P3.423: Multi-omics Analysis Reveals the Role of MAT2A in Metabolic Reprogramming of Non-Small Cell Lung Cancer 1752

Yimin Chen[1],XuyuGu[2],Jia Yu[2], Shen Chen[2], Shuo Yang[2],Bin Chen[2], Qian Liu[1],Qiyu Fang[2]
[1]Analytical Research Center for Organic and Biological Molecules, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China, [2]Department of Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China;
Correspondence: Qiyu Fang, MD, Associate Professor, Email:qyFang.work@outlook.com

IASLC 2026 World Conference on Lung Cancer
SEPTEMBER 12 – 15, 2026
SEOUL, REPUBLIC OF KOREA

INTRODUCTION

Metabolic reprogramming in cancer is often regulated by epigenetic modifications.Methionine adenosyltransferase 2A (MAT2A) plays a key role in this process by synthesizing S-adenosylmethionine (SAM), the primary methyl donor for epigenetic methylation. However, the regulatory role of MAT2A in metabolic reprogramming in NSCLC (non-small cell lung cancer)remains to be fully elucidated, with only one study focusing on its function in tumor-initiating cells. Current MAT2A inhibitors face challenges due to metabolic plasticity and compensatory upregulation of the enzyme, highlighting the need for further investigation to improve therapeutic strategies.

METHODS

We employed quantitative proteomics and metabolomics to investigate MAT2A-driven metabolic reprogramming in NSCLC following MAT2A knockout or treatment with inhibitor AG-270. This study aimed to uncover its potential regulatory role in lipid metabolism, glycolysis, and transport pathways, and to explore potential combination therapeutic strategies.

DISCUSSION AND CONCLUSION

Actionable Take Away Message

- **Our multi-omics analysis demonstrates MAT2A's role in regulating lipid metabolism, glycolysis, and transport pathways in NSCLC, and we demonstrates a highly synergistic combination strategy involving AG-270 and the LXR agonist LXR-623..**

Future Direction for Research

- Further explore its mechanism
- Clinical Strategies for Combination Drug Therapy

REFERENCES & ACKNOWLEDGEMENTS

National Natural Science Foundation of China (No 22425703),Natural Science Foundation of Shanghai (25ZR1401308), Tongji University Independent and Original Basic Research Project (No. 22120240374).

• Artificial Intelligence (AI) Use Disclaimer

This presentation was prepared with AI-assisted language editing; all scientific content reflects the authors' independent medical judgment.

RESULTS

- Fatty acid biosynthesis, cholesterol metabolism, glycolysis, and transsulfuration pathway are disrupted upon knockout and inhibition of MAT2A significantly .
- In fatty acid biosynthesis, MAT2A affects the expression of key genes FASN and SCD, as well as the levels of key metabolites palmitic acid (PA) and oleic acid (OA), as exogenous PA reverses the cell growth inhibition caused by AG-270.
- In cholesterol metabolism, MAT2A regulates biosynthesis and efflux, binding AG-270 to liver X receptor agonists(LXR-623) to promote cholesterol efflux and enhance anti-tumor efficacy.
- In energy metabolism, MAT2A affects glycolysis by regulating HIF1A. GLUT1 inhibitors(BAY-876)that inhibit glucose uptake exhibit a synergistic effect when combined with AG-270.
- In the sulfur conversion pathway, MAT2A transcriptionally regulates the key enzyme CBS involved in cysteine biosynthesis. The combination therapy of AG-270 upregulated gene PHGDH inhibitor (NCT-503) and SLC7A11 inhibitor (HG106) showed synergistic effects.

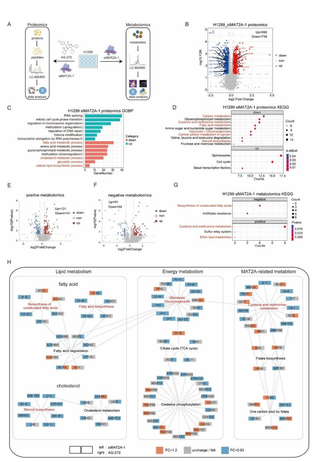


Figure 1. Proteomics and metabolomics analysis reveal patterns of MAT2A-driven metabolic reprogramming
A, workflow of proteomics and untargeted metabolomics. H1299 was treated with siMAT2A-1 or 5 μM AG-270, and then collected for subsequent omics experiment. B, volcano plot of siMAT2A-1 group in proteomi GOBP enrichment of siMAT2A-1 group in proteomics. D, KEGG enrichment of siMAT2A-1 group in proteomics. E, F, volcano plot of siMAT2A-1 group in negative metabolomics (E) and positive metabolomics (F. 0.05, FC > 1.5 or < 0.67, VIP > 1). G, KEGG enrichment of untargeted metabolomics (P < 0.05, FC > 1.5 or < 0.67, VIP > 1). H, the metabolism network shows three major pathways including lipid metabolism, en metabolism and MAT2A-related metabolism in proteomics of siMAT2A-1 and AG-270, all datasets were derived from the KEGG database, genes shown in network were significant (P < 0.05, FC < 0.83 or FC > 1.2).

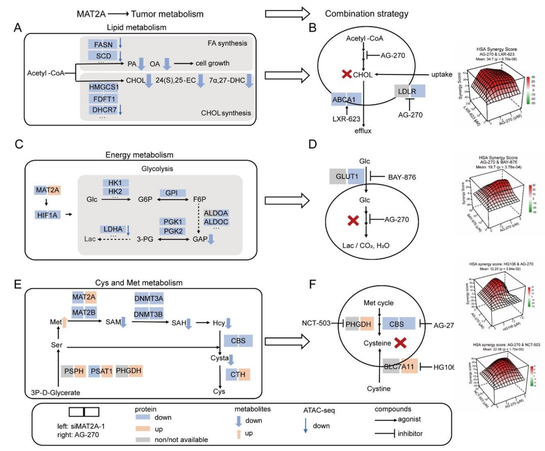


Figure 2. MAT2A regulates tumor metabolism and potential combination strategies are proposed.
A, C, E, MAT2A regulates lipid metabolism including fatty acid biosynthesis and cholesterol homeostasis (A), glycolysis in energy metabolism (C) and Cys and Met metabolism (E).
B, D, F, MAT2A inhibition AG-270 exhibits potential combination effect with LXR agonist LXR-623 (B), GLUT1 inhibitor BAY-876 (D), PHGDH inhibitor NCT-503 and SLC7A11 inhibitor HG106 (F).
Abbreviation: malate, Mal; nicotinic acid riboside, NAR; reduced nicotinamide mononucleotide, NMNH; nicotinamide mononucleotide, NMN; flavin mononucleotide, FMN; serine, Ser, cysteine, Cys.