

Gut Microbiota and Metabolomic Profiles Predict the Response to Immune Checkpoint Inhibitor Therapy in Lung Squamous Cell Carcinoma

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Background

- Lung squamous cell carcinoma (LUSC) is the second most prevalent histological subtype of lung cancer.
- Immune checkpoint inhibitors (ICIs) have emerged as the first-line therapeutic strategy for LUSC patients.
- Clinically available approaches for predicting immunotherapy efficacy remain insufficient in comprehensiveness and precision.
- The regulatory effects and mechanisms of gut microbiota and its metabolites on ICI response in LUSC are not fully elucidated.

Objective

To investigate the impacts of gut microbiota and associated metabolites on ICI treatment efficacy in LUSC patients and to explore their clinical predictive value for immunotherapy outcomes.

Study Hypothesis

Baseline gut microbial composition and fecal metabolomic signatures differ between responders and non-responders to ICI therapy, enabling the development of predictive biomarkers.

Methods

Cohort

30 LUSC patients receiving ICI therapy

Grouping

Responders: PFS ≥ 6 mo (n=15)
Non-responders: PFS < 6 mo (n=15)

Sampling

Fecal samples collected prior to immunotherapy initiation

Metagenomics

Microbial composition and differential taxa analysis

Metabolomics

Non-targeted metabolomic profiling

Bioinformatics

Machine learning for biomarker screening

Key Microbial Findings

Although overall gut microbiota composition did not differ significantly between groups, genus-level differential abundance analysis identified 15 taxa with significantly different mean relative proportions between responders (R) and non-responders (NR) (all $p < 0.05$, Figure 1A).

Representative R-enriched genera included:

- Faecalicatena** ($p = 0.0431$)
- Luxibacter** ($p = 0.0232$)
- Anaerococcus** ($p = 0.0338$)
- Cryptobacterium** ($p = 0.00891$)
- Lactimicrobium** ($p = 0.0204$)
- Aerococcus** ($p = 0.00665$)

LEfSe analysis further identified taxonomic biomarkers discriminating responders from non-responders (Figure 1C).

Results

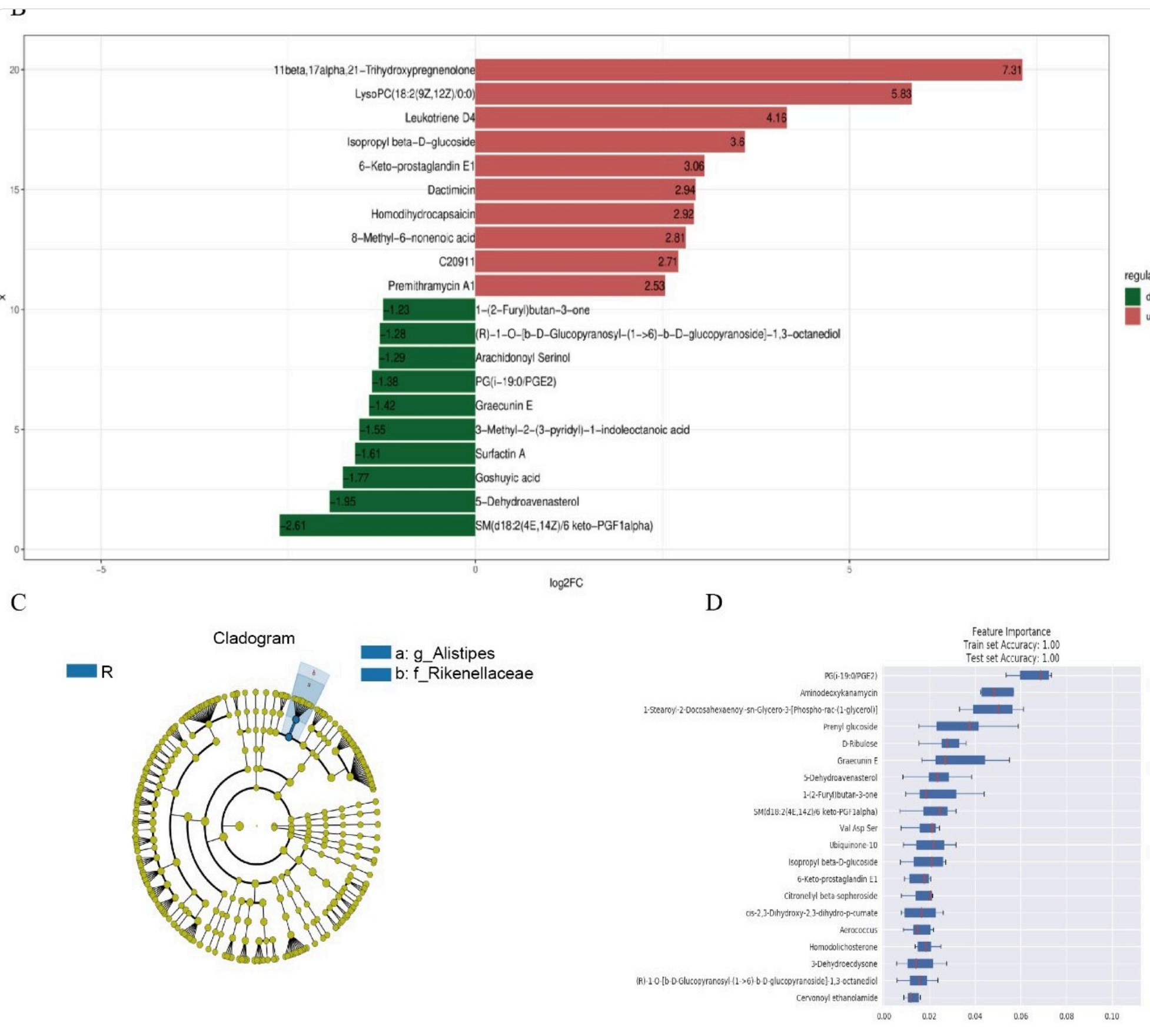
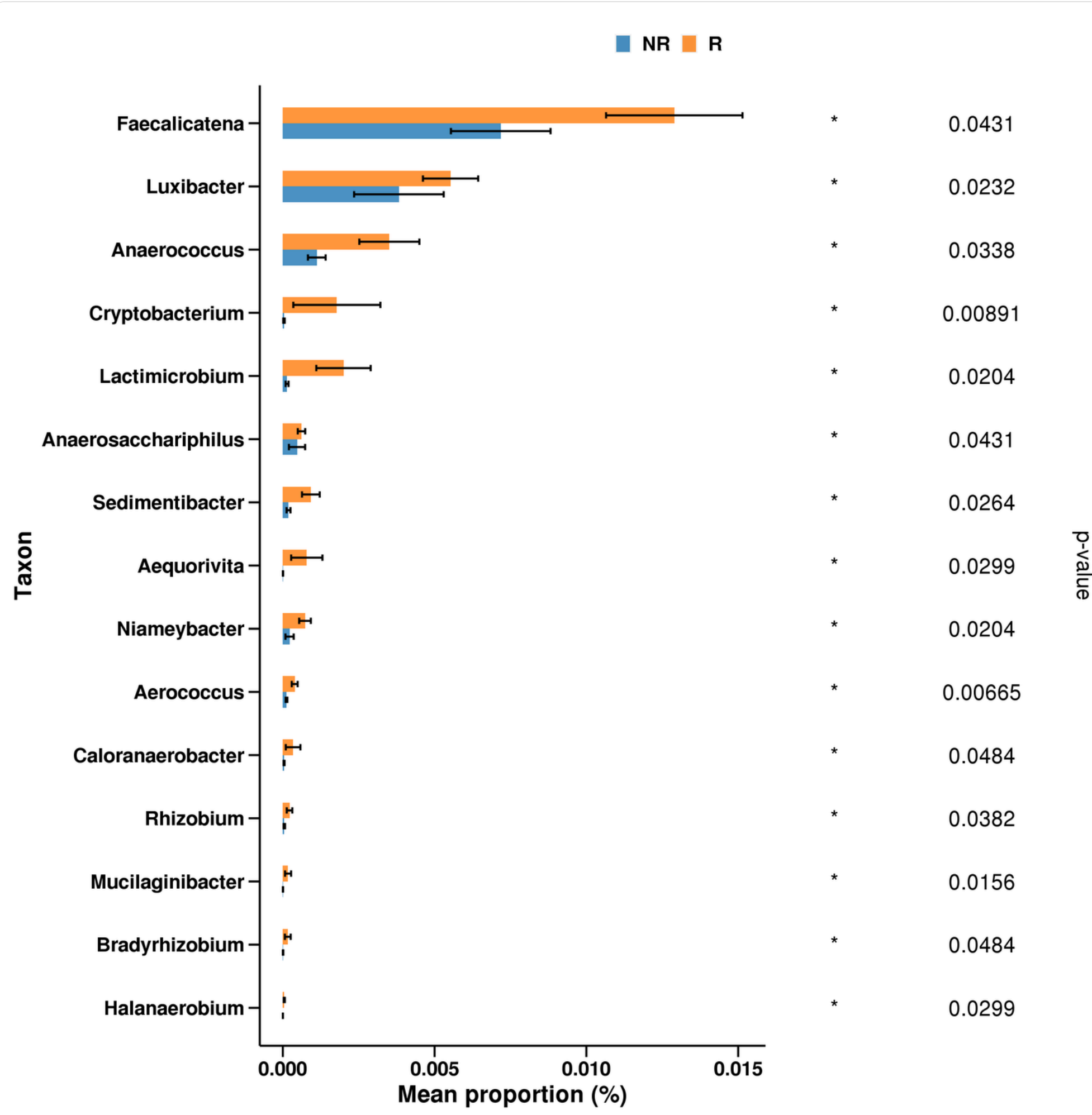


Figure 1. Multi-omics characterization of baseline fecal samples in LUSC patients treated with ICIs. **(A)** Genus-level differential abundance analysis showing mean relative proportions of taxa significantly different between non-responders (NR, blue) and responders (R, orange); p-values are indicated on the right. **(B)** Differential metabolites ranked by log₂ fold change, showing upregulated (red) and downregulated (green) metabolites. **(C)** Cladogram of taxonomic biomarkers distinguishing responders from non-responders. **(D)** Machine learning feature importance ranking identifying top predictive metabolites.

Metabolomic Insights

- Lipid metabolic pathways played a central regulatory role in ICI treatment for LUSC.
- Marked differences in expression levels of multiple lipid metabolites were observed between responders and non-responders.
- Prostaglandin and sphingolipid-related metabolites emerged as top differential features.
- Machine learning models identified high-quality static biomarkers with strong predictive performance.

Machine Learning Biomarkers

Two high-quality static biomarkers were identified as reliable indicators for predicting immunotherapy efficacy and monitoring disease progression:

PG(i-19:0/PGE2)

Prostaglandin metabolite associated with ICI response

SM(d18:2(4E,14Z)/6 keto-PGF1α)

Sphingomyelin/prostaglandin-derived metabolite with predictive value

Clinical Implications

- Baseline gut microbiota and metabolomic profiles can modulate ICI efficacy in LUSC.
- Specific microbial genera may serve as non-invasive predictive indicators before treatment initiation.
- Static metabolite biomarkers offer a reliable approach for early prediction of immunotherapy response.
- Integration of multi-omics data supports personalized treatment decision-making.

Conclusions

This study confirms that the gut microbiota and its metabolites can modulate the efficacy of ICI therapy in LUSC patients. The identified specific static biomarkers possess promising clinical potential for the early prediction of ICI treatment responses and can provide valuable evidence to guide individualized clinical treatment regimens.

Take-Home Message

Baseline fecal multi-omics signatures, particularly lipid metabolites including PG(i-19:0/PGE2) and SM(d18:2(4E,14Z)/6 keto-PGF1α), represent promising non-invasive biomarkers for predicting ICI response in LUSC patients.

Future Directions

- Validate identified biomarkers in independent, multi-center cohorts.
- Investigate mechanistic links between lipid metabolism, gut microbiota, and anti-tumor immunity.
- Develop a clinically applicable multi-omics prediction model.
- Explore microbiota-targeted interventions to enhance ICI efficacy.

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