

TEAD Upregulation Promotes Osimertinib Resistance in NSCLC

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Abstract

Osimertinib, a third-generation tyrosine kinase inhibitor (TKI), is the first-line standard therapy for EGFR-mutated non-small cell lung cancer (NSCLC). However, acquired resistance is inevitable, with underlying mechanisms incompletely elucidated, leading to limited subsequent treatments and posing major clinical challenges. This study established osimertinib-resistant NSCLC models in vitro and in vivo, revealing a novel resistance mechanism mediated by TEAD upregulation but independent of the classical Hippo pathway. Osimertinib treatment enhances TEAD protein stability by inhibiting its ubiquitination-mediated degradation. Upregulated TEAD promotes YAP nuclear translocation, strengthens YAP/TEAD intranuclear co-localization and liquid-liquid phase separation (LLPS) capacity. The elevated YAP/TEAD condensates collectively upregulate downstream target gene expression and compromise the anti-proliferative activity of osimertinib. Based on this mechanism, we developed ET825, a novel YAP/TEAD interaction inhibitor to overcome osimertinib resistance. ET825 effectively disrupts the TEAD/YAP interaction in cells, significantly suppresses YAP transcriptional activity, and inhibits NSCLC tumor proliferation. Additionally, since SHP2 is a critical signaling node in the EGFR pathway, the combination of SHP2 inhibitor ET0038 and ET825 exhibited significant synergistic anti-tumor effects in osimertinib-resistant NSCLC models in vitro and in vivo. This study elucidates a previously uncharacterized osimertinib-induced resistance mechanism mediated by TEAD upregulation and YAP-TEAD activation, and provides a translationally promising therapeutic strategy to overcome osimertinib resistance.

Keywords

Non-small Cell Lung Cancer (NscLC), Osimertinib, Tead, Yap, Liquid-liquid Phase Separation (Llps)