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"The effect of TLE1 in drug resistance in Lung Adenocarcinoma"

Lung cancer is the second most frequent cancer diagnosis in the world. Among men it is the most common cancer and the third most common cancer in women. There are two major groups of lung cancer, small cell lung carcinoma (SCLC), and non-small cell lung carcinoma (NSCLC). NSCLC comprises approximately 85% of all diagnosed cases of lung cancer and is divided into three variants, adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Lung adenocarcinoma (LUAD) patients that carry the epidermal growth factor receptor (EGFR) activating mutation are treated using EGFR inhibition therapy involving EGFR tyrosine kinase inhibitors (EGFR-TKI). This represents the gold standard treatment. While EGFR-TKI's are initially effective in the initial phase of therapy, many patients eventually develop tolerance and eventual resistance. EGFR-TKI resistance remains a major clinical problem, thereby novel insights are needed to examine the molecular mechanisms underlying EGFR-TKI resistance in lung cancer. Here, we present experimental data indicating an important role of the transcriptional corepressor Transducin-Like Enhancer of Split 1(TLE1) in mediating EGFR-TKI-induced tolerance and resistance in LUAD cells. Using the drug tolerant persistor (DTP) cell model system, we found that TLE1 expression is upregulated both at the mRNA and protein levels in EGFR-mutant, EGFR-TKI sensitive parental cells upon 9 days of EGFR-TKI treatment. Importantly, acute downregulation of TLE1 in parental cells resulted in reduced DTP formation and survival. Conversely, overexpression of exogenous TLE1 promoted further development of DTP cells. Collectively, these data indicate the critical expression of TLE1 in initiating EGFR-TKI tolerance, likely due to the survival promoting transcriptional and epigenetics of TLE1.