Editorial

Lung cancer and chronic obstructive pulmonary disease: understanding the complexity of carcinogenesis

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Lung cancer (LC) carries a high mortality and has a 5-year survival of around 15% (1). Chronic obstructive pulmonary disease (COPD) has a 10% prevalence, also involving high mortality rates (2). Both entities have a series of common characteristics (3). The first, their high mortality, with important associated comorbidity. In addition, both diseases share underlying etiologies such as tobacco, gene expressions, environmental factors and inflammation. COPD has proven to be a common comorbidity in patients with LC, with a very variable prevalence among studies, ranging between 28% and 40%, due mainly to methodological differences in the definition of COPD, the null differentiation in some cases with the existence of emphysema, and the high underdiagnosis of this disease, both in patients with LC and in the general population (4). Also, emphysema is present in more than 45% of LC cases (4).

Evidence of an association between COPD and the development of LC has been observed in several studies, describing an increase in the incidence and mortality of LC in patients with airflow obstruction (5). Several subsequent studies have confirmed this fact, with an increase of between 2 and 4 times in the risk of developing LC (6). This higher mortality may be also related to the fact than when airflow is below (FEV_1 <30%) it is not recommended any surgical procedure for LC patients.

Most studies show that adenocarcinoma is the leading histological kind of LC (7). However, squamous LC and small-cell LC (SCLC) still are more prevalent in patients with underlying COPD and emphysema, probably because of smoking (8). Tobacco affects SCLC risk in COPD patients, compared with controls. Also, COPD status has been independently associated with the odds of developing SCLC after adjusting for age, gender, and tobacco (8). Patients with emphysema have a higher risk of squamous carcinoma, even after adjusting for age, sex, COPD, and smoking history (8-10).

Any tobacco history is frequent among patients with COPD, emphysema or LC. Young *et al.* (6) found that COPD prevalence was of 50% amongst LC patients, so they suggested that if 20% of smokers could develop COPD and 10% of smokers could develop LC, then, with that prevalence of 50%, one out of four COPD-smoking patients might develop LC. This agrees with the fact that 85% of LC occur in smokers, and 95% of LC occurs in COPD-smoking patients (6).

Airway chronic inflammation is one of the pathophysiological mechanisms that plays a key role in the amplification of the initial mutagenic response of LC. It is possible that persistent airway inflammation in COPD patients induces alterations in the bronchial epithelium that favor carcinogenesis (11). Also, an excess in the production of oxygenated and nitrogenous radicals could induce structural and functional modifications in lipids, proteins and DNA, thus negatively affecting the signaling cascades and metabolic pathways dependent on them. Several studies have found high levels of oxidants and decreased

antioxidants in tissues (12). In addition, epigenetic alterations play a role in LC development. To date, many genes are suspected to play a role in the appearance of LC, such as *CYP1A1*, *CYP2D6*, *CYP2A6*, *CYP2C9*, *CYP3A4* and *CYP2E1*, *GSTM1*, *GSTT1* and *GSTP* (13). Deletion of genes such as *GSTM1* and *GSTT1* also increase the risk of LC (13).

Until now, it is unclear how metabolic pathways having a role in tobacco carcinogenesis might differently affect COPD onset and LC onset in the former patients. To have a clearer picture on the LC onset in COPD patients it would be relevant to differentiate the importance of carcinogenic-related pathways from those related with chronic inflammation. To do this, it would be very interesting to have powerful studies based in COPD which are never smokers and how LC is developed in this subpopulation. Due to the low incidence of COPD in never smokers, these studies are not currently available but would provide important insights on how LC arises from COPD.

There is an increasing interest in performing multi-omic approaches to LC development. Studies to date suggest that non-small cell LC (NSCLC) consists of epithelial cells which have been genetically altered, showing transcription alterations, which might be the trigger to cancer initiation (14). Other studies state that protein profiles identified in the bronchoalveolar lavage of patients with COPD, COPD + LC, LC and controls, might help to understand the relationship between LC and COPD, providing potential new biomarkers for LC early diagnosis (15). It is known that lung tumors in COPD patients have different methylated and expressed genes than patients without COPD (16). Some works have even developed a genome-wide transcriptome map of NSCLC based on gene expressions in lung tumors and epithelia cells of the lung (17).

A tumor is defined not only of carcinogen cellularity, but is also made of stromal cells around (14). This stromal environment is composed of microorganisms, white cells, fibroblasts, pericytes, endothelial cells, stromal nerves and adipocytes, as well as the extracellular matrix (18). The belief that tumors relate to their microenvironment is becoming increasingly important, as extracellular matrix (ECM) and stroma may promote tumor progression (18). In fact, senescent human fibroblasts have shown to stimulate both malignant and premalignant epithelial cells to proliferate, thus playing an active role in tumor cell recruitment, growth and spread (14). Also, abnormal ECM is a common feature in COPD, since elevated elastolytic proteases disrupt the ECM in this disease (14).

Sandri *et al.* have recently published the study "*Multi-omic molecular profiling of lung cancer in COPD*" (14). They conducted a multi-omic analysis to identify gene expression patterns that distinguish COPD stroma in patients with or without LC, including samples of tumor and adjacent tissues from 32 cases with adenocarcinoma and COPD and lung samples from 32 individuals with COPD without LC, and they analyzed transcriptome, translatome and proteomic data in them. They included quantitative mass spectrometry proteomics along with RNASeq in total cytoplasmic mRNA (transcriptomics) and polysomal-associated mRNA (translatomics).

They found that predictive variables associated with the tumor, compared to adjacent stroma were mainly represented in the transcriptomic data, whereas, predictive variables associated with adjacent tissue compared to controls were represented at the translatomic level. Also, they found that the ECM and PI3K-Akt signaling pathway was potentially pre-malignant, as its over-representation was habitual in the tumor and adjacent tissue but not in controls.

This study has two main limitations. First, they have assessed tissue samples from lung adenocarcinoma, but other histological types that are traditionally associated with COPD, such as squamous or SCLC have not been included in the study. In addition, controls had graver COPD than cases. However, the authors state that the same pathways (ECM and PI3K/Akt) were represented in the distinction of tumor tissue from matched adjacent tissue, suggesting that these are related to carcinogenesis and not COPD severity.

The PI3K/Akt/mTOR pathway stimulation leads to the assembly of the eukaryotic translation initiation factor 4 (eIF4) complex (14). The eIF4 forms a complex that enables translation (19). The finding of increased expression of eIF4 indicates a likely mechanism responsible for the immune response, being the gene for eIF4 amplified in about 40% of squamous cell lung carcinomas (19). Some studies hypothesize that gene amplification of eIF-4 causes elevated protein expression that elicits an immune response to eIF4 in the patient (19). Therefore, eIF4 can serve both as a genetic marker in the form of gene amplification and as an immunologic marker in the form of an antibody response (19). However, information about the role of AKT in COPD is scarce. It seems that PTEN is a negative regulator of AKT, and that there is a loss of PTEN in stromal fibroblasts, due to a single nucleotide polymorphism (SNP) of PTEN. This might be the link between COPD and LC development (14).

The study by Sandri *et al.* provides new information about the characterization of patients with COPD and LC, underlying the importance of transcriptomic, translatomic and proteomic data, and stablishing ECM and PI3K-Akt as potential premalignant pathways.

There is increasing evidence about the existence of several genetic alterations which lead to the development of LC, in general population but also in COPD patients. In fact, LC is no longer defined solely by its histological type and its stage. Molecular characterization of NSCLC is becoming increasingly important with the advent of molecular testing (as tumors harboring somatic mutations in genes such as epidermal growth factor receptor-EGFR, anaplastic lymphoma kinase-ALK, or ROS1 have shown better responses to new targeted therapies) and immunotherapy (20). In addition, progress is being made through the spreading use of liquid biopsies and massive genetic sequencing. With the arrival of new treatments targeting tumor-stroma interactions, multi-omic approaches of lung carcinogenesis in COPD patients are necessary to deepen in tumor progression and response to therapy. Therefore, genome-wide approaches are necessary to understand the complexity of carcinogenesis, specifically on COPD population, as they are those subjects with a greater probability of benefiting from computed tomography screening of LC. Nevertheless, we must continue deepening in the relationship between COPD and LC, on a combined approach, based on clinical, functional, analytical, radiological, and multi-omic features.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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