



Category: Cancer Genomics

# Integrated multi-omics analysis reveals potential mechanisms of acquired resistance to erlotinib in head and neck cancer cells

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## Abstract

Epidermal growth factor receptor (*EGFR*) is overexpressed in 90% of head and neck squamous cell carcinomas (HNSCC). However, most clinical trials with tyrosine kinase inhibitors (TKIs) have shown modest response rates due to development of acquired resistance. We performed whole exome sequencing (WES) of an isogenic pair of erlotinib-sensitive (SCC-S) and resistant (SCC-R) HNSCC cell lines to elucidate the molecular mechanisms that govern acquired resistance to erlotinib. Exome sequencing resulted in identification of 148 non-synonymous single nucleotide variants (SNVs) in 139 genes and copy number alterations (CNA) ( $\geq 2$  fold) affecting 339 genes in SCC-R cells compared to SCC-S cells. Comparison of SNVs from SCC-R against post-translational modification databases resulted in identification of loss of ubiquitinylation site at *p.K57E* in dual specificity mitogen-activated protein kinase kinase 1 (*MAP2K1*) which was validated using *in-house* high-throughput proteomic data. Substitution mutation K57N in *MAP2K1* is shown to result in its constitutive activation and subsequent gefitinib resistance in lung adenocarcinoma. We also identified a well-known driver mutation p.G13R in Harvey rat sarcoma viral oncogene homolog (*HRAS*) (AIF: 20.41%). In addition, we also observed CNA in other genes of this pathway including RAC-beta serine/threonine-protein kinase (*AKT2*), glycogen synthase kinase-3 alpha (*GSK3A*), Rho guanine nucleotide exchange factor 1 (*ARHGEF1*) amongst others. Corresponding protein expression changes of these genes were also observed in proteomics data. Quantitative phosphoproteomics revealed hyperphosphorylation of other proteins involved in MAPK pathway such as serine/threonine-protein kinase B-raf (*BRAF*), *MAP2K2*, mitogen-activated protein kinases such as *MAPK1* and *MAPK3*. Integrative multi-omic analysis revealed constitutive activation of key intermediates of MAPK pathway in SCC-R cells compared to SCC-S cells which may be essential in the development of acquired resistance to erlotinib in these cells. We hypothesize that combinatorial treatment regime involving inhibition of putative targets such as *MAP2K1* with erlotinib therapy may aid in tackling acquired erlotinib resistance in HNSCC patients.

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