ISSN (Print) 1225-9918
ISSN (Online) 2287-3406
Journal of Life Science **2017** Vol. 27. No. 8. 958~964 DOI : https://doi.org/10.5352/JLS.2017.27.8.958

- Review -

Autophagy and Oral Cancer

Seung Hwa Son[1] and Eun-Jung Kim[2]*

[1]*Department of Dental hygiene, Gangdong College, Eumseong, Chungbuk 27600, Korea*
[2]*Department of Biomedical Laboratory Science, Sangji University, Wonju 26339, Korea*

Received July 29, 2017 /Revised August 28, 2017 /Accepted August 28, 2017

Autophagy plays an important role in cellular homeostasis and survival for cell recycling and various stresses within the cell. Recent studies have shown that autophagy activity modulates the expression of oncogene and tumor suppressor genes, leading to the development or suppression of cancer. Induction of autophagy is involved in preventing cancer development in normal cells and plays an important role in prompting a specific cell death mechanism in cancer cells with damaged cell death function. It is also known that autophagy inhibition increases the therapeutic efficacy by sensitizing cancer cells that are resistant to chemotherapy. However, the role of autophagy has not yet been fully understood in cancer treatment. Oral squamous cell carcinoma accounts for more than 90% of oral cancer and is the sixth most common cancer in the world. The incidence of oral cancer has increased by 50% over the last 20 years and the mortality rate is over 40% within 5 years after the onset. In oral cancers, the role of autophagy are described to look for tumor inhibitory in the early stages of tumor formation, like other cancers, indicating the dual functions involved in tumor cell survival include tumor progression stages. This review summarizes the various roles of autophagy in cancer cells and suggests the possibility of autophagy as a promising target for effective oral cancer therapy.

Key words : Autophagy, cancer therapy, oral squamous cell carcinoma

Introduction

In 1963, de Duve presented the term autophagy, which is derived from the Greek words 'auto' and 'phagy' sense 'self' and 'eating', to describe the happening of obvious intracellular, membranous vesicles that included degraded cytoplasmic material [44]. Autophagy has been shown to play an important role in maintaining homeostasis and cellular integrity in normal cells. In addition to these physiological conditions, it has been found to be involved in a variety of pathological manners, and there is a growing interest in its role as an important regulator in the growth and treatment of malignant tumors [36, 44]. Autophagy is a self-digestive progression that confirms the lysosomal degradation of superfluous or damaged organelles and misfolded proteins [22]. Depending on the pathway to the lysosomes, three different autophagy types are well-defined: microautophagy, chaperone-mediated autophagy and macroautophagy [29]. This review specially focuses on macroautophagy, which is henceforth simply named autophagy. Autophagy begins with the formation of double membrane vesicles, known as autophagosomes, which surround cytoplasmic components. The autophagosomes then merge with lysosomes where the isolated contents experience degradation and recycling [11]. Many studies on the cellular biologic mechanisms of autophagy in recent decades have been implicated in both human health and disease. Autophagy is significant for the elimination of damaged or long-lived proteins and organelles in all cells. Autophagy defects are related with susceptibility to genomic damage, metabolic stress, and tumorigenesis in mice demonstrating a role for autophagy in tumor suppression [32]. This deficiency of autophagy is known to play an important role in the pathology of many diseases. For example, autophagy dysregulation is associated with the development of a variety of diseases, including degenerative brain diseases such as Parkinson's disease or Alzheimer's disease, congenital muscular disorders such as pemphigus, congenital heart disease and various types of cancer [23, 30]. However, the role of autophagy in cancer is more complex, sometimes leading to cancer and in others it seems to inhibit cancer. Several results suggest that autophagy may act as a tumor suppressor in the early stage of tumor development, but it may contribute to the survival of the tumor if the cell

***Corresponding author**
Tel : +82-33-738-7683, Fax : +82-33-738-7683
E-mail : jung0724@sangji.ac.kr

becomes malignant and developed. Hormone therapy, chemotherapy, and radiation therapy, which are used in the treatment of cancer, often cause autophagy, which acts as a survival response and contributes to depressing the potential cancer cure rate [18, 24]. In contrast, there is also an observation that cancer cells that are resistant to apoptosis will be able to suggest a new anti-cancer strategy through overexpression of autophagy. Thus, it is the major problem to decide how best to use autophagy to maximize the effect of cancer treatment due to the role of contradictory autophagy in the development and treatment of cancer.

Oral cancer incidence has been reported to account for 2-5% of all malignant tumors that occur in the human, and 2-3% of all cancer deaths are caused by oral cancer mortality [20]. The most common type of oral cancer is oral squamous cell carcinoma (OSCC), which accounts for about 80-90% [27]. Treatment of oral malignancies includes surgical resection, radiotherapy and chemotherapy, and immunotherapy. For progressive carcinoma, combined therapy with surgery and radiation therapy or chemotherapy is being performed to increase the survival rate [19]. The 5-year survival rate of oral cancer is upgraded by the study and development of the treatment, and the survival rate is increased when the disease is found early and treated properly [19]. For this reason, basic research data are urgently required for the early detection and early treatment of oral cancer, and the better quality of life of the patient.

In this review, we describe autophagy's newest findings and express how autophagy behaves in the process of cancer development and growth. In particular, we will discuss the possibility of autophagy as an alternative to new cancer therapy in situations of oral cancer treatment.

Comparison of programmed cell death

Based on the morphology of cell death by Clarke, 4 types of cell death have been suggested, and so far programmed cell death has been studied in detail [14, 9]. The first type, known as type I or apoptosis, is known to be regulated by the caspase family due to the formation of so-called apoptotic bodies, which characterize cell types such as cell shrinkage, chromatin condensation, nucleosomal DNA degradation and fragmentation. The second type, called type II or autophagic cell death is characterized by the formation of an autophagic vesicle in the cell and degradation of intracellular macromolecule similar to the lysosomal system. When autophagosome formation is stimulated, some chromatin condensation appears similar to apoptosis, but it is established as autophagy, which means self-eating by inducing apoptosis without detecting DNA fragmentation (Table 1). The third type is type III, which is defined as nonlysosomal vesiculate degradation. Type III programmed cell death is known as type IIIA and type IIIB, and is classified into nonlysosomal degradation and cytoplasmic type of degeneration [9]. Methods for evaluating type II or autophagic cell death systems have been developed, including microscopic observation of cell morphology, degradation assay for long-lived proteins, and monodansylcadaverine [14].

The process of autophagy

Previously known apoptosis, necrosis only deals with the death of whole cells, but autophagy is a new type of programmed cell death which is related to the death and regeneration of intracellular organelles such as mitochondria and endoplasmic reticulum. In other words, it has been thought that the intracellular organelles in the human are maintained in a static state at normal periods, but it has been revealed that the intracellular organelles constantly die and regenerate even when the cells are kept static. Through this procedure, the old and degenerated intracellular organelles are eliminated and become a necessary nutrient source to

Table 1. Comparison of autophagy and apoptosis among programmed cell death

	Autophagy	Apoptosis
Nucleus morphology	Fractional chromatin condensation Nucleus undamaged until late stages No DNA laddering	Chromatin condensation Nuclear fragmentation DNA laddering
Detection methods	Research of augmented lysosomal activity Research of increased long-lived protein degradation Research of amplified cytoplasmic sequestration Finding of LC3 mobilization to autophagy membranes	Nuclear/cellular fragmentation detection DNA laddering detection Increased in sub G1 content measured FACS analysis Annexin-V staining

regenerate new intracellular organelles, thus forming a cycle in which new cells are regenerated [39]. Some of the cytoplasm, including organelles, is surrounded by a phagophore or isolation membrane to arrange an autophagosome. The external membrane of the autophagosome consequently melts with the lysosome, and the internal material is degraded in the autolysosome. Amino acids and other small molecules formed through autophagy degradation are recycled back to the cytoplasm or used for energy production [30, 45]. Hence, autophagy is a complex process, which can be divided into five stages: initiation, elongation, closure, maturation, and degradation (Fig. 1). At each stage, several autophagy-related genes (ATGs) are closely coordinated [18, 30]. More than 35 ATGs regulating various processes in autophagosome formation were found on yeast genetic screens [18]. ATGs were originally found in yeast, but almost ATGs now have heterologous homologous genes in mammalian cells. In fact, since autophagy is activated for cell survival, it is likely to increase tumor cell survival in many cases and stimulate tumorigenesis. In many other cases, however, a strong death signal that transcends this survival advantage kills the tumor cells and eventually inhibits the tumor. From an objective point of view, it is reasonable to assume that autophagy is in the process of cell death but not directly contributing to cell death [37]. Although autophagy does not make cell death by itself, there is a sight that autophagy promotes cell death as a necessary process in situations where it is associated with signals that induce other cell deaths.

Autophagy as a therapeutic target in cancer

In cancer, autophagy has a diversity of functions, including the removal of unnecessary substances and the supply of nutrients, depending on the genotype and stage of the cancer [7, 37, 43, 45]. The understanding of the diversity of autophagy under these conditions is very significant in the development of cancer drugs. Increasing the activity of autophagy may lead to cancer suppression. Autophagy plays an important role in maintaining the genetic stability by preventing the transformation of normal cells into cancer cells, inhibiting the development of cancer, and removing the damaged cellular organelles so as not to generate active oxygen [12]. On the other hand, recent studies have shown that the activity of autophagy is regulated by the expression of oncogene and tumor suppressor genes and cancer is either developed or inhibited (Table 2). In particular, the mammalian target of rapamycin (mTOR) kinase, which is known to be an autophagy inhibitor in human cells, inhibits the activity of autophagy by maintaining hyperphosphorylation in the protein necessary for the initiation of the autophagic cascade [13]. Conversely, mTOR expression was suppressed in stress conditions such as nutrient insufficiency and autophagy activity was reported to increase. NF-1, PI3K, and Ras have been known as oncogenes that regulate the expression of these mTORs. Although Ras inhibits autophagy as a signal transducer in the RTK-mTOR pathway, neurofibromin-1 (NF-1), an antagonist of Ras, is predictable to increase the autophagy by inhibiting the RTK-mTOR pathway, but a clear mechanism has been described not [38]. Bec-1 as a tumor suppressor is a major modulator of autophagy, suggesting that when the expression of Bec-1 is promoted, smARF regulates p53 and activates autophagy independent of the RTK-mTOR pathway [25, 26, 34, 42]. Therefore, it can be summarized that oncogene and tumor suppressor control autophagy by several signaling. It is proposed that autoph-

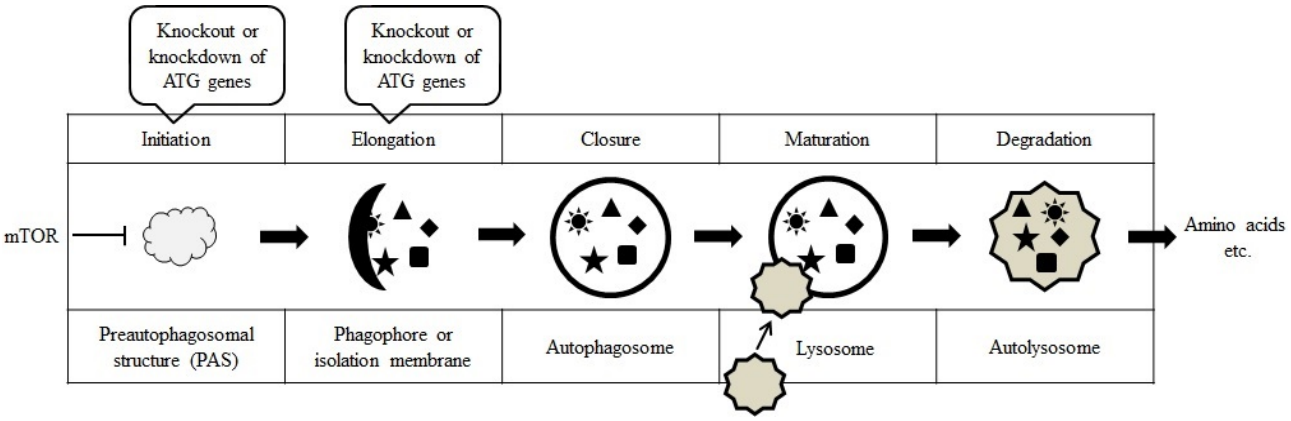

Fig. 1. Five stages in the formation of autolysosome during autophagy.

Table 2. Patterns of autophagy directive by oncogenes and tumor suppressor genes

Oncogenes	Join to autophagy	Relation to tumor formation
PI3K	mTOR activating kinase	Gain-of-function mutations or augmentations of PI3K are public to several human cancers
NF1	Ras antagonist, negatively controls the RTK-mTOR pathway	Functional loss mutations result in type I neurofibromatosis.
Ras	RTK-mTOR pathway signal converter	Overexpressed in most human cancers
Akt1	Structurally active Akt1 functions as an autophagy inhibitor *in vitro* and *in vivo*	Gain-of-function mutations or augmentations shown in high fractions of human cancers
Tumor suppressor genes	Join to autophagy	Relation to tumor formation
p53	Cellular p53 exerts tonic inhibition of autophagy Nuclear p53 transactivates autophagy-stimulating factors	Mutations in more than 50% of all human tumors
Bec-1	Crucial modulator of autophagy	Brain tumors are characterized by decreased expression of Bec-1
smARF	By releasing Bex-1 as a Bcl-X_L mediated inhibition, it probably promotes autophagy independent of p53	Mutated or missing in various types of human cancer

agy may be an attractive scheme for future cancer treatment approach by studying inhibitor or activator for gene and protein expression and signaling.

Since the mechanism and function of autophagy associated with cancer is caused by an inclusive variety of pathways, the possibility of developing an anticancer drug targeting autophagy is considered to be unlimited. Autophagy is mainly activated in hypoxia and stress states of cancer. Consequently, it is expected that the use in combination with various anticancer agents and autophagy activating substances will further maximize the therapeutic effect [11, 17]. In addition, the use of an inhibitor for the regulator inhibiting the autophagy system described above may be useful for the development of various anticancer adjuvants. Inhibition of cancer cell growth in chronic myelogenous leukemia cells caused by the combination of 3-methyladenine (3-MA), a known inhibitor of class III phosphoinositide 3-kinase (PI3K), and suberoylanilide hydroxamic acid (SAHA), a known histone deacetylase inhibitor, has been testified [6]. According to other studies, autophagy was inhibited in cancer cells showing resistance to radiation [3]. The effect of autophagy-activating substances on radiation tolerant cancer is expected to inhibit tolerance.

Autophagy in oral squamous cell carcinoma

The oral cancer is one among the common malignancies in numerous parts of the world. Around 90% of these diagnosed cases are OSCC [1]. OSCC results due to a complicated interaction between several environmental and genetic factors and is thus a complex multistage course [35]. Even though abundant has been found about autophagy and its role in several carcinomas, not much has been found about the portion it plays in OSCC.

A current immunohistochemical study of 195 oral squamous cell cancers revealed higher levels of cytoplasmic p62, suggesting damaged autophagy, and its correlation with reduced general and disease specific survival [10]. A high level of autophagy-related protein light chain 3 (LC3)-II was found in these patients, suggesting augmented basal levels of autophagy may be associated to autophagy re-activation in later advanced stage cancers. This has been revealed in other cancers such as melanoma and backs the concept of an autophagy contradiction [10]. Tumors of the head and neck are highly heterogeneous cancers with variable genetic mutations contribute toward tumorigenesis [21]. However, some consistencies in somatic aberrations have been shown by well-known genomic sequencing [5]. Some of these aberrations are in processes which are identified to play an important role in autophagy. Phosphoinositide-3-kinase, catalytic, alpha polypeptide (PIK3CA) gene is generally mutated in head and neck cancers and stimulation of PI3K and downstream effectors have been found to promote autophagy [5].

It has been also demonstrated that despite the absence of cytotoxicity, oral cancer cells experience inhibited proliferation following Porphyromonas gingivalis (P. gingivalis)

infection, compared to non-infected control cells [8]. P. gingivalis, a main etiologic micro-organism of chronic periodontitis, settles inside the tumor microenvironment of patients with oral cancer. Apoptosis could not explain inhibited proliferation in infected cells as only some of cells had the sub-G1 DNA content expressive of apoptosis. Conversely, P. gingivalis induced significant accumulation of oral cancer cells in the G1 phase with a reduction in S phase [8]. This phenomenon is in contrast to the continuous growth that appears in non-infected cells. In the blockade of autophagy pathway via 3-MA, P. gingivalis failed to suppress the cell cycle or arrest the cell cycle in the G1 phase. This suggests that P. gingivalis induced cell proliferation by inducing autophagy and disrupting the cell cycle [8]. Recent studies have shown that 2′-benzoyloxycinnamaldehyde(BCA) induces apoptosis and autophagy in p53 null cells, human Oral Squamous Carcinoma YD-10B cells, and inhibits cell proliferation [15]. Previous studies have revealed that autophagy promotes apoptosis leading to cell death, while autophagy inhibits apoptosis and is involved in cell survival [28]. In another study, p53 mutation and c-myc amplification were observed in OSCC [33]. Various cells have been reported that have been exposed to have mutations in p53 and caspases to enhance resistance to apoptotic stress and a multi-targeting strategy against tumor cells [40, 41, 46]. This suggests that the opportunity for cancer treatment will increase. Most cancers that are resistant to chemotherapy, including specific oral cancers, have demonstrated autophagy to avoid cell death. The system of autophagy and apoptosis is inversely related, but their molecular association is much more complex and requires further evaluation [16, 31]. Some studies have used agents other than 3-MA to encourage apoptosis directly or indirectly by inhibiting cellular autophagy. Bai et al. used G15, an antagonist to G protein-coupled receptor 30 (GPR30), a recognized cancer cell proliferator to induce apoptosis in OSCC [4]. Apicidin, a histone deacetylase inhibitor, was used to initiate apoptosis in OSCC cells [2].

Autophagy slows down and interferes with the development of various therapies to reduce and eliminate cancerous tumors. Lymphocyte-induced autophagy has been shown to help survival of cancer cells [1]. Autophagy is induced by radiation therapy to a large amount beyond the limits of carcinoma cells, leading to autophagy-mediated cell death. Therefore recognizing the molecules mediating autophagy may help as therapeutic agents by either directly or indirectly inducing apoptosis in chemotherapy resistant cancers cells containing oral cancer.

Conclusions

Autophagy is a programmed cell death type II, known as self-eating, which induces cell death by forming an auto-phagosome within a cell. Generally autophagy action is tumor suppression and tumor formation, which reports dual function. The role of tumor suppression is to remove the damaged mitochondria by several factors, thereby alleviating oxidative stress or eliminating various risk factors and suppressing the cancerous phenomenon. However, most tumor cells are known to undergo tumorigenesis by activating autophagy as a mechanism for survival in conditions such as limited nutrition, hypoxia and radiation exposure. Recent studies have stated that autophagy inhibitors have been used in combination with anticancer drugs to stimulate apoptosis and improve the therapeutic effect. However, the molecular mechanism for the regulation and role of autophagy in tumors has not been fully revealed. Furthermore, the autophagy inhibition may be more involved in the survival of tumor cells, so more vigorous research is required in the future.

References

1. Adhauliya, N., Kalappanavar, A. N., Ali, I. M. and Annigeri, R. G. 2016. Autophagy: A boon or bane in oral cancer. *Oral Oncol.* **61**, 120-126.
2. Ahn, M. Y., Ahn, S. G. and Yoon, J. H. 2011. Apicidin, a histone deaceylase inhibitor, induces both apoptosis and autophagy in human oral squamous carcinoma cells. *Oral Oncol.* **47**, 1032-1038.
3. Apel, A., Herr, I., Schwarz, H., Rodemann, H. P. and Mayer, A. 2008. Blocked autophagy sensitizes resistant carcinoma cells to radiation therapy. *Cancer Res.* **68**, 1485-1494.
4. Bai, L. Y., Weng, J. R., Hu, J. L., Wang, D., Sargeant, A. M. and Chiu, C. F. 2013. G15, a GPR30 antagonist, induces apoptosis and autophagy in human oral squamous carcinoma cells. *Chem. Biol. Interact*. **206**, 375-384.
5. Cancer Genome Atlas Network. 2015. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature* **517**, 576-582.
6. Carew, J. S., Nawrocki, S. T., Kahue, C. N., Zhang, H., Yang, C., Chung, L., Houghton, J. A., Huang, P., Giles, F. J. and Cleveland, J. L. 2007. Targeting autophagy augments the anticancer activity of the histone deacetylase inhibitor SAHA to overcome Bcr-Abl-mediated drug resistance. *Blood* **110**, 313-322.
7. Choi, K. S. 2012. Autophagy and cancer. *Exp. Mol. Med.* **44**,

109-120.
8. Cho. T. J., Wee, S. W., Woo, V. H., Choi, J. I., Kim, S. J., Shin, H. I., Lee, J. H. and Park, H. R. 2014. Porphyromonas gingivalis-induced autophagy suppresses cell proliferation through G1 arrest in oral cancer cells. *Arch. Oral Biol.* **59**, 370-378.
9. Clarke, P. G. 1990. Developmental cell death: morphological diversity and multiple mechanisms. *Anat. Embryol. (Berl)* **181**, 195-213.
10. Cosway, B. and Lovat, P. 2016. The role of autophagy in squamous cell carcinoma of the head and neck. *Oral Oncol.* **54**, 1-6.
11. Degenhardt, K., Mathew, R., Beaudoin, B., Bray, K., Anderson, D., Chen, G., Mukherjee, C., Shi, Y., Gelinas, C., Fan, Y., Nelson, D. A., Jin, S. and White, E. 2006. Autophagy promotes tumor cell survival and restricts necrosis, inflammation, and tumorigenesis. *Cancer Cell* **10**, 51-64.
12. Denton, D., Xu, T. and Kumar, S. 2015. Autophagy as a pro-death pathway. *Immunol. Cell Biol.* **93**, 35-42.
13. Galluzzi, L., Vicencio, J. M., Kepp, O., Tasdemir, E., Maiuri, M. C. and Kroemer, G. 2008. To die or not to die: that is the autophagic question. *Curr. Mol. Med.* **8**, 78-91.
14. Gozuacik, D. and Kimchi, A. 2004. Autophagy as a cell death and tumor suppressor mechanism. *Oncogene* **23**, 2891-2906.
15. Kim, H. W. and Kim, S. A. 2014. Cinnamaldehyde derivative, 2′-benzoyloxycinnamaldehyde (BCA), Induces Apoptosis and Autophagy in Human Oral Squamous Carcinoma YD-10B Cells. *Kor. J. Oral. Maxillofac. Pathol.* **38**, 247-256
16. Jiang, L. C., Xin, Z. Y., Deborah, B., Zhang, J. S., Yuan, D. Y., Xu, K., Liu, X. B., Jiang, H. Q., Fan, Q. C., Zhang, B. and Li, K. Y. 2015. Inhibition of autophagy augments apoptosis in human oral squamous cell carcinoma under nutrient depletion. *J. Oral Pathol. Med.* **44**, 361-366.
17. Karantza-Wadsworth, V., Patel, S., Kravchuk, O., Chen, G., Mathew, R., Jin, S. and White E. 2007. Autophagy mitigates metabolic stress and genome damage in mammary tumorigenesis. *Genes Dev.* **21**, 1621-1635.
18. Kimmelman, A. C. 2011. The dynamic nature of autophagy in cancer. *Genes Dev.* **25**, 1999-2010.
19. Klug, C., Berzaczy, D., Voracek, M. and Millesi, W. 2008. Preoperative chemoradiotherapy in the management of oral cancer: a review. *J. Craniomaxillofac. Surg.* **36**, 75-88.
20. Kujan, O., Glenny, A. M., Duxbury, J., Thakker, N. and Sloan, P. 2005. Evaluation of screening strategies for improving oral cancer mortality: a Cochrane systematic review. *J. Dent. Educ.* **69**, 255-265.
21. Leemans, C. R., Braakhuis, B. J. and Brakenhoff, R. H. 2011. The molecular biology of head and neck cancer. *Nat. Rev. Cancer* **11**, 9-22.
22. Levine, B. and Klionsky, D. J. 2004. Development by self-digestion: molecular mechanisms and biological functions of autophagy. *Dev. Cell* **6**, 463-477.
23. Levine, B. and Kroemer, G. 2008. Autophagy in the pathogenesis of disease. *Cell* **132**, 27-42.
24. Li, Y. J., Lei, Y. H., Yao, N., Wang, C. R., Hu, N., Ye, W. C., Zhang, D. M. and Chen, Z. S. 2017. Autophagy and multidrug resistance in cancer. *Chin. J. Cancer* **36**, 52.
25. Liang, C., Lee, J. S., Inn, K. S., Gack, M. U., Li, Q., Roberts, E. A., Vergne, I., Deretic, V., Feng, P., Akazawa, C. and Jung, J. U. 2008. Beclin1-binding UVRAG targets the class C Vps complex to coordinate autophagosome maturation and endocytic trafficking. *Nat. Cell. Biol.* **10**, 776-787.
26. Liang, X. H., Jackson, S., Seaman, M., Brown, K., Kempkes, B., Hibshoosh, H. and Levine, B. 1999. Induction of autophagy and inhibition of tumorigenesis by beclin 1. *Nature* **402**, 672-676.
27. Lo-Muzio, L., Santarelli, A., Panzarella, V., Campisi, G., Carella, M., Ciavarella, D., Di-Cosola, M., Giannone, N. and Bascones, A. 2007. Oral squamous cell carcinoma and biological markers: an update on the molecules mainly involved in oral carcinogenesis. *Minerva. Stomatol.* **56**, 341-347.
28. Martin-Ezquerra, G., Salgado, R., Toll, A., Gilaberte, M., Baro, T., Alameda, Q., F., Yebenes, M., Sole, F., Garcia-Muret, M. and Espinet, B. 2010. Multiple genetic copy number alterations in oral squamous cell carcinoma: study of MYC, TP53, CCDN1, EGFR and ERBB2 status in primary and metastatic tumours. *Br. J. Dermatol.* **163**, 1028-1035.
29. Mizushima, N., Levine, B., Cuervo, A. M. and Klionsky, D. J. 2008. Autophagy fights disease through cellular self-digestion. *Nature* **45**, 1069-1075.
30. Mizushima, N., Yoshimori, T. and Levine, B. 2010. Methods in mammalian autophagy research. *Cell* **140**, 313-326.
31. Patil, S., Rao, R. S. and Raj, A. T. 2015. Dual role of autophagy in oral cancer. *J. Int. Oral Health* **7**, i-ii.
32. Qu, X., Yu, J., Bhagat, G., Furuya, N., Hibshoosh, H., Troxel, A., Rosen, J., Eskelinen, E. L., Mizushima, N., Ohsumi, Y., Cattoretti, G. and Levine, B. 2003. Promotion of tumorigenesis by heterozygous disruption of the beclin 1 autophagy gene. *J. Clin. Invest.* **112**, 1809-1820.
33. Ravikumar, B., Sarkar, S., Davies, J. E., Futter, M., Garcia-Arencibia, M., Green-Thompson, Z. W., Jimenez- Sanchez, M., Korolchuk, V. I., Lichtenberg, M., Luo, S., Massey, D. C., Menzies, F. M., Moreau, K., Narayanan, U., Renna, M., Siddiqi, F. H., Underwood, B. R., Winslow, A. R. and Rubinsztein, D. C. 2010. Regulation of mammalian Autophagy in physiology and pathophysiology. *Physiol. Rev.* **90**, 1383-1435.
34. Reef, S. and Kimchi, A. 2008. Nucleolar p19ARF, unlike mitochondrial smARF, is incapable of inducing p53-independent autophagy. *Autophagy* **4**, 866-869.
35. Roepman, P., Wessels, L. F., Kettelarij, N., Kemmeren, P., Miles, A. J., Lijnzaadm, P., Tilanus, M. G., Koole, R., Hordijk, G. J., van der Vliet, P.C., Reinders, M. J., Slootweg, P. J. and Holstege, F. C. 2005. An expression profile for diagnosis of lymph node metastases from primary head and neck squamous cell carcinomas. *Nat. Genet.* **37**, 182-186.
36. Rosenfeldt, M. T. and Ryan, K. M. 2009. The role of autophagy in tumour development and cancer therapy. *Expert Rev. Mol. Med.* **11**, e36.
37. Rosenfeldt, M. T. and Ryan, K. M. 2011. The multiple roles of autophagy in cancer. *Carcinogenesis* **32**, 955-963.
38. Shaw, R. J. and Cantley, L. C. 2006. Ras, PI(3)K and mTOR

signalling controls tumour cell growth. *Nature* **441**, 424-430.
39. Singletary, K. and Milner, J. 2008. Diet, autophagy, and cancer: a review. *Cancer Epidemiol. Biomarkers Prev.* **17**, 1596-1610.
40. Soung, Y. H., Lee, J. W., Kim, S. Y., Jang, J., Park, Y. G., Park, W. S., Nam, S. W., Lee, J, Y., Yoo, N. J. and Lee, S. H. 2005. CASPASE-8 gene is inactivated by somatic mutations in gastric carcinomas. *Cancer Res.* **65**, 815-821.
41. Soussi, T. and Lozano, G. 2005. p53 mutation heterogeneity in cancer. *Biochem. Biophys. Res. Commun.* **331**, 834-842.
42. Tasdemir, E., Maiuri, M. C., Galluzzi, L., Vitale, I., Djavaheri-Mergny, M., D'Amelio, M., Criollo, A., Morselli, E., Zhu, C., Harper, F., Nannmark, U., Samara, C., Pinton, P., Vicencio, J. M., Carnuccio, R., Moll, U. M., Madeo, F., Paterlini-Brechot, P., Rizzuto, R., Szabadkai, G., Pierron, G., Blomgren, K., Tavernarakis, N., Codogno, P., Cecconi, F and Kroemer, G. 2008. Regulation of autophagy by cytoplasmic p53. *Nat. Cell. Biol.* **10**, 676-687.
43. White, E. 2012. Deconvoluting the context-dependent role for autophagy in cancer. *Nat. Rev. Cancer* **12**, 401-410.
44. Yang, Z. and Klionsky, D. J. 2010. Eaten alive: a history of macroautophagy. *Nat. Cell Biol.* **12**, 814-822.
45. Yang, Z. and Klionsky, D. J. 2010. Mammalian autophagy: core molecular machinery and signaling regulation. *Curr. Opin. Cell Biol.* **22**, 124-131.
46. You, J., He, Z., Chen, L., Deng, G., Liu, W., Qin, L., Qiu, F. and Chen, X. 2010. CH05-10, a novel indinavir analog, is a broad-spectrum antitumor agent that induces cell cycle arrest, apoptosis, endoplasmic reticulum stress and autophagy. *Cancer Sci.* **101**, 2644-2651.

초록 : 자가포식작용과 구강암

손승화[1] · 김은정[2]*
([1]강동대학교 치위생학과, [2]상지대학교 임상병리학과)

Autophagy는 세포 내에서 세포의 재활용과 다양한 스트레스에 세포 homeostasis와 survival에 중요한 역할을 한다. 최근 연구에서는 autophagy 활성이 oncogenes과 tumor suppressor genes의 발현이 조절됨으로써 암이 발달되거나 억제됨이 보고되고 있다. Autophagy의 유도는 정상세포에서는 암 발생을 예방하는데 관여하며, 손상된 세포사멸 기능을 가진 암세포에서는 특정세포사멸기전을 유발하는데 중요한 역할을 한다. 또한 autophagy 억제는 항암약물과 치료법에 저항을 나타내는 암세포를 민감하게 만들어 치료효능을 증가시킨다고 증명되고 있다. 그러나 cancer 치료에서의 autophagy의 역할은 아직까지 완전히 이해되지 않았다. Oral squamous cell carcinoma (OSCC)는 구강암의 90% 이상을 차지하고 있으며, 전세계적으로 6th 가장 흔한 암중의 하나로, 최근 2배 이상 증가하고 있으며 높은 mortality rate를 보이고 있다. 구강암에서의 autophagy의 역할은 다른 암들과 마찬가지로 종양형성의 초기 단계 동안 종양억제성을 보이나, 종양진행 동안은 종양세포 생존에 관여하는 두 가지의 기능을 나타내는 것으로 보고되고 있다. 본 리뷰에서는, 암에서의 autophagy의 조절에 대한 다양한 역할을 요약하고, 이를 바탕으로 효과적인 암 치료를 위한 유망한 target으로 autophagy의 가능성을 제시하고자 한다.