

HJURP-Yap1-Wisp1 Axis Drives Lung Adenocarcinoma Brain Metastases through Tumor-supportive Microglial Reprogramming

Zhanming Ma^{1,2,3}, Chaoqiang Deng^{1,2,3}, Wangyang Zhu^{1,2,3}, Haiquan Chen^{1,2,3*}, Yang Zhang^{1,2,3*}

Fudan University Shanghai Cancer Center, Shanghai, China * Corresponding author

Introduction

Brain metastasis (BrM) is a catastrophic complication of lung adenocarcinoma (LUAD), characterized by a unique immunosuppressive niche dominated by reprogrammed microglia. However, the molecular cues orchestrating this microglial plasticity remain elusive. This study aimed to identify specific drivers of LUAD brain metastasis and elucidate the molecular mechanism by which metastatic tumor cells remodel the microglial phenotype to facilitate colonization.

Methods

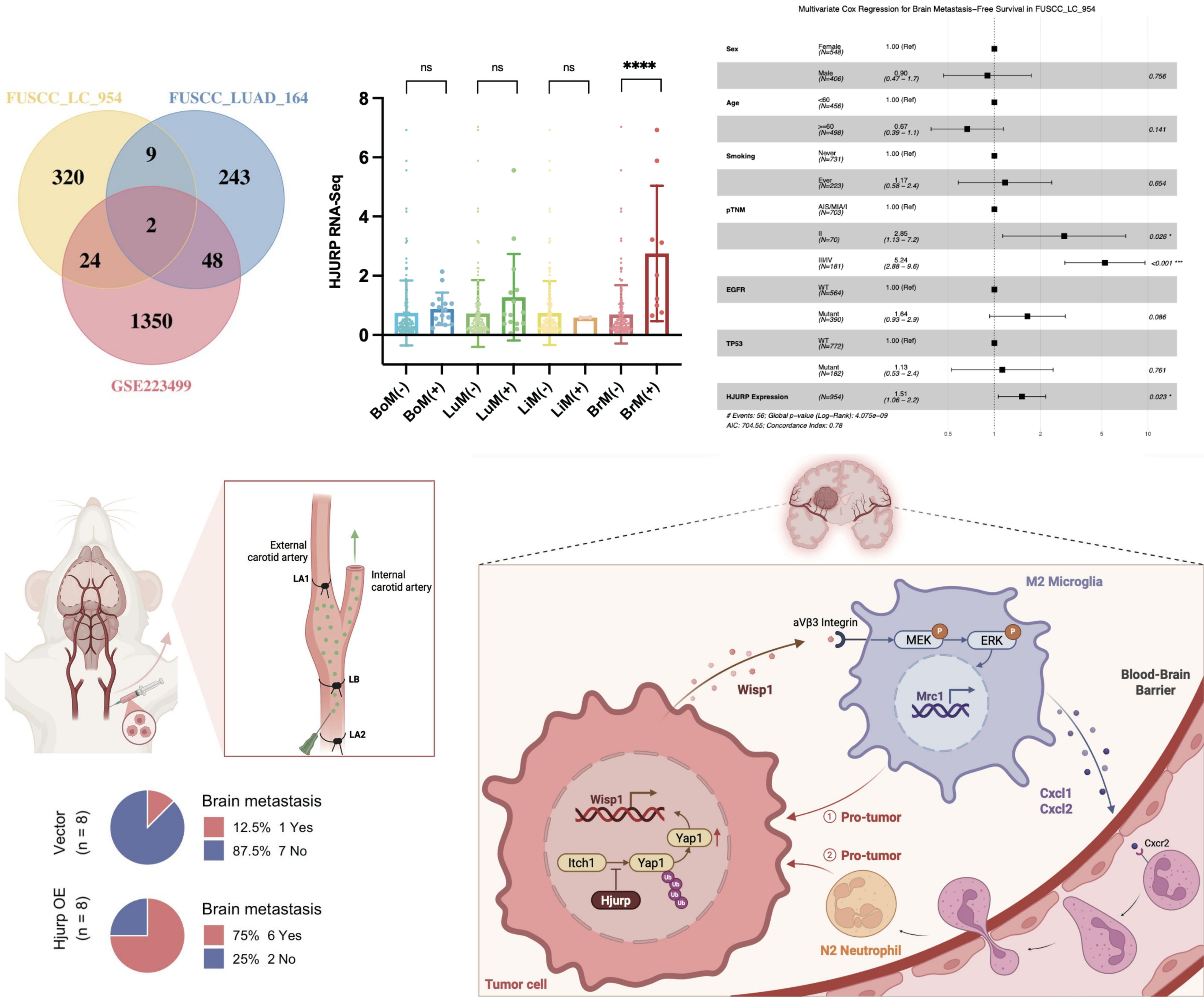
An integrated analysis of multi-cohort bulk and single-cell transcriptomics from clinical samples was performed to screen for BrM-specific candidate genes. Functional roles were validated in vivo using intracarotid artery injection mouse models with HJURP-overexpressing and Wisp1-knockout lung cancer cell lines. The immune landscape was comprehensively characterized using scRNA-seq, spatial transcriptomics. Mechanistically, chromatin immunoprecipitation, co-immunoprecipitation, and luciferase reporter assays were conducted to dissect intracellular signaling, while transwell co-cultures and ligand-receptor analyses investigated intercellular crosstalk. The therapeutic potential of targeting the identified axis was evaluated using pharmacological inhibition with Simvastatin.

Results

HJURP (Holliday Junction Recognition Protein) was identified as a specific driver of BrM, with high expression significantly correlating with poor brain metastasis-free survival in patients. Mechanistically, HJURP functioned as a non-canonical scaffold that stabilized the Hippo pathway effector YAP1 by obstructing its ITCH-mediated ubiquitination, thereby driving the transcriptional activation and secretion of the matricellular protein. Crucially, tumor-derived WISP1acted as a paracrine ligand that selectively engaged Itgav/Itgb3 receptors on microglia. This interaction triggered MEK/ERK signaling, driving microglia toward a distinct pro-tumoral M2-like phenotype. Genetic depletion of Wisp1 or pharmacological disruption of the HJURP-YAP1-WISP1 axis using Simvastatin significantly reversed microglial polarization and reduced brain metastatic burden.

Conclusions

This study demonstrates that the HJURP-YAP1-WISP1 axis drives lung adenocarcinoma brain metastasis by orchestrating tumor-supportive microglial reprogramming. HJURP acts beyond its histone chaperone role to stabilize YAP1, inducing WISP1 secretion which educates microglia via Integrin-MAPK signaling. These findings reveal a critical mechanism of tumor-microglia crosstalk and suggest that Simvastatin intervention targeting the HJURP-YAP1-WISP1 axis represents a promising therapeutic strategy for overcoming lung adenocarcinoma brain metastasis.



1 Department of Thoracic Surgery and State Key Laboratory of Genetics and Development of Complex Phenotypes, Fudan University Shanghai Cancer Center, Shanghai, 200032, China;

2 Institute of Thoracic Oncology, Fudan University, Shanghai, 200032, China;

3 Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, 200032, China