DBT-ILS study finds potential target for drug resistance in OSC Cancer

New Delhi, Feb 23: Rewiring tumor cells to undergo drug-induced apoptosis is a promising way to overcome chemoresistance. Thus, identifying causative factors for chemoresistance is of high importance.

The cancer research group at DBT-Institute of Life Sciences (DBT-ILS), Bhubaneswar led by Dr Rupesh Dash has identified CMTM6 (CKLF-Like MARVEL Transmembrane Domain-Containing Protein 6) as a stabilizer of ENO-1 thereby facilitating cisplatin resistance in tumor cells.

Unbiased global proteome-profiling of cisplatin sensitive and resistant OSCC lines identified CMTM6 as top ranked upregulated protein in cisplatin resistant Oral Squamous Cell Carcinoma (OSCC) as compared to the sensitive lines. CMTM6 is a type-3 transmembrane protein with a MARVEL domain consisting of four transmembrane helices.

Analyses of OSCC patient tumor samples demonstrated significantly higher CMTM6 expression in chemotherapy-non-responders as compared to chemotherapy-responders. In addition, a significant association between higher CMTM6 expression and poorer relapse-free survival in Esophageal Squamous Cell Carcinoma, Head and Neck Squamous Cell Carcinoma and Lung Squamous Cell Carcinoma.

CMTM6 depletion restored the cisplatin-induced cell death and reduced the tumor burden significantly in xenograft models. The transcriptome analysis of CMTM6 depleted and the control cisplatin resistant cells depicted Wnt signaling pathway to be one of the most dysregulated pathways in cisplatin resistant lines. CMTM6 interaction with membrane-bound Enolase-1 stabilized its expression, leading to activation of Wnt signaling mediated by AKT–glycogen synthase kinase-3β. As CMTM6 facilitates tumor cells for immune evasion and mediates cisplatin resistance, it can be a promising therapeutic target for treatment of therapy resistant OSCC. The detailed results are accepted for publication in JCI insight.

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