



KEAP1 Mutation Drives Immune Evasion via SGK1 Regulation and Metabolic Reprogramming in NSCLC

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INTRODUCTION

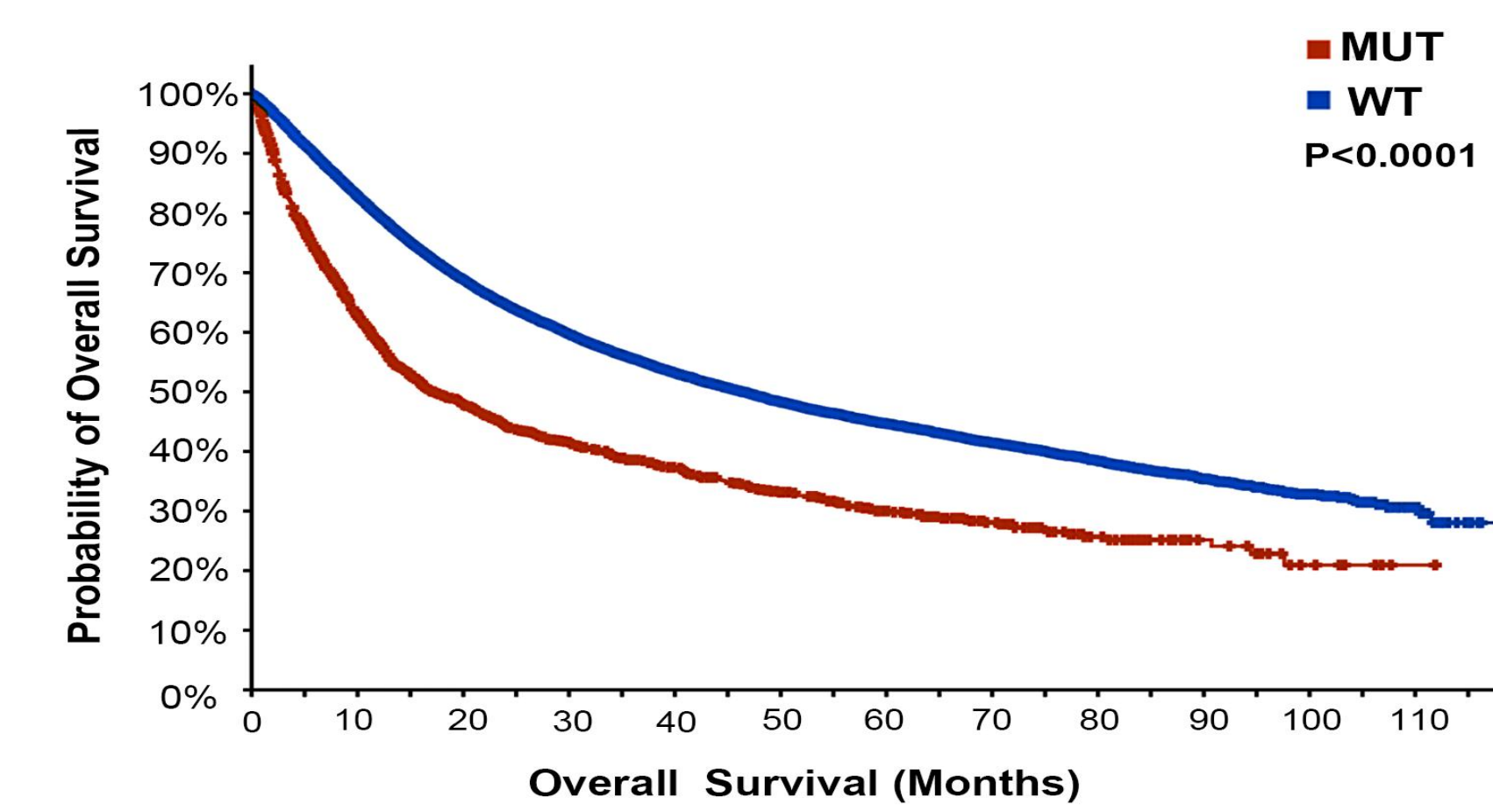
Immune checkpoint inhibitors (ICIs) have achieved remarkable progress in the clinical treatment of non-small cell lung cancer (NSCLC). However, KEAP1 loss-of-function mutations markedly limit the efficacy of PD-1/PD-L1 immune checkpoint blockade. Emerging evidence indicates that KEAP1 loss-of-function mutations are closely correlated with metabolic reprogramming and the tumor microenvironment (TME). Therefore, it is essential to elucidate the underlying resistance mechanisms and explore novel combination therapeutic strategies.

METHODS

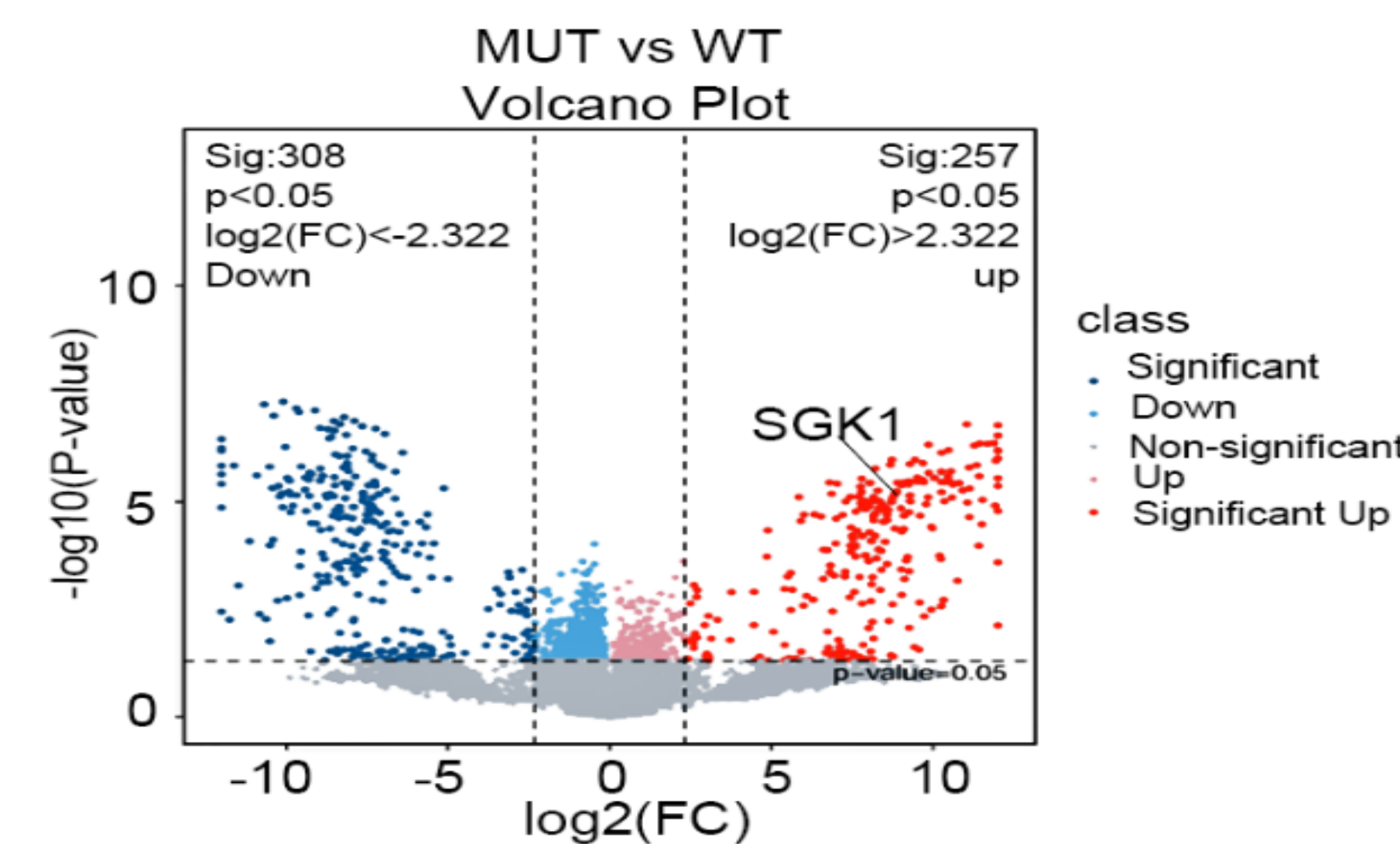
- Clinical data from multiple cohorts of NSCLC patients receiving immunotherapy were analyzed to evaluate the association between KEAP1 expression and immunotherapeutic response.
- Integrated RNA-seq and proteomic analyses were conducted in KEAP1 wild-type (WT) and mutant (MUT) models to identify downstream regulators and metabolic pathways.
- Expression levels and correlation of KEAP1 and its downstream target SGK1 were assessed via public databases, RT-PCR, Western blotting, Elisa and immunofluorescence.
- Functional assays were performed in KEAP1 WT and MUT cell lines, as well as SGK1 overexpression and knockout cell lines.
- The therapeutic efficacy and safety of combination treatment with multiple KEAP1 pathway inhibitors and ICIs were further evaluated in murine models.

RESULTS

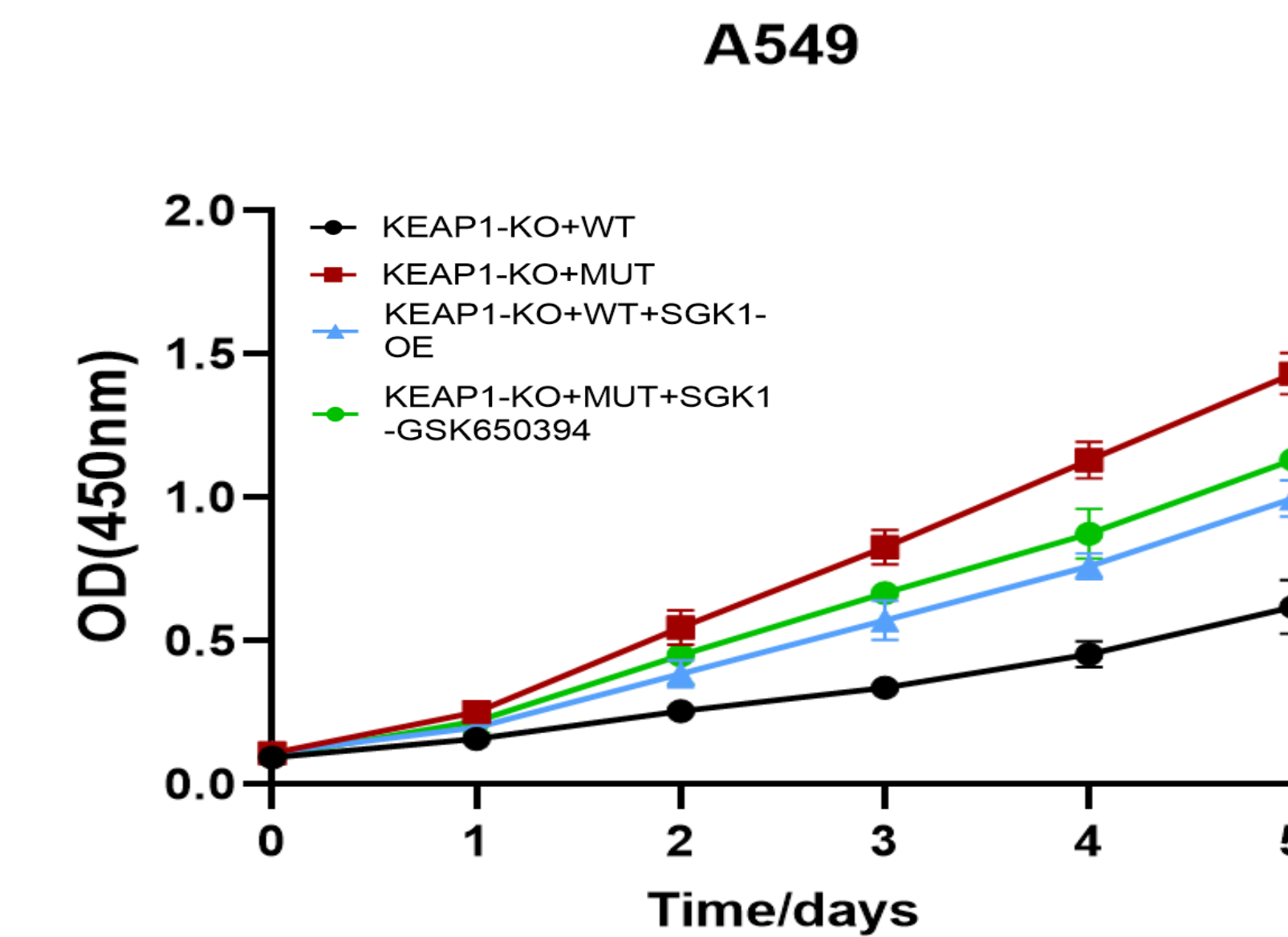
Clinical data indicate a negative correlation between KEAP1 mutation and patient survival, as well as insensitivity to single-agent anti-PD-1/PD-L1 treatment.



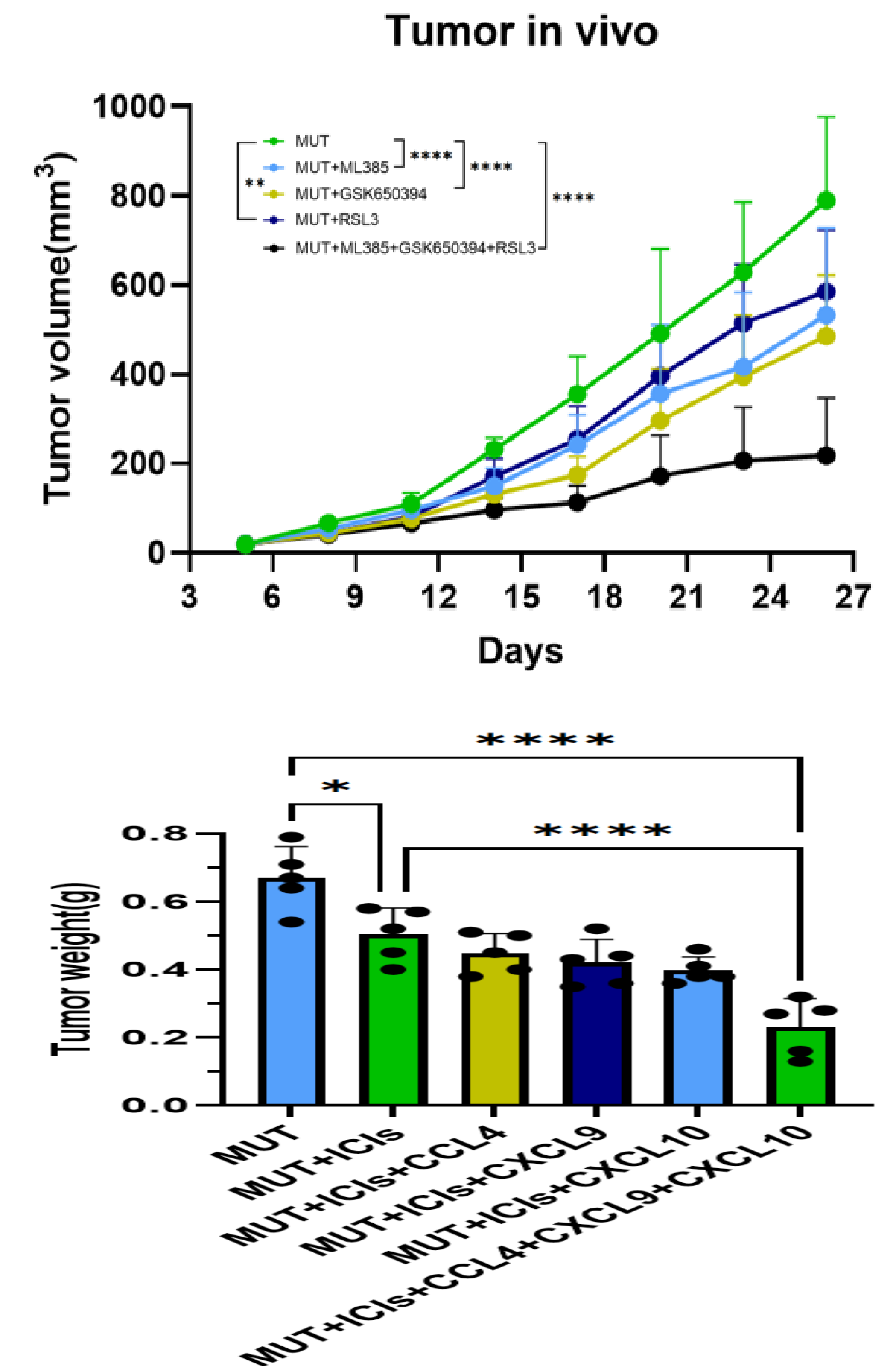
Multi-omics analyses demonstrate that KEAP1 mutation is positively associated with high expression of membrane protein SGK1.



In vitro assays confirm that KEAP1 mutation and SGK1 upregulation synergistically drive tumor cell proliferation, migration and invasion. In vitro co-culture further demonstrates that KEAP1-mutant cells upregulate SGK1 in the tumor microenvironment, suppress oxidative stress and ferroptosis in tumor cells.



In mouse models, the triple combination of ML385, GSK650394, and RSL3 synergizes with ICIs to prominently reverse immunotherapy resistance in KEAP1-MUT tumors. Meanwhile, the immunotherapeutic efficacy of the chemokine combination (CCL4, CXCL9, CXCL10) in conjunction with ICIs is significantly improved.



CONCLUSION

SGK1 serves as a pivotal driver of KEAP1 mutation-driven immune escape and a promising predictive biomarker for immunotherapy response in NSCLC. The triple combination of ML385/GSK650394/RSL3 plus chemokines synergizes with ICIs to effectively reverse immune resistance in this subtype, providing a novel strategy for precise immunotherapy stratification and targeted sensitization.

REFERENCES & ACKNOWLEDGEMENTS

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