



P3.323: Construction of Molecular Regulatory Network of Pulmonary Carcinoid Tumors Based on Multi-omics Analysis and Screening of Therapeutic Targets.

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INTRODUCTION

- Pulmonary neuroendocrine tumors (PNETs) are a heterogeneous group of epithelial neoplasms arising from neuroendocrine cells in the bronchopulmonary tract.
- Trefoil factor 3 is a pivotal secreted small polypeptide belonging to the trefoil factor family, mapped to chromosomal region 21q22.3.
- Based on our previous whole-transcriptome sequencing data of pulmonary neuroendocrine tumor cell lines, we found that TFF3 and other genes were significantly highly expressed in pulmonary carcinoid. Combined with single-cell sequencing data of neuroendocrine tumors from public databases, these findings suggested that TFF3 may function in highly malignant tumor cell subpopulations. Accordingly, we focused on TFF3 and performed comprehensive bioinformatic analyses, including pan-cancer and expression profiling. Our results verified TFF3 upregulation in pulmonary carcinoid and demonstrated that elevated TFF3 expression is associated with poor survival in patients with this tumor.

METHODS

Design:

- Transcriptome sequencing of cell lines: Three pulmonary carcinoid and two normal bronchial epithelial cell lines were cultured for whole-transcriptome sequencing. Bioinformatic analyses were performed to characterize the transcriptomic features of pulmonary carcinoid cells.
- Construction of ceRNA regulatory network: miRNA-centered co-expression analysis was applied to screen target mRNAs and circRNAs. Cytoscape was used to construct and visualize lncRNA-mRNA regulatory networks.
- Single-cell sequencing and tumor subpopulation analysis: Single-cell data from three pulmonary carcinoid specimens were analyzed. CNV profiling was used to identify tumor subpopulations, followed by differential expression and functional enrichment analyses for each subgroup.
- Functional validation of candidate genes: Carcinoid-specific differentially expressed genes were selected for validation. CCK-8, colony formation, migration and EDU assays were used to assess cell malignant phenotypes, while flow cytometry detected cell apoptosis and cell cycle alterations.

DISCUSSION AND CONCLUSION

- Transcriptomic profiling revealed distinct gene expression patterns: In pulmonary carcinoids, 2491 upregulated mRNAs were enriched in cyclic nucleotide signaling and neuropeptide ligand-receptor interactions, whereas 2629 downregulated mRNAs were mainly involved in MAPK and PI3K pathways.
- Key ceRNA axes mediate core signaling pathways: let-7 family miRNAs served as core hubs of the lncRNA-miRNA-mRNA axis regulating MAPK and cAMP signaling. miR-1224-5p/3p dominated the circRNA-miRNA-mRNA axis and modulated RAP1 and cAMP pathways.
- Single-cell analysis identified tumor heterogeneity: Four CNV-based tumor subpopulations were defined. Subgroup 1 was prominently associated with DNA replication and vesicle secretion, indicating intrinsic tumor heterogeneity.
- TFF3 and MUC13 regulate malignant behaviors: Integrated multi-omics analysis screened TFF3 and MUC13 as candidate genes. Functional experiments confirmed that both genes induce cell cycle arrest and suppress pulmonary carcinoid proliferation and migration.

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RESULTS

Integrated transcriptomic analyses identify TFF3 as a key regulator in pulmonary carcinoid (PC). Multi-omics integration of bulk and single-cell RNA-sequencing uncovered TFF3 and MUC13 as candidate genes, supported by differential-expression screening, single-cell profiling and GO functional enrichment. In-vitro assays confirmed that TFF3 silencing induces cell-cycle arrest and suppresses proliferation and migration of pulmonary carcinoid cells.

