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2022 Medical Research Day Posters

Oct 13th, 12:00 AM

Investigating the role of HER3 in the resistance to EGFR tyrosine kinase inhibitors in non-small cell lung cancer

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Recommended Citation

Larsen, Margaret; Lyu, Hui; and Liu, Bolin, "Investigating the role of HER3 in the resistance to EGFR tyrosine kinase inhibitors in non-small cell lung cancer" (2022). *Medical Research Day*. 48.

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Investigating the role of HER3 in the resistance to EGFR tyrosine kinase inhibitors in non-small cell lung cancer

Margaret Larsen, Hui Lyu, Bolin Liu

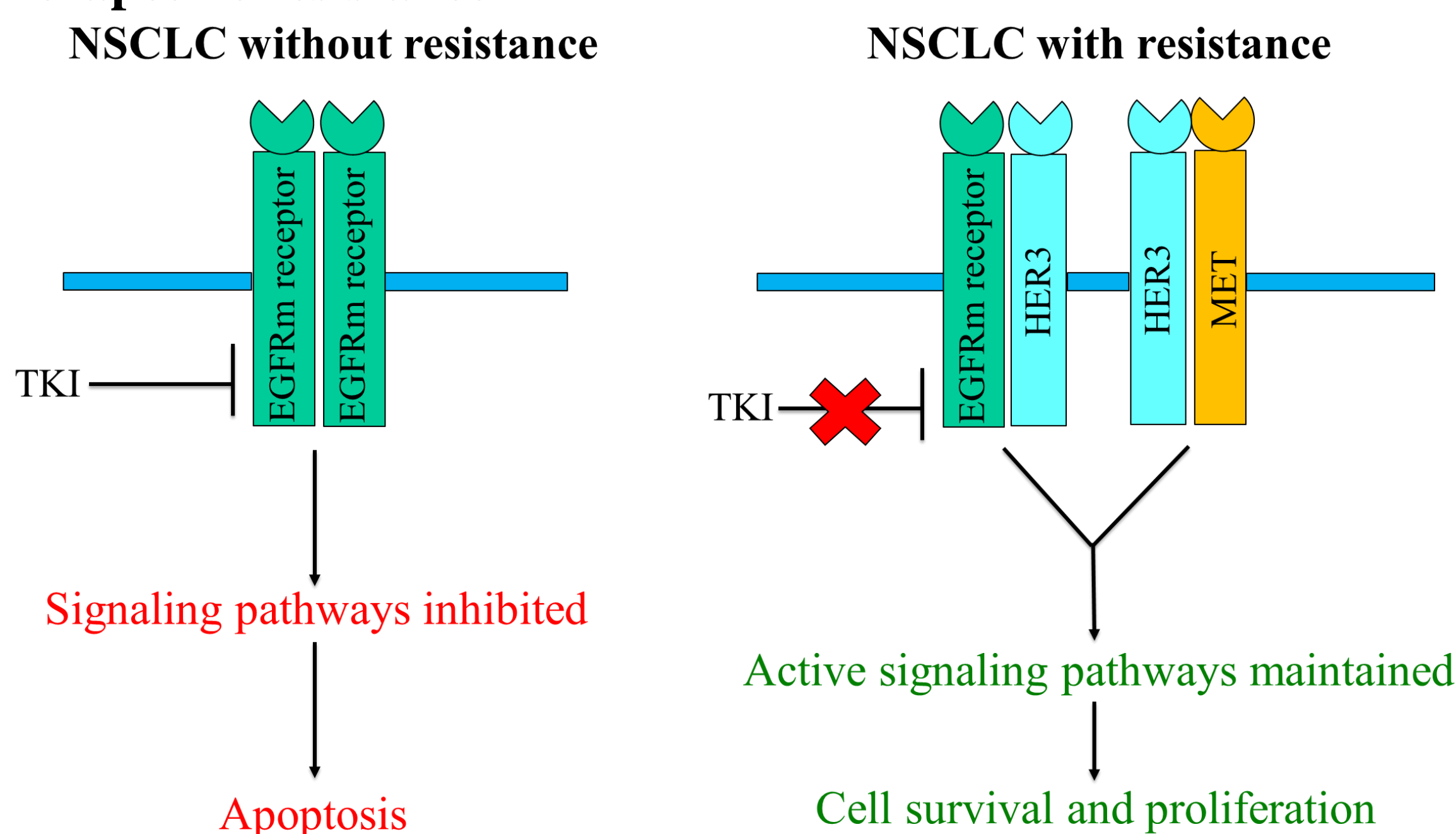
LSUHSC-New Orleans, Stanley S. Scott Cancer Center, Departments of Interdisciplinary Oncology and Genetics

Introduction

- Non-small cell lung cancer (NSCLC) comprises 80% of lung cancer cases.
- NSCLC has a 5-year survival rate of approximately 19%.
- Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have shown promise in the treatment of NSCLC patients with EGFR activating mutations.
- Patients frequently develop resistance to EGFR-TKIs emphasizing the significance of studying the underlying mechanism.
- Human epidermal growth factor receptor 3 (HER3) is a member of the EGFR family and is unique in that it has little to no intrinsic tyrosine kinase activity.

Hypothesis

We hypothesize that EGFR mutants (EGFRm) are working in conjunction with HER3 and other membrane receptors to continue activating the downstream signaling pathways in order to evade the effects of EGFR-TKIs, resulting in therapeutic resistance.



Methods

EGFRm PC9 (Exon 19del) and HCC827 (Exon 19del) parental NSCLC cell lines

Exposure of cells to increasing concentrations of either 1st generation (erlotinib or gefitinib) or 3rd generation (osimertinib/AZD9291) EGFR-TKI

Establishment of EGFR-TKI resistant cell lines (PC9 AR, PC9-GR/AR, HCC827 AR, HCC827 ER)

Cell proliferation (MTS) assays to ensure resistance phenotype is present

Western blot and quantitative reverse transcriptase polymerase chain reaction (RT-qPCR) performed

Cell proliferation

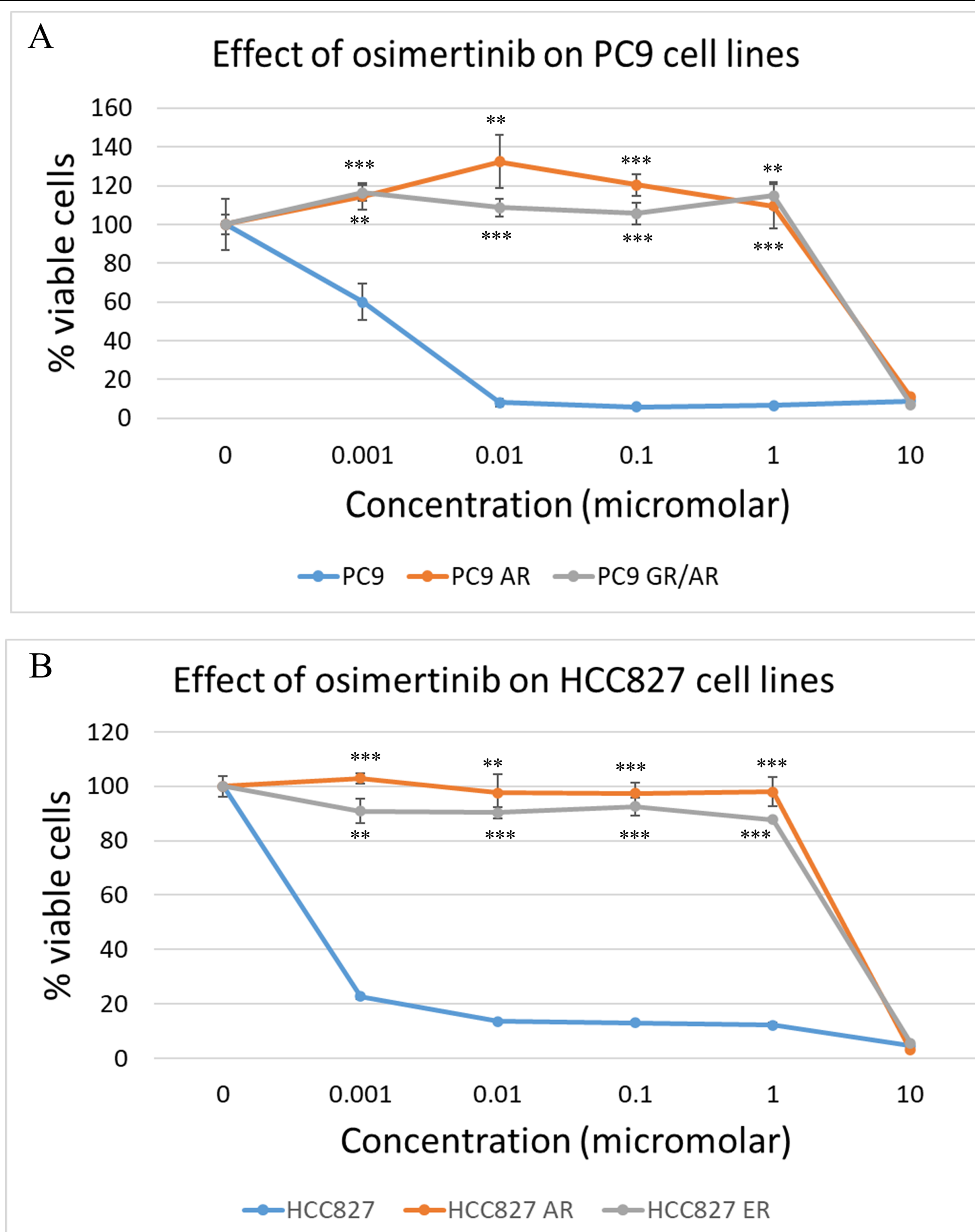


Figure 1. MTS assays performed with NSCLC parental and EGFR-TKI resistant cell lines. Cell proliferation (MTS) assays were used to determine the effect of osimertinib (3rd generation EGFR-TKI) on both parental and EGFR-TKI resistant cell lines. **A-B**, EGFR-TKI resistant HCC827 and PC9 cell lines (HCC827 AR, HCC827 ER, PC9 AR, PC9 GR/AR) are shown to maintain the resistance phenotype even in increasing concentrations of osimertinib (AZD9291) compared to parental cell lines. (**, $p \leq 0.01$; ***, $p \leq 0.001$)

Expression of membrane receptors

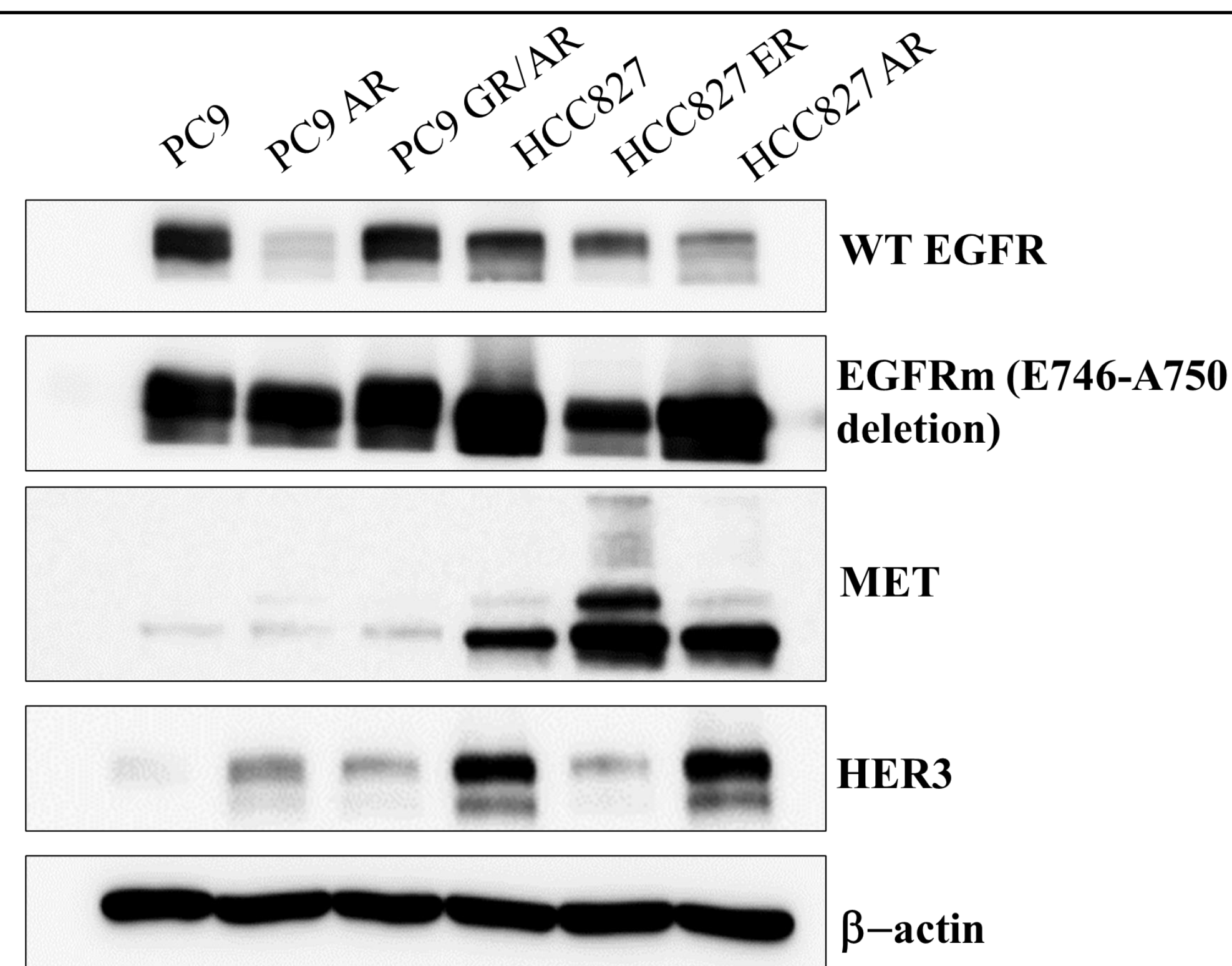


Figure 2. Western blot assays showing the levels of protein expression of several membrane receptors in resistant and parental NSCLC cell lines. Wild-type EGFR (WT EGFR) levels vary among the cell lines, while mutant EGFR (EGFRm) levels remain relatively constant. Mesenchymal-epithelial transition (MET) protein amplification is seen strongly with HCC827 resistant cell lines. HER3 levels increase in PC9 resistant cell lines, while they stay the same or decrease in HCC827 resistant cell lines. β -actin is used as a loading control.

Activation of downstream signaling

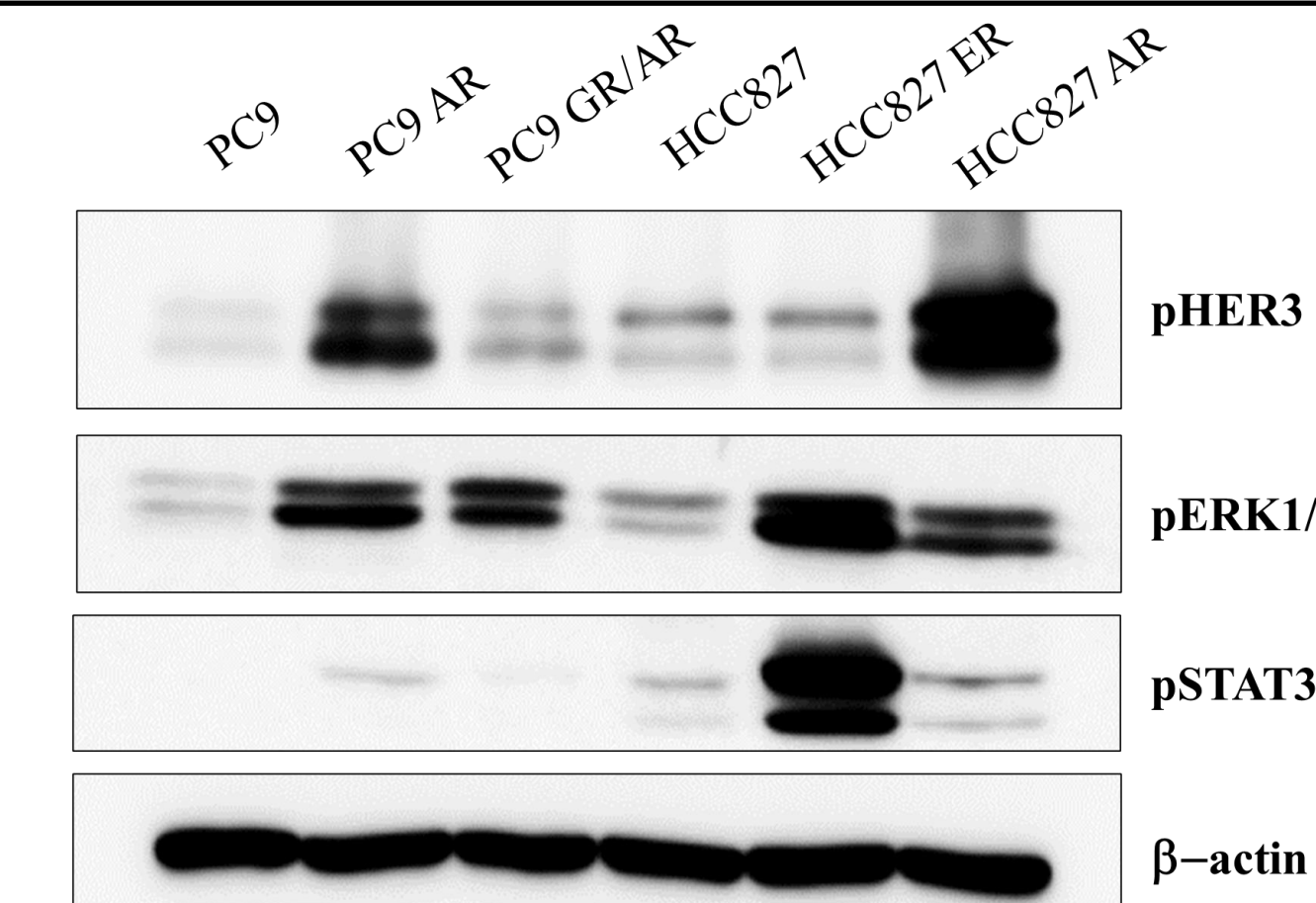


Figure 3. Western blot assays showing the levels of phosphorylated proteins for several downstream signaling pathways of HER3 in resistant and parental NSCLC cell lines. Phosphorylated HER3 (pHER3), ERK1/2 (pERK1/2), and STAT3 (pSTAT3) are upregulated in most of the resistant cell lines compared to the parental cell lines. β -actin is used as a loading control.

mRNA expression changes

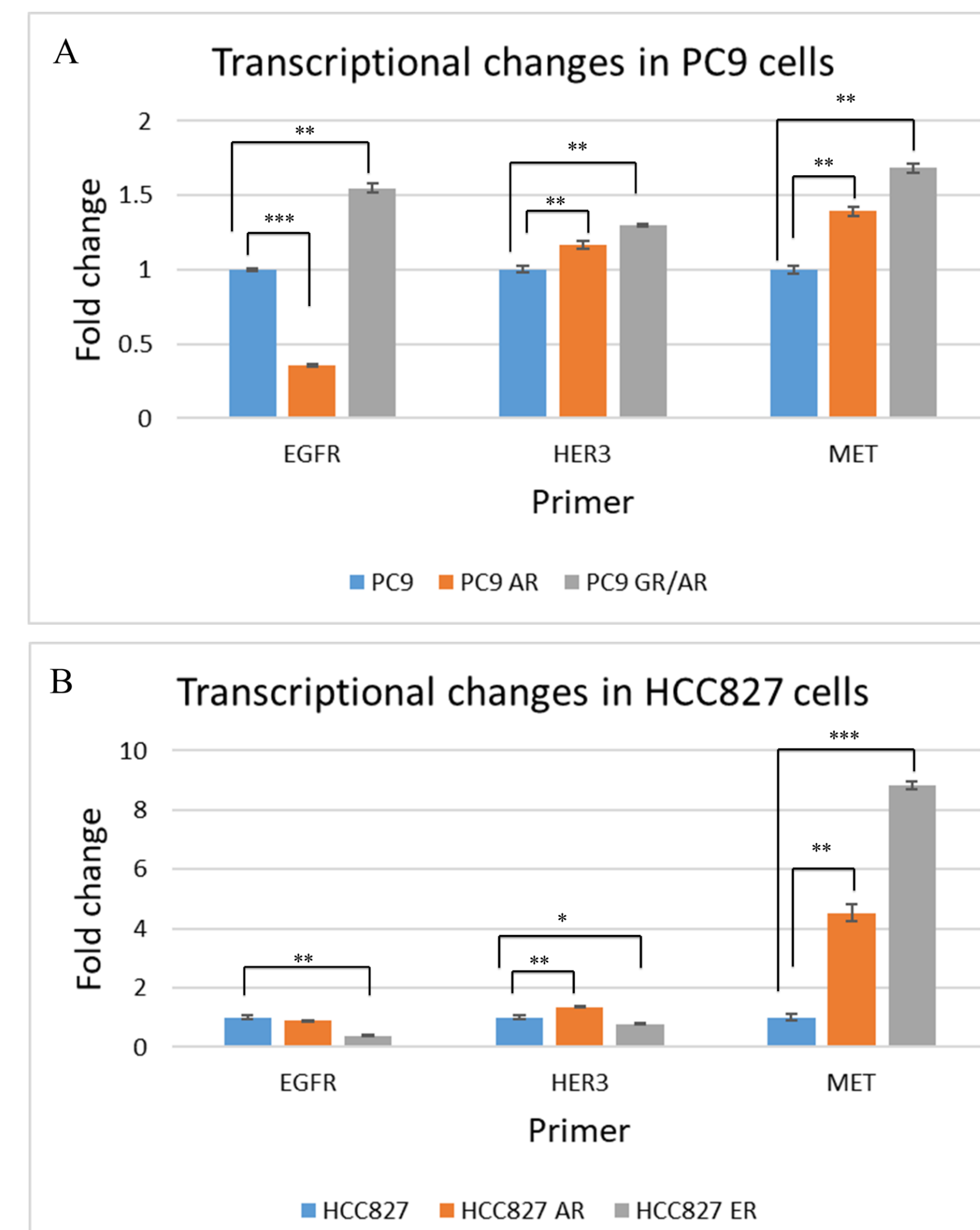


Figure 4. Quantitative reverse transcriptase polymerase chain reaction (RT-qPCR) showing mRNA expression levels for several membrane proteins. PC9 (A) and HCC827 (B) resistant cell lines show statistically significant mRNA amplification of MET, while transcriptional changes of EGFR and HER3 are variable between the two resistant cells lines compared to the control. (*, $p \leq 0.05$; **, $p \leq 0.01$; ***, $p \leq 0.001$)

Conclusions

- Cell lines resistant to EGFR-TKIs maintain their resistance phenotype as indicated by the MTS results.
- HER3 and MET overexpression is shown in several of the resistance cell lines compared to the parental in both Western blots and RT-qPCR, indicating possible involvement of these two receptors in EGFR-TKI resistance.
- Increased levels of p-STAT3 and p-ERK1/2 in resistance cell lines versus control suggest continued activation of downstream signaling pathways as a way to compromise the efficacy of EGFR-TKIs.
- Future studies will continue to define the role of HER3-mediated signaling in the resistance to EGFR-TKIs in NSCLC.