



P3.138: RAB37-LRRK2 Axis Orchestrates Lysosomal Reprogramming and Pre-Metastatic Niche Formation to Drive Early Colonization of Brain Metastasis

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IASLC 2026 World
Conference on Lung Cancer

SEPTEMBER 12 - 15, 2026
SEOUL, REPUBLIC OF KOREA

INTRODUCTION

Brain metastasis (BrM) remains a devastating complication of non-small cell lung cancer (NSCLC), with limited mechanistic understanding and therapeutic options. Pre-metastatic niche (PMN) establishment in the brain is critical for metastatic colonization, yet the molecular regulators linking lysosomal dysfunction, secretory autophagy, and immune-vascular remodeling in NSCLC BrM remain largely unknown.

METHODS

To identify master regulators of BrM in lung cancer, we established an optimized NSCLC brain metastasis mouse model via 5 cycles iterative left ventricular injection and employed LC-MS/MS analysis. Top candidates were validated through multi-omics (Single-cell sequencing, spatial proteomics and time-lapse photography etc.) to define their roles in shaping the PMN formation. Furthermore, an immune system-tumor double humanized lung cancer patient-derived BrM xenograft (hu-PBMC-BrM PDX) models were established to recapitulates the human brain PMN and evaluate the therapeutic potential of targeting this critical signaling axis.

DISCUSSION AND CONCLUSION

Main Message

- This study uncovers an essential signalling bridge connecting tumor cell lysosomal reprogramming and brain PMN formation. It furnishes prognostic biomarkers and novel therapeutic targets for clinicians to identify high-risk individuals and inhibit BrM at its earliest seeding stage. Targeting RAB37-LRRK2 axis disrupts PMN, providing a promising therapeutic strategy to suppress brain metastatic colonization.

Future Direction for Research

- Core scientific breakthrough and advancement over existing brain-metastasis knowledge.
- Early stage risk stratification for high-risk BrM patients.
- Novel therapeutic targets for metastasis-preventive therapy.

ACKNOWLEDGEMENTS

Funding

This study was supported by the National Natural Science Foundation of China (Grant no. 82573623, no.82403508).

Medical Ethics Committee

Human primary lung cancer tissues and paired brain metastatic tissues were obtained from Nanfang Hospital of Southern Medical University (Guangzhou, China). All tissue samples were collected in accordance with the hospital's informed consent policy and with approval from the hospital's institutional research ethics committee.

RESULTS

- We identified small G-protein RAB37 as a novel potential target for NSCLC brain metastases via LC-MS/MS analysis.
- Genetic ablation of RAB37 in BrCs significantly inhibit angiogenesis and early colonization of brain metastases in lung cancer *in vivo* BrM models.
- RAB37 recruits LRRK2 to inhibit the lysosomal membrane protein TMEM175 ion channel activity and disrupts lysosomal H⁺ efflux and acidification.
- Therapeutically, pharmacological inhibition of RAB37-LRRK2 signaling markedly reduced brain metastases in hu-PBMC-BrM PDX systems.

