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# It Takes (At Least) Two To Tango: Dual Regulation Of Tumor Suppressor *CDC73* And Its Implications In Cancer Therapeutics

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**Abstract**

*CDC73* is a tumor suppressor gene loss of which is linked to hyperparathyroidism jaw tumor syndrome. Its role in oral squamous cell carcinoma (OSCC or oral cancer) remains elusive. Oral squamous cell carcinoma, a subtype of HNSCC, is leading cancer in Indian males and third most common malignancy in Indian females. Also, the oral cancer prognosis still continues to be worse demanding the identification of a specific therapeutic target in OSCC. Having said that we tried to address the role of CDC73 in OSCC. In our study, we found that CDC73 has dual mode of regulation in OSCC. Despite its significant downregulation, loss of heterozygosity, promoter methylation and mutation (hallmarks of tumor suppressor gene, TSG) are not the major mechanisms of its downregulation. Using bioinformatics and biochemical assays, we found that WT1 and mir155 regulate its expression at transcriptional and translational levels, respectively. Using ChIP and EMSA, we found that WT1 knocks down CDC73 by binding its promoter. mir155 knocks down its expression by binding its 3'UTR. Using an antagomiR-155, we not only restored CDC73 levels but also suppressed the cancer phenotype in mir-155 overexpressing cell line. Further, a xenograft study in nude mice showed that antagomiR-155 could reduce tumor burden *in vivo.* Together, our study not only validates CDC73 a TSG but also could be an effective and promising therapeutic target in oral cancer.

***Key words:*** *CDC73, miR-155, Tumor suppressor gene, WT1, OSCC.*