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Genomic profiling and molecular targeting of lung cancer brain metastases

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Background

Approximately 40%-50% of cancer patients who develop brain metastases have lung cancer. There is very limited information on genetic signatures associated with lung cancer brain metastases and prior studies mostly included small cohorts of cases.

Methods

We analyzed a large collection of lung cancer cases (n = 47215 for all NSCLC; 29438 for lung adenocarcinoma LUAD) that underwent comprehensive genomic profiling (FoundationOne), and identified potential key genetic alterations involved in loco-regional lesions (Loco) vs extracranial metastases (EM) vs brain metastases. We then performed preclinical studies to determine their functional roles and downstream pathways.

Results

Compared to Loco, the top 3 most enriched genetic alterations were *CDKN2A/2B* loss and *SMARCA4* mutation in EM, and amplifications of *NFKB1A*, *RICTOR* and *KRAS* in brain metastases. Previous studies suggested that the aberrant activation of PI3K/AKT/mTOR pathway was associated with the development of BM. We also found significantly more frequent alterations of the overall PI3K/AKT/mTOR pathway in the BM (Loco 13.0% vs EM 14.5% vs brain metastases 18.1%), which was primarily driven by the enrichment of *RICTOR* amplification (Loco 3.6% vs EM 6.2% vs brain metastases 8.6%) in LUAD. *In vitro* studies showed that both genetic and pharmacological ablation of RICTOR in *RICTOR*-amplified NSCLC cells significantly reduced migration and invasion, whereas upregulation of RICTOR facilitated these processes. Mechanistic studies suggested that RICTOR may regulate the metastatic process through modulating the AKT, MET, EMT and CXCL12 chemokine-CXCR4 pathways. *In vivo* studies in orthotopic mouse models further revealed that both inducible RICTOR knockdown (with doxycycline) and TAK228 (mTOR1/2 inhibitor) significantly inhibited lung cancer tumor growth and spread in the brain.

Conclusions

RICTOR amplification is the most enriched actionable genomic target in NSCLC brain metastases, and its ablation can lead to reduced local invasion and tumor progression in the brain. Our study provides a foundation for the development of RICTOR-targeted therapeutic strategies for the treatment and/or prevention of lung cancer brain metastases.

Legal entity responsible for the study

The authors.

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Disclosure

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