



Differential Gut Metabolites Associated with Immunotherapy Response in Small Cell Lung Cancer: A Non-targeted Metabolomics Study

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INTRODUCTION

Immunotherapy, particularly immune checkpoint inhibitors, offers promise for small cell lung cancer (SCLC). However, many patients do not respond and reliable biomarkers are scarce. The gut microbiome and its metabolites are emerging as modulators of immunotherapy efficacy. Here, we performed untargeted fecal metabolomics to identify differential metabolites associated with treatment response in SCLC.

METHODS

A total of 41 SCLC patients receiving immune checkpoint inhibitor therapy were enrolled. Based on RECIST criteria, patients were dichotomized into responders (R, n=20) and non-responders (NR, n=21). Fecal samples were collected prior to immunotherapy initiation. Non-targeted metabolomic analysis was conducted using liquid chromatography-tandem mass spectrometry. Orthogonal partial least squares discriminant analysis was employed to identify differential metabolites between groups, with variable importance in projection ≥ 1.0 and fold change ≥ 1.0 (or adjusted $P < 0.05$) as thresholds for statistical significance.

CONCLUSION

This study demonstrates that non-targeted metabolomic profiling distinguishes SCLC patients with favorable immunotherapy response from those with poor response. The identified differential metabolites may serve as potential non-invasive biomarkers for predicting immunotherapy efficacy and provide insights into the metabolic pathways underlying microbiota-mediated immunomodulation. Further validation in larger cohorts and mechanistic investigations are warranted to translate these findings into clinical practice.

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The authors confirm that all aspects of this study, including experimental design, data acquisition, statistical analysis, result interpretation, and the writing of the abstract/poster, were carried out without the use of any generative artificial intelligence tools. All scientific conclusions and statements are entirely original to the authors and adhere to the standards of academic integrity.

RESULTS

Non-targeted metabolomic profiling revealed distinct metabolic signatures between responders and non-responders, with OPLS-DA demonstrating clear separation between two groups. A total of 34 differential metabolites were identified, among which 21 were elevated in responders and 13 were enriched in non-responders. KEGG pathway enrichment analysis performed on the complete set of differential metabolites identified several significantly enriched pathways, including sphingolipid metabolism, amino sugar and nucleotide sugar metabolism, and O-antigen nucleotide sugar biosynthesis. Within these pathways, metabolites upregulated in responders and those upregulated in non-responders exhibited distinct distribution patterns, suggesting divergent metabolic reprogramming associated with differential clinical outcomes.

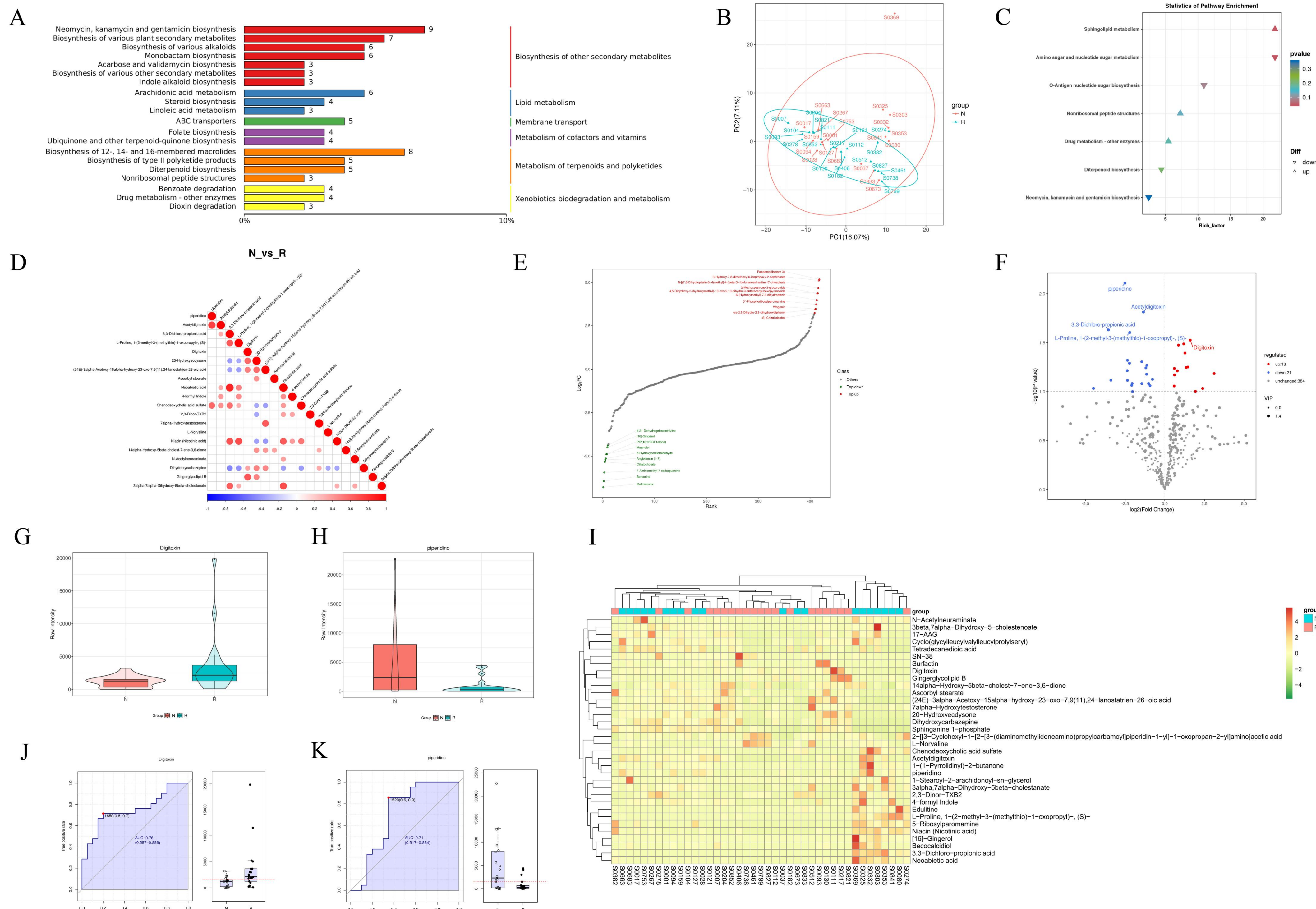


Figure (A) Summary of KEGG database classification. (B) PCA of differential group. (C) KEGG enrichment plot of differential metabolites. (D) Differential metabolite correlation plot. (E) Dynamic distribution of differential metabolite abundance. (F) Volcano plot of metabolites. (G-H) Differential metabolite violin plot. (I) Hierarchical clustering heatmap of differential metabolite union. (J-K) ROC curve and boxplot of differential metabolite.

Disclosure

Artificial Intelligence (AI) Use Disclaimer

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