Role of BRG1 (SMARCA4) in the resistance of lung cancer to EGFR inhibitors

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ABSTRACT: Mutations in the BRG1, resulting in attenuation and nonfunctional protein production, have been reported frequently in non-small cell lung cancer (NSCLC). Due to its essential function as an ATPase core subunit of the SWI/SNF complex in regulating gene expression, BRG1 has been extensively studied for its role in response to conventional cancer therapies. However, little is known about its function in response to targeted therapy (e.g., EGFR-TKIs). To date, EGFR-targeted tyrosine kinase inhibitors (TKIs) have shown clinical benefit in NSCLC patients harboring activating mutations in the kinase domain of the receptor but not in patients with amplified wild-type (wt)-EGFR, suggesting the existence of unexplored resistance mechanisms.

In this study, we demonstrate BRG1 status in wt-EGFR NSCLC cells dictates the response to EGFR-TKIs both in vitro and in vivo. Molecular studies revealed cross-talk between EGFR and BRG1, and the formation of wt-EGFR and pAKT(Ser473) complex governed by BRG1 mutation status, contributed to resistance. Our study results demonstrate that pre-screening of wt-EGFR NSCLC patients for BRG1 status will result in a subset of patients benefitting from EGFR-TKI therapy. Further, our study offers a rationale for designed combinatorial therapy for NSCLC patients.