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"Role of the intra-tumor microbiome in the non-small cell lung cancer immune microenvironment through a multi meta-omics analysis in Chilean patients"

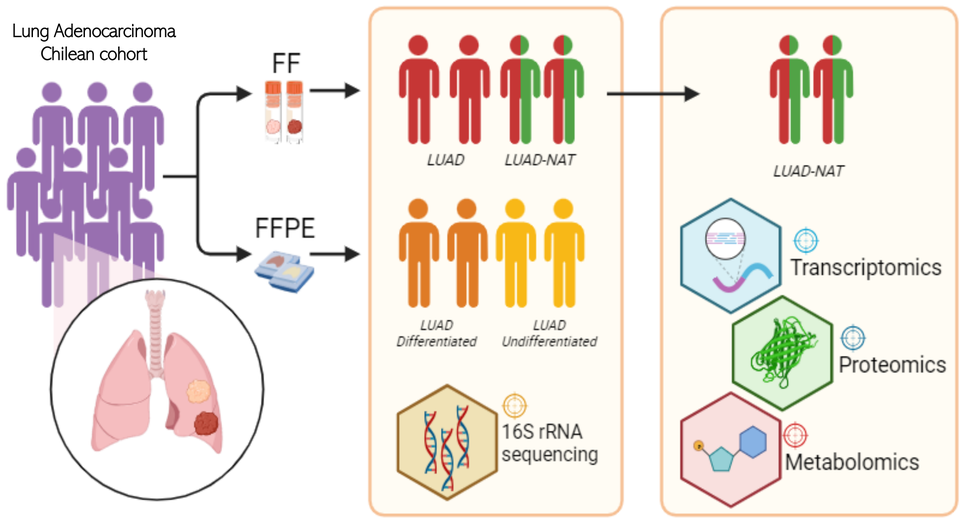
Ivania Valdés[1,2], Alberto J. Martin[3,4], J. Eduardo Martínez[5], Erick Riquelme[2]

[1]Universidad Mayor, Facultad de Ciencias, Vicerrectoría de investigación, Programa de Doctorado en Genómica Integrativa, Santiago, Chile; [2]Pontificia Universidad Católica de Chile, Departamento de Enfermedades Respiratorias, Facultad de Medicina, Santiago, Chile; [3]Fundación Ciencia & Vida, Centro Científico y Tecnológico de Excelencia Ciencia & Vida, Laboratorio de Redes Biológicas, Santiago, Chile; [4]Universidad San Sebastián, Facultad de Ingeniería, Arquitectura y Diseño, Escuela de Ingeniería, Santiago, Chile; [5]Corporación CGNA, Temuco, Chile.

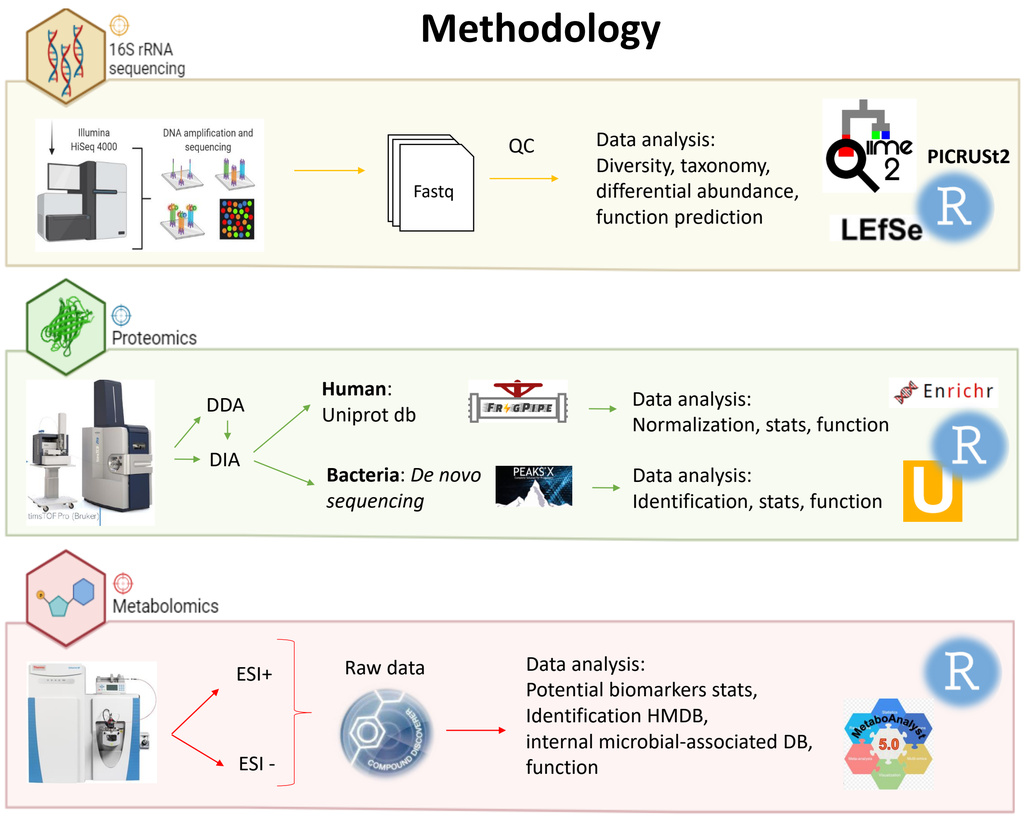
Background

In Chile and worldwide, lung cancer is one of the leading causes of death; therefore, research in this field is of vital importance. Microbiome research in lung cancer has revealed that the tumor microenvironment harbors a distinct microbial community. Within the tumor microenvironment, the microbiota are thought to exert influence on tumor development and progression. The intricate interplay between the tumor microbiome and the immune system adds complexity to our understanding of cancer, as these two factors interact and influence one another in ways that are still being unraveled. The tumor microbiome´s role in cancer has underscored its capacity to influence and modulate immune surveillance, although the functional mechanisms remain elusive.

Multi-omic approaches, such as integrating meta genomics, transcriptomics, proteomics and metabolomics data, provide a holistic view of the tumor microbiome, enabling the identification of key microbial players and their functional roles in cancer. Here, we outline how the tumor microbiota can impact the host´s immune response to lung cancer. We explored the microbiome in lung adenocarcinoma tumors (LUAD) and non-tumoral adjacent tissues (NAT).



Methodology



Results and discussion

Different microbial components differentiate tumor samples from non-tumor adjacent tissue

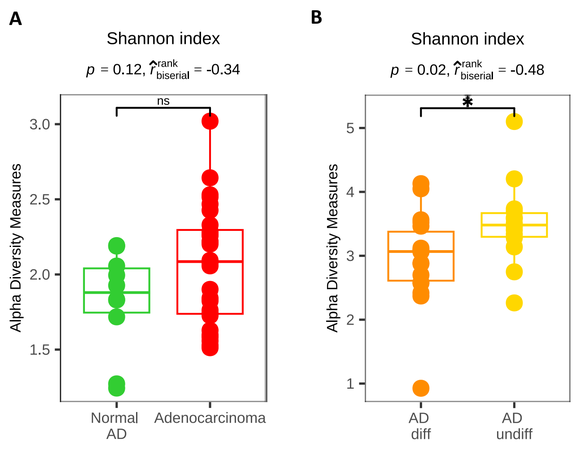


Figure 1. Alpha diversity analysis using Shannon index and Wilcoxon rank sum test. A Comparison between fresh-frozen samples for adenocarcinoma and non-tumor adjacent tissue. B Comparison between formalin-fixed paraffin-embbeded simples from adenocarcinoma differentiated and undifferentiated.

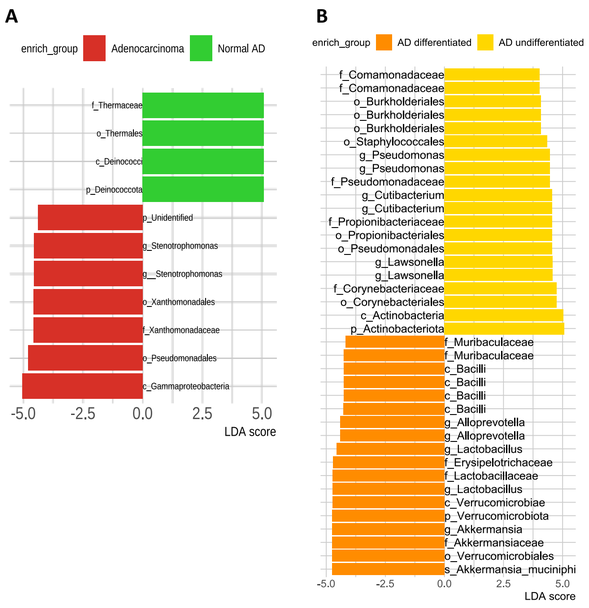
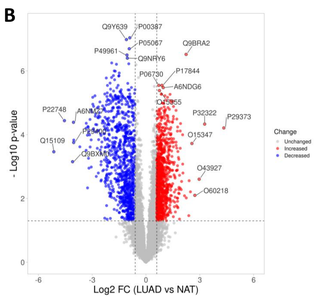


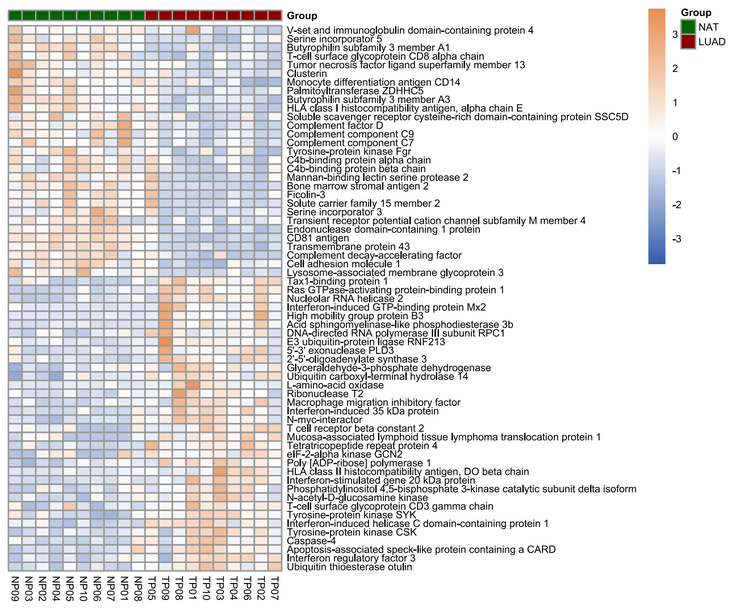
Figure 2. Differential abundance analysis using LDA score from LEfSe. A Comparison between fresh-frozen samples for adenocarcinoma and non-tumor adjacent tissue. B Comparison between formalin-fixed paraffin-embbeded simples from adenocarcinoma differentiated and undifferentiated.

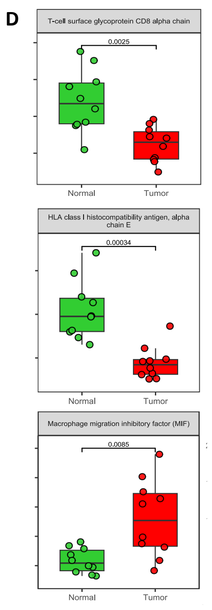
Host immune-related proteins differ between groups and promote an immune-evasion profile

A

Human protein identification source	Number
DDA mode	7109
DIA mode	6709
Presence 50% per group	6390
Paired t-test LUAD vs NAT (pval < 0.05)	2155
FC +1.5 up	749
FC -1.5 down	871
Immune filtered KW0391 up	34
Immune filtered KW0391 down	29







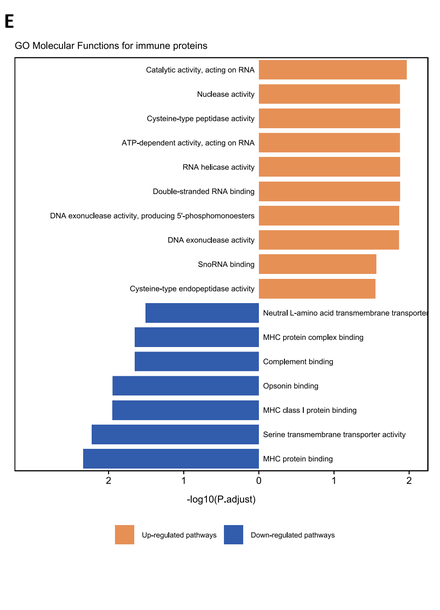
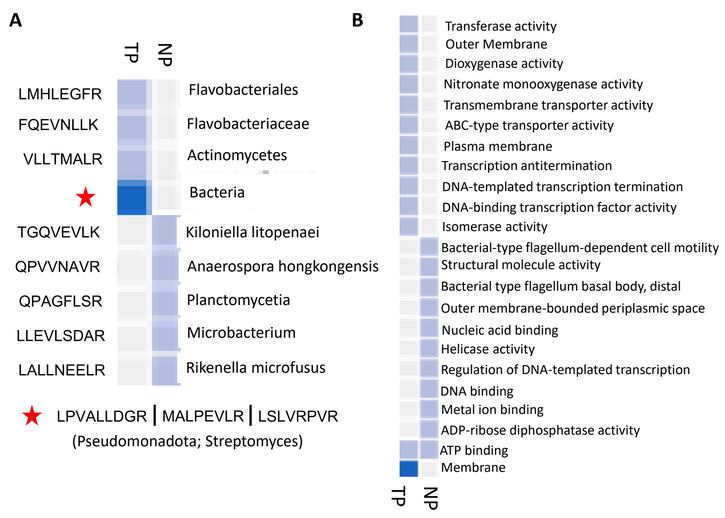


Figure 3. Proteomics analysis for Adenocarcinoma and non-tumor adjacent tissue of fresh frozen samples. A Table of protein counts in each analysis. B Volcano plot of fold change and pvalue (FC > 1.5, padjusted < 0.05) for all proteins. C Heatmap of intensity values of immune-related proteins. D Boxplot of intensity values from up and downregulated host proteins (Wilcoxon rank sum test, pval < 0.05). E Gene ontology molecular functions enrichment analysis of immune-related set of proteins up and downregulated in Adenocarcinoma.

Microbial derived-molecules (peptides and metabolites) promote an immune-suppression profile



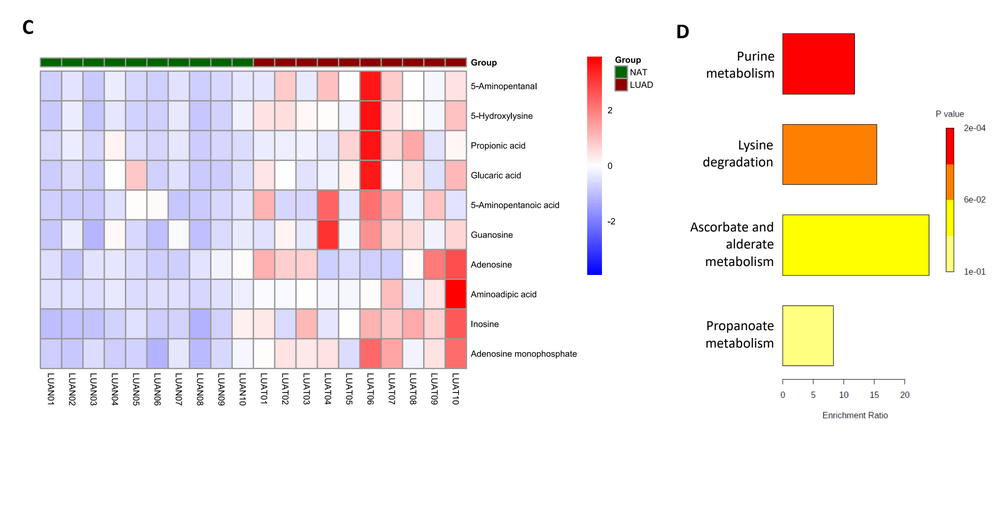


Figure 4. Metaproteomics and metabolomics analysis for Adenocarcinoma and non- tumor adjacent tissue of fresh frozen samples. A Heatmap of microbial-related peptides and the last common ancestor identified. B Heatmap of peptide set enrichment for Gene ontology analysis. C Heatmap of microbial-associated metabolites intensities. D Metabolite Sets Enrichment Overview in Adenocarcinoma.

Conclusions

- The differences in microbial composition between adenocarcinoma and non-tumor adjacent tissue are evident through the increased presence of *Pseudomonas* within the tumor, potentially giving rise to a pro-inflammatory profile. Furthermore, the absence of *Akkermansia* in tumors may contribute to an undifferentiated state, worsening the disease.
- A reduction in T CD8 cells and HLA class I-related proteins in adenocarcinoma samples suggests that the downregulation pathways within the tumor related to MHC complex binding that would contribute to tumor evasion and ultimately contributing to tumor progression.
- Microbial peptides associated with *Pseudomonadota* and *Streptomyces* in tumor samples, consistent with our initial findings, and their involvement in transmembrane transport activity, along with an increase in purine microbial metabolites (adenosine and inosine), could foster an immunosuppressive microenvironment that contribute to the tumor progression.

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