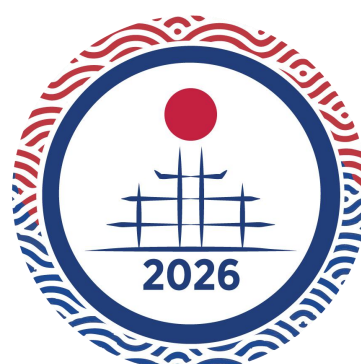




Baseline Gut Metagenomic Signatures Predict Immune Checkpoint Inhibitor-Related Pneumonitis

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INTRODUCTION

Immune checkpoint inhibitors (ICIs) greatly improve cancer treatment, but can cause serious immune-related adverse events. IC-related pneumonitis (CIP) is a life-threatening complication, and reliable pre-treatment predictive biomarkers are still lacking.

The gut microbiome regulates host systemic immunity and affects ICI-related toxicities. Most researches focus on microbial taxonomy, while the predictive value of baseline gut microbiome function for CIP remains unclear. This study aimed to identify baseline fecal metagenomic taxonomic and functional signatures linked to subsequent CIP occurrence.

METHODS

Thirty-two cancer patients receiving ICI therapy were enrolled, including 9 who subsequently developed CIP and 23 CIP-free controls. Baseline fecal samples collected before ICI initiation underwent deep metagenomic sequencing.

Following DNA extraction and quality filtering, high-quality reads (mean Q30 > 93%) were used to construct a non-redundant microbial gene catalog for downstream annotation.

Taxonomic profiling was performed using the NR database. Functional annotation was conducted against KEGG, eggNOG, CAZy, CARD, VFDB and PHI-base databases.

For statistical analyses, Shannon and Chao1 indices were calculated for alpha diversity. Beta diversity and compositional differences were assessed via PCoA, NMDS and ANOSIM. LEfSe (LDA > 2.0) identified differential taxa and modules, and PLS-DA visualized sample clustering by metagenomic profiles.

DISCUSSION AND CONCLUSION

This study provides metagenomic evidence that baseline gut microbial communities differ intrinsically between cancer patients who develop immune checkpoint inhibitor-related pneumonitis (CIP) and non-CIP controls. PLS-DA and PCoA revealed significant separation of metagenomic profiles, indicating distinct baseline microbial architectures before ICI treatment.

Functional annotation delineated the molecular basis of this compositional disparity. CIP-associated metagenomes showed marked enrichment in antimicrobial resistance genes (CARD), carbohydrate-active enzymes (CAZy), and virulence factors (VFDB), reflecting heightened microbial metabolic capacity and pathogenic potential. PHI-base identified divergent pathogen-host interaction signatures, further supporting the link between gut microbial traits and CIP susceptibility. Alpha and beta diversity metrics corroborated significant between-group divergence in community composition.

From a translational perspective, fecal metagenomic profiling may serve as a non-invasive tool to stratify CIP risk before ICI initiation, enabling proactive monitoring and personalized toxicity management. However, limitations exist: the modest sample size constrains statistical power and generalizability, and the observational design only supports association, not causation. The mechanistic pathways linking gut microbial functions to pulmonary immune toxicity remain incompletely defined.

In conclusion, baseline gut metagenomic signatures—particularly those related to antimicrobial resistance, virulence factors, and metabolic pathways—are significantly associated with subsequent CIP development. Fecal metagenomics is a promising non-invasive biomarker for CIP risk prediction, but prospective validation in larger multi-center cohorts is required before clinical translation.

RESULTS

