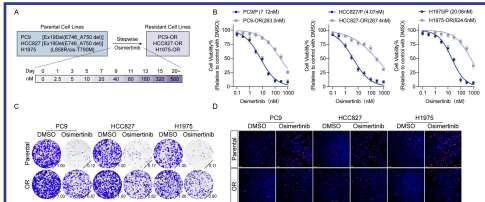


INTRODUCTION

EGFR tyrosine kinase inhibitors (EGFR-TKIs), particularly osimertinib, have significantly improved the treatment of EGFR-mutant non-small-cell lung cancer (NSCLC). However, acquired resistance remains inevitable and represents a major clinical challenge. Mechanistically, SNAP47 promotes MMP3 secretion, which facilitates extracellular maturation of pro-HGF into active HGF, thereby activating MET, enhancing EGFR–MET signaling, and sustaining downstream AKT activity. Targeting this SNAP47–MMP3–HGF–MET axis restores sensitivity to osimertinib, revealing a previously unrecognized secretion-dependent mechanism of EGFR-TKI resistance and a potential therapeutic vulnerability in EGFR-mutant NSCLC.

METHODS



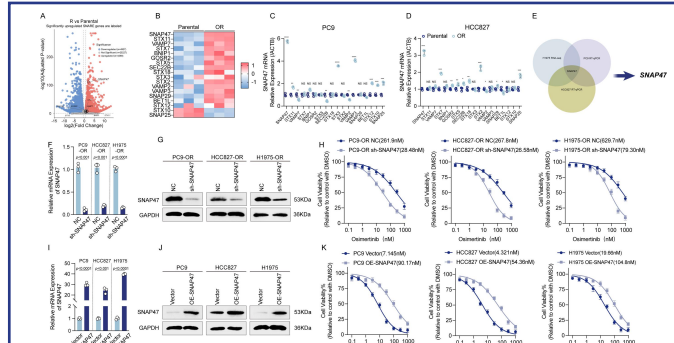
Establishment of EGFR-TKI Acquired Resistance Models with Multiple Genetic Backgrounds: To model acquired EGFR-TKI resistance, we established osimertinib-resistant cell lines PC9-OR, HCC827-OR, and H1975-OR via stepwise dose escalation. These models spanning diverse EGFR mutation backgrounds provide a robust platform for dissecting resistance mechanisms.

RESULTS

SNAP47 is consistently elevated in EGFR-TKI-resistant models and clinical resistant specimens

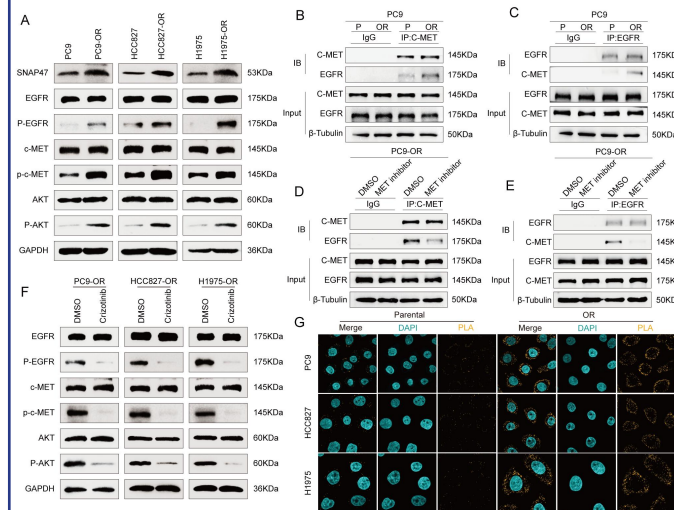
Section 1: Functional studies demonstrated that SNAP47 is both required for the maintenance of EGFR-TKI resistance and sufficient to promote resistance in EGFR-mutant NSCLC. SNAP47 depletion restored sensitivity to osimertinib and gefitinib, reduced IC50 values, and enhanced apoptosis in resistant cells and patient-derived organoids, whereas SNAP47 overexpression conferred drug tolerance in parental cells. These supporting SNAP47 as a functional driver of EGFR-TKI resistance and a potential therapeutic target.

RESULTS



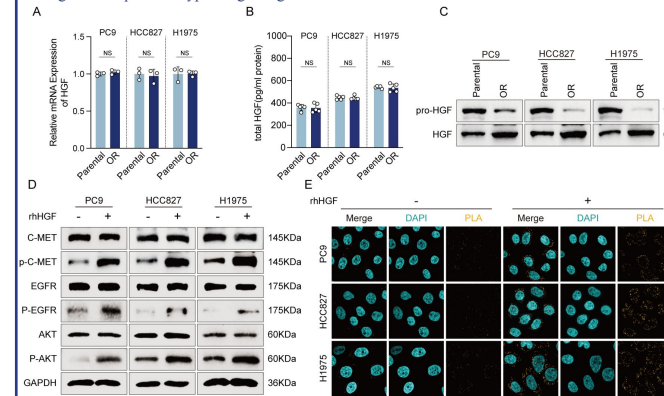
MET-dependent EGFR–MET receptor complexes sustain PI3K–AKT signaling in EGFR-TKI-resistant cells

Section 2: EGFR-TKI-resistant NSCLC cells exhibit persistent activation and enhanced coupling of MET and EGFR, which sustains downstream AKT signaling and cell survival. Pharmacological or genetic inhibition of MET disrupted EGFR–MET interactions, suppressed EGFR/AKT phosphorylation, and restored sensitivity to osimertinib. Moreover, combined EGFR and MET inhibition produced greater growth suppression than either treatment alone, identifying MET-dependent EGFR–MET signaling as a key bypass mechanism underlying EGFR-TKI resistance.



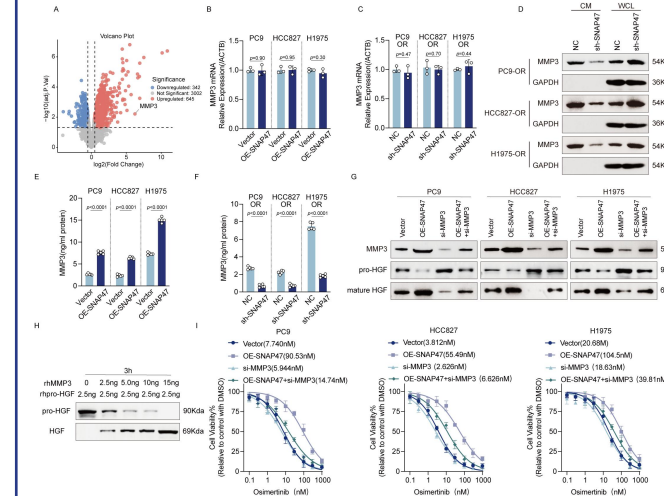
Enhanced pro-HGF processing generates mature HGF to activate MET-dependent signaling in EGFR-TKI-resistant cells

Section 3: EGFR-TKI-resistant NSCLC cells exhibit enhanced extracellular maturation of HGF without increased HGF expression or secretion. Mature HGF activates MET, promotes EGFR–MET receptor association, sustains downstream EGFR–AKT signaling, and reduces sensitivity to osimertinib. These findings identify increased HGF maturation, rather than HGF overproduction, as a key mechanism driving MET-dependent bypass signaling and EGFR-TKI resistance.



SNAP47-dependent MMP3 secretion promotes pro-HGF maturation and sustains EGFR/MET–AKT signaling

Section 4: SNAP47 promotes EGFR-TKI resistance by enhancing the secretion of MMP3 rather than increasing its transcription. Secreted MMP3 directly facilitates pro-HGF processing into mature HGF, thereby activating MET–EGFR–AKT signaling and reducing osimertinib sensitivity. Genetic depletion of MMP3 reverses SNAP47-driven resistance in cells, organoids, and xenografts, while mature HGF rescues this effect, establishing a SNAP47–MMP3–HGF axis as a key mechanism sustaining EGFR-TKI resistance.



DISCUSSION AND CONCLUSION

Actionable Take Away Message

- SNAP47 is identified as a bona fide functional driver of EGFR-TKI acquired resistance across multiple genetic backgrounds. Targeting SNAP47 — either genetically or pharmacologically — resensitizes resistant NSCLC cells and tumors to EGFR inhibition, offering a promising therapeutic strategy to overcome treatment failure in EGFR-mutant lung cancer.

Future Direction for Research

- Moving forward, elucidating the precise molecular mechanism by which SNAP47 mediates vesicle trafficking to sustain EGFR signaling survival will be critical. Developing selective SNAP47 inhibitors and validating SNAP47 as a predictive biomarker for resistance in larger clinical cohorts could ultimately translate this discovery into a precision combination therapy, directly benefiting clinicians and patients facing EGFR-TKI relapse.

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Artificial Intelligence Use Disclosure

Generative AI tools were used solely to assist with language refinement and text condensation. All scientific content, data interpretation, and conclusions were independently assessed, verified, and approved by the authors.