



P3.265: Microglial RAB7-Mediated Lipid Transfer Overcomes Adaptive Resistance to Osimertinib in Lung Cancer Brain Metastases

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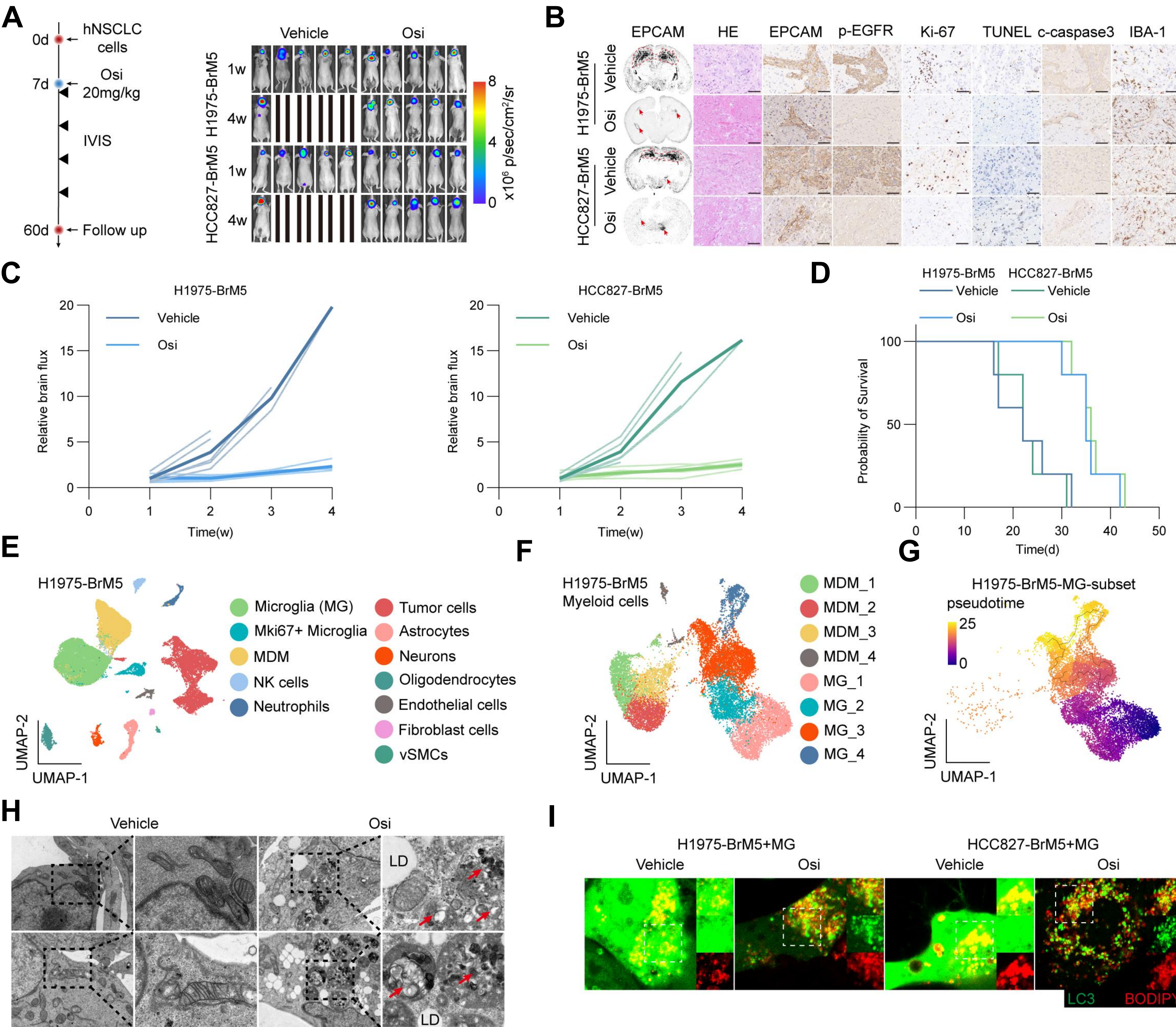
INTRODUCTION

- Brain metastases remain a major clinical challenge in EGFR-mutant lung adenocarcinoma, despite the initial intracranial efficacy of Osimertinib.
- Adaptive resistance within the brain microenvironment limits durable therapeutic benefit, but the contribution of resident microglia remains poorly understood.
- We investigated whether microglia promote adaptive Osimertinib resistance through intercellular lipid trafficking and identified the underlying molecular mechanism.

DISCUSSION AND CONCLUSION

- Microglia are active contributors to adaptive Osimertinib resistance in EGFR-mutant lung adenocarcinoma brain metastases.
- RAB7-dependent transfer of lipid structures from microglia to tumor cells provides a previously unrecognized mechanism supporting tumor survival under therapeutic pressure.
- Targeting microglia–tumor metabolic crosstalk may represent a complementary strategy to delay adaptive resistance to Osimertinib.

RESULTS



METHODS

- EGFR-mutant lung adenocarcinoma brain metastasis models were established by left ventricular injection and longitudinally monitored by BLI during Osimertinib treatment.
- ScRNA-seq was performed on resistant brain metastases to identify resistance-associated microglial populations, followed by in vitro and in vivo functional validation.
- Mechanistic studies examined RAB7-dependent lipid transfer from microglia to tumor cells, which was also a potential biomarker of treatment response.

REFERENCES & ACKNOWLEDGEMENTS

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- Osimertinib-resistant brain metastases were supported by a distinct lipid-enriched microglial population.
- Microglia transferred lipid-containing structures to tumor cells through RAB7-dependent vesicular trafficking.
- RAB7 expression was associated with Osimertinib response and may serve as a potential predictive biomarker and therapeutic target.