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REVIEW ARTICLE

AUTOPHAGY AND ORAL CANCERS: A SHORT REVIEW

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ABSTRACT

The catabolic process of autophagy involves recycling of cellular elements and is thought to play a major role in etiopathogenesis of cancers. Autophagy is thought to buffer metabolic stress, thereby aiding in cell survival. Also, it is found that inhibiting autophagy under deficient nutrition can restore cell death to apoptosis. Therefore, autophagy has a dual role in cancer therapeutics. As oral cancers are major concern of worldwide deaths much research is required in the field of its progression and to determine positive treatment modalities. There exists a huge gap of knowledge to understand the process of autophagy, and it is beyond doubt that further research in this field would open up new doors of cancer prevention and treatment.

INTRODUCTION

Oral squamous cell carcinoma is the most common type of cancer of the head and neck region. Cancers of the oral cavity accounts for 48% of all head and neck cancers. Oral cancer is a global public health problem, ranking 11th among most common type of cancer, with over 2,00000 new cases reported annually worldwide, 2/3 of which occur in developing countries.[1]

The overall mortality rate remains quite high at 50% even with modern treatment modalities. In India, oral cancer is the most common and fatal cancer among males and ranks 3rd among cancers affecting Indian women. Etiological studies show use of tobacco in any form, along with consumption of alcohol and infection by HPV (Human papilloma virus) are the major causes for development of oral cancers. [2]

Surgery, radiation along with combination of chemotherapeutic agents are typical treatment standards that have often reduced morbidity. However there still remains a need to identify prognostic biomarkers and targeted treatment approaches towards treatment of oral cancers. [3]

Autophagy and its mechanism*(Figure 1)*

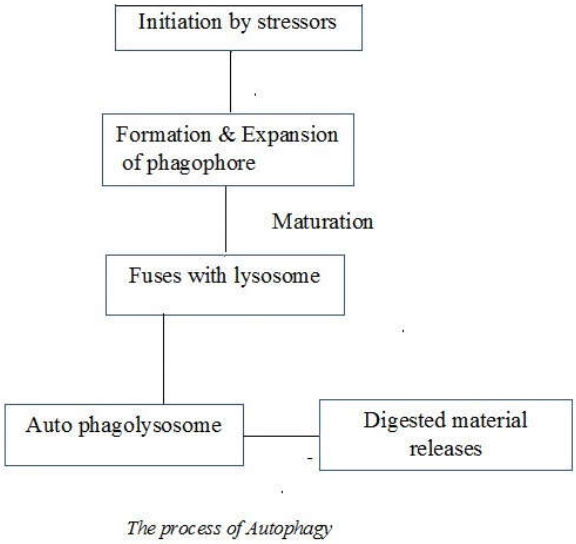
Autophagy is a catabolic homeostatic intercellular mechanism associated with recycling of damaged or dysfunctional cell organelles or proteins. Autophagy is a five-stage process, essentially controlled by Atg (autophagy) regulatory proteins, and the interaction of essential protein kinase complexes. [4]

mTOR (mammalian target rapamycin) is the central regulator of autophagy. mTOR maintains basal levels of autophagy, when sufficient nutrient is available, and initiates formation of a double lipid isolation bilayer from ER, termed as phagophore. The phagophore along with damaged and sequestrated cytoplasmic material are entrapped together into a double membrane structure known as autophagosome. This autophagosome combines with a lysozyme resulting in formation of autolysozyme, thereby marking the beginning of enzymatic degradation of sequestrated material of the cytosol, into free building blocks which are essentially the by-products of autophagy, *viz.* amino acids and sugars, which are later recycled back into the cytosol to sustain cellular haemostasis.[5] Studies by Suzuki and Ohsumi using yeast genetics helped to decode more than 30 autophagy related genes. This process is regulated by Atg genes, along with ULK (Serine / Threonine) ½ protein kinase complex and class III P13 kinase complex, containing VPS (Vacuolar protein sorting) 34, beclin 1 and Ambra-1. Along with these complexes Atg 12/ Atg 5/ Atg 6 and LC3 (light chain 3) proteins maintains the optimum autophagic flux.[6]

Autophagy and cancers

There have been many studies conducted to show the role of autophagy mediated cell survival in progression of several cancers. It is suggested that at a basal level autophagy, cancer cell contributes to cell survival but prolonged activation of autophagy leads to cell-death by self-degradation and is

therefore referred as the double-edged sword in tumorogenesis.[6]

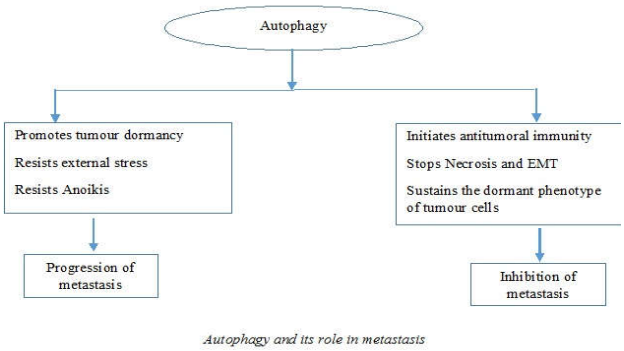


The process of Autophagy

Figure 1

Autophagy in tumour progression

Autophagy helps in metastasis of tumours by resisting anoikis, an apoptotic process that is associated with detachment of cells from ECM (extra cellular matrix). Also, autophagy regulates migration and cellular invasion.[4] On the contrary it has been found that autophagy reduces metastasis too. Autophagy deficiency stabilizes the transcription factor TWIST 1 through SQSTM 1 (Sequestosome 1) / p62 accumulation. TWIST 1 stabilization by SQSTM 1 promotes EMT (Epithelial to mesenchymal transition) that regulates cancer development and progression [7]. Autophagy also induces anti-tumour immunity by releasing HMBG1 (high mobility group 1) protein from tumour cells that are destined to die. Autophagy reduces macrophage infiltration by inhibiting tumour cell necrosis. Autophagy shows the phenomena to maintain dormant phenotype of tumour cells, which aids to prevent its entry from replicating cell cycles, ultimately preventing macrometastasis. [5]*(Figure 2)*



Autophagy and its role in metastasis

Figure 2

Tobacco, alcohol and autophagy

Consumption of tobacco and alcohol simultaneously results in large cellular changes that induces cancer. Tobacco smoking induces autophagy by SIRT-1(Sirtun) and PARP-1 (Poly [ADP ribose] polymerase 1) mechanism *(Hwang et al, 2010),* whereas areca nut, a form of chewable tobacco also induces autophagy like symptoms like inflammation, acidic vesicles and accumulation of LCII, OCEM 1. Tobacco smoking too is also known to cause accumulation of LC3II. Smoking marijuana which contains cannaboids enhances progression of oral cancers in association with alcohol and tobacco. But it has also been found that cannaboids speeds up autophagic death of human cancer cells, although more research is required in this field. [4-5] [8]

HPV and autophagy[4]

Griffin et.al 2013 found that HPV- 16 infection gets enhanced due to break down of autophagy genes as well as due to biochemical inhibition of autophagy. HPVE6 and HPV E7 are thought to regulate autophagy in opposing ways. HPV 16 E6 activity results in sustained mTOR activity, indicating slowing down of autophagy (*Spangle and Munger 2010*), [9] whereas HPV 16 E7 shows initiation of autophagy (*Zwerschkeet.al*) [10]

Oral cancers and autophagy

Head and neck tumours are quite heterogenous with several genetic mutations. But with genomic sequencing some stability in somatic aberrations has been identified. Few of these aberrations and changes are well known to play a part in autophagy. *E.g.* Mutation of PIK3CA gene is commonly associated with head and neck cancers and activation of PIK3 and mTOR have been found to promote autophagy.[5] [11-12] IHC study on 195 OSCC patients, showed high levels of P62 suggesting impaired autophagy. But it has also been reported, that there has been an increase in LC3II in patients, suggesting increased levels of autophagy in these tumours, thereby indicating reactivation of autophagy in later advanced stages of cancer. [5] Ma *et al*. in their study showed that by inhibiting autophagy using 3MA, CQ or Beclin 1 shRNA, resulted in enhanced cell death in adenoid cystic carcinoma treated with cis-diamminedichloroplatinum.[6]

Autophagy and cancer treatment

Autophagy decelerates and hinders various treatment techniques that are intended to reduce and erase off cancerous tumour. It has been shown that autophagy induced by lymphocyte, aids in survival of cancer cells. [5]Autophagyis induced massively by radiotherapy beyond the threshold limit of carcinoma cells, that leads to autophagy mediated cell death. However, overexpression of antiautophagic proteins (BCl-2 and p63) leads to radioresistant tumors. Autophagy at basal level results in chemoresistance, so using drugs that inhibit autophagy and/ or induces massive autophagy might inhibit carcinogenesis.[4] [13]

References

1. Albert Thomas, Oral Cancer, Screening & Vaccine topics, IARC screening group, International Agency for research on Cancer, World Health Organisation. http://screening.irac/oralindex/oralindex.php
2. Diana V Messadi, Diagnostic aids for detection of oral precancerous conditions, *International Journal of Oral Science* (2013) 5, 59-65 doi:10.1038/ijos.2013.24; published online 7 June 2013
3. Szu-Yuan Wu1, Yi-Wen Liu, Yang-Kao Wang, Tsung-Hsing Lin, Yi-Zhen Li, Shu-Hsin Chen, Ying-Ray Lee, Ionizing radiation induces autophagy in human oral squamous cell carcinoma, *JBUON* 2014; 19(1): 137-44
4. MK Sannigrahi, V Singh, R Sharma, NK Panda1, M Khullar, Role of autophagy in head and neck cancer and therapeutic resistance, *Oral Diseases* (2014) doi:10.1111/odi.12254

5. Namrata Adhauliya, Anupama N. Kalappanavar, I.M. Ali, Rajeshwari G. Annigeri, Autophagy: A boon or bane in oral cancer, *Oral Oncology* 61 (2016) 120-6
6. Shankargouda Patil, Roopa S Rao, A Thirumal Raj, Dual Role of Autophagy in Oral Cancer, *Journal of International Oral Health* 2015; 7(6):i-ii
7. Lei Qiang and Yu-Ying He, Autophagy deficiency stabilizes TWIST1 to promote epithelialmesenchymal transition, *Autophagy* 10:10, 1-2; October 2014
8. Hwang JW, Chung S, Sundar IK et al (2010). Cigarette smokeinduced autophagy is regulated by SIRT1-PARP-1-dependent mechanism: implication in pathogenesis of COPD. *Arch BiochemBiophys* 500: 203-9.
9. Spangle JM, Munger K (2010). The human papillomavirus type 16 E6 oncoprotein activates mTORC1 signaling and increases protein synthesis. *J Virol* 84: 9398-9407.
10. Zwerschke W, Mazurek S, Massimi P, Banks L, Eigenbrodt E, Jansen-Durr P (1999). Modulation of type M2 pyruvate kinase activity by the human papillomavirus type 16 E7 oncoprotein. *Proc Natl Acad Sci USA* 96: 1291-6.
11. Leemans CR, Braakhuis BJM, Brakenhoff RH. The molecular biology of head and neck cancer. *Nat Rev Cancer* 2011; 11(1):9-22.
12. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature* 2015; 517(7536):576-82.
13. Kondo Y, Kanzawa T, Sawaya R, Kondo S. The role of autophagy in cancer development and response to therapy. *Nat Rev Cancer* 2005; 5(9):726-34.

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