Editorial

Dual Role of Autophagy in Oral Cancer

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How to cite the article:

Patil S, Rao RS, Raj AT. Dual role of autophagy in oral cancer. J Int Iral Health 2015;7(6):i-ii.

Autophagy represents a self-repair mechanism in which the defective or damaged cellular components, including the cytoplasmic organelles are entrapped in a double lipid bilayer termed phagophore.[1] The phagophore and the material entrapped together are referred to as autophagosome. Once combined with a lysosome, it is referred to as an autolysosome, marking the initiation of enzymatic degradation of the sequestered content.[2,3] By-products of autophagy including amino acids and sugars are recycled back into the cytosol.[1] Failure in autophagy leads to cell death either through apoptosis or necrosis. Common pathologies including infections, degenerative disorders, heart disease have been linked to an overall failure in the cells autophagic system.[4,5] Suzuki and Ohsumi utilized yeast genetics to decode more than 30 autophagy-related genes.[6] Studies have shown that autophagy is not a non-specific mechanism, but that it follows an organelle specific disposal process targeting substrates, including peroxisomes, ribosomes, mitochondria, invading bacteria and protein aggregates.[7-10] Though the molecular mechanism of autophagy is not fully elucidated, studies including that of Bjørkøy *et al*. have shown that ubiquitination plays a major role in aggregate targeting.[11] Several studies have also shown that specific proteins tag the cytoplasmic organelle inducing autophagic degradation.[1] Though the cytoprotective role of autophagy serves to prevent cell death under physiological conditions, its self-repair mechanism is exploited by cancer cells to resist therapeutic modalities. Most of the chemotherapy-resistant cancers including specific oral cancers have demonstrated autophagy to evade cell death. Though the process of autophagy and apoptosis are inversely related, their molecular conjunctions are far complex and require further appraisal.[2] Autophagy suppresses tumour initiation by degrading the accumulated damaged organelles, thus preventing genomic instability.[12,13] In contrary autophagy aids in the progression of advanced cancer by rendering the cancer cells resistant to therapeutic agents. Several studies have shown that inhibiting autophagy may render the cancer cells more susceptible to treatment modalities. Subjecting cancer cell lines to 3- 3-methyladenine (3-MA) treatment inhibited autophagy as indicated by dysregulation of its key modulators. Suppression of autophagy can be determined by monitoring its modulators including Beclin 1 and p62 density, light chain 3 (LC3)-II/LC3-I ratio and GFP-LC3 level.[14-16] Jiang *et al*. demonstrated that the cells cultured in Earle's balanced salt activated its autophagic mechanism to compensate for the nutritional deficiency. Following activation of the cells autophagic system, the cells were further subjected to 3-MA treatment. The results showed marked dysregulation in Beclin 1, microtubule-associated protein LC3, p62, and green fluorescent protein–light indicating that the cells are directed away from autophagy toward apoptosis.[1] Several studies have used agents other than 3-MA to induce apoptosis by directly or indirectly suppressing cellular autophagy. Bai *et al*. used G15, an antagonist to GPR30, a known cancer cell proliferator to induce apoptosis in oral squamous cell carcinoma (OSCC).[17] Ahn *et al*. used apicidin, a histone deaceylase inhibitor, to initiate apoptosis in OSCC cells.[18] Ma *et al*. showed that inhibiting autophagy using 3MA, CQ, or Beclin 1 shRNA enhanced cell death in adenoid cystic carcinoma cells treated with cis-diamminedichloroplatinum.[19] Thus identifying the molecules inhibiting autophagy may serve as therapeutic agents by either directly or indirectly inducing apoptosis in chemotherapy resistant cancers cells including oral cancer.

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