INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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SHORT ABSTRACT

Oral cancer is the sixth most prevalent cancer of the world and is the second highest cancer type in India. The increase rise in the consumption both smoking and smokeless tobacco is one of the major reasons behind the rise in oral cancer cases in India. Moreover, in spite of the different therapies available such as surgery, chemotherapy and radiotherapy, there are always problems associated with it such as chemoresistance, side effects and tumor recurrence. Several studies have shown that ATP citrate lyase, the first enzyme involved in the first step of *de novo* lipogenesis (accountable for the production of oxaloacetate and acetyl-CoA in the cytosol) played an important role in the tumorigenesis of various types of cancer. ACLY is also known to form crossroads between glucose metabolism and fatty acid synthesis pathway. It has been evidenced that upregulated expression of ACLY enhanced tumor growth and proliferation in different cancers such as breast cancer, brain cancer, bladder cancer, lung cancer, prostate cancer and ovarian cancer. However, the role of ACLY is still unknown in oral cancer. Therefore, understanding the role of ACLY in oral carcinogenesis might prove significant for the early detection and prevention of oral malignancy. Here, in our study an attempt has been made to investigate the role of ACLY in oral cancer. In a study conducted in the cbioportal of cancer genomics, we found that alterations in ACLY gene of patients with HNSCC had a lesser median month survival rate as compared to patients without alterations indicating that ACLY might play an important role in the development and progression of oral cancer. We observed upregulated expression of ACLY both in the mRNA as well as the protein level of ACLY in oral cancer cells as compared to normal cells suggesting its important role in the tumorigenesis of oral cancer. IHC analysis using tissue micro array slides showed upregulation in the expression of both ACLY and p-ACLY in oral cancer tissues as compared to the normal tissues of the oral cavity. Several studies have also shown increased expression of ACLY in various types of cancer. This is the first report showing ACLY is upregulated ‘in oral cancer. In addition, tobacco and its components also enhanced the expression of ACLY thereby leading to the progression of tumorigenesis in oral cancer. The IHC analysis using

tissue microarray slide also showed that the increase expression of ACLY is correlated with the different stages of development of oral cancer. Moreover, increased expression of the protein was also observed with the increase in stages and grades of oral cancer as compared to normal. Further, knockout of ACLY using CRISPR/Cas 9 system of gene editing in oral cancer cells inhibited the survival, proliferation and migration of the tumor cells. Moreover, downregulation in the expression of the important signalling molecules involved in the cancer metabolism such as phospho-S6, Akt1, Akt2, mTOR was observed in ACLY knockout HSC-3 cells as compared to the scrambled control suggesting the involvement of Akt/mTOR/s6 pathway. Therefore, further *in vivo* studies are requisite to confirm and strengthen our findings and provide valuable information thereby validating the effect of ACLY in the development and progression of oral cancer.