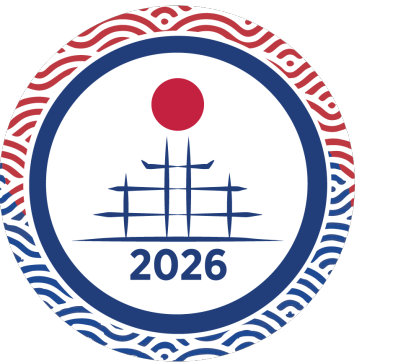


P2.038 Riboflavin Preference Promotes Extracellular Matrix Degradation and Metastasis in Lung Adenocarcinoma via the FLAD1-AMBP-uPA Axis



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Background

Metastatic lung adenocarcinoma (LAUD), characterized by poor prognosis and limited therapeutic options, remains a major clinical challenge. Identifying novel biomarkers and therapeutic targets is crucial to improving patient outcomes.

Methods

We established a multi-omics LAUD cohort, incorporating proteomic, transcriptomic, and metabolomic data, alongside single-cell transcriptomic data from metastatic samples, to identify metabolic features associated with metastasis. The role of riboflavin metabolism in invasion and metastasis was further validated both in vivo using mouse models and in vitro with cell line models.

Results

Significant metabolic differences were observed between primary and metastatic lesions at the single-cell transcriptomic level, particularly in tumor cells. Multi-omics integration identified that riboflavin metabolism was most active in metastatic lesions and closely correlated with prognosis. FLAD1, a key enzyme in riboflavin metabolism involved in FAD synthesis, was observed to be overexpressed in various lung metastatic lesions, including malignant pleural effusion and brain metastases. In vitro, forced overexpression of FLAD1 significantly enhanced cell migration and invasion.

Subcutaneous tumor-bearing mouse models exhibited a significant increase in tumor volume in the FLAD1 overexpression group, with Masson's staining revealing a notable reduction in extracellular matrix content within the tumor tissue. Mechanistically, FLAD1 downregulates AMBP, thereby relieving its inhibition of urokinase-type plasminogen activator (uPA), which activates the fibrinolytic ability of tumor cells and promotes the degradation of the extracellular matrix.

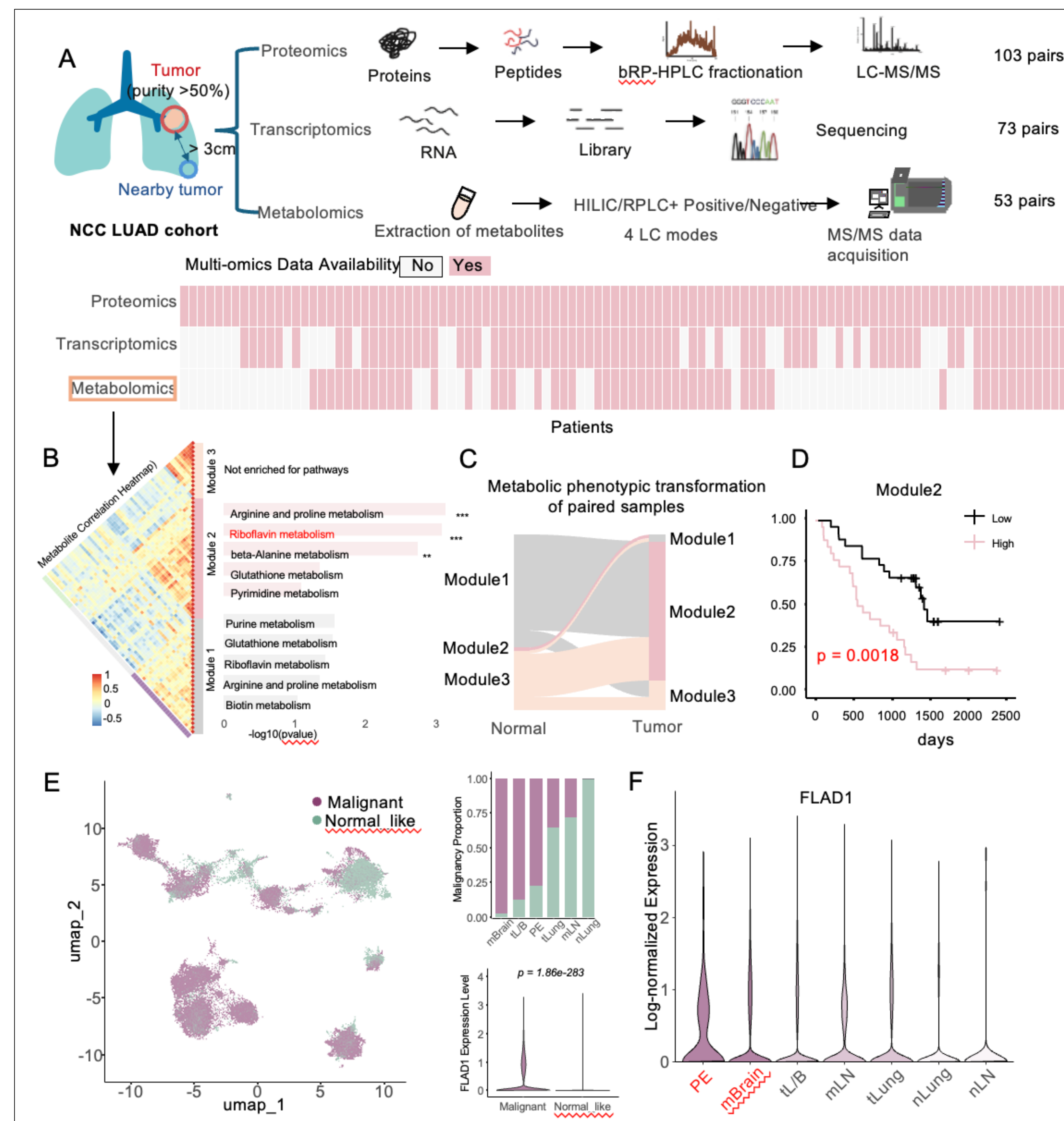


Figure 1. Multi-omics analysis identifies riboflavin metabolism and FLAD1 as metastasis-associated features in lung adenocarcinoma. (A) Cohort design and multi-omics data availability. (B–D) Metabolic module analysis highlights riboflavin metabolism and its association with prognosis. (E,F) Single-cell analysis shows elevated FLAD1 expression in malignant cells and metastatic lesions.

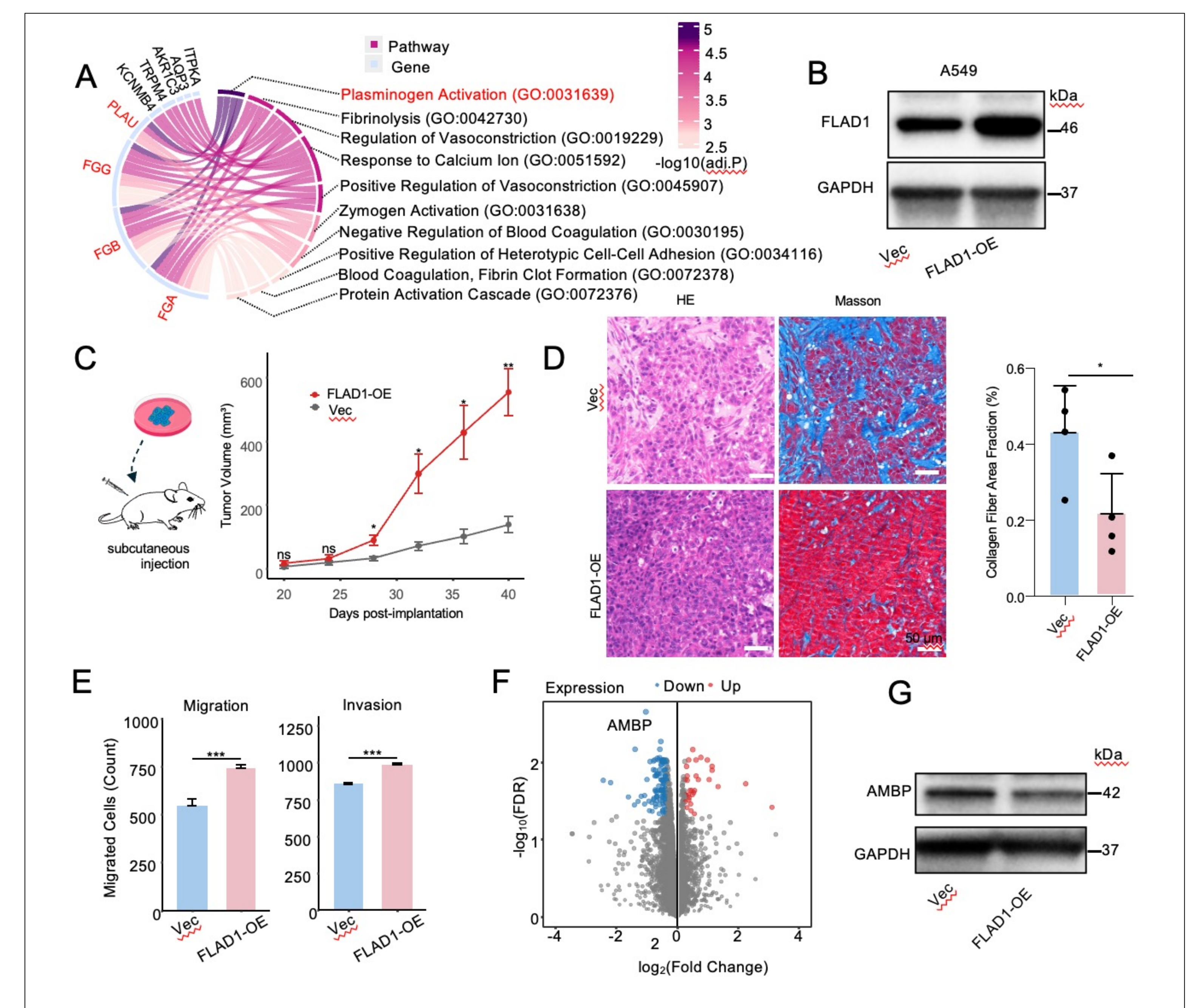


Figure 2. FLAD1 promotes tumor growth, migration, invasion, and extracellular matrix degradation. (A) Functional enrichment highlights plasminogen activation and fibrinolysis. (B–E) FLAD1 overexpression enhances tumor growth and invasive phenotypes while reducing collagen content. (F,G) AMBP is identified and validated as a downregulated protein following FLAD1 overexpression.

Conclusion

FLAD1 promotes extracellular matrix degradation by downregulating AMBP and activating the uPA fibrinolytic pathway. Targeting FLAD1 offers a promising strategy to inhibit lung adenocarcinoma metastasis.

AI Use Disclosure:

ChatGPT (OpenAI) was used solely for language editing and polishing to improve grammatical accuracy, clarity, and readability. All scientific content, interpretations, and conclusions were independently developed and reviewed by the authors.