



P3.141: Priestia Is Associated with TLS Formation and Spatial Immune Remodeling in Lung Adenocarcinoma

Z. Zhao¹, Y. Lei^{2,3}, Y. Zhang¹, L. Yao¹, C. Cai¹, Y. Wang^{4,5}, H. Zhou¹
¹Department of Thoracic Surgery, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou/CN, ²School of Medicine, South China University of Technology, Guangzhou/CN, ³Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou/CN, ⁴Youth Innovation Team of Medical Bioinformatics, Shenzhen University Health Science Center, Shenzhen/CN, ⁵College of Basic Medicine, Shenzhen University Health Science Center, Shenzhen/CN
Correspondence: Lungcancer@163.com



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INTRODUCTION

BACKGROUND:

Tertiary lymphoid structures (TLS) are associated with improved prognosis and favorable immunotherapy responses in lung adenocarcinoma (LUAD).

MICROENVIRONMENT:

Intratumoral microbiota actively shape the local tumor immune microenvironment, but their specific role in driving or influencing TLS formation remains unclear.

KNOWLEDGE GAP:

The complex molecular, spatial, and clinical features linking specific intratumoral bacterial communities to TLS assembly are not yet well defined.

OBJECTIVE:

To identify intratumoral microbiota associated with TLS formation and to characterize the molecular and spatial features linked to this process in LUAD.

METHODS

Study Design:

A multimodal cross-validation study of 605 LUAD patients across 4 independent cohorts. We designed an integrative framework combining spatial transcriptomics, bulk RNA-sequencing, and matched microbiome profiling. Advanced computational pipelines—including weighted gene co-expression network analysis (WGCNA) and bidirectional causal mediation analysis—drove the evaluation of complex pathways linking bacterial abundance to TLS formation and overall survival. The framework's molecular and microenvironmental findings were then rigorously evaluated using two external transcriptomic cohorts and an independent clinical tissue subset via fluorescence in situ hybridization (FISH) spatial mapping.

DISCUSSION AND CONCLUSION

Actionable Take Away Message

- **Microbial-Immune Crosstalk:** This study establishes *Priestia* as a key intratumoral bacterial genus significantly linked to Tertiary Lymphoid Structure (TLS) formation, effectively capturing a highly immune-active microenvironment and improved overall survival in LUAD.
- **Spatial Sensing Mechanism:** Advanced spatial transcriptomics and FISH mapping reveal that *Priestia* and LBP-related signaling preferentially localize at the TLS periphery, uncovering a structured, microecological interface that likely supports TLS assembly.

Future Direction for Research

- **Mechanistic Causal Validation:** Execute in vivo and in vitro functional experiments to definitively establish the unidirectional causal pathways by which *Priestia* modulates LBP-related signaling and induces TLS formation.
- **Prospective Clinical Translation:** Conduct large-scale, prospective multicenter studies to validate the real-world clinical utility of integrating microbial abundance (*Priestia*) and TLScore as dual-biomarkers for personalized prognostic risk stratification.
- **Microbiome-Modulated Immunotherapy:** Investigate the therapeutic potential of manipulating the intratumoral microbiome to enhance TLS assembly, aiming to boost the local immune response and improve patient efficacy with immune checkpoint inhibitors.

KEY REFERENCE

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RESULTS

Key Findings

- **A. Prognostic Value of TLScore:** High TLScore effectively identified a highly immune-active microenvironment enriched for B and T cells, demonstrating a significant association with improved overall survival (log-rank $p=0.014$) in the discovery cohort.
- **B. Discovery of Priestia as a Key Biomarker:** The bacterial genus *Priestia* was identified as strongly TLS-associated, showing a significantly higher detection rate in TLS-High compared to TLS-Low tumors (49.0% vs. 30.8%) and a robust positive correlation with TLScore (Spearman $r=0.18$, $p=0.017$).
- **C. Structural Mediation of Survival:** Causal mediation analysis revealed that the positive association between *Priestia* and patient survival is driven primarily through its influence on TLS formation (ACME=161.0, $p=0.002$), highlighting an indirect microecological benefit.
- **D. Spatially Organized Microenvironment:** Spatial transcriptomics and exploratory FISH analysis demonstrated that both LBP-related signaling and intra-tumoral *Priestia* preferentially clustered directly at TLS boundaries (closer peri-TLS proximity within 50 μm , $p<0.0001$), uncovering a highly structured spatial sensing interface.

