

Additional Trametinib Delays and Overcomes Acquired Resistance to Lorlatinib in ALK-Rearranged Lung Cancer

Shiyou Wei¹, Lunxu Liu¹

¹Department of Thoracic Surgery, Institute of Thoracic Oncology, West China Hospital, Sichuan University, Chengdu, China

Correspondence: Lunxu Liu, MD, PhD, FRCS (Engl.) (lunxu_liu@aliyun.com)

INTRODUCTION

- Molecular mechanisms driving resistance to the third-generation ALK tyrosine kinase inhibitor lorlatinib in *ALK*-rearranged non-small cell lung cancer (NSCLC) are not well understood.
- This study aims to elucidate these mechanisms and explore potential therapeutic strategies to delay and overcome resistance to lorlatinib in *ALK*-rearranged NSCLC.

METHODS

- Integrated analyses of RNA sequencing (RNAseq) and reverse phase protein array (RPPA) data were conducted to uncover the underlying mechanisms of resistance.
- The underlying molecular mechanisms were validated using immunohistochemistry, western blotting, and flow cytometry.
- Additionally, lorlatinib-resistant cell line and a cell line-derived xenograft (CDX) model were generated to validate the therapeutic efficacy of combination therapies.

DISCUSSION AND CONCLUSION

Actionable Take Away Message

- Our findings suggest that activation of MAPK signaling confers acquired resistance to lorlatinib in ALK-rearranged NSCLC.

Future Direction for Research

- The combination of lorlatinib with trametinib may offer a promising therapeutic strategy to delay and overcome this resistance, thereby improving treatment outcomes for patients with ALK-rearranged NSCLC.

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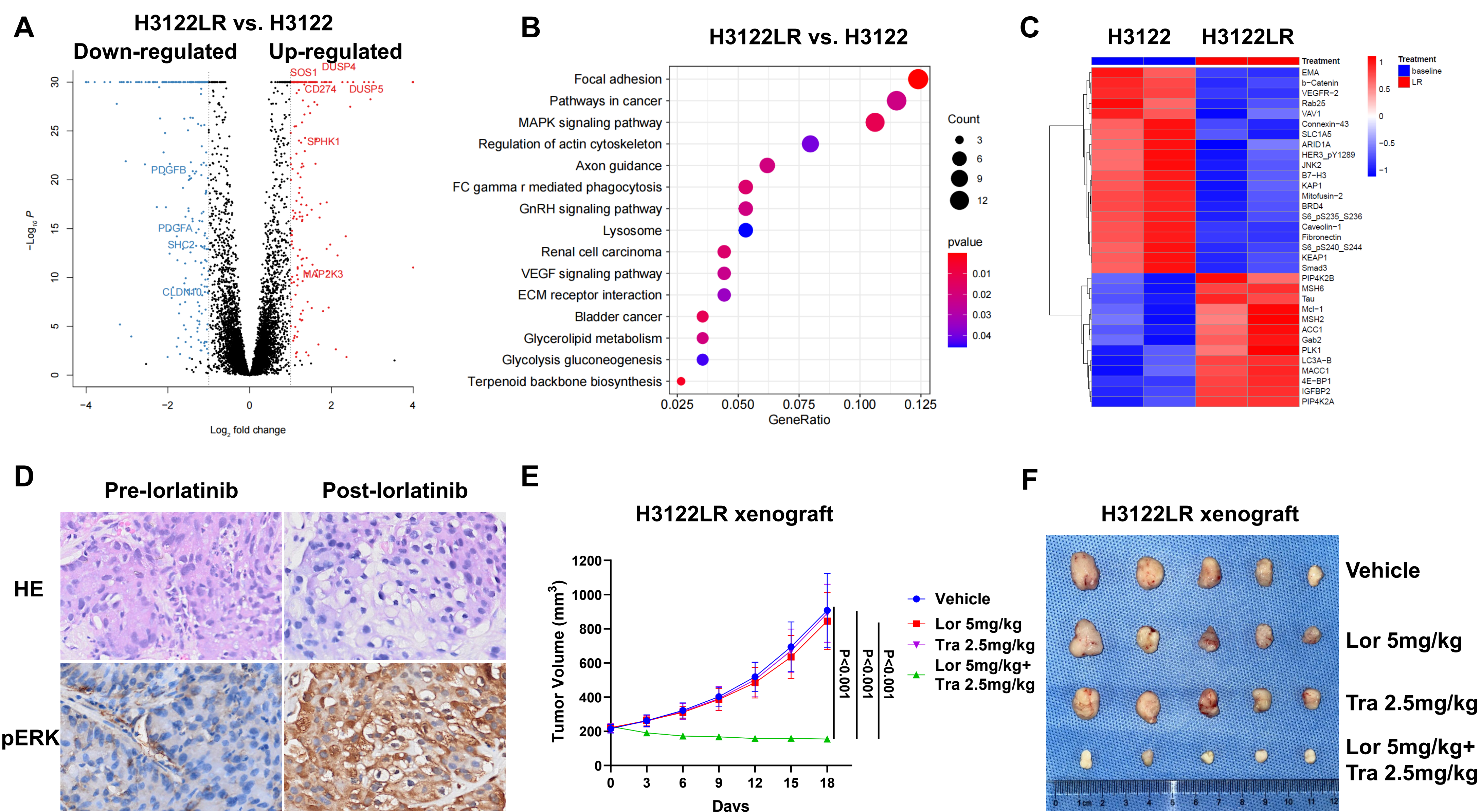
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The authors declare no conflicts of interest related to this study.

RESULTS

- Integrated analyses of RNAseq and RPPA data indicated the MAPK signaling pathway was activated in lorlatinib-resistant H3122LR cells.
- The IHC staining of paired pre- and post-lorlatinib specimens from four patients showed a significant increase in pERK1/2 levels after the development of acquired resistance to lorlatinib.
- Combining lorlatinib with the MEK inhibitor trametinib significantly delayed the formation of resistant tumors, and reduced tumor proliferation and reversed resistance in both H3122-LR cells and CDX models.



(A) Volcano plots depicting differentially expressed genes between H3122LR and H3122 cells.

(B) Gene Set Enrichment Analysis (GSEA) of differentially expressed genes between H3122LR and H3122 cells.

(C) Analysis of pathways associated with differentially expressed proteins between H3122LR and H3122 cells.

(D) Specimens before and after lorlatinib treatment stained with hematoxylin and eosin (HE) and immunohistochemistry (IHC) to assess ERK expression.

(E and F) Tumor growth curve (E) and tumor images (F) of H3122LR tumors in mice treated with vehicle, lorlatinib at 5mg/kg, trametinib at 2.5mg/kg, or a combination of lorlatinib at 5mg/kg and trametinib at 2.5 mg/kg daily.