Molecular links between COPD and lung cancer: new targets for drug discovery?

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ABSTRACT

Introduction: COPD and lung cancer are leading causes of morbidity and mortality worldwide, and they share a common environmental risk factor in cigarette smoke exposure and a genetic predisposition represented by their incidence in only a fraction of smokers. This reflects the ability of cigarette smoke to induce an inflammatory response in the airways of susceptible smokers. Moreover, COPD could be a driving factor in lung cancer, by increasing oxidative stress and the resulting DNA damage and repression of the DNA repair mechanisms, chronic exposure to pro-inflammatory cytokines, repression of innate immunity and increased cellular proliferation.

Areas covered: We have focused our review on the potential pathogenic molecular links between tobacco smoking-related COPD and lung cancer and the potential molecular targets for new drug development by understanding the common signaling pathways involved in COPD and lung cancer.

Expert commentary: Research in this field is mostly limited to animal models or small clinical trials. Large clinical trials are needed but mostly combined models of COPD and lung cancer are necessary to investigate the processes caused by chronic inflammation, including genetic and epigenetic alteration, and the expression of inflammatory mediators that link COPD and lung cancer, to identify new molecular therapeutic targets.

Article highlights

- COPD and lung cancer share common risk factors represented by smoke exposure and genetic predisposition but only a proportion of lifelong smokers will develop COPD and lung cancer.
- Smoking behavior in susceptible patients causes genetic and epigenetic alterations, mitochondria dysfunction and oxidative stress, and alteration of immune response.
- COPD is likely a driver of lung cancer, by increasing oxidative stress and resulting DNA damage, chronic exposure to proinflammatory cytokines, repression of the DNA repair mechanisms and increased cellular proliferation.
- Persistent chronic airway inflammations with several pathways of activation are processes that link COPD and lung cancer.
- Defective innate immune responses in COPD provide an environment conducive to the onset of carcinogenesis.
- Combining risk models of lung cancer and COPD with molecular phenotyping of young and 'healthy smokers' are essential to identify molecular targets for new therapies.
- Combined experimental models of COPD and lung cancer may provide a better model of human lung cancer.

1. Introduction

Chronic obstructive pulmonary disease (COPD) and lung cancer are leading causes of morbidity and mortality worldwide. COPD is the third commonest cause of death and lung cancer the seventh most common cause of cancer worldwide [1]. Cigarette smoke exposure is a shared environmental risk factor whilst the incidence of these diseases in only 15–20% of smokers indicates a genetic predisposition [2]. The prevalence of lung cancer in COPD patients is greater than the prevalence of lung cancer in general population [3] and COPD is a major independent risk factor for lung carcinoma in smokers and increases the risk of lung cancer up to 4.5-fold [2]. This risk is even greater in patients with α1-antitrypsin deficiency [4]. Recently a nested case–control study of Genetic Epidemiology of COPD (COPDGene) demonstrated that the degree of COPD severity, including airflow obstruction, emphysema, and respiratory exacerbations, is independently predictive of lung cancer [5]. Pulmonary emphysema, particularly in patients with severe COPD [5], is associated with an increased risk of lung cancer, even in lifelong nonsmokers [6]. Quantitative chest computed tomography (CT), therefore, could identify COPD patients at greater risk of lung cancer [7]. Improving selection criteria for lung cancer screening requires determination of the presence and quantification of emphysema in order not to miss a significant number of lung cancer cases [8]. The mechanisms that link emphysema and lung cancer are currently debated and may include mutations in telomerase and sheltering genes [9]. The presence of static hyperinflation, defined by functional residual capacity (FRC) values, is another independent risk factor for lung cancer in COPD patients [10].

Lung cancer is also a leading cause of morbidity and mortality in patients with COPD [11] and 50–70% of lung cancer patients have spirometric evidence of COPD [12]. Smoking-associated COPD is linked to the development of a specific subtype of NSCLC termed squamous cell carcinoma (SCC) [13] and with small cell lung cancer (SCLC) [14]. Since >90% of COPD and lung cancer cases are smoking related and only a proportion of lifelong smokers will develop COPD and/or NSCLC, here we initially discuss the role of cigarette smoke as causative factor but focus on the potential pathogenic molecular links between these diseases and the potential molecular targets for new drug development. Potential shared pathogenic mechanisms between COPD and lung cancer are shown in Figure 1.

2. Defining pathogenetic features of COPD and lung cancer

2.1. Human studies and models of COPD and lung cancer

Clearly, the assessment of human tissues comparing samples from lung cancer and COPD patients with age- and sex-matched controls provides critical information on disease features. Diseased tissues include lungs resected during lung transplantation and control lungs not suitable for transplant [15]. Sputum, bronchoalveolar lavage (BAL) and bronchoscopy samples can be collected. Specific cell types such as macrophages, neutrophils, fibroblasts, and bronchoepithelial cells can be specifically isolated and assessed [16,17]. Bronchoepithelial cells can also be cultured at the air-liquid interface and grown into differentiated airway epithelium maintaining their disease phenotype [18,19]. Blood samples can also be assessed, but the data do not always correlate with observations in the lung [20,21].

2.2. Animal models of COPD with lung cancer

Since COPD is a major risk factor for NSCLC, superimposing carcinogens on an experimental model of COPD may provide a better model of human lung cancer [20–30]. Few studies have modeled the induction of lung cancer on the background of COPD. One cigaratte smoke-induced model showed emphysema-like alveolar enlargement and the development of tumors A/J mice administered the tobacco carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) followed by cigarette smoke exposure showed emphysema-like alveolar enlargement and the development of tumors [31]. Mice exposed to cigarette smoke for 5 months with 1 month air periods in-between had the highest tumor multiplicity and incidence and alveolar size. In addition, mice expressing a mutant Kras allele exposed to aerosolized nontypeable Haemophilus influenzae (NTHi) lysate weekly for eight weeks developed lung tumors, whereas the lysate alone resulted in COPD-like airway inflammation [32].

However, lung function was not measured in either of these models and both resulted in adenomas/adenocarcinomas rather than SCC. The development of animal models to investigate the relationships between the two diseases was determined to be a high priority because these models are currently lacking [2].

3. Commonalities in genetics and epigenetics of COPD and lung cancer

3.1. Genetics, smoking behavior, and NSCLC and COPD susceptibility

Two single-nucleotide polymorphisms (SNPs) in chromosome 15 (15q25.1) are associated with lung cancer risk. This region contains a cluster of six genes: nicotinic acetylcholine receptor alpha subunits 3 (CHRNA3) and 5 (CHRNA5), the β4 nicotinic acetylcholine receptor (nAChR) subunit (CHRNB4), proteasome alpha 4 subunit isoform 1 (PMSA4), the IREB2 iron-sensing response element, and LOC123688, a gene of unknown function [33].

Fourteen percent of lung cancer risk is associated with this region with the strongest association with rs16969968 in exon 5 of CHRNA5 that induces an amino acid substitution (D398N). The functional effect of this substitution is unknown [33]. A synonymous variant in exon 5 (rs1051730) of CHRNA3 is also strongly associated with lung cancer. There is a fivefold greater risk of lung cancer in subjects who have both a family history of lung cancer and two copies of the high-risk alleles rs8034191 (odds ratio [OR] = 7.20) or rs1051730 (OR = 5.67), which are located in the 15q24-25.1 locus [34].

Other smoking-associated SNP variations have also been identified in both COPD and lung cancer including rs200616965 (CHRNA5), rs56317523 (CHRNB4), rs6495309 (CHRNA3), or rs1051730 (CHRNA5-CHRNA3) [35]. Of these, rs6495309 (CHRNA3) genotypes conferred poor survival in lung cancer patients [36]. The three risk SNPs reported in Caucasians are not associated with lung cancer risk in Chinese patients [37] but rs1051730 and rs16969968 polymorphisms are associated with cigarette smoking, COPD and lung cancer in Mexicans [38].

It is unknown whether these polymorphisms increase lung cancer risk independently of their effects on smoking behaviour [39]. Importantly, rs16969968 is the most significant SNP associated with nicotine dependence although it is strongly linked with an increased risk of lung cancer independent of pack-years smoked [40].

Acetylcholine (Ach) is released by both normal human bronchial epithelial cells and by SCC cell lines [41]. Ach promotes the proliferation of neoplastic cells by acting on nAChRs [42] and of lung fibroblasts and myofibroblasts via muscarinic ACh receptors (mAChRs) [43]. Multiple subtypes of nAChRs and mAChRs exist, but most SCLC and NSCLC cells express α7 nAChR and heteromeric α3, α4, and α5 containing nAChR [44] SCLC cells express all five mAChR subtypes, whilst SCC cells express only the M2R, M3R, and M4R subtypes [42].

Overall, cancer cells express different levels of Ach receptors as well as increased ACh and reduced cholinesterase activity [45]. Smoking modulates nAChR expression in lung cancers [46] and nicotine enhances Ach release from squamous cells, increasing tumor cell proliferation and invasion via activation of nAChR [47]. The effect of nicotine is mediated by the mitogen activated protein kinase (MAPK) (p44/42) and Akt pathways and by an NF-κB-dependent anti-apoptotic process [48].

NSCLC cells overexpress the transcription factor hypoxia inducible factor (HIF)-1α which correlates with advanced tumor grade, increased angiogenesis, and resistance to chemotherapy and radiotherapy. Nicotine enhances the expression of HIF-1α and of vascular endothelial growth factor (VEGF) in SCC and adenocarcinoma cell lines. VEGF is a key angiogenic and vascular remodeling factor in both COPD and lung cancer [49].

Data are lacking on the possible actions of smoking or nicotine on ACh release from the non-neuronal cholinergic system in the airway. Theoretically, increased Ach release produced by either autocrine or paracrine loops could cause small airway fibrosis, a characteristic of COPD [50], and enhance cholinergic signaling on the bronchial/bronchiolar epithelium thus contributing to COPD and carcinogenesis in chronic cigarette smokers.

Sequencing of RNA, or RNA-Seq, is a recently developed and now common method to analyze transcriptomic expression [51]. Using this approach many genes and pathways associated with COPD

and lung cancer have been identified in the respective tissues [52–54]. These results provide new information for further investigation of the COPD and lung cancer microenvironment and may help develop new diagnostic or therapeutic strategies targeting both COPD and associated lung cancer.

Multi-omics analysis of non-malignant lung tissue in COPD identified cancer-associated differentially expressed proteins often in the absence of corresponding changes in mRNA levels. The molecular mechanisms driving these changes varied according to lung function with the mammalian target of rapamycin (mTOR) pathway being prevalent in subjects with normal to mildly impaired lung-function and pathways downstream of extracellular matrix (ECM) formation with severe airflow obstruction [55]. ECM and mTOR gene expression programs were up-regulated in line with pro-cancer markers such as senescence (IL-6) and bone morphogenetic protein-1 (BMP1) in patients with mild and severe airflow obstruction, respectively.

A transcriptomic and outcome analysis of 3,553 NSCLC samples was used to identify 14 mitochondrial-related genes whose lung tumor expression correlated with patient mortality. One of these, PGAM5 which regulates mitophagy, was only expressed in alveolar macrophages, with the highest expression in smokers with COPD. In cancerous tissue, PGAM5 was detected in malignant and pre-malignant epithelial cells as well as in associated macrophages at the periphery of the cancer. Macrophages at the edge of cancers from COPD patients showed a trend toward a higher expression of PGAM5, and PGAM5 expression in cancer tissue was associated with specific macrophage subsets and linked to patient mortality [56].

Table 1 summarizes the genes potentially involved in lung carcinogenesis and COPD pathogenesis.

3.2. Genetics of cell cycle regulation, apoptosis and NSCLC, and COPD susceptibility

Inherited polymorphisms may regulate the differential susceptibility to COPD and squamous cell lung carcinoma but direct mutagenesis induced by cigarette smoke (acquired somatic mutations) may also be important [57]. Acquired somatic mutations in tumor suppressor genes including tumor protein p53 (TP53) may alter cell cycle regulation and programmed cell death resulting in malignant transformation [58]. DNA damage triggers a ‘danger response’ regulated by ataxia telengectasia mutated (ATM) and TP53 proteins. This rapid response, induced by oxidative stress, for example, reduces the resulting cellular damage as cells wait for DNA repair. However, cell damage can become permanent in cells with shortened telomeres resulting in cellular senescence, i.e., a cell that is metabolically active, resistant to apoptosis but unable to proliferate beyond the G1 stage of the cell cycle [58]. Recent evidence demonstrates reduced expression of another DNA damage-repair protein, xeroderma pigmentosum group C (XPC) in SCC [59].

The tumor-suppressor gene p21WAP/CIP1 is transcriptionally activated by TP53 during oxidative stress-inducing cell cycle arrest and DNA repair. Progression of the cell cycle through to S phase is controlled by cyclins and cyclin-dependent kinases (CDKs). p21WAP/CIP1 inhibits the cyclin E-CDK2 and cyclin D1-CDK4 complexes to enable G1 arrest and block entry into the S phase. p21WAP/CIP1 forms complexes in the cytoplasm with cyclins and Cdks but can also complex with proliferating cell nuclear antigen (PCNA) within the nucleus to inhibit DNA synthesis [58]. A moderate-risk allele for SCC is predicted to have a functional effect on p21WAP/CIP1 [60]. Taiwanese subjects with p21WAP/CIP1 R/R and R/S genotypes compared to the S/S genotype [odds ratios (OR) = 2.07] were at higher risk of developing COPD compared to healthy smokers [61]. The expression of p21WAP/CIP1 is increased cells in immune and structural cells of COPD patients [62] and oxidative stress enhanced cytoplasmic p21WAP/CIP1 expression prevents apoptosis [62]. Targeted disruption of the p21WAP/CIP1 gene in mice prevents cigarette-smoke-mediated lung inflammatory responses [63] and p21WAP/CIP1 deficient mice spontaneously develop lung cancer [64].

The retinoblastoma gene (RB1) encodes the protein p105 Rb, which regulates cell-cycle checkpoint control. The ability of CDK4 and cyclin D-CDK6 complexes to phosphorylate p105 Rb during the cell cycle is regulated by a family of inhibitors, including p16INK4a. There are no reports of p105 Rb expression in the COPD lung, but greater levels of proinflammatory senescent type 2 alveolar cells that co-express p16INK4a and phosphorylated NF-κB are found in COPD peripheral lungs compared to

control subjects [65]. Furthermore, the promoter of p16INK4a is frequently methylated in the bronchial epithelium of NSCLC patients and cancer-free controls and is unaffected by smoking cessation [66]. Defects in RB1 results in the rare childhood tumor retinoblastoma and carriers of RB1 germline mutations who survive have a greater risk of late-onset lung cancer [67]. More research is needed in this area.

3.3. Epigenetic alterations and NSCLC and COPD susceptibility

Epigenomics is the large-scale study of epigenetic modifications, i.e., heritable changes in gene expression without DNA sequence alterations [68]. These epigenetic changes include DNA methylation, non-coding and microRNA expression (ncRNA and miRNA) and post-translational modifications of histones which together with chromatin remodeling enzymes complexes control chromatin structure and the transcriptional output of the cell [69]. Lung cancer has been associated with changes in all of these mechanisms [70].

DNA methylation controls gene silencing and nuclear architecture [71] and is now recognized as a dynamic process. De novo addition of a methyl residue to the 5′ position of cytosine is controlled by DNA methyltransferase (DNMT)1, whilst DNMT3a and DNMT3b maintain methylation status. Conversely, cytosines are demethylated by 10–11-translocation (TET) enzymes [72]. DNA methylation varies between cell types and is associated with altered gene expression. Although CpG-rich regions (CpG islands) within the promoter region can regulate gene expression [71], the majority of the >16,000 differentially methylated regions (DMRs) in different cells/tissues are associated with alternative transcriptional start [73].

Combined DNA methylation profiling and mRNA expression analysis on a genome-wide scale has emphasized the importance of DNA methylation status on controlling the differential gene expression seen in NSCLC [72]. Suppression of DNA methylation increases the expression of numerous genes involved in cell differentiation, EMT, Wnt pathway activation and cell cycle regulation in many cancers [74]. The first genome-wide epigenetic study of COPD patients identified 349 CpG sites that were significantly associated with the disease [75]. Similarly, a genome-wide methylation screen in NSCLC patients identified >400 tumor-specific DMRs some of which regulated genes involved in cell proliferation, differentiations, and self-renewal [76].

DNA hypomethylation also occurs at repetitive sequences in SCC. However, single-copy sequences rarely become demethylated [77]. Despite this, hypomethylation of the aryl hydrocarbon receptor repressor (AHRR) gene on chromosome 5 occurs with tobacco smoking and indicates a high risk for COPD exacerbations and lung cancer [78].

The link between DNA methylation changes and expression of some tumour-suppressor genes has been utilized in cancer diagnosis [72]. Aberrant DNA methylation patterns in sputum and breath are early detection markers of [79]. p16INK4a inactivation is the most effective means of blocking the cyclin D–Rb pathway and methylation of its promoter can be detected in sputum up to 3 years before clinical diagnosis of SCC [80]. Hypermethylation of the p16INK4a promoter in histologically negative lymph nodes is also associated with an elevated risk for the recurrence of NSCLC following resection [81]. In addition, numerous immune genes are hypermethylated in COPD and these may be involved in the transformation from COPD to lung cancer [82].

Other forms of DNA methylation exist such as N6-mA DNA methylation which acts as a repressive mark to silence transcription of long interspersed nuclear element (LINE) transposons [83]. This mark is abnormal in glioblastoma but whether it varies in COPD and/or lung cancer is unknown.

4. Pathogenetic mechanisms of COPD and lung cancer association: epithelial–mesenchymal transition and inflammation

4.1. Epithelial–mesenchymal transition (EMT) and lung cancer in COPD

EMT is a repair process caused by chronic inflammation whereby epithelial cells transform into a mesenchymal phenotype that is associated with invasive and metastatic lung cancer thereby linking COPD and lung cancer [84]. The hallmarks of EMT are the loss of the epithelial adhesion molecule

CDH1 (E-cadherin) and β-catenin [85] and/or a gain of mesenchymal markers such as N-cadherin (CDH2), vimentin (VIM) and alpha-smooth muscle actin (αSMA) [86]. Genetic studies have identified many pathways involved in EMT including the transforming growth factor beta (TGF-β), fibroblast growth factor (FGF), epidermal growth factor (EGF), nuclear factor-κB (NF-κB), and the Wnt pathways [86]. TGF-β-induced EMT in airway epithelial cells is a potential pro-tumorigenic event in COPD-associated-lung cancer [87] and is characterized by increased deposition of type I collagen, through the production of connective tissue growth factor (CTGF) and phosphoinositide 3-kinase (PI3K) signaling. PI3K inhibitors significantly attenuate the effects of TGF-β on EMT [88].
Cigarette smoke-induced EMT is associated with Akt signaling, intracellular reactive oxygen species (ROS) and enhanced TGF-β1. The Akt inhibitor MK-2206 inhibited EMT in a mouse model of COPD and in bronchial epithelial cells [89]. Cytokines such as IL-17A and GDF15 are also implicated in EMT, are upregulated in COPD lung, and their expression correlates with EMT markers [90]. Regulation of EMT formation may, therefore, be a possible target for COPD-NSCLC development.

4.2. Lower airways inflammation in COPD and NSCLC

The airways, particularly the small airways, of COPD patients are chronically inflamed with recruitment and activation of macrophages, CD4+ and CD8+ T cells, dendritic cells, B cells and neutrophils [91]. The degree of inflammation correlates with COPD severity [50] and a causal relationship between inflammation and cancer is suggested [92], although the mechanism(s) underlying this association are not completely understood [93].
Inflammatory mediators released into the bronchial/bronchiolar epithelial stem cell niche can induce proneoplastic mutations, proliferation, resistance to apoptosis, angiogenesis, invasion, metastasis, and secretion of immunosuppressive factors. In addition, macrophages and T lymphocytes have a feed-forward interaction with neoplastic cells resulting in increased growth and resistance to immune destruction due to a loss of tumor immunogenicity and/or a reduced local antitumor immune response [94]. COPD-like airway inflammation promotes lung carcinogenesis (adenocarcinoma) in a mouse model with a G12D mutation activated Kras allele in airway secretory cells [32].
Tumor necrosis factor α (TNF-α), which is upregulated in COPD, promotes lung cancer by inducing an immunosuppressive response to myeloid-derived suppressor cells within the tumor microenvironment [95]. Lung samples from tumors and non-tumors in the parenchyma of lung cancer patients with or without COPD revealed significantly increased TNF-α levels in tumor lesions compared to non-tumor specimens in the lung cancer-COPD group [96]. Furthermore, bioinformatic analysis of DNA methylation patterns highlighted innate defense, dendritic cell, and lymphocyte trafficking pathways as being enriched in COPD associated lung cancer. This is consistent with the hypothesis that the COPD inflammatory microenvironment influences lung cancer by impacting the epigenome [82]. Indeed, a specific subtype of macrophage, the M2 macrophage, is the predominant macrophage phenotype in both COPD [91] and in lung cancer [97].
Lymphocytes, particularly cytotoxic CD8+ T cells, are an important link in both COPD and lung cancer. The cytotoxic T cell-dependent growth of implanted cancer cells is enhanced in smoking mice with emphysema. CD11c+ dendritic cells were unable to efficiently stimulate the cytotoxic responses of naive T lymphocytes towards the tumor carcinoma in vivo; however, T-cell activation was enhanced by PDL1 blockade. This suggests that emphysema patients may be optimal candidates for cancer immunotherapies [98].
Small airway remodeling in COPD is regulated, at least in part, by the actions of proteases and anti-proteases and these may impact upon carcinogenesis. Matrix metalloproteinases (MMP)s, particularly MMP-2, are constitutively expressed whilst MMP-9 is induced during tissue remodeling and is overexpressed in COPD where it is thought to contribute to the development of emphysema. MMP-2 and MMP-9 act on basal membranes to facilitate tumor invasiveness and metastasis [99].
Osteopontin (OPN), a matrix protein also involved in tissue remodeling, cell-mediated immunity, and malignant transformation, is upregulated in COPD and correlates with lung cancer stage and tumor differentiation [100]. OPN levels may predict the presence of lung cancer in patients with COPD [101].

We next review some of the inflammatory mediators and intracellular signaling pathways potentially relevant in the pathogenetic links between COPD and lung cancer.

4.3. Inflammatory mediators in COPD and lung cancer

4.3.1. Oxidants and mitochondria in COPD and lung cancer

COPD and lung cancer are both associated with chronic inflammation and oxidative stress. Oxidative stress causes proliferation(lung cancer) and inflammation (COPD) [102]. Mitochondrial damage in COPD patients increases oxidative stress and chronic inflammation increases the risk of carcinogenesis [103]. The former may reflect a shift in the apoptosis/proliferation balance toward hyperproliferation [48] and the transition from normal epithelial to hyperplastic to carcinomatous cells in COPD. Oxidative stress also promotes somatic mutations [80] and affects DNA methylation by forming 8-hydroxy-2'-deoxyguanosine (8-OHdG) residues. ROS and reactive nitrogen species (RNS) also induce single or double stranded DNA breaks and abnormal DNA cross-linking [104]. The presence of the modified guanine base 7,8-dihydro-8-oxoguanine (8-oxoG) is elevated in the genome of COPD patients. 8-OxoG is primarily recognized by 8-oxoguanine glycosylase 1 (OGG1), which catalyzes the first step in the DNA base excision repair pathway. However, cellular oxidative stress represses the activity of substrate-bound OGG1 enabling NF-κB DNA binding and the enhanced expression of both innate and adaptive immunity. Interestingly, OGG1 is mechanistically linked to oncogenesis via KRAS [105].

Mitochondria are the major source of intracellular ROS, and mitochondrial superoxide dismutase (SOD) 2 protein is elevated in the parenchyma from tumor compared to non-tumor patients with and without COPD. SOD2 expression correlated with smoking intensity [96]. Enhanced systemic oxidative stress and reduced anti-oxidants are seen in lung cancer patients with COPD compared to those without. Thus, increased oxidative stress in COPD may predispose to a higher risk of developing lung cancer [106]. Increased oxidative stress also induces cellular senescence which is increased in emphysema and is linked to accelerated aging with shortened telomeres and a decrease in antiaging molecules [107].

Mitochondrial-derived ROS is important for cellular signaling, but excess production affects cell wall integrity and damages lipids, proteins and DNA [108]. Dysregulation of mitochondrial genes [109] and transcription factors [110] is seen in SCC patients with COPD. Mitochondrial function also controls oxygen homeostasis, and hypoxia and hypoxia-inducible factor (HIF)-1α is expressed in the large airways of COPD patients and in 32–56% of NSCLCs [111]. Given the association between COPD, lung cancer, inflammation, and mitochondrial dysfunction, restoration of mitochondrial function may be a therapeutic target.

4.3.2. Interleukins in COPD and lung cancer

Increased IL-17 levels are associated with the severity of COPD and promote chronic inflammation. In murine models of lung cancer, IL-17A deficiency [112] or reduced Toll-like receptor (TLR)-2 and −4 expression [113] reduces tumor proliferation and inflammatory mediator expression. COPD is characterized by increased levels of TLR2, neutrophilia and the bacteria NTHi, Moraxella cattarhalis and S. pneumoniae [114] suggesting a link between neutrophilia, IL-17 and pathologic microbiota with lung cancer.

IL-6 induces tumor cell proliferation and orchestrates an immune suppressive lung microenvironment via signal transducer and activator of transcription (STAT3) pathway activation. STAT3 activation occurs in COPD lung tissues [115]. The systemic expression of IL-2 and IL-1 was higher in those with lung cancer and COPD, whilst the levels of IL-4 were significantly lower [96].

4.4. Chemokines, their receptors and heterogeneous nuclear ribonucleoproteins (hnRNP) in COPD and lung cancer

The CXCR4/CXCL12 (SDF-1) axis is implicated in lung cancer pathogenesis. Neutralization by anti-CXCL12 or anti-CXCR4 monoclonal antibodies significantly decreased NSCLC metastases in in vivo

models [116]. CXCR4/CXCL12 activation induces heterogeneous nuclear ribonucleoprotein A2/B1 nuclear export [117] which impacts upon cell migration [118]. Heterogeneous nuclear ribonucleoproteins (HnRNPs) regulate mRNA processing, transport, subcellular localization and stability, cell cycle regulation, telomere stability, and cellular senescence [117].
Most hnRNPs drive cancer progression, whilst hnRNP A2/B1 also causes cell migration [118]. Overexpression of the splice variant hnRNP A2/B1 in plasma and bronchial epithelium is detected many years prior to the diagnosis of lung cancer in high-risk smokers and has a high sensitivity for the presence of SCC and for better prognosis [119]. The pathogenic mechanisms underlying the CXCR4/CXCL12 axis and hnRNP A2/B1 in COPD and NSCLC are unknown. In antibody blocking experiments using COPD sera, CCL21 has an important role in NSCLC cell migration. These results offer an interesting therapeutic strategy against lung cancer [120].
Smoking enhanced CXCL14 expression by airway epithelial cells and its expression is further increased in COPD smokers with hyperplastic/metaplastic lesions. Epithelial presence of CXCL14 could represent a molecular link between airway epithelial cells and COPD and lung cancer [121].

4.4.1. Prostaglandins in COPD and lung cancer

Prostaglandin E2 (PGE2) produced by the activity of the cyclooxygenase-2 (COX-2) enzyme may be important in the pathogenesis of both COPD and lung cancer. PGE2 modulates the inflammatory response in COPD and may promote carcinogenesis by regulating cell proliferation, apoptosis, and angiogenesis. COX-2 is expressed in several lung cancers and promotes cancer growth through microsomal PGE synthase-1 (mPGES-1) and PGE2 receptor EP1 [122]. Smokers with COPD have increased levels of COX-2 and PGE2 in their sputum and the latter inversely correlates with FEV1% predicted [123]. In addition, increased COX-2 expression is observed in COPD lung parenchyma [124]. Epidemiological data suggest a 36% reduction in the incidence of adenocarcinoma in subjects who regularly use aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) [125]. Ibuprofen may have an even greater anti-lung cancer effect than aspirin [125]. There is a significantly increased risk of lung cancer in subjects with an SNP within the COX-2 3′-UTR that is linked to reduced COX-2 expression [126].

5. Intracellular signaling pathways in COPD and lung cancer

NF-κB is a critical pro-inflammatory transcription factor [127] and its activation is increased in immune cells and the epithelium of the lower airways in COPD patients and also in premalignant lesions in the bronchial epithelium and in neoplastic cells of squamous cell lung carcinomas [128]. NF-κB activation and STAT3 are crucial in the development of lung cancer from COPD [129]. NF-κB also suppresses p53 expression [102], stimulates proliferation and inhibits cell death possibly by enhancing ROS production [130]. The generation and maintenance of a protumorigenic inflammatory environment consisting of alternatively activated macrophages and regulatory T cells is NF-κB-dependent and links COPD with lung cancer [131]. NF-κB p65 activity is regulated by phosphorylation and acetylation [132]. The expression of the deacetylase Sirtuin 1 (SIRT1) is reduced in COPD [133]. The Akt/mTOR pathway, which is negatively regulated by SIRT1, is upregulated in lung cancer in subjects with mild COPD [55].
Peroxisome proliferator–activated receptor (PPAR)γ regulates cell growth by inducing differentiation and apoptosis in an NF-κB-dependent manner [134]. The expression of PPARγ is reduced in lung cancer whilst rosiglitazone, a PPARγ ligand, inhibited lipopolysaccharide (LPS)-induced neutrophilia and reduced chemoattractants and survival factors in vivo [134].

The pathogenetic mechanisms linked to the association of COPD and lung tumor are summarized in Table 2.

6. Innate immune defects in COPD and lung cancer

There is evidence formarked dysregulation of innate immunity in COPD [135]. COPD patients have a profound immune dysfunction related to enhanced activity of regulatory T cells, CD4+PD-1+

exhausted effector T cells and myeloid-derived suppressor cells (Figure 2). Targeting these cells can be therapeutically effective in NSCLC and may restore appropriate immune responses in COPD and thereby reduce exacerbations and prevent the risk of cancer [136]. It is also evident that mast cell activation is aberrant in the lungs of patients with COPD and in lung cancer [137]. This may reflect altered interactions with airway structural cells and targeting these cells and associated mediators may prove effective in these diseases. In addition, natural killer T (NKT) cells, a cellular interface between innate and adaptive immunity, are dysregulated in COPD [138].

Specific mediators implicated in the links between COPD and lung cancer include serum amyloid A (SAA) whose expression is increased in COPD. It can increase the production of tumors as well as the function of the N-formylpeptide receptor on phagocytes [139]. This receptor is expressed on immune and epithelial cells and may provide a mechanistic link between COPD and lung cancer and be a novel therapeutic target. In addition, IL-22 has a pivotal role in lung antimicrobial defense via the induction of β-defensins and protect against tissue damage [140]. Influenza virus increases the bronchial epithelial cell expression of IL-22R, and this can be cleaved by neutrophil proteases to impair IL-22 immune signaling. IL-22 and its receptors and IL-22R cleavage products are enriched in human and experimental COPD tissues and sputum reflecting an abnormal innate immune response to infection which may impact on lung cancer development [141].

Alveolar macrophages (AM) from COPD patients have an impaired phagocytic capacity which is linked to deregulated release of extracellular sphingosine-1-phosphate (S1P) from airway epithelial cells in response to cigarette smoke exposure [142]. AMs from COPD and lung cancer patients also have a defect in efferocytosis – phagocytosis of apoptotic cells [143,144]. Interestingly, in lung cancer this is mediated, at least in part, by the release of PGE2 from cancer cells whilst PGE2 expression is also increased in COPD/emphysema.

The HMG-CoA reductase pathway also known as the mevalonate pathway, is responsible for the production of cholesterol, haem, coenzyme Q10 and all steroid hormones [145]. Mitochondrial dysfunction which occurs in COPD and lung cancer results in deregulation of this pathway and subsequent defects in autophagy and a failure to kill defective cells [146]. Defects in the mevalonate pathway also affect innate immune responses to smoke which may link COPD with increased incidence of lung cancer [145]. This data also suggest a potential benefit of statins and dietary fiber in preventing lung cancer in COPD patients. Recent data highlighted the links between P53 expression, the mevalonate pathway and tumorigenesis [147].

Activation of the adaptive immune system, autoimmunity under the control of reactive carbonyls [148] and expansion of the B-cell pool occurs in COPD [149]. B cell expansion is driven by a proliferation-Inducing ligand (APRIL) which is associated with the onset and progression of NSCLC. The number of alveolar macrophages, epithelial cells and B cells expressing APRIL is greatest in subjects with COPD and NSCLC compared to patients with COPD or NSCLC alone or in control subjects implicating it as a possible therapeutic target.

7. High-throughput genome-wide technologies for measuring gene expression for early diagnosis of lung cancer in COPD patients

Genome-wide analysis of mRNA and miRNA expression provides powerful insights into the mechanisms underlying lung carcinogenesis [150]. Indeed, molecular classification of human lung carcinomas is based on gene expression profiling used for determining the optimal therapeutic approach for each cancer [151]. Expression profiling of histologically normal large-airway epithelial cells from at-risk smokers identified an 80-gene signature that could predict smokers with and without lung cancer with 83% accuracy and 90% sensitivity for stage 1 lung cancer [152]. RNA sequencing has replaced gene arrays and provide a greater depth of information regarding molecular processes in lung cancer cells [153,154]. A similar analysis can be performed to assess genome-wide epigenetic marks [155] and of miRNA profiles [156] to differentiate between cancer cell types.

Differentially expressed genes from airway epithelial cells and lungs of emphysema patients have been used to determine a signal in blood [157]. There was significant overlap between blood and the

airways/lungs, although the expression of some of the genes was altered in opposite directions. In addition, blood miRNA profiles from COPD patients who developed lung cancer compared to matched subjects who did not identify nine differentially expressed miRNAs including members of the miR-320 family that target cancer-related pathways including the MAPK pathway [158].

Gene profiling of laser microdissected lungs identified 374 differentially expressed probes in SSC lung cancer patients with and without COPD. Over 10% of the probes were for genes involved in mitochondrial function [159]. Combining expression data with chromosomal aberrations showed significant associations with the 5q31.2–31.3 region. This analysis highlights the importance of combining genetics with the expression of mRNAs and miRNAs that may better reflect the effect of tobacco smoking. Twelve out of 34 differentially expressed miRNAs in small airway epithelial cells, linked predominantly to Wnt pathways, remained differentially expressed after 3 months of smoking cessation [110]. There have been some attempts at analyzing the airway proteome and glycome to determine markers that distinguish adenocarcinoma from COPD [160].

Detection of volatile organic compounds in breath collected using breath sensors has enabled the discrimination between patients with COPD and those with or without NSCLC with a success rate of almost 90% [161]. It is unclear what metabolites (isoleucine, acetoacetate, creatine, N-acetylated glycoproteins and glycerol) differentiate between disease types and lung cancer (Deja, 2014) [162].

Single-cell whole-genome sequencing is revolutionizing our understanding of the disease. Whole-exome sequencing of 100 early-stage NSCLC tumors revealed widespread intratumor heterogeneity with respect to somatic copy number and mutations [163]. EGFR, MET, BRAF, and TP53 driver mutations were mostly clonal, but heterogeneous drivers in PI3KCA, chromatin modification, and DNA damage response pathways were found in >75% of the tumors. Deep sequencing of individual lung cancer cells from a patient with EGFR-mutant lung cancer discerned concurrent events that were associated with genetically driven therapy resistance [164]. Events involved in the failure to respond to EGFR inhibitors included Wnt/β-catenin alterations, CDK4 and CDK6 mutations, and PIK3CA function. These studies emphasize the importance of questioning the single-gene driver hypothesis of oncogenesis and explains, in part, clinical responses.

Examination of circulating tumor DNA (ctDNA) in 100 tracking NSCLC evolution through therapy (TRACERx) subjects demonstrated that phylogenetic ctDNA profiling tracks the subclonal nature of lung cancer relapse and metastasis and gives insight into future approaches to personalized therapies [165]. The future of personalized medicine for lung cancer requires the precise delineation of each cancer's global genomic and epigenomic profiles.

8. New potential pharmacological therapies for both lung cancer and COPD

Many new chemical entities and biologics (Table 3) are effective in preventing lung cancer in animal models. Efficacy in small clinical trials, however, has rarely translated into larger multicenter studies and, as stated above, better disease models are required. It must be noted that both of the new anti-PD-1 and anti-CTLA4 checkpoint inhibitors that are highly effective in treating 20–30% of patients were discovered using mouse models. We indicate below the data for drugs currently used to treat COPD and those that may impact upon COPD inflammation and thereby influence lung cancer.

Many drugs used to treat COPD may have potential in preventing lung cancer. Inhaled corticosteroids (ICS) reverse DNA hypomethylation and modulate mRNA expression of oncogenes in animal models of lung cancer [166] and epidemiological studies indicate that the risk of lung cancer is reduced by regular ICS [167]. However, there was no regression of bronchial dysplasia or secondary carcinogenesis markers in smokers after 6 months high dose ICS [168]. Long-term studies with ICS show either no effect or a reduced risk of lung cancer in COPD patients [169], rather the use of ICS or oral corticosteroids (OCS) is associated with lung cancer risk, especially in men [170]. A case–control study demonstrated that smoking cessation is crucial in reducing the risk of lung cancer especially in men [171].

Nicotinic and M3 mAChR receptor antagonists inhibit SCC cell growth in vitro but three years of treatment with inhaled tiotropium (a potent M3 antagonist) had no effect on the risk of lung cancer

in moderate to severe COPD patients [172]. Future studies should examine whether combined treatment with bronchodilators and ICS improve cancer risk.

Other drugs used predominantly to treat COPD comorbidities have been proposed to be useful in treating COPD and thereby prevent lung cancer. Statins have anti-inflammatory effects, but clinical trials show variable efficacy in COPD [173]. They improve cardiovascular and respiratory cancer morbidity/mortality, reduce the rate of lung function decline and lower the risk of lung cancer. There was a 63% dose-dependent reduction in lung cancer risk with rosuvastatin, simvastatin, and atorvastatin [174]. In addition, selective COX-2 inhibitors significantly reduced lung cancer risk, although there was a concomitant increase in the risk of cardiovascular disease [175].

Prevention of COPD exacerbations should affect the risk of lung cancer in COPD patients. Statins have anti-inflammatory effects, but clinical trials show variable efficacy in COPD [176]. Statins improve cardiovascular and respiratory cancer morbidity/mortality, reduce the rate of lung function decline and lower the risk of lung; there was a 63% dose-dependent reduction in lung cancer risk with rosuvastatin, simvastatin and atorvastatin [174]. The phase 2 IMPULSE study evaluated lefitolimod, a TLR9 agonist, as maintenance treatment in extensive-stage SCLC and COPD patients showed a median overall survival of 316 vs 246 days in the lefitolimod and control groups, respectively, and a hazard risk of 0.48 [177]. Further studies using TLR antagonists should be performed.

The complexity of NF-κB signaling and the paradoxical induction of inflammasome activation with genetic knockout and pharmacological ablation of NF-κB initially stalled the development of NF-κB drugs for the treatment of COPD and lung cancer [178]. The ubiquitin-proteasome pathway is essential for regulating NF-κB activity and has been targeted in lung cancer. Proteasome inhibitors induce apoptosis in NSCLC cell lines [179] and clinical trials with bortezomib showed limited efficacy as a monotherapy in NSLCL. Subsequent studies have focused on combination therapies. Other small molecule NF-κB inhibitors are under development [111] and edesalonexent (CAT-1004), a bifunctional oral small molecule that links salicylic acid and docosahexaenoic acid, is safe and well tolerated in man [180]. The PI3K pathway is activated in bronchial airway cells of smokers with lung cancer and targeting the PI3K pathway in lung cancer and COPD may be useful, including during influenza-induced exacerbations [23].

Phytoceutals such as curcumin and the polyphenolic compound resveratrol [3,5,4'-trihydroxystilbene] derived from red wine reduce tumor cell viability and colony formation in vitro and protect against lung carcinogenesis and inflammation in animal models. Epidemiological studies suggest a benefit of moderate wine intake on the risk of developing COPD, airflow obstruction in long-term smokers and lung cancer development [181]. These effects are thought to be due to their antioxidant properties, and antioxidant therapy should also be effective in COPD and lung cancer but clinical studies have generally not been effective due to the poor bioavailability of the drugs [[182]. Paradoxically, mouse COPD studies indicate that treatment with antioxidants is associated with an increased cancer risk [102]. Immune checkpoint inhibitors (ICIs) (Figure 2) are novel and effective therapies in some NSCLC and smokers are more likely to respond to these immune therapies [183–185].

Recent studies showed that the presence of COPD is associated with longer progression-free intervals in patients treated with ICIs [186] and higher sensitivity to ICIs and better overall survival of NSCLC patients with COPD, compared with those without COPD [187]. Given the role of the immune system in both COPD and lung cancer and the increasing use of ICI, better understanding of the connections between COPD and NSCLC is fundamental to improving treatments.

9. Conclusions

A greater understanding of the molecular pathology of advanced NSCLC has led to clinical trials of personalized targeted therapies. Unraveling the complexity of the molecular links between COPD and NSCLC requires studies of the molecular and immune pathobiology of smokers with premalignant bronchial lesions of SCC compared to smokers with and without COPD. Early detection of both diseases is critical for effective therapy and combining risk models of lung cancer and COPD with molecular phenotyping of young and 'healthy smokers' is essential. This will elucidate new

molecular targets in early carcinogenesis and enable the development of early diagnostic tests and novel therapies. The goal is either the prevention of invasive NSCLC or transforming this to a treatable chronic disease.

10. Expert opinion

Chronic obstructive pulmonary disease (COPD) and lung cancer are leading causes of morbidity and mortality worldwide. They share a common environmental risk factor in cigarette smoke exposure and a genetic predisposition represented by their incidence in only a fraction of smokers. COPD could be a driving factor in lung cancer, by increasing chronic inflammation and oxidative stress. Superimposing carcinogens on an experimental model of COPD may provide a better model of human lung cancer. Cigarette smoke-induced EMT, caused by chronic inflammation, links COPD and lung cancer, and its hallmarks are the loss of the epithelial adhesion molecule and/or a gain of mesenchymal markers. Particularly, TGF-β-induced EMT in airway epithelial cells is a potential pro-tumorigenic event in COPD-associated-lung cancer. Several SNPs in candidate gene families (e.g., detoxifying enzymes, proteinases, anti-proteinases, and cytokines) have been implicated in the pathogenesis of both COPD and lung cancer but only confer a proportion of the risk.

Different epigenetic changes, such as DNA methylation, noncoding and microRNA expression (ncRNA and miRNA) and post-translational modifications of histones, have been also associated with lung cancer. Certainly, chronic inflammation, and small airways inflammation correlated with COPD, are others links with lung cancer, though the mechanisms underlying this association are not completely understood.

Particular emphasis is focused on mitochondrial dysfunction/damage that lead to an imbalance between oxidants and antioxidants pathways, with resulting DNA damage, and the restoration of mitochondrial function may be a therapeutic target. Increase levels of interleukins 17 and 6 are associated with the severity of COPD and cells proliferation inducing a suppressive lung microenvironment, the repression of the DNA repair mechanisms and increased cellular proliferation. Chemokines and their receptors as CXCR4/CXCL12 are involved in lung cancer driving cell migration, but the pathogenic mechanism linking COPD and lung cancer is unknown. Increased expression of PGE2 produced by COX-2 in inflammatory response in COPD may promote carcinogenesis, and it could be therapeutic target. At least, the alteration of intracellular signaling pathways, as NF-κB transcription factor activation in immune cells and epithelium of lower airways in COPD patients and also in neoplastic cells of squamous cell lung cancer.

By understanding the common signaling pathways involved in COPD and lung cancer the hope is that treatments will be developed that not only treat the underlying disease process in COPD, but also reduce the currently high risk of developing lung cancer in these patients. As more molecular mechanisms linking COPD to lung cancer are discovered, the opportunity for chemoprevention will arise. Although an association between both of these diseases has been established, therapeutic approaches for preventing lung cancer in COPD patients remain limited. Ideally, new therapies will be developed that have the ability to suppress COPD progression while reducing lung cancer risk.

New potential pharmacological therapies are focused on molecular links between COPD and lung cancer. Many new chemical entities and biologics are effective in animal models but there are no larger multicentre studies. Many other studies are required on molecular and immune pathobiology of smokers with premalignant bronchial lesions of NSCLC compared to smokers with and without COPD. Combining risk models of lung cancer and COPD with molecular phenotyping of young and 'healthy smokers' are essential to identify molecular targets for new therapies.

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Declaration of interest

The Authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Table 1. Genes potentially involved in lung carcinogenesis and COPD pathogenesis*.

CHRNA3
CHRNA5
CHRNB4
p53
XPC
p21WAP/CIP1
RB1
SERPINA1
MMP
CYP1A1
EPHX1
MPO

* It is still unknown if there is an increased risk of the squamous cell carcinoma histological subtype.

CHRNA3: nicotinic acetylcholine receptor alpha subunits 3; CHRNA5: nicotinic acetylcholine receptor alpha subunits 5; CHRNB4: nicotinic acetylcholine receptor beta subunits 4; RB1: retinoblastoma gene; MMP: matrix metalloproteinase; CYP1A1: cytochrome P450 1A1; EPHX1: microsomal epoxide hydrolase 1; MPO: myeloperoxidase; XPC: xeroderma pigmentosum group C.

Table 2. Main pathogenetic links between COPD and lung cancer.

- Common susceptibility genes (see Table 1)
- Epithelial–mesenchymal transition (EMT)
- Lower airways inflammation
- Inflammatory mediators

Oxidative stress, mitochondrial damage
Acetylcholine
Cytokines (IL-1, IL-2, IL-6, IL-17)
Chemokines (CXCL14, CXCR4/CXCL12, CCL21)
Prostaglandin E2,
Proteases (MMPs)

- Intracellular signaling pathways

NF-κB
PPARsγ

EMT: epithelial–mesenchymal transition; NF-κB: nuclear factor-κB; MMPs: matrix metalloproteinase; PPARsγ: peroxisome proliferator–activated receptors γ

Table 3. Potential therapies for the treatment of both COPD and lung cancer.

Wide-spectrum anti-inflammatory compounds:
- Inhaled glucocorticoids
- COX-2 selective inhibitors
- Novel anti-inflammatory compounds (curcumin, resveratrol, statins).

Selective antagonists of inflammatory mediators:
- Anti-oxidants
- Muscarinic M3 receptor antagonists
- CXCR4/CXCL12 axis blockers
- Cytokine blockers

Transcription factor modulators:
- NF-κB blockers
- PPARγ agonists

Immune checkpoint inhibitors

COX-2: cyclooxygenase-2; NF-κB: nuclear factor-κB; PPARsγ: peroxisome proliferator–activated receptors γ

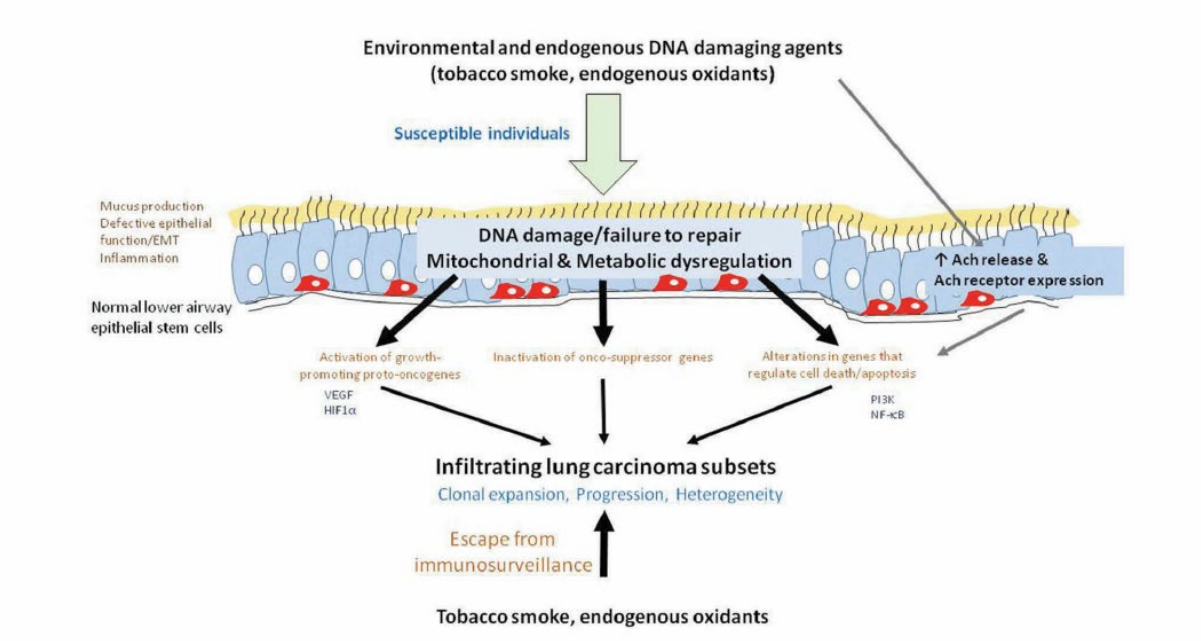

Figure 1. The potential molecular basis of lung carcinogenesis in COPD patients.
DNA damage/repair imbalance leads to the activation of growth-promoting proto-oncogenes, inactivation of oncosuppressor genes, and alteration of genes that regulate cell death. Escape of immunosurveillance escape finally leads to infiltrating lung cancer cell subsets.
Ach: acetylcholine; DNA: deoxyribonucleic acid; EMT: epithelial–mesenchymal transition; HIF1α: hypoxiainducible factor 1α; NF-κB: nuclear factor-κB; PI3K: phosphoinositide 3-kinase; VEGF: vascular endothelial growth factor.

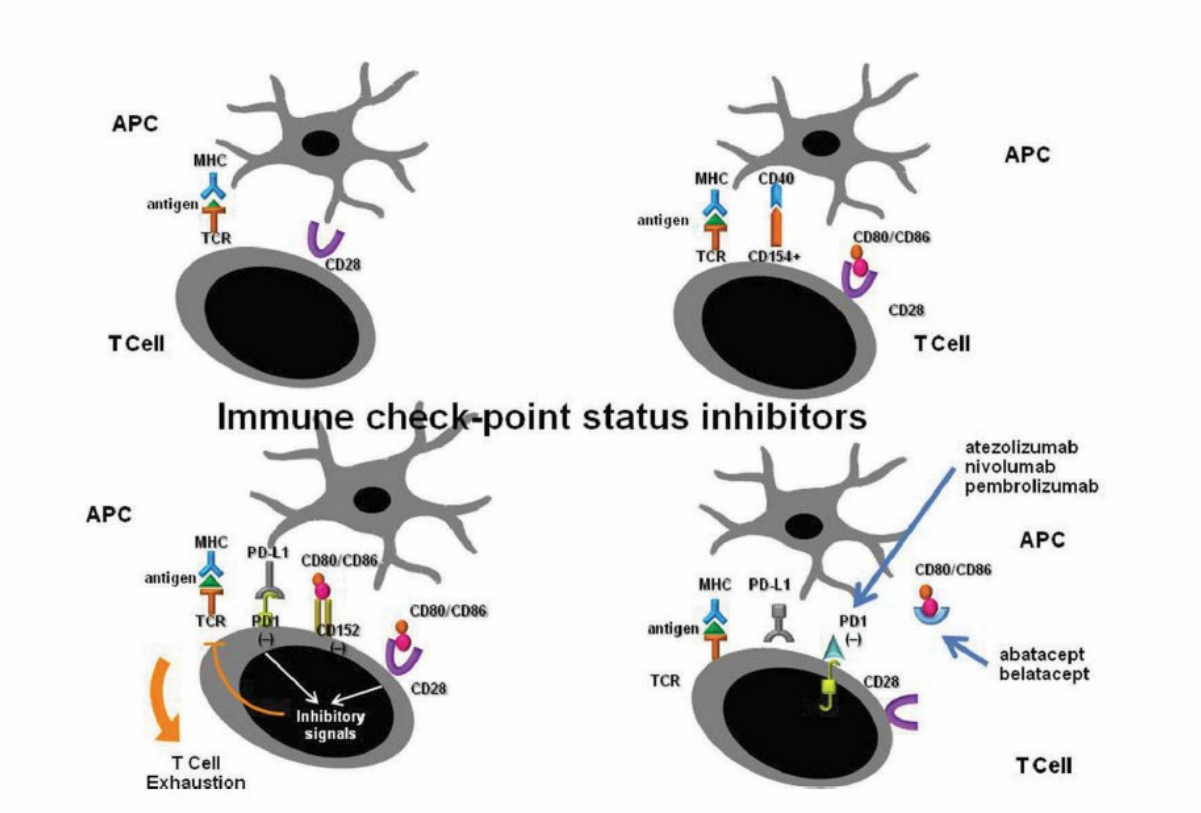

Figure 2. Immune checkpoint status inhibitors.
Immune checkpoints regulate cell-mediated responses in tissues where antigen-presenting cells (APCs) express checkpoint ligands such as PD-L1. Antigenic stimulation and checkpoint ligand expression contribute to a balance of immune activation and control.
APC: antigen presenting cell; CD: cluster of differentiation; MHC: major histocompatibility complex; PD-1: programmed cell death-1; PD-L1: programmed death-ligand-1; TCR: T cell receptor.