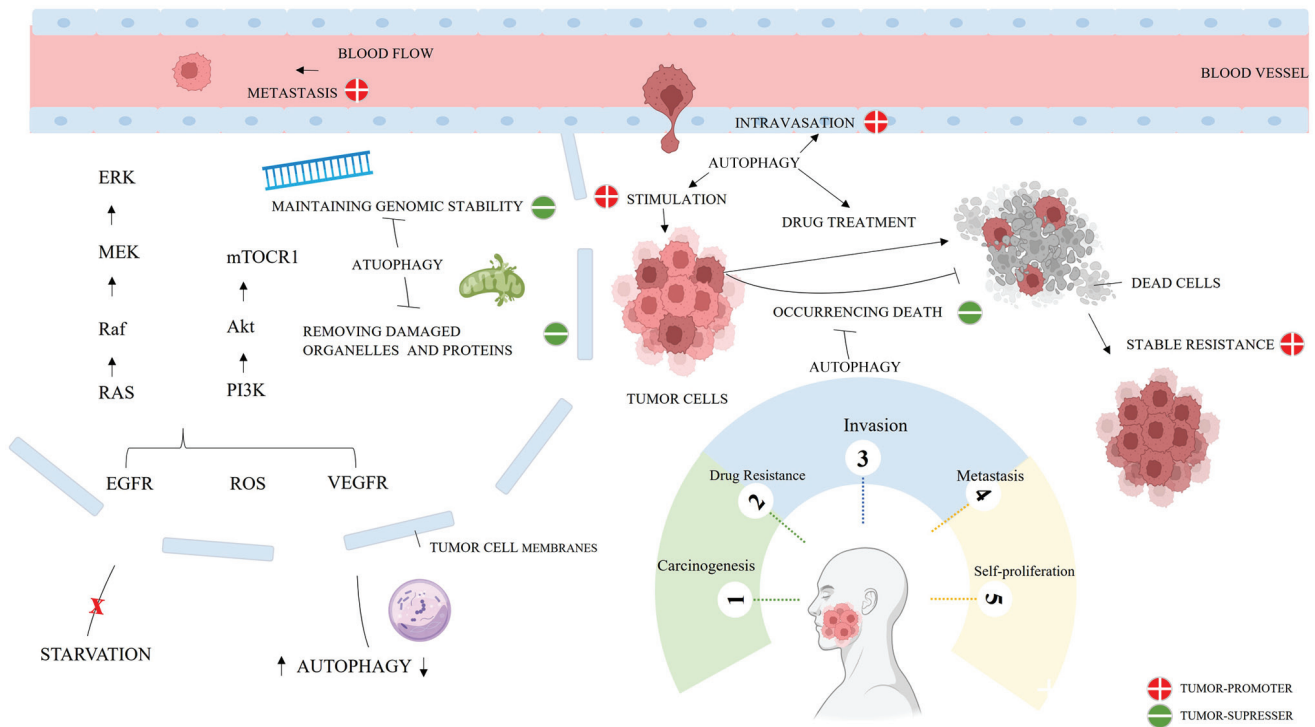


Figure 5. Mechanism of autophagy in oral cancer. Autophagy can promote or inhibit oral cancer by regulating carcinogenesis, drug resistance, invasion, metastasis and self-proliferation. Specifically, the anti-tumorigenic features of autophagy exhibit reduced DNA damage, maintenance of genome stability, occurrence of cell death, oncogene-induced senescence, and removal of damaged organelles and proteins. Conversely, autophagy can promote cancer by facilitating cancer invasion and metastasis, decreasing cancer cell sensitivity to stimuli, enhancing drug resistance and enhancing stem cell expansion. Figure created in Microsoft Powerpoint (Microsoft Corporation). AKT, protein kinase B; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; MEK, mitogen-activated extracellular signal-regulated kinase; mTORC1, mTOR complex; PI3K, phosphoinositide 3-kinase; Raf, serine/threonine kinase protein; RAS, renin-angiotensin system; ROS, reactive oxygen species; VEGFR, vascular endothelial growth factor receptor.

oral cancer, thus promoting the progression of oral cancer (83). A previous study showed that the ratio of autophagy-related LC3-II/LC3-I and Beclin-1 protein in OC2 and SCC4 cells treated with stelletin B increased, while p62 decreased, thus promoting cell death (84). Anethole, a scented plant extract, could induce the autophagy of Ca9-22 cells to promote anti-cancer activity by affecting several signaling pathways and triggering apoptosis. Increasing autophagy can promote the ability of intracellular glutathione activity and increase the expression of the p53 gene (85). The inhibition of epidermal growth factor receptor (EGFR) signal transduction reduces the expression of stem cell marker transcription factor 2 by promoting autophagy degradation. Gefitinib is an inhibitor of EGFR tyrosine kinase, which has protective effects on oral cancer cells *in vitro* and *in vivo* (86); it can increase the subsequent autophagy degradation and inhibit the development of cancer stem cells by inhibiting the phosphorylation of transcription factor 2 at the Y277 site and increasing its ubiquitination (86). When autophagy inhibitor Autophaginib was used to treat the cells with overexpression of circadian clock gene aryl hydrocarbon receptor nuclear translocator-like protein 1 (ARNTL), it reversed the increased expression of apoptosis-related factors BAX and BCL-2, decreased the cell proliferation index and increased the apoptotic index, and promoted cell viability. *In vivo*, the tumorigenesis test also showed that overexpression of ARNTL-induced autophagy inhibited tumor growth (87).

The possible mechanism mediated by autophagy and the matrix metalloproteinase-9 (MMP-9)/Rho-related

GTP-binding protein RhoC (RhoC) signaling pathway may be responsible for the chemopreventive impact of serine/threonine kinase (AKT) inhibitors on carcinogen 4-nitroquinoline 1-oxide (4NQO)-induced tongue carcinogenesis in mice (88). In a previous study, pRhoC and MMP-9 expression was suppressed by MK2206 2HCl, whilst the autophagy gene LC3II was stimulated. In this investigation, it was also discovered that MK22062HCl could increase autophagy and apoptosis, and decrease the expression of phosphorylated (p-) AKT (88). Thus, it was hypothesized that the chemopreventive action of MK22062HCl on 4NQO-induced tongue carcinogenesis in mice is associated with the stimulation of autophagy and apoptosis. Studies have revealed that autophagy acts as an inhibitor of OSCC chemically induced by 4NQO in the early stage of OSCC (88,89). The 4NQO-induced OSCC model can accurately simulate the morphology and histopathology of human OSCC. Autophagy induced by spermidine and a reduction of neuroamine levels reduced the severity of lesions and the incidence of oral small cell carcinoma in mice exposed to 4NQO (89).

Autophagy is not only a process of promoting cell survival, but also a known mechanism for inducing cell death (90). Autophagy is a potential therapeutic target for cancer due to its capacity to modulate cell death. It is well known that there is a complex relationship between apoptosis and autophagy. Autophagy can antagonize apoptosis to allow tumor cells to survive, and apoptosis-related caspase activation can reduce autophagy as a feedback response. Nevertheless, by activating caspase-8 and consuming endogenous apoptosis inhibitors,

autophagy can also occasionally cause apoptosis. Research has indicated that one method is that p62, which is integrated into autophagosomes by attaching to LC3 in autophagy-activated cells, can control autophagy and apoptosis. Autophagy then leads to the breakdown of p62 (91). lncRNA CASC9 enhances p62 protein expression and inhibits autophagy-mediated apoptosis through the AKT/mTOR pathway (92). Autophagy in oral cancer is induced by chlorpromazine through exogenous death receptors and internal mitochondrial pathways, while autophagy products promote tumor cell apoptosis and enhance the anticancer effect of chlorpromazine (93). The metformin derivative HL156A induces autophagy, as demonstrated by autophagy vacuole staining and quantification of autolysosome-associated LC3BI/II proteins. CQ treatment of cells and oral cancer xenogeneic models has been shown to increase apoptosis, reduce proliferation and inhibit tumor growth *in vivo*, thus HL156A induces autophagy to protect cells from apoptosis (94). The inhibition of autophagic flux by gallic acid, the active ingredient of *Terminalia bellirica* in tuberculosis extract leads to the increase of autophagosome accumulation in tuberculosis, which makes *Terminalia bellirica* unable to fuse with lysosome without changing the activity of lysosome (95). On the other hand, the use of autophagy inhibitors can regulate the stage-specific progress of autophagy after treatment with tuberculosis extract, and cells temporarily acquire autophagy as a survival-promoting mechanism, which is then beneficial to autophagy-dependent apoptosis (95). In tongue SCC (TSCC) cells, glaucocalyxin A (GLA)-induced apoptosis, autophagy and ROS production was observed in a concentration- and time-dependent manner. In order to prevent the viability and proliferation of TSCC cells, GLA causes ROS-dependent apoptosis and autophagy (96). Hinokitiol inhibits the proliferation of OSCC cells by inducing apoptosis and autophagy (97). MTP, an inhibitor of pyruvate kinase M2, increases ROS production and regulates the expression of autophagy gene products. Overexpression of Janus kinase 2 can partially reverse MTP-mediated apoptosis and autophagy (98). Polyphyllin G from rhizome of *Paris yunnanensis* Franch induced the formation of autophagosomes in oral cancer SAS and OECM-1 cells in a dose-dependent manner, and the expression of LC3-II and beclin-1 increased (98). Polyphyllin G induced autophagy by activating extracellular signal-regulated kinase (ERK) and c-Jun n-terminal kinase (JNK), and the use of autophagy inhibitor CQ reduced the death of OSCC cells induced by polyphyllin G (99).

The change of cell fate from autophagy to apoptosis depends on the severity of stress. By controlling pathways, natural substances can control autophagy and apoptosis in OSCC cells. Radix Astragali is a natural plant antitoxin, which has a unique molecular mechanism for inducing autophagy. By activating JNK1/2 and inhibiting Akt, ERK1/2 and p38, it can trigger autophagy, form acidic vesicle organelles, produce LC3-II, induce cell cycle arrest and apoptosis, and effectively inhibit the growth of human oral cancer cells (100). Platyphyllenone gradually increased apoptosis and autophagy of oral cancer cells through JNK and AKT signaling pathways in a dose-dependent manner, indicating that platyphyllenone grandiflorum ketene can promote autophagy of OSCC (101). The combination of autophagy inhibitors and piperlongumine therapy induced apoptosis and protective autophagy in human oral cancer MC-3

and HSC-4 cell lines through the JNK-mediated mitogen-activated protein kinase (MAPK) pathway, which helps to inhibit cell proliferation (102). Rhubarb protein extracted from Chinese herbal medicine can inhibit the expression of related proteins in the Akt/mTOR signaling pathway in OSCC cells and mouse xenografts, and induce autophagy to play an anticoagulant effect, suggesting that autophagy is related to the inhibition of the Akt/mTOR signal pathway by rhubarb protein (103). Piperine inhibits the PI3K/Akt/mTOR signal pathway in a dose-induced manner to induce the increase of acidic vesicle organelles, autophagy marker proteins and apoptosis, thus inducing autophagy and apoptosis *in vitro* and inhibiting tumor growth *in vivo* (104). Inhibition of lncRNA HOTAIR by nimbolide increases the expression of miR-126, which leads to the activation of GSK-3 β , thereby affecting the shielding effect of cytoprotective autophagy (105). Nimbolide also induced normal autophagic features, such as the build-up of acidic vesicles, the upregulation of Beclin-1 and ATG5, the conversion of LC3-I to LC3-II and p62 degradation (105). The angular furanocoumarin oroselol can induce autophagy, reduce the expression of LC3-II and p62 in human oral cancer cells, and downregulate the PI3K/AKT signaling pathway to exert its anti-proliferative activity (106). *Gardenia* fruit genipin and rhubarb chrysophanol both inhibit the PI3K/AKT/mTOR pathway, which in turn causes OSCC cells to undergo autophagy. After co-incubation with autophagy inhibitor 3-methyladenine (3-MA), the change in the autophagy labeled protein (LC3-II and p62) was alleviated (107,108). However, when autophagy induced by 3-MA chrysophanol was used, the apoptosis rate increased significantly (107). Apoptosis and autophagy-related proteins in western blotting have been shown to be elevated in glycyrrhizin-induced tumors, indicating that the compound inhibits tumor growth by promoting autophagy in cancer cells and mouse oral xenograft cancer models. Autophagy-related apoptosis may be inhibited by glycyrrhizin through the PI3K/AKT/mTOR pathway and exert an antitumor effect (109). The expression of lncRNACASC9 was positively correlated with p-AKT in OSCC and negatively correlated with LC3B. In oral squamous cells with low CASC9, p62 protein combined with LC3B was degraded after incorporation into autophagosomes, which enhanced autophagy, positively regulated apoptosis and increased early apoptosis. Through enhancement of cell proliferation and inhibition of autophagy-mediated apoptosis via the AKT/mTOR pathway, CASC9 facilitates the advancement of OSCC. lncRNA-APTCSC3 inhibits the proliferation of oral cancer by inducing autophagy, as the development of autophagy vesicles and the expression of autophagy-related proteins in SCC-1 and SCC-9 cells are increased (110). The smooth initiation of the autophagy signaling pathway is triggered by melatonin and erastin, while autophagy is blocked downstream. The combination of melatonin and erastin enhanced the level of apoptosis and ferroptosis in tumor tissue *in vivo* and *in vitro*, while the level of autophagy decreased autophagy and apoptosis, and played an anticancer effect without adverse reactions (80).

In contrast with the aforementioned evidence, some scholars have shown that resveratrol can induce the autophagic death of OSCC cells, but that it cannot induce apoptosis; the specific mechanism remains unknown (111). However, resveratrol can cause oral cancer cells to undergo autophagy by blocking lipid metabolism and the signal route for cell

survival that is controlled by the transcription factor sterol regulatory element binding protein 1 (111). Therefore, in the aforementioned examples discussed, whether autophagy inhibition in cancer cells does help to enhance tumor apoptosis remains to be determined. The complex interaction between cancer cell autophagy and apoptosis reflects some complexity in deciphering the role of autophagy in human cancer and its treatment.

Although apoptosis is the most studied PCD related to autophagy, there are other cell death signal patterns, such as necrotizing apoptosis. Necrotizing apoptosis, a type of PCD controlled by several cytokines and pattern recognition receptors, is typified by caspase independence and is commonly considered a 'fail-safe' form of cell death (112). Latifolin isolated from tangerine peel can effectively block cell invasion and adhesion by inactivating focal adhesion kinase/non-receptor tyrosine kinase, thus causing anti-metastatic activity. Latifolin inhibits autophagy and increases apoptotic cell death. Latifolin also inhibits necrotizing apoptosis by dephosphorylating necrotizing apoptotic regulatory proteins and exerts anticancer effects through apoptotic cell death (113). Herbaceous lignin Machilin D inhibits the PI3K/AKT/mTOR/p70S6K pathway and MAPKs, leading to apoptotic cell death and increased autophagy. Further studies have shown that Machilin D regulates the survival of OSCC cells by inducing apoptosis and autophagy, and reducing necrotizing apoptosis mediated by focal adhesion molecules (114). Xanol increases the expression of beclin-1 and LC3, and decreases the expression of p62, inhibiting the PI3K/AKT/mTOR/p3S62K pathway and causing autophagy. Autophagy and apoptosis play a coordinated role in cancer (115). Xanol increases autophagy by inhibiting the AKT signal pathway in human OSCC, thus promoting apoptotic cell death and inhibiting necrotizing apoptotic cell death (115).

It is worth noting that nanoparticles (NPs) have been proposed as a new autophagy activator, and both physical and chemical properties may greatly affect the autophagy regulation ability of NPs (116,117). The biomimetic nanomaterial PCN-CQ@CCM (the metal-organic framework material PCN-224 was used as a carrier to load CQ and it was coated onto the surface with isolated OSCC cell membranes) enhances ROS damage induced, and LC3-II increases significantly, triggering the apoptotic pathway (118). An active targeting strategy significantly inhibits the fusion, formation and degradation of autophagosomes and lysosomes, triggers higher autophagic flux, and further inhibits damage repair, thus synergistically inhibiting oral cancer (118). A tumor-targeted biomimetic nano-platform combines photodynamic therapy with autophagy inhibition to treat oral cancer. 3,5-Bis (4-hydroxy-3-methoxybenzylidene)-N-methyl-4-piperidine promotes autophagy of oral cancer cells by targeting LC3B and p62 protein expression (118). *Usnea barbata* dry acetone extract-loaded mucoadhesive oral films significantly increased oxidative stress nuclear condensation autophagy cell cycle and anticancer potential against oral invasion in CLS-354 tumor cells (119). In the majority of the cells treated with Fe@Au, which triggers autophagy, the cytoplasm contained double-membrane autophagosomes. Although there was evident ROS activity, the inclusion of ROS scavengers was insufficient to shield the cancer cells from the cytotoxicity caused by Fe@Au. The cytotoxicity caused by Fe@Au was effectively decreased

by the addition of CQ or the autophagy inhibitor 3-MA. Therefore, autophagy mediated by mitochondria was identified as the cause of the cancer-specific cytotoxicity of Fe@Au (120). RC-GMN consists of GE11 peptide-modified small micelles (RCGM) and HA nanogels (NG). Autophagy induced by laser irradiation is excessive autophagy, resulting in autophagic cell death (120). RC-GMN loaded with resveratrol induces cell protective autophagy, overcomes the inhibition of the tumor hypoxic environment in photodynamic therapy (PDT), induces higher autophagy cell death, and further promotes the synergistic effect of tumor cell death and apoptosis in PDT therapy (121). By contrast, other NPs, such as nano-diamonds, may inhibit autophagic activity (122,123). Compared with polylactic acid (PLA) plus cisplatin NPs (CDDP-PLANPs), PLA plus cisplatin-CQ NPs (CDDP/CQ-PLANPs) demonstrated reduced autophagy, increased ROS and an increased rate of death in CAL-27 cells (124). The dysfunction of the autophagy pathway has gradually become a new mechanism to evaluate the toxicity of NPs. It is undeniable that some NPs will adversely affect autophagy and lysosome pathways, resulting in toxicological consequences (125). One of the functions of the pheophorbide A-diamino quinoline conjugate iron core-gold shell is that the formed NPs realize the phase transformation of NPs and improve the biological distribution while being protonated in tumor cell lysosomes (126). Research has demonstrated that LC3B-II and p62 levels are elevated in OSC-3 OSCC cells and oral OSC-3 tumor-bearing nude mice *in situ*, along with a greater degree of vacuolization and decreased proliferative activity. These findings suggest that pheophorbide a-bisaminoquinoline conjugate inhibits tumor growth by inhibiting autophagy and inducing vacuolization (126). The cobalt-ferrocene metal-organic framework (Co-Fc) is a type of NP synthesized from ferrocene and cobalt. HydroxyCQ (HCQ) is loaded to construct CoFc@HCQ NPs, and oral cancer cell membrane (CM) is extracted to synthesize CM@Co-Fc@HCQ NPs. When Co-Fc@HCQ is used *in vivo* and *in vitro*, the fusion of autophagy vesicles and lysosomes is inhibited, the autophagy function induced by Co-Fc is decreased, autophagy inhibition plays a dominant role in cells and ROS is accumulated in tumor cells (127). It is important to note that a variety of nano-drugs can be easily categorized based just on the nanomaterials they contain and have an immense amount of potential for precisely controlling tumor cell autophagy, as displayed in Table I. Since NP medications have a smaller clinical utility than conventional pharmaceuticals, not all of them are included in this list. Therefore, from the perspective of autophagy, the biological safety and anticancer treatment mechanism of NPs can be better explained, which is also the second reason for the further study of autophagy and its mechanism of oral cancer.

Regulation of tumor invasion and metastasis. The most common reason for death from numerous malignancies, including OSCC, is the invasion and metastasis of the cancer, or the migration of the cancer cells from the original tumor to distant areas with subsequent growth (128,129). *Clostridium* outer membrane vesicles activate autophagy, which increases the expression of autophagy-related factors. By blocking autophagic flux, autophagy inhibitors not only reduce the migration and invasion induced by *Fusarium* outer membrane

Table I. Nanomaterials for the regulation of autophagy in oral squamous cell carcinoma.

First author, year	NPs	Material type	Package	Mechanisms	(Refs.)
Dai <i>et al</i> , 2022	PCN-CQ@CCM	Bionanomaterials	Metal-organic skeleton PCN as a carrier loaded with CQ- encapsulated CCM	Trigger the apoptotic pathway in mitochondrial damage, while released CQ inhibits protective autophagic flux effectively.	(118)
Popovici <i>et al</i> , 2022	<i>Usnea barbata</i> dry acetone extract (UBA)- loaded mucoadhesive oral films	Mucoadhesive Oral Films	-	Significantly increase cellular oxidative stress, nuclear condensation and autophagy	(119)
Lima <i>et al</i> , 2021	Chitosan/polycaprolactone microparticles	Composite Sponge	Chitosan	Stimulate autophagy	(161)
Ma <i>et al</i> , 2022	Pheophorbide a-bisamino-quinoline conjugate	Nanofiber	-	Lysosomal dysfunction, autophagy inhibition and unusual cytoplasmic vacuolization	(126)
Wu <i>et al</i> , 2011	Iron core-gold shell nanoparticles	Complex NPs	Gold	Induce autophagy, and autophagy inhibitors block cytotoxicity	(120)
Li <i>et al</i> , 2020	RC-GMN	Complex NPs	nano gel	Induce protective autophagy	(124)
	Cisplatin@ultra-short single-walled carbon nanotube	Complex NPs		Inhibit autophagy	
Chen <i>et al</i> , 2023	Oral cancer cell membranes@cobalt-ferrocene metal-organic framework@hydroxychloroquine	Complex NPs	CM@Co	Fusion of autophagic vesicles with lysosomes is inhibited, suppressing autophagic accumulation of ROS	(127)
Wang <i>et al</i> , 2021	HuR gene-editing plasmid of CRISPR-Cas9	Complex NPs	Solid lipid NPs and liposomes	Promote autophagy and regulate drug resistance	(162)
NP, nanoparticle.					

vesicles *in vitro*, but also reverse the homeostasis of epithelial-mesenchymal transformation (EMT)-related proteins, thus inhibiting the induction of EMT (20). Caffeic acid phenethyl ester derivatives 26G or 36m inhibit malignant phenotypes, including cell migration, colony formation and angiogenesis, through ROS generation-activated mTOR-ULK1-p62-LC3 autophagy signal transduction, which is related to changes in cellular oxidative stress. In oral cancer cells treated with 26G or 36M, autophagy lysosomes were formed by 26G or 36M stimulation to degrade cytoplasmic substances at a relatively late stage of autophagy. The expression of LC3-II increased significantly due to the reduction of non-phosphorylated p62 protein (130). Nucleoprotein 1 was most significantly upregulated in patients with OSCC with or without lymphatic metastasis and was positively correlated with metastasis and poor prognosis of OSCC according to highly sensitive quantitative unlabeled quantitative proteomic analysis. Knockdown of nucleoprotein 1 in Cal27 and HN6 cells reduced the activity of transcription factor E3 promoter and inhibited transcription, and the key steps, such as autophagy formation, maturation and autophagosome-lysosome fusion, worked normally, only because lysosome dysfunction led to autophagic flux damage and inhibition of cancer progression (131). Fibroblast activation, myofibroblast differentiation and senescence are particularly associated with genetically unstable OSCC. Aging fibroblasts from genetically unstable OSCC contain more autophagosomes than those from normal human oral fibroblasts and fibroblasts from genetically stable OSCC, which may be due to increased autophagic flux. Human oral fibroblasts treated with autophagy inhibitor TGF- β 1 enhanced the migration of oral squamous cells (132). Fusarium diol induces autophagy by controlling AKT and MAPK signal transduction. Autophagy affects apoptotic cell death through Beclin-1 expression, LC3-II conversion and autophagosome formation, thus preventing OSCC proliferation, migration and invasion (133). The downregulation of retinol-binding protein 1 decreased the expression of autophagy-related proteins Beclin-1, ATG5 and LC3-II, as well as autophagy and the autophagic flux of OSCC cells. Retinol binding protein 1 regulates autophagy by destroying downstream autophagy-lysosome fusion, inhibits malignant biological behavior *in vitro* and inhibits tumor growth *in vivo*. Knockout of ATG5 inhibits cells co-transfected with retinol-binding protein 1 and knockout cytoskeleton-related protein 4, and further reduces the growth, migration and invasion of OSCC cells (134). The extract of *Tribulus Terrestris* fruit inhibits the autophagy, migration and invasion of TSCC cells (135). Surfactin induces the autophagy and apoptosis of OSCC cells through NADPH oxidase/endoplasmic reticulum stress/calcium-downregulated extracellular signal-regulated kinase 1 and 2 pathways in a ROS-dependent manner. Autophagy and apoptosis pathways share a common regulatory signal to calcium lymph nodes (136). δ -8-tetrahydrocannabinol and δ -9-tetrahydrocannabinol cause irreparable damage to OSCC cells and cause genomic instability, which can trigger cell cycle arrest and enhance apoptosis and autophagy to reduce cell viability/proliferation (137); they also inhibit migration by inhibiting EMT markers, reducing ROS production and increasing the expression of glutathione (137). For ease of understanding, the present review also lists the OSCC-related

compounds/drugs studied in recent years (Table II), and their connections and functions with autophagy.

Hsa_circ_0000378 (circ-LRP6) promotes EMT and autophagy in OSCC. Increasing autophagy can reverse the EMT process in OSCC cells inhibited by LRP6, including an increase in E-cadherin and a decrease in vimentin levels (138). One type of lncRNA is gastric cancer associated transcript 1 (GACAT1). In cancer tissues and cell lines of patients with OSCC, GACAT1 is highly expressed, while its target tumor suppressor gene, microRNA-149 (miR-149), is not as well expressed (139). GACAT1 silencing on OSCC cells was reversed by knocking down the lncRNA GACAT1 and transfecting the cells with miR-149 inhibitors. This resulted in the stimulation of autophagy and death while inhibiting migration and proliferation. OSCC cells multiplied and migrated more when lncRNA LINC01207 was overexpressed, although autophagy and apoptosis were suppressed. LINC01207 competitively inhibits miR-1301-3p and upregulates the expression of its endogenous target LDHA in OSCC, which promotes the malignant behavior of cancer (140). Therefore, elucidating how these pathways regulate cell death interact at the molecular level and how to map and integrate these pathways will provide a new direction for systematic research in this field. Identifying key factors such as ncRNA should make these processes treatment-targeted and highly needed.

Regulation of radiation tolerance and chemical resistance.

Autophagy is an important lysosome-dependent pathway, which ultimately leads to tumor cell survival and drug resistance. Chemotherapy is part of the conventional first-line therapy for most tumors. However, the effectiveness of radiotherapy is limited by the adaptation of tumor cells, which makes tumor cells have the ability to tolerate radiotherapy (141). Ubiquitin-specific protease 14 (USP14) knockdown increased autophagy induction in radiation-treated OSCC cells, whereas ATG14 knockdown decreased autophagy induction. Inhibition of USP14 reduces the radioresistance of OSCC *in vitro* and *in vivo* through autophagy-dependent apoptosis (142). Blocking autophagy with lysosomal inhibitors has become a promising method for solving the therapeutic radiation tolerance induced by autophagy. In one study, LC3 was significantly increased in SAS cancer cells and xenograft tumors co-treated with bortezomib and radiation compared with radiation alone, thus reducing the expression of tumor necrosis factor receptor-related factor 6 to improve its carcinogenicity and improve the poor prognosis. The use of 3-MA significantly reduced the cytotoxicity indicating the death-promoting effect of autophagy in the cytotoxicity induced by combined therapy. The accumulation of LC2-II induced by combination therapy in the presence of autophagosome-lysosome fusion inhibitors indicated that autophagic flux increased (143). Autophagy of human TSCC cells is upregulated by radiation or cisplatin. The sensitivity of human TSCC to cisplatin and radiation can be increased by using CQ to inhibit autophagy (144).

Traditional single-drug chemotherapy is a common treatment for all types of cancer. World War II gave rise to the concept of utilizing hazardous chemicals to cure cancer, and numerous chemotherapeutic medications have subsequently been found or created (145). Chemotherapeutic drugs include cisplatin, a platinum drug that can induce DNA-platinum

Table II. Autophagy in cancer.

A, Natural compounds					
First author, year	Drugs	Oral cancer cell lines	Function/mechanism	Influence on autophagy	(Refs.)
Kuo <i>et al</i> , 2022	Stelletin B	OC2 and SCC4	Induce endoplasmic reticulum stress, mitochondrial stress, apoptosis and autophagy, leading to OSCC cell death.	Induce	(84)
Patra <i>et al</i> , 2020	<i>Terminalia bellirica</i>	Cal33	Increase the accumulation of ROS to promote autophagy and apoptosis.	Induce	(95)
Shi <i>et al</i> , 2021	Glaucocalyxin A	CAL27, Tca8113 and HGE	Production of ROS induces apoptosis and autophagy in TSCC cells.	Induce	(96)
Hsieh <i>et al</i> , 2016	Polyphyllin G	SAS and OECM-	Apoptosis and autophagy were induced by ERK and JNK.	Induce	(99)
Ko <i>et al</i> , 2015	Pterostilbene	SAS and OECM-1	Activation of JNK1/2 and inhibition of Akt-ERK1/2p38 induces autophagy and cell cycle arrest.	Induce	(100)
Semlali <i>et al</i> , 2023	PAC	Ca9-22	PAC combined with cisplatin can further induce apoptosis and autophagy, and alleviate cisplatin resistance.	Induce	(157)
Shih <i>et al</i> , 2023	Caffeic acid phenethyl ester	SAS and OECM-1	Activation of mTOR-ULK1-P62-LC3 autophagy signaling pathway through ROS generation inhibits cell migration, colony formation and angiogenesis.	Induce	(130)
Zhang <i>et al</i> , 2023	Rhein	YD-10B and Ca9-22	Inhibit autophagy by inhibiting the AKT/mTOR signal pathway.	Inhibit	(103)
Han <i>et al</i> , 2023	Piperine	HSC-3	Induce the increase in acidic vesicles by inhibiting the PI3K/Akt/mTOR pathway.	Induce	(104)
Sophia <i>et al</i> , 2018	Nimbolide	SCC131 and SCC4	Inhibit tumor growth by regulating the ncRNAHOTAIR/miR-126/PI3K/Akt/GSK3 signaling axis to transform cell protective autophagy into apoptosis-induced autophagy.	Induce	(105)
Wang <i>et al</i> , 2022	Oroselol	SSC-4	Inhibit cell migration, cell invasion and the PI3K/AKT signaling pathway.	Induce	(106)
Park <i>et al</i> , 2022	Chrysophanol	CAL-27 and Ca9-22	Inhibition of the PI3K/AKT/mTOR pathway induces autophagy of OS CC cells.	Induce	(107)
Wei <i>et al</i> , 2020	Genipin	SCC-25 and SCC-9	Inhibition of PI3K/AKT/mTOR pathway induces autophagy of OSCC cells.	Induce	(108)
Ji <i>et al</i> , 2021	Liquiritigenin	CAL-27	Induce autophagy by inhibiting the PI3K/AKT/mTOR pathway	Induce	(109)
Fukuda <i>et al</i> , 2022	Resveratrol	Ca9-22	Induce autophagy-related apoptosis and inhibit lipid metabolism.		(111)
Yun <i>et al</i> , 2022	Latifolin	YD-8 and YD-10B	Inhibit the formation of autophagy-associated proteins and autophagosomes.	Inhibit	(113)

Table II. Continued.

A, Natural compounds					
First author, year	Drugs	Oral cancer cell lines	Function/mechanism	Influence on autophagy	(Refs.)
Yun <i>et al</i> , 2023	Machilin D	YD-10B	Inhibit the PI3K/AKT/mTOR/p70S6K pathway, and induce autophagy and apoptosis.	Induce	(114)
Yun <i>et al</i> , 2023	Xanol	YD-10B	Inhibit the PI3K/AKT/mTOR/p70S6K pathway, induce autophagy and reduce necrotizing apoptosis.	Induce	(115)
Park <i>et al</i> , 2022	Falcarindiol	YD-10B	Regulate the formation of autophagy vacuoles induced by Atg7, LC3 and Beclin-1 through the AKT and MAPK signaling pathways.	Induce	(133)
Shu <i>et al</i> , 2021	<i>Tribulus terrestris</i> fruit	SAS and TW2.6	Inhibition of autophagic flux, cell growth and metastasis of oral cancer cells.	Inhibit	(135)
Vo <i>et al</i> , 2023	Surfactin	SCC4 and SCC25	Autophagy induced by the NADPH oxidase/ROS/ER stress/calcium downregulated extracellular signal-regulated kinase 1 and 2 pathways. Regulation of ROS activating apoptosis, autophagy and ferroptosis.	Induce	(136)
Semlali <i>et al</i> , 2021	Tetrahydro-cannabinol	Ca9-22	Cause genomic instability and increase its apoptosis and autophagy to reduce cell viability.	Induce	(137)
B, Others					
First author, year	Drugs	Oral cancer cell lines	Function/mechanism	Influence	(Refs.)
Chen <i>et al</i> , 2024	<i>Fusobacterium nucleatum</i>	CAL27 and HSC3	Activate autophagic flux, thereby promoting cancer metastasis and invasion.	Induce	(20)
Wang <i>et al</i> , 2023	Melatonin and erastin	SCC-15	Regulation of ROS activating apoptosis, autophagy and ferroptosis.	Induce	(80)
Liu <i>et al</i> , 2022	MAP3K11	W2.6 and SAS	Stimulation of autophagy leads to malignant cancer cells.	Induce	(83)
Lv <i>et al</i> , 2020	Epidermal growth factor receptor	CAL-27	Reduce the ubiquitination of SOX2, inhibit the binding to p62 and prevent the autophagy degradation of SOX2.	Induce	(86)
Jhou <i>et al</i> , 2021	Chlorpromazine	Ca9-22, HSC-3	Induce autophagy through the PI3K/Akt/mTOR/p70S6K pathway, promote apoptosis and inhibit tumor growth <i>in vivo</i> ERK.	Induce	(93)

Table II. Continued.

B, Others	First author, year	Drugs	Oral cancer cell lines	Function/mechanism	Influence	(Refs.)
	Nguyen <i>et al.</i> , 2022	Metformin derivative HL156A	YD-15, YD-10B and YD-8	Induce autophagy to protect cells from apoptosis and inhibit the growth of the mouse model.	Induce	(94)
	Lin <i>et al.</i> , 2023	Hinokitiol	SCC4 and SCC25	Promote LC3B accumulation and sequestosome-1 (p62/SQSTM1) expression to induce autophagy.	Induce	(97)
	Choi <i>et al.</i> , 2023	Piperlongumine	MC-3 and HSC-4	Activation of protective autophagy through the MAPK signaling pathway.	Induce	(102)
	Fan <i>et al.</i> , 2022	Nucleoprotein 1	Cal27 and HN6	Inhibit the activity of transcription factor E3 promoter and destroy the function of the lysosome.	Induce	(131)

AKT, protein kinase B; ERK, extracellular signal-regulated kinase; ER, endoplasmic reticulum; GSK3, glycogen synthase kinase-3; JNK, c-Jun n-terminal kinase; LC3, light chain 3; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated extracellular signal-regulated kinase; mTOR, mammalian target of rapamycin; NADPH, nicotinamide adenine dinucleotide phosphate; p70S6K, 70-kDa ribosomal protein S6 kinase; PI3K, phosphoinositide 3-kinase; PAC, 3,5-bis(4-hydroxy-3-methoxybenzylidene)-N-methyl-4-piperidine; ROS, reactive oxygen species; SQSTM1, sequestosome 1; SOX2, SRY-box transcription factor 2 gene; ULK1, UNC51-like kinase-1.

adducts to block DNA repair, the mitotic inhibitors paclitaxel and docetaxel, and topoisomerase II inhibitors (anthracycline) doxorubicin and epirubicin (146,147). Autophagy also has dual functions in the process of tumor chemotherapy. On the one hand, chemotherapy-induced autophagy can make tumor cells escape the effects of various treatments and promote chemotherapy resistance and tumor survival (148,149). On the other hand, some chemotherapeutic drugs can treat tumors by inducing autophagy (150). Beclin1 is the first key factor found to be related to autophagy, and it is also an important protein regulating autophagy; it promotes autophagy by locating the precursor of autophagy. Beclin-1 is the core participant of autophagy regulation and one of the most important protein complexes in the autophagy formation pathway. Previous studies have found that the loss of alleles in human prostate, breast and ovarian cancer promotes the activation of p53 and significantly promotes proliferation *in vitro* and *in vivo* (151). The expression of Beclin-1 in CAL-27 cells was significantly inhibited before chemotherapy but increased after chemotherapy (152). It has been reported that frameshift mutations in some autophagy-related genes are present in gastric and colorectal cancer (153). These mutations are involved in the occurrence and development of tumors by dysregulating autophagy. These findings suggest that Beclin-1 is a tumor suppressor gene that is involved in both OSCC and autophagy. When low-power laser irradiation is applied to oral cancer cells, ROS cause the cells to undergo apoptosis and protective autophagy signal transduction. This increases the transcriptional activity of RelA and Beclin-1 expression in the exposed cells (154). The pharmacology and genetic ablation of autophagy become the resistance mechanism to enhance the apoptosis of oral cancer cells induced by low-power laser irradiation (154). During cisplatin treatment, Beclin-1 was upregulated, while the inhibition of Beclin-1 significantly weakened the self-renewal potential, cancer cell stemness and resistance to cisplatin-induced cytotoxicity of oral CD44⁺ tumor stem cells (155). Cisplatin therapy enriches the tumor stem cell population and autophagic flux by accelerating autophagosome-lysosome fusion and stimulating lysosome activity (155). By contrast, autophagy defects reduce the increased level of ROS, enhance the cancer cell stemness, and reduce the cisplatin resistance of tumor stem cells. Inhibition of autophagy increases the cytotoxicity of cisplatin, thus inhibiting the expansion of oral CD44⁺ cells (155).

The secretion of aggregates promotes mitochondrial autophagy under the condition of serum starvation through the AMPK/Akt/mTOR signaling pathway to protect cells from nutritional deprivation. Inhibition of autophagy in CAL33 cells secreting aggregates significantly increases cell death, indicating that autophagy plays a role in promoting survival in oral cancer, resulting in cisplatin-induced inhibition of cell death in oral cancer (156). Bis(4-hydroxy-3-methoxybenzylidene)-N-methyl-4-piperidine is a new curcumin analogue. As a supplementary therapy of cisplatin, it enhances autophagy and inhibits the mitochondrial membrane potential of oral cancer cells (157). On study showed that the inhibition of glucose transporter-1 in OSCC and cisplatin-treated cisplatin-resistant cells made the cells sensitive, and induced apoptosis and autophagy (158). The overexpression of mitochondrial fission protein 1 leads to mitochondrial autophagy, and its inhibitor

Table III. Strategies and mechanisms for modulating chemical resistance through the regulation of autophagy.

First author, year	Chemotherapy drugs	Autophagic compounds/materials	Goal of targeted regulation	Mechanisms	(Refs.)
Prabharaj <i>et al</i> , 2023	Cisplatin		BECN1 and NRF2	Defective autophagy in CD44 ⁺ cells activates NRF2 signaling to enhance cancer stemness.	(155)
Naik <i>et al</i> , 2021	Cisplatin	Secretory clusterin	Akt/mTOR/ULK1	Activation of autophagy to inhibit apoptosis.	(156)
Semlali <i>et al</i> , 2023	Cisplatin	PAC		Combination of PAC and cisplatin further induces apoptosis, autophagy and alleviates cisplatin resistance.	(157)
Kumari <i>et al</i> , 2023	Cisplatin	GLUT1/3	c-Jun	Blockade of the GLUT1 receptor sensitizes CisR-OSCC cells to cisplatin.	(158)
Tsai <i>et al</i> , 2022	Cisplatin	MTH-3	Transcription factor EB	Decreases mitochondrial membrane potential and induces autophagy.	(163)
Yang <i>et al</i> , 2023	Cisplatin		F-box/WD repeat protein 7	Upregulates autophagy expression after overexpression and inhibits colony formation.	(164)
Lima <i>et al</i> , 2021	5-Fluorouracil	Chitosan solution/polycaprolactone		Promotes autophagy and inhibits cell proliferation and survival.	(161)
Wang <i>et al</i> , 2021	Pirarubicin	Epi-loaded liposomes-HPR	HuR (ELAVL1)	Promotes apoptosis, necrosis, autophagy and leads to cancer cell death.	(162)
Panigrahi <i>et al</i> , 2022	Adriamycin and paclitaxel	S28	MTP18 inhibitor	Lysosomal membrane permeabilization leads to a decrease in lysosomal pH, which impairs autophagosomal lysosomal fusion.	(159)
	5-Fluorouracil, doxorubicin and cisplatin	Capsaicin	Mitochondrial fission protein 1	Promotes cell death by eliminating DNA damage caused by chemotherapeutic drugs.	

GLUT, facilitative glucose transporter; NRF2, nuclear respiratory factor 2; PAC, Bis (4-hydroxy-3-methoxybenzylidene)-N-methyl-4-piperidine.

S28 can also activate autophagy and affect the autophagic flux of oral cancer cells, but it cannot lead to mitochondrial autophagy, due to the difficulty of low perfusion mitochondrial phagocytosis (159). ROS induced by S28 promote lysosomal membrane permeability, which leads to the decrease of lysosomal pH, thus destroying autophagy-lysosomal fusion, leading to the accumulation of activated lysosomes in oral cancer cells and promoting apoptosis, therefore improving the efficiency of chemotherapy (159). Capsaicin has been found to enhance autophagy, and decrease glycoprotein II in human OSCC HSC-3 and SAS cell lines, but has no significant effect on apoptotic cell death (160). The expression of ribonucleoprotein II induced by capsaicin is consistent with the use of autophagy inducers and inhibitors, revealing a new mechanism by which capsaicin makes oral cancer cells sensitive to anticancer drugs (160). The synthesis of polycaprolactone modified by chitosan solution can reduce the early and local recurrence of head and neck SCC induced by 5-fluorouracil in head and neck cancer cell lines (161). Composite sponges and particles containing 5-FU induce LC3 activation and apoptosis marker PARP1 expression in a manner similar to that of individual drugs and enhance the therapeutic efficacy of 5-fluorouracil interference drugs (161). HuR (ELAVL1) is an RNA-binding protein. The HuR gene editing plasmid of RISR-cas9 (HuRCRISR) is encapsulated and delivered by solid lipid NPs, and epirubicin is encapsulated by liposomes. Their co-treatment in SAS cells further promotes apoptosis, necrosis and autophagy, leads to cancer cell death and regulates drug resistance (162). Curcumin derivative MTH-3 increases autophagy of oral cancer CAL27 cisplatin-resistant cells by regulating the target transcription factor EB, which triggers intrinsic apoptosis and is sensitive to cisplatin (163). Transfection of F-box/WD repeat protein 7 (FBXW7) into SCC7 and CAL9 cells increased sensitivity to cisplatin therapy, with lower colony formation and invasion, slower cell proliferation, and higher apoptosis and autophagy (164). FBXW7 overexpression in mouse tumors with CAL27 xenografts was correlated with increased autophagy and apoptosis (164). The strategies and mechanisms of regulating chemical resistance by regulating autophagy are summarized (Table III).

5. Conclusions and prospects

In summary, autophagy is a key therapeutic option for malignancies, including oral cancer. The expression of therapeutic targets in tumor cells plays a major role in the selection of particular medications, as numerous natural and clinical pharmaceuticals are altered or employed in conjunction with tiny molecular inhibitors. Tumors exhibit diverse levels of gene expression for different autophagy regulating genes. The fact that conventional medications have been repurposed in targeted autophagy is also intriguing (162). This acts as an indication that with advances in science, the uses of certain medications may become more widespread. The way in which to regulate autophagy is a big unresolved issue in terms of controlling oral cancer through autophagy. Autophagy regulation, including activation and inhibition, is now being sought and intensively investigated. By controlling the autophagic response to cancer, these strategies will also help those suffering from the disease. However, the general regulation of autophagy may lead to

unnecessary systemic side effects. For example, the regulation of autophagy in cancer treatment can lead to deterioration of renal function (165). Thus, it is especially crucial to create targeted treatments to control cancer cell autophagy without causing negative systemic effects. NP autophagy regulators offer special benefits in this respect (166). It might be possible to utilize this method to improve treatment, or cure or prevent cancer if these particular types of autophagy can be controlled. This could also provide predictive insights into the functions of autophagy in human diseases.

The exact role of autophagy in cancer needs to be further clarified. For further research development, the different stages, tumor microenvironment and treatment of autophagy cancer can be further studied in the future. It is unclear what the signals, molecules and mechanisms are that allow autophagy to act as an anticancer process in some situations while having the opposite effect in others.

It is expected that in the following years, new findings will be made that will help us understand the process underlying this intriguing cellular autophagy and aid us to develop effective cancer treatments. It should be noted that attempts to impede processes deemed essential may be hampered if cancer cells modify how they carry out cellular tasks. For instance, even though autophagy is considered to be crucial for the formation of cancer, cancer cells may be able to evade effective strategies to block or stimulate autophagy if they are able to retain healthy mitochondria, endoplasmic reticulum and lysosomes in methods other than autophagy. This appears plausible given the evolutionary conservatism of autophagy, the control of its signaling pathway, its molecular mechanism and its physiological function, but formal evidence is lacking. In the near future, more links between autophagy and human diseases may be confirmed.

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ZL performed the literature search and wrote the review. YZ, JHL and YXW provided suggestions and revised the present review. All authors critically reviewed the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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