

Semaphorin 7A promotes EGFR-TKI resistance in EGFR mutant lung adenocarcinoma cells

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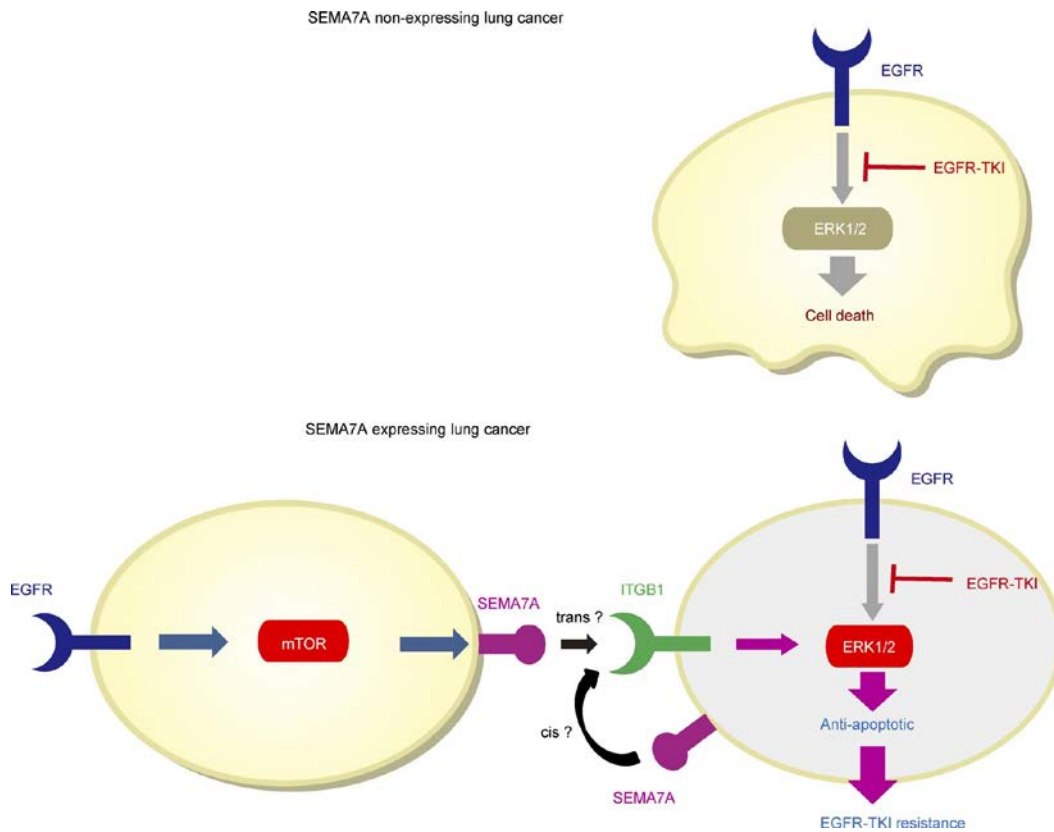
Although responses to EGFR tyrosine kinase inhibitors (EGFR-TKIs) are initially positive, 30%–40% of patients with EGFR-mutant tumors do not respond well to EGFR-TKIs, and most lung cancer patients harboring EGFR mutations experience relapse with resistance. Therefore, it is necessary to identify not only the mechanisms underlying EGFR-TKI resistance, but also potentially novel therapeutic targets and/or predictive biomarkers for EGFR-mutant lung adenocarcinoma.

The research group of Atsushi Kumanogoh (Immunopathology, IFRc and Graduate School of Medicine) found that the GPI-anchored protein semaphorin 7A (SEMA7A) is highly induced by the EGFR pathway, via mTOR signaling, and that expression levels of SEMA7A in human lung adenocarcinoma specimens were correlated with mTOR activation. Investigations using cell culture and animal models demonstrated that loss or overexpression of SEMA7A made cells less or more resistant to EGFR-TKIs, respectively. The resistance was due to the inhibition of apoptosis by aberrant activation of ERK. The ERK signal was suppressed by knockdown of integrin $\beta 1$ (ITGB1). Furthermore, in patients with EGFR mutant tumors, higher SEMA7A expression in clinical samples predicted poorer response to EGFR-TKI treatment. Collectively, these data show that the SEMA7A–ITGB1 axis plays pivotal roles in EGFR-TKI resistance mediated by ERK activation and apoptosis inhibition. Moreover, our results reveal the potential utility of SEMA7A not only as a predictive biomarker, but also as a potentially novel therapeutic target in EGFR-mutant lung adenocarcinoma.

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Expression of SEMA7A in human lung adenocarcinoma is regulated by the EGFR–mTOR axis and is involved in development of resistance to EGFR-TKIs. Resistance is mediated by inhibition of apoptosis by the SEMA7A–ITGB1–ERK axis.