Idiopathic pulmonary fibrosis (IPF) and lung cancer

Ivana Persico*, Maria Cristina Sini*, Stefania Casula*, Antonella Manca, Giambattista Maestrale, Giuseppina Casu, Maria Grazia Doro, Laura Frogheri, Giuseppe Palmieri

Collaborating Institutions: Università degli Studi di Sassari; Sassari; Azienda Ospedaliero Universitaria (AOU), Sassari; Azienda Ospedaliero Brotzu, Cagliari; Italy - Lung Cancer MDT, AOU Sassari.

*These authors contributed equally

Idiopathic Pulmonary Fibrosis (IPF) is a specific, chronic and progressive form of interstitial pneumonia with severe prognosis and poor survival rates (2/3 years from diagnosis). IPF incidence is estimated in 2/30 cases per 100,000 persons/years, mainly affecting over 65 years old individuals. Although pathophysiological mechanisms are not fully understood, environmental and occupational factors, smoking, viral infections, and traction injury of the lung are recognized as causative elements leading to chronic damage to the alveolar epithelium.

IPF is considered an epithelium-driven disease where recurring micro-injuries in lung epithelia promote an imbalance between profibrotic (TGF-β, PDGF, bFGF, IL-1, TNF-α) and anti-fibrotic (KGF, HGF, EPC) mediators. In this scenario, chronic fibrosis replaces normal repair mechanisms: excessive fibroblasts proliferation and aberrant extracellular matrix remodeling determine an irreversible distortion of lungs architecture and subsequent evolution in honeycombing areas. IPF shares several molecular, pathophysiological and clinical aspects with lung cancer, including high mortality rates; in particular, both diseases share genetic and epigenetic factors, enhanced proliferation and abnormal activation of specific signaling transduction pathways. The prevalence of lung cancer, particularly adenocarcinoma, in patients with IPF in clinical studies ranges from 31% in older reports to 10-17% in more recent reports. Nevertheless, these figures were consistently lower in epidemiological studies, ranging from 4% to 7%. IPF patients affected by lung cancer are commonly male, smokers or ex-smokers, at their 6th or 7th decade of life; lung cancer arises generally 2-3 years after the diagnosis of IPF, and affects mostly the peripheral aspect of the lower lobes of the lungs where fibrosis is more frequent and consistent.

Considering the above-mentioned similarities, we started a comparative study of the mutational landscape in IPF and lung cancer tissue biopsies. We have already collected formalin-fixed, paraffin embedded (FFPE) IPF tissues samples (28 cases over 49 recorded in our database), 15% of which has progressed to lung cancer (IPF/K). In addition, we aim to carry out further comparisons using as a reference sample a previously analyzed cohort of IPF-unrelated lung adenocarcinomas. Our study is structured in 3 steps: a) clinical and pathological data collection: comorbidity, lifestyle (e.g. smokers/non-smokers), respiratory parameters (PFT, FEV, FVC, TLC, DLCO, BPCO, chronic respiratory failure degree and pulmonary hypertension); b) histopathologic classification and centralized FFPE sections processing; c) DNA and RNA extraction from FFPE followed by NGS mutational analysis using a multi-genic panel (52 main oncogenes and tumor suppressor genes involved in tumorigenesis).

Our preliminary results on 28 DNA/RNA from FFPE IPF tissue biopsies, we found 16 missense variants spreading on 11 genes. Among them, 3 are filtered out as pathogenic by prediction algorithms in FGFR3, MTOR and PIK3CA genes respectively, that play a pivotal role in cellular growth and proliferation mechanisms.

Once completed the mutational analyses in all collected samples (IPF and IPF/K), we plan to evaluate correlation between different molecular profiles and clinical-pathological parameters in order to define potential patients subgroups. Furthermore, all results will be compared with the reference sample of lung adenocarcinoma previously processed using the the same panel.

Defining consistent patients sub-groups is indeed crucial for better understanding the molecular mechanisms underlying the IPF pathogenesis and its progression to lung cancer.

Keywords: Idiopathic Pulmonary Fibrosis, Lung Cancer, NGS