4393P Smoking-associated gene expression changes in paired tumor and normal lung specimens from resected NSCLC: a TITANIA subset analysis

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CONFLICTS OF INTEREST: H. Juhl is founder of Indivumed GmbH; N. Gabelia is an Indivumed employee.

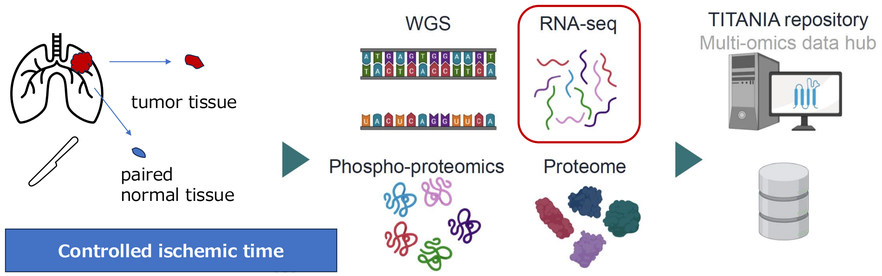
Background

- Smoking affects both tumor and surrounding normal lung tissue[1, 2].
- Tumor-only comparisons may mix background lung effects with tumor-associated changes[3].

Objective: To characterize smoking-associated transcriptomic changes in normal lung, tumor tissue, and paired tumor–normal transition.

Materials and Methods

TITANIA (multi-omics data cancer diagnostics therapies) framework



Cohort: TITANIA prospective multi-omics study (National Cancer Center Hospital East, IRB 2020-079)
Differential expression: DESeq2-normalized expression compared between smokers and never-smokers
Directional DEG definition: P<0.001 and |fold change|>1.5
Functional enrichment: GO Biological Process over-representation analysis (clusterProfiler) on directional DEG sets; Benjamini-Hochberg adjusted P reported

- **Paired Tissue Design:** Tumor and normal lung tissues were analyzed from the same patient.
- **Within-Patient Δ Analysis:** Tumor–normal expression differences were calculated for each patient.
- **Three-Track Analysis:** Smoking-associated expression was evaluated in tumor, normal, and paired-delta analyses.

Key Takeaways

- **Smoking-Signal Direction Reversal:** Smoking-associated expression patterns differed in direction between normal lung and paired delta.
- **Tumor-Only Misses Field Effects:** Smoking-related signals in normal lung were not fully represented by tumor-only analysis.
- **Paired Analysis Reveals Transition:** Within-patient analysis captured changes from normal lung to tumor that were not evident from tumor-only comparison.
- **Future Directions:** Validate key smoking-associated pathways using interaction models, WGS, ssGSEA, and proteomic data.

Results

Characteristics	Tumor	Paired non-tumor
Patients	23	16
Age, years, median [IQR]	72.0 [70.0, 78.0]	73.5 [71.0, 78.5]
Male	14 (60.9)	9 (56.2)
Female	9 (39.1)	7 (43.8)
Smoker	18 (78.3)	11 (68.8)
Ad	12 (52.2)	8 (50.0)
Sq	10 (43.5)	8 (50.0%)

Smoking classification: smoker (any smoking history) vs never-smoker

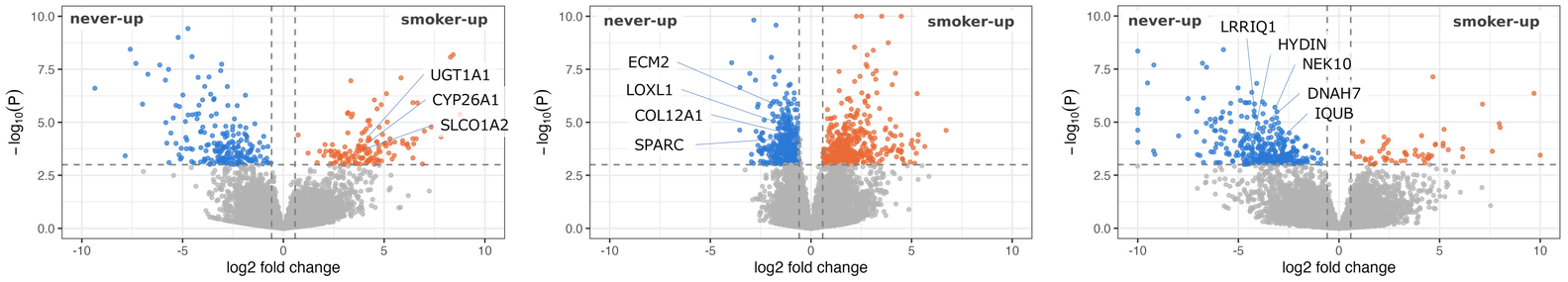
Summary of Results

Tumor
215 never-smoker-up
170 smoker-up
smoker-up genes enriched for
- xenobiotic metabolic process

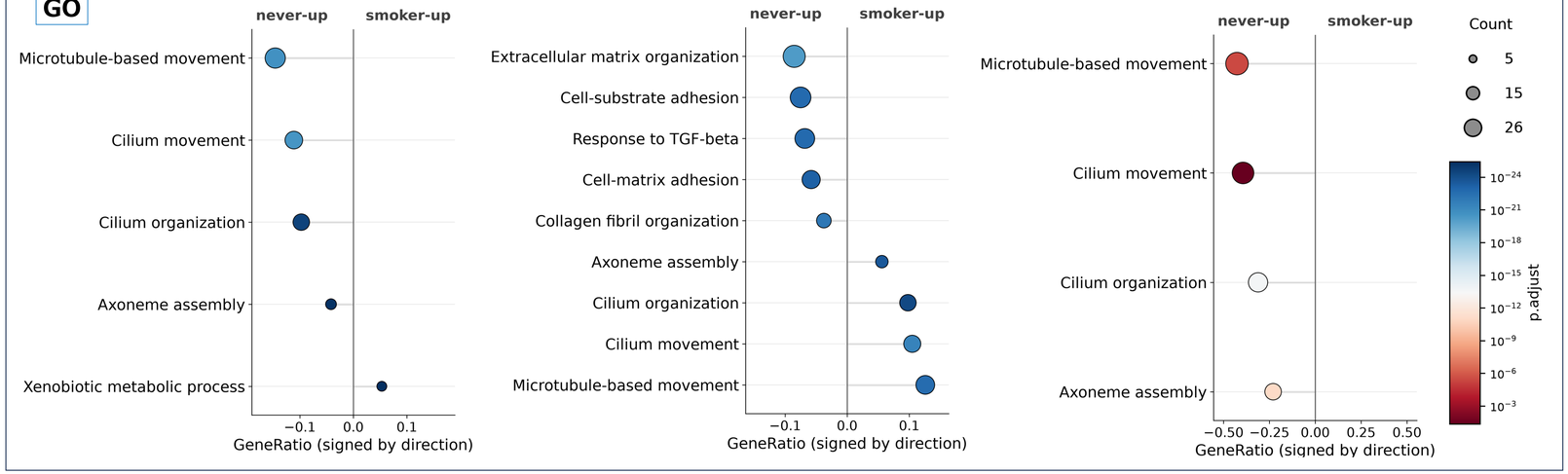
Normal
335 never-smoker-up
257 smoker-up
never-smoker-up genes enriched for
- extracellular matrix organization
- collagen fibril organization
- response to TGF-β

Paired delta
132 never-smoker-up
26 smoker-up
never-smoker-up genes enriched for
- cilium movement
- microtubule-based movement
- cilium organization
- axoneme assembly

DEG



GO



1. Landi MT, Dracheva T, Rotunno M, et al. Gene expression signature of cigarette smoking and its role in lung adenocarcinoma development and survival. PLoS One. 2008
2. Pintarelli G, Cotroneo CE, Noci S, et al. Cigarette smoke alters the transcriptome of non-involved lung tissue in lung adenocarcinoma patients. Sci Rep. 2019
3. Spira A, Beane JE, Shah V, et al. Airway epithelial gene expression in the diagnostic evaluation of smokers with suspect lung cancer. Nat Med. 2007