Multi-omic Profiling Identifies p63 as a Novel Genetic Determinant Driving Lung Fibrosis and Cancer, Targetable for Treatment

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Lung cancer is the leading cause of cancer-related mortality worldwide. Scleroderma-related interstitial lung disease (SSc-ILD) and lung carcinoma are forms of fibrotic-originating lung diseases responsible for 85% of lung malignancies. Their rapid metastasis limits treatment options and highlights the need for developing effective therapeutic modalities to treat lung fibrosis and revert its progression to cancer. Tumor protein 63 (TP63) belongs to the p53 family of transcription factors regulating stem cell commitment in squamous epithelia. Prior studies have shown that p63 is involved in tumorigenesis and metastasis; however, its direct role in lung fibrosis and carcinomas remains unknown. Our study utilized bioinformatics and cell perturbation to identify p63's role in lung fibrosis and cancer proliferation. Using a single-cell RNA sequencing dataset in >50 patients with Idiopathic pulmonary fibrosis (IPF), we identified p63 as a critical protein enriched in disease relative to normal. Furthermore, quantitative gene expression analyses revealed high enrichment of p63 in rapidly proliferating fibroblasts. Moreover, we showed that CRISPR-mediated p63 knockdown substantially reduces lung cancer cell and primary lung fibroblast viability by 37% and 23%, respectively, relative to untransformed cells (control). Alternatively, overexpression of p63 increased proliferation of cancer cells by 14% and SSc fibroblasts by 51%. Using multi-omics profiling and molecular biology assays, we analytically confirmed p63 as an integral regulator of cell growth, survival, and metastasis driving lung fibrosis and cancer. Our study suggests that therapeutically targeting p63 could be a novel mode of treatment for lung fibrosis and subsequent carcinomas with significant clinical impact.