Development of miRNA therapeutics targeting ATP citrate lyase (ACLY) for the treatment of oral cancer

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Background: The global incidence of oral cancer (OC) has seen a consistent rise, with India accounting for nearly one-third of reported cases. Thus, there is an urgent need to gain a comprehensive understanding of the underlying pathophysiology of OC and develop effective and novel therapeutic interventions for the prevention and treatment of this deadly disease. Lipogenesis, a primary metabolic alteration in cancer cells, is linked to ACLY, a key enzyme in lipid biogenesis making it a promising target for OC treatment. Aberrant expression of ACLY regulates vital signaling pathways in tumorigenesis, indicating its potential as a novel therapeutic strategy against OC. MicroRNAs (miRNAs) are recognized as primary regulators of gene expression for their ability to modulate the diverse hallmarks of tumorigenesis. The proposed study aims to investigate the role of microRNAs in the regulation of ACLY and to develop microRNA therapeutics for the treatment of OC. The therapeutic potential of the candidate microRNA mimics that regulate ACLY expression will be tested in OC models.

Methods: *In silico* studies were conducted to determine the expression levels of ACLY mRNA, protein, and phospho(p)-protein in HNSCC patients obtained from GEO-HNSC (Gene Expression Omnibus-HNSC), TCGA-HNSC (The Cancer Genome Atlas-HNSC), and CPTAC-HNSC (Clinical Proteomic Tumor Analysis Consortium-HNSC) datasets. Moreover, ACLY expression was examined in OC cell lines via immunoblotting technique. Further, the microRNAs targeting ACLY were identified using various online web-based computational tools and further validated via the qRT-PCR method. To determine the functional effect of miR-655-3p on several hallmarks of OC, different assays were carried out to determine its therapeutic relevance.

Results: The analysis revealed that the expression of ACLY was significantly high in HNSC patients in various and had lower median survival compared to those with low ACLY-expressing groups. Moreover, ACLY is highly expressed in OSCC cell lines when compared to normal cells. ACLY targeting microRNA mimic i.e. miR-655-3p exhibited a downregulation of ACLY in oral cancer cells. As anticipated, the knockdown of ACLY via miR-655-3p resulted in a considerable inhibition of oral cancer cell proliferation, decreased oral cancer cell migration, and caused S-phase arrest. It also led to the modulation of various proteins implicated in critical cellular processes such as growth, survival, autophagy, EMT, etc. Furthermore, the silencing of ACLY by mir-655-3p resulted in the dysregulation of various components of the Akt/mTOR signaling pathway. The Akt/mTOR signaling pathway is a crucial regulator of cellular growth, and its constitutive activation is a well-known contributor to the development and progression of various cancers, including OC, through the activation of survival and proliferative genes.

Conclusion: In light of these findings, our results suggest that ACLY is highly expressed in OC and miR-655-3p might play an important role in suppressing the different hallmarks of OC. Thus, targeting ACLY via a-miR-655-3p serves as a potential strategy to inhibit oral carcinogenesis.

Keywords: miRNAs, oral cancer, ACLY, miR-655-3p