

Chronic obstructive pulmonary disease and lung cancer: underlying pathophysiology and new therapeutic modalities

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Abstract

COPD and lung cancer are major lung diseases affecting millions worldwide. Both diseases have links to cigarette smoking, and exert a considerable societal burden. People suffering from COPD are at a higher risk of developing lung cancer than those without COPD and are more susceptible to poor outcomes after diagnosis and treatment. Lung cancer and COPD are closely associated, possibly sharing common traits such as an underlying genetic predisposition, epithelial and endothelial cell plasticity, dysfunctional inflammatory mechanisms including the deposition of excessive extracellular matrix, angiogenesis, susceptibility to DNA damage and cellular mutagenesis. In fact, COPD could be the driving factor for lung cancer, providing a conducive environment that propagates its evolution. In the early stages of smoking, body defences provide a combative immune/oxidative response and DNA repair mechanisms are likely to subdue these changes to a certain extent; however, in patients with COPD with lung cancer the consequences could be devastating, potentially contributing to slower post-operative recovery after lung resection and increased resistance to radiotherapy and chemotherapy. Vital to the development of new-targeted therapies is an in-depth understanding of various molecular mechanisms that are associated with both pathologies. In this comprehensive review, we shall provide a detailed overview of possible underlying factors that link COPD and lung cancer and current therapeutic advances from both human and pre-clinical animal models that can effectively mitigate this unholy relationship.

Running head – COPD and lung cancer: understanding and treatments

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Key points –

There is consistent evidence that COPD and lung cancer share common pathological mechanisms. A greater understanding of these mechanisms may allow the development of new therapeutic targets.

Since 90% of cancers in the human body are of epithelial origin, it is possible that epithelial mesenchymal transition (EMT) is the link between COPD and lung cancer, being further exaggerated by associated pathologies such as angiogenesis, oxidative stress, infections and inflammation.

Inhaled corticosteroids suppress EMT in patients with COPD and decrease lung cancer risk in observational studies. If such effects are confirmed prospectively, EMT may be a possible new therapeutic target for management of both COPD and lung cancer, but this warrants further studies.

Small airway fibrosis and obliteration occur quite early in COPD. Therefore, it is important to understand mechanisms that are switched on early in the disease, in order to enable the possibility of early-personalised intervention.

Smoking cessation and exercise training should be promoted and considered as part of the multidisciplinary management of patients with both COPD and lung cancer.

1. COPD and lung cancer

Chronic obstructive pulmonary disease (COPD) is a systemic inflammatory condition associated with several comorbidities, including lung cancer. It is a major cause of global morbidity and mortality with 328 million affected worldwide and 3.5-4 million deaths annually. According to the World Health Organization (WHO) COPD is currently the third leading cause of death globally and within 15 years is expected to become the leading cause of death. [1]. Cigarette smoke is the major etiological factor but air pollution and smoke from biomass fuels are also major contributors, especially in low- and middle-income countries [1]. Smokers with COPD are twice as likely to develop lung cancer as smokers without COPD, and lung cancer is a common cause of death in COPD [2]. Patients with lung cancer and concomitant COPD have a worse survival than patients with lung cancer without COPD [3-5]. Although an association between both of these diseases has been established for decades, therapeutic approaches for preventing lung cancer in patients with COPD remain limited. Co-existing COPD may limit treatment options for lung cancers and thus must be assessed and managed in a timely manner. Lung cancer is one of the most common forms of cancer in the world, with 1.8 million new cases detected annually (as of 2015) and 1.6 million deaths worldwide annually [6]. The current 5 year average survival rate (18.6%) for patients with lung cancer is much lower than for other leading causes of cancer, with regional differences being attributed to variations in treatment and diagnostics [6, 7]. Worldwide, smoking prevalence has steadily increased and is currently the major contributor, with about 80% of lung cancer related deaths linked to smoking in the United States and France [8], 61% in Asia and 40% in sub-Saharan Africa. Second hand tobacco smoking (SHS) is also a risk factor, with over 21,400 lung cancer deaths in non-smokers annually attributed to SHS [9]. In low and middle income countries, indoor air pollution mostly due to combustion of wood or coal used for cooking and heating purposes, is another important risk factor [10]. The Australian Institute of Health and Welfare [11] found that lung cancer was the leading cause of death for both male and female Australians followed by colorectal, breast, prostate, and pancreatic cancers. In 2017, nearly 12,500 Australians were diagnosed with lung cancer, which is 34 people every day [11]. Lung cancer was also responsible for the highest overall burden among cancers [11].

Lung cancers are broadly classified into two major types; non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) [12, 13]. NSCLC constitutes 85% of all lung cancers, and is further characterised into squamous cell carcinoma (SqCC), adenocarcinoma, and large cell

carcinoma. While SqCC typically arises from large airway bronchial squamous epithelium [14], adenocarcinoma (40% of all cancers) arises from the secretory (glandular) cells that are located in the distal epithelial lining of the lung bronchi [15]. Although adenocarcinoma is most often found in smokers, it is also the more prevalent variant of NSCLC in non-smokers. Large-cell carcinoma consists of large-sized cells that are anaplastic and arises from large airways [16]. In addition to these common subtypes of NSCLC, there are also other variants, including bronchoalveolar or “lepidic predominant adenocarcinoma”, mixed and undifferentiated carcinomas.

Small-cell lung cancer (SCLC) usually arises centrally in the chest (large airways or lymph nodes) [17]. It contains dense neurosecretory granules and is associated with paraneoplastic syndromes at presentation such as inappropriate secretion of antidiuretic hormone. SCLCs have traditionally been staged into limited and extensive stage disease [18]. They are divided into typical and atypical and can grow either in the airways or in the lung periphery [17, 18]. Like SCLC, carcinoid tumours are characterised as neuroendocrine tumours, which are commonly located in the gastrointestinal tract, and less commonly in the lung [19].

2. Chemoprevention for lung cancer in COPD

To date, smoking cessation is the only proven effective approach for preventing lung cancer in patients with COPD [20-22]. In view of the potential shared mechanism of chronic inflammation in both diseases, the chemoprotective effect of anti-inflammatory agents in COPD population has been assessed. Three retrospective studies of patients with COPD from different countries found a reduced risk of lung cancer in those using inhaled corticosteroids [23-25], with a negative dose-response relationship between the dose of inhaled corticosteroids and the risk of developing lung cancer [23-25], **Table 1**. A meta-analysis of seven randomized controlled trials assessing the effects of inhaled corticosteroids in COPD (n = 5085) revealed a trend towards decreased lung cancer mortality in the treatment group compared to the placebo group [26]. In contrast, inhaled corticosteroids have not been shown to exert significant chemopreventive effects in smokers with premalignant lung lesions [27, 28]. The exact mechanisms through which inhaled corticosteroids exert these apparent anti-cancer effects are not clear, however, we will discuss potential mechanisms later in this review.

Statins have also been shown to have a possible role in preventing lung cancer in patients with COPD [29]. A retrospective cohort study of more than 40,000 patients with COPD reported that the use of statins reduced lung cancer risk by 63% [30]. However, neither inhaled corticosteroids nor statins have been evaluated in prospective controlled trials. Given the lack of definitive evidence, neither agent should be used solely for their potential chemoprotective effects in patients with COPD. Chemoprevention for lung cancer has also been investigated in ever-smokers who may have COPD. Pre-clinical and epidemiologic studies indicated potential protective roles of antioxidants in preventing cancers [31]. However, randomised controlled trials on lung cancer prevention using antioxidant supplements in ever-smokers have been disappointing. Neither combination supplementation with alpha-tocopherol, beta-carotene and retinol, nor the individual components was found to reduce lung cancer risk in major randomised controlled trials, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study (ATBC) [32] and the Beta-Carotene and Retinol Efficacy trial (CARET)[33]. Indeed, the ATBC and CARET studies, which included over 47,000 ever-smokers in total, consistently showed an *increased* risk of lung cancer with beta-carotene supplementation in ever-smokers [32, 33]. A recent prospective cohort study of vitamin B supplementation for lung cancer found that high-dose vitamin B6 or B12 supplementation increased lung cancer risk in male smokers [34]. The mechanism of increased lung cancer risk with micronutrient supplementations is unclear. Some of the recent studies are listed in.

3. Impact of COPD and lung cancer on exercise capacity

Exercise capacity in patients with chronic respiratory diseases such as COPD and/or lung cancer is impaired and often limited by symptoms such as dyspnoea and leg fatigue [35]. In patients with COPD, exercise intolerance can result from one or a combination of the following: ventilatory limitation, impaired gas exchange, atrophy of peripheral muscles and/or peripheral muscle weakness and cardiac dysfunction [35]. In those with concomitant lung cancer, exercise capacity can be further reduced by the tumour(s) itself, which disrupts pulmonary mechanics and gas exchange, as well as a result of the lung cancer treatment, which can include lung resection, chemotherapy, radiotherapy and other options [36].

Exercise capacity of patients with COPD and/or lung cancer can be measured using either laboratory-based exercise tests (such as the maximal incremental cardiopulmonary exercise test [CPET]) or field-based exercise tests (such as the six-minute walk test [6MWT] and

incremental shuttle walk test [ISWT]). The importance of assessing exercise capacity in these populations is well-established. In both patients with COPD and patients with lung cancer the peak rate of oxygen consumption ($\text{VO}_{2\text{peak}}$) measured during a CPET has been shown to be a strong predictor of mortality [37, 38]. Furthermore, $\text{VO}_{2\text{peak}}$ measured before surgery is a strong predictor of postoperative pulmonary complications for patients undergoing lung resection for NSCLC [37]. Of note, performance during field-based walking tests also has prognostic implications. A systematic review of 13 studies reported an association between six-minute walk distance and mortality in patients with COPD [39]. In patients undergoing lung resection for NSCLC, poor performance in the 6MWT or the ISWT before surgery is associated with an increased risk of postoperative pulmonary complications [40, 41].

4. The role of exercise training/therapy

Exercise training has been shown to improve exercise capacity in both patients with chronic lung diseases and patients with different types of cancer. In fact, exercise training, which is the cornerstone of pulmonary rehabilitation, is an integral component for management of patients with COPD. [42] When compared to COPD, research on exercise training in patients with lung cancer is in its infancy. However, recent studies have demonstrated its value across the whole lung cancer continuum, especially in patients with NSCLC [43-46].

Pulmonary rehabilitation, including exercise training, should be offered to patients with stable COPD or following an exacerbation of their disease [35, 47]. A Cochrane review of 65 randomised controlled trials (RCTs) concluded that pulmonary rehabilitation significantly improves exercise capacity, health related quality of life (HRQoL), and symptom control in patients with COPD [48]. Of note, there was no difference in outcomes between exercise training only and more complex pulmonary rehabilitation programmes [48]. Pulmonary rehabilitation following an exacerbation of COPD has been shown to reduce hospital readmissions [49]. In patients with early stage NSCLC, both preoperative and postoperative exercise training programmes have been demonstrated to be effective at improving health outcomes [50, 44]. However, despite the growing evidence of the benefits of exercise training in this population, referral of such patients to exercise training programmes is still uncommon [51]. A standard pulmonary rehabilitation exercise program is 6 to 8 weeks in duration. To minimise surgical delay, a modified exercise program of shorter duration with more frequent sessions is more appropriate for patients with lung cancer. Preoperative exercise training

predominantly comprises aerobic training and is usually conducted whilst patients await surgery. In most studies to date, this timeframe ranged between 1 to 4 weeks [44]. In both cohort studies and a systematic review of RCTs, short-term (2 to 4 weeks) intensive pre-operative pulmonary rehabilitation (or ‘pre-habilitation’) significantly improved baseline lung function, exercise capacity and symptoms in patients with lung cancer [52, 53, 44]. In addition, pre-operative exercise training was associated with improved lung function recovery after surgery and reduced post-operative pulmonary complications (51, 73). In a study by Licker et al that investigated the effectiveness of preoperative exercise training on postoperative outcomes in people undergoing lung resection for NSCLC, independent predictors of postoperative pulmonary complications were preoperative peakVO₂, pre-operative exercise training, and COPD [56, 57].

A decline in exercise capacity and lung function, both important prognostic factors, is commonly observed following lung resection for NSCLC [54, 55, 37]. Postoperative exercise training programmes should be tailored to improve exercise capacity and health outcomes that may have been negatively affected by the lung resection. The usual duration and characteristics of the postoperative programme are derived from the COPD pulmonary rehabilitation literature. Programmes range between 8 to 12 weeks; with sessions 2 to 3 times/week, including both aerobic and resistance training. Postoperative exercise training has been shown to improve exercise capacity (VO₂peak and six-minute walk distance), [50, 43, 45] total muscle mass[45] and HRQoL [45].

In patients with advanced lung cancer exercise training programmes should aim to prevent deterioration in important clinical outcomes, control symptoms and maximise independence. This is an area of growing interest amongst researchers and clinicians, and there are several RCTs being conducted to investigate effectiveness of exercise training in this population [56-58]. To date, exercise training has been shown to be feasible and safe in patients with advanced lung cancer [59].

5. Perioperative care for surgical candidates

Surgical resection remains the treatment of choice for patients with early-stage NSCLC and co-existing COPD who have adequate physiologic reserve. Patients with COPD have higher post-operative morbidity and mortality following lung resection [60-63]. The degree of lung

function impairment correlates with post-operative complications. Patients with lung cancer may have undiagnosed COPD or under-treated COPD. Timely assessment and management of COPD during the perioperative period are important for optimisation of baseline lung function and fitness in order to minimise potential surgical morbidities. Evidence regarding the short-term effects of these approaches for improving perioperative outcomes is limited.

Long-acting bronchodilators, including long-acting muscarinic antagonists (LAMAs) and long-acting beta₂-agonists (LABAs), are the mainstay therapy for long-term management of patients with COPD. Both agents have been shown to improve dyspnoea, lung function, exercise capacity and health-related quality of life, and to reduce exacerbation rate in patients with stable COPD [64, 65]. Perioperative commencement of long-acting bronchodilators, within 1 to 2 weeks prior to thoracic surgery significantly improved pre-operative lung function [66, 67]. Initiation of LAMAs or LABAs prior to surgery has also been shown to reduce post-operative cardiorespiratory complications in patients with lung cancer [68, 69]. A randomized controlled trial by Suzuki et al demonstrated that the perioperative use of combined LAMA and LABA improved post-operative lung function and health-related quality of life in patients with COPD, particularly in those with moderate-to-severe disease [70].

Cardiovascular complications are common following thoracic surgery, particularly in those with COPD who are at high risk of cardiovascular events [62, 71]. Concerns have been raised that cardiovascular adverse events could be associated with the use of long-acting bronchodilators. Muscarinic receptor antagonists have been associated with cardiovascular events in observational and clinical trials [68, 72]. However, an increased incidence of post-operative cardiac complications, including arrhythmias, with the use of LABAs and LAMAs has not been reported in retrospective studies [68, 72].

Although long-term use of inhaled corticosteroids has been shown to reduce exacerbations in patients with moderate-to-severe COPD, they have also been demonstrated to be associated with an increased risk of pneumonia [73-75] [76-79]. A retrospective study by Yamanashi et al revealed no association between perioperative use of inhaled corticosteroids and post-operative respiratory complications [80]. Further, addition of inhaled corticosteroids to dual long-acting bronchodilators was associated with improved pre-operative lung function and reduced post-operative pulmonary complications in patients with COPD [67].

To achieve the best outcomes for patients with lung cancer and COPD, optimising management of COPD should be integrated into routine care. Smoking cessation and short-term intensive preoperative pulmonary rehabilitation should be advocated. Warner et al reported that patients who had stopped smoking for two months or less had a pulmonary complication rate almost four times that of patients who had stopped for more than two months. They recommend at least two months of smoking cessation should occur to maximize the reduction of postoperative respiratory complications [81]. Kuri et al reported that preoperative smoking cessation of longer than three weeks has the potential to reduce the incidence of impaired wound healing among patients who have undergone reconstructive head and neck cancer surgery [82]. Very little work has been done in this area therefore, more studies looking at the beneficial effects of smoking cessation are warranted. Dual bronchodilation with LAMA and LABA is the preferred therapy for improving patients' baseline clinical status. Pre-operative use of inhaled corticosteroids may have additional clinical benefits, particularly in those with moderate-severe COPD.

6. Lung cancer radiotherapy

Radiotherapy improves loco-regional disease control and survival in patients with lung cancer. However, radiation pneumonitis is a concerning side effect of thoracic radiotherapy, consequent upon the lungs' exquisite sensitivity to ionizing radiation. The incidence of radiation pneumonitis in lung cancer varies depending upon irradiation techniques and regimens. The reported incidence of clinically symptomatic radiation pneumonitis is up to 17% among patients undergoing radical radiotherapy [83, 84]. Patients with lung cancer are commonly being treated using newer irradiation techniques such as intensity-modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT) which provide more optimal radiation dose distribution and lower impact to normal tissue. In comparison to conventional radiotherapy, IMRT uses an involved-site technique to alter the intensity of radiation in different parts of a single radiation beam. On the other hand, SBRT, also referred to as stereotactic ablative radiation, administers higher doses of radiation over fewer fractions to an accurately delineated target. The use of IMRT has been shown to reduce rates of severe pneumonitis when compared to conventional radiotherapy (3.5% vs 7.9%) [85]. Clinically significant radiation pneumonitis develops in fewer than 10% of patients receiving SBRT for lung cancer [86, 87].

Data are conflicting regarding the effect of COPD on the risk of radiation pneumonitis. Previous retrospective studies reported that COPD was associated with an increased incidence of radiation pneumonitis, including in those who received SBRT [88, 89]. However, in patients with lung cancer treated with radiotherapy, patients with severe COPD experienced milder radiation pneumonitis compared to those with normal lung function or milder COPD [90, 91]. It is possible that the lack of lung tissue associated with the presence of emphysema in patients with severe COPD reduces the potential for radiation-induced lung toxicity. Systemic glucocorticoids remain the mainstay therapy for patients with symptomatic radiation pneumonitis, with limited evidence suggesting that high-dose inhaled budesonide 800 µg twice daily may be a potential alternative therapeutic option [92].

Other local therapies such as radiofrequency ablation (RFA) and thermal ablative therapies have been used for treatment of lung cancer and other types of cancers [93]. In a retrospective, case-controlled observational study, Chi et al reported that both RFA and microwave ablation were equally effective and safe for patients with primary and metastatic lung tumours. Ablation was successfully completed in all patients with no procedure-related death. Mu and colleagues reported that CT-guided percutaneous RFA appeared to be a safe and effective treatment option for lung malignancies adjacent to the pericardium [94].

7. Systemic therapies

While systemic chemotherapy is the standard of care for patients with advanced lung cancer, the recent development of tyrosine kinase inhibitors (TKIs) and immunotherapy has revolutionised management for these patients. Tyrosine kinase inhibitors are small molecule inhibitors of enzymes that regulate cellular growth factor signalling, while immunotherapies are monoclonal antibodies directed against immune checkpoint proteins to enhance endogenous immune responses against tumour cells [95]. The current approach to systemic therapies in lung cancer focuses on tailoring treatment choice according to tumour histology and molecular profiles. Compared to chemotherapy, TKIs and immunotherapies show promising results with sustained responses in selected patients. Although new systemic therapeutic agents are generally less toxic than systemic chemotherapy with favourable safety profiles, their unique mechanisms of action can result in a different array of side effects.

Drug-related pneumonitis has been reported with the use of TKIs and immunotherapies. Systematic reviews found that the incidences of drug-related pneumonitis were 1.2% for epidermal growth factor receptor (EGFR) TKIs, 2.1% for anaplastic lymphoma kinase (ALK) TKIs and 1.3-3.6% for immunotherapies [96-98]. The mortality rates of drug-related pneumonitis were 22.8% for EGFR TKIs and 9% for ALK TKIs. Although COPD per se has not been identified as a risk factor for drug-induced pneumonitis, cigarette smoking is associated with an increased incidence of pneumonitis [99]. Interstitial lung disease, another risk factor for drug-induced pneumonitis, not uncommonly co-exists in patients with COPD [100]. In addition, long-term use of inhaled corticosteroids may increase the risk of *Pneumocystis jiroveci* pneumonia in patients with lung cancer and co-existing COPD who are treated with systemic therapies [101, 102]. This possible risk should be weighed against any potential improvement in lung function or symptoms achievable through the use of inhaled corticosteroids in individual patients, after considering other risk factors for opportunistic infection. It is important to monitor symptoms and lung function in patients with COPD and lung cancer who receive these agents in order to detect possible drug-related adverse effects early.

As immunotherapies can modulate T-cell response via inhibition of immune checkpoints, they may be of potential therapeutic value for COPD. There are emerging data suggesting a potential role of dysregulated immune checkpoints leading to excessive T cell response in COPD [103]. Given the complex interplay of various inflammatory pathways in COPD, further investigations are required before translating this knowledge into clinical management.

8. Mechanisms linking COPD and lung cancer

The major mechanisms linking COPD and lung cancer are likely related to common traits of both diseases, such as: oxidative stress, inflammation, genetic predisposition, epigenetics in lung cancer and COPD, extracellular vesicles (EVs), epithelial-mesenchymal transition (EMT), endothelial to mesenchymal transition (EndoMT), extracellular matrix (ECM) and angiogenesis (**Figure 1**). COPD has been shown to be a risk factor for lung cancer [104]; COPD patients are at a six-fold higher risk of developing lung cancer as compared to smokers with normal pulmonary function [105]. Here, we discuss common mechanisms shared by both of these diseases.

8.1 Oxidative stress

Cigarette smoke contains more than 4000 different types of poisonous chemicals and is known to generate greater than 1000 oxidants per puff; oxidative stress can cause damage to lung tissue by inducing cellular proteomic and transcriptomic changes. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are among the more potent molecular candidates that interact with vital cellular organelles such as mitochondria and endoplasmic reticulum to cause potentially devastating imbalances in cellular metabolism.

In both COPD and lung cancer, there is substantial evidence that points to increased ROS and RNS activity causing systemic cellular breakdown as well as inducing irreversible DNA damage. ROS generated through cigarette smoke directly affects inflammatory cells, systematically reducing their ability to mount an immune response to infections as well as obliterating cancer cells. In smokers and COPD patients Morlá et al [106] observed that peripheral lymphocytes had shorter telomere length compared to normal healthy subjects, thus leading to a shorter cellular lifespan. This has been attributed to ROS, which are known to accelerate the process of cellular aging. Similar studies by Ceyalan et al. [107] also identified that circulating leukocytes in this population had severely damaged DNA with a considerable increase in lipid peroxidation mutagen markers such as plasma malondialdehyde and TBA-reactive substances. Thus, decreasing life span and DNA damage in lymphocytes in smokers and in patients with COPD make them more susceptible to cancer, in part due to weakened immune response resulting in inability to remove transformed or mutated cells. This fits with our recent findings of decreases in key inflammatory cell populations in early COPD [108], thus increasing such individuals' susceptibility to respiratory infections as well as to cancer [109-111, 78, 79].

In lung cancer, elevated levels of ROS induce single or double-stranded DNA breaks and abnormal DNA crosslinking [112]. This would result in arrest or induction of unwarranted transcription, replication errors, and genomic instability, all of which could lead to cancer induction and spread. In fact, common toxic oxidative chemicals from smoking such as B(a)P diol epoxide (BPDE) cause irreversible damage to the DNA by forming DNA adducts through covalent binding or oxidation. The formation of BPDE–DNA adducts, if left unrepaired by nucleotide excision repair mechanisms, can block the transcription of essential genes, leading to unwarranted cellular effects [113]. Genome-wide association studies (GWAS) have also

revealed suboptimal DNA repair capacity (DRC) as a major determinant for genetic susceptibility to lung cancer although there is considerable inter-individual variation in DRC partly due to the variability in DNA repair genes [114].

Increased ROS levels also induce cellular senescence via DNA damage, arrest cellular growth and alter cellular function. Senesced immune cells have activated protein complexes leading to a condition termed senescence-associated secretory phenotype (SASP) which produces proinflammatory substances such as IL-1, IL-6, and IL-8 [115]. The cytokines produced are potent attractors and activators of innate immune cells, which cause tissue damage by producing even more oxidizing molecules, released mainly to destroy pathogens which are not necessarily present [116]. In NSCLC, cytokines that are enhanced in SASP complex are also known to be markers of prognosis. Interestingly, among them IL-6 is known to initiate growth and spread of lung cancer in mouse models, which has been attributed to the IL-6/STAT3 pathways [117].

The impact of ROS and their relationship with smoking, lung cancer and COPD is of paramount importance and further understanding the mechanisms underlying these relationships could possibly provide new therapeutic opportunities for early interventions.

8.2 Inflammation

Airway inflammation is known to play a critical role in COPD and cancer [118]. Over many years, the literature has provided important insight into the increases of both innate and adaptive immune cells in both bronchoalveolar lavage (BAL) and sputum samples in COPD [119, 120]. However, evidence suggests substantial contradiction about the actual picture of the type of inflammation in the airway wall wherein hypo-cellularity [121] or cellular dysfunctionality/abnormalities are observed [120].

It remains to be deciphered whether inflammation plays a causal role in enhancing mutations in lung cancer. However, inflammatory factors can enhance the progressive capacity of cancer cells. For examples, increased activation of NF- κ B activity results in lung inflammation and substantial pro-tumorigenic effect. The effector cell population that mediates tumorigenicity is the macrophages, which could be recruited to the lungs because of epithelial cell induced NF- κ B activation [122]. A number of studies have reported increases in alveolar and luminal macrophages in smokers with both normal lung function and COPD when compared to non-

smoker controls [123]. Further, sub-phenotyping the macrophages in these patients groups also revealed predominantly M2 macrophages, with increased expression of the phagocytic receptor CD163/CD206 [124, 120]. This increase in M2 macrophages switch was identified to be promoted by pro- Th2/M2 cytokines such as IL-4, IL-10, IL-13, CCL22, and IL-6 among others [120]. Interestingly, in the tumour microenvironment itself, tumour-associated macrophages were shown to be predominantly M2 as well, which suggests that polarization of macrophages observed in mild-moderate COPD patients could be pro-tumorigenic [125]. A recent meta-analysis with over 2500 NSCLC patients [126], observed that M2 macrophages were indeed the dominant macrophage phenotype and specifically patients' survival was attributed to the dominant sub-type of macrophages in the tumour microenvironment [126, 125]. The authors concluded that patients with larger numbers of M2 macrophages had lesser chances of survival than those with M1 macrophage phenotype. Almatroodi et al demonstrated that differences in M1 and M2 predominance varied according to NSCLC subtype [127].

Other than macrophages, lymphocytes, especially cytotoxic CD8⁺ T cells, also form an important link in both COPD and lung cancer. Interestingly, CD8⁺ T cells are the dominant T cell phenotype in patients with mild-moderate COPD over CD4⁺ T cells and this dominance may be partly due to increased susceptibility of COPD patients to viral infections [119]. Recently, McKendry et al [128] provided evidence of increased expression of programmed cell death (PD)-1 in CD8⁺ T cells and the ligands PD-L1 on macrophages in ex-vivo samples from patients with mild-moderate COPD. The interaction between PD-1 and its ligand PD-L1 induces cell cycle arrest resulting in T cell anergy. Further, external administration of influenza virus led to an increased propensity of dysfunctional CD8⁺ T cells, estimated by their decreased ability to degranulate [128]. Similarly, increased expression of PD-1 on CD8⁺ T cells was found to be higher in peripheral blood of patients with NSCLC- and their interaction with PD-L1 in the tumour milieu is now an established target for antibody based therapeutic interventions such as pembrolizumab in advanced stages of cancer [129, 130]. These studies suggest that orientation of immune cell expression patterns towards lung cancer is observed quite early in both smokers and patients with COPD and that detecting these changes could help to design more effective future diagnostics and therapies.

8.3 Role of extracellular vesicles

Extracellular vesicles (EVs) are small membranous vesicles that are secreted or shed by cells. In humans, EVs can be detected in body fluids including blood, urine, saliva, breast milk,

ascites, and cerebrospinal fluid, among others. They are categorized as exosomes, ectosomes, microvesicles, or apoptotic bodies depending upon size [131]. The size of EVs varies from 30-1000 nm, with exosomes being the smallest (30-100 nm) and larger apoptotic bodies ranging up to 1000 nm [132]. Exosomes can play a crucial role in both COPD and lung cancer. EVs in general, are known to actively regulate tumour microenvironment (TME) by directly altering the immune response or through modulating epithelial transition, fibroblast activation or angiogenesis [133]. Changes to the TME could take place through selective transfer mechanisms and would ideally involve both proteins and nuclear materials such as RNA. For example, McCready et al [134] observed that HSP90 α , in tumour associated secretory exosomes, increases invasiveness of cancer cells through the activation of plasmin and annexin-II. HSP90 α protein is abundant in patients with COPD and acts as a potent biomarker along with HSP 27 and 70 [135]. It potentiates EMT in several forms of cancer [136], a phenomenon which is also active in patients with early stage COPD, pointing towards a possible association. Similar to transfer of proteins, miRNA-containing exosomes can be a determining factor in both lung cancer and other chronic lung disease [137]. MiRNAs are known to selectively inhibit or silence the mRNA translational process, thus acting as an important cellular modulator. For example, the miR-200 family of miRNA can actively inhibit TGF- β 1 induced EMT activity in airway epithelial cells [138] and forms a double negative feedback loop with a family of EMT-inducing transcription factors, ZEB [139]. Studies in both lung cancer and COPD suggest a significant reduction in cellular miR-200 and an increase in extracellular exosomal miR-200 [140, 141]. The decrease in cellular miRNA suggests active cellular expulsion through exocytosis of this essential regulator, leading to an increase in epithelial cell plasticity and mobility. Although recent studies have implicated EV in the pathophysiology of lung cancer, a connection to COPD could lead to the discovery of potential biomarkers and novel therapeutic interventions for management of lung cancer [142].

8.4 Extracellular matrix (ECM) and proteinases

ECM has important roles in maintaining tissue functionality and stability and in regulating cell activities. The ECM is organised in two main structural types: 1) basement membranes in epithelia and endothelia and 2) interstitial network of fibrous proteins, glycosaminoglycans and matricellular proteins that provides structural support for cell types in the lung and maintains three-dimensional appearance and biomechanical characteristics [143, 144]. Key ECM proteins maintaining tissue integrity are, for example, elastin, collagens and specific

proteoglycans. The ECM is also an important storage source for different growth factors and cytokines, which are crucial for cell differentiation and proliferation [145, 146]. One of the major producers and regulators of ECM are the fibroblasts. These cells synthesise large amounts of matrix components, different growth factors and inflammatory mediators. Fibroblasts may thereby have important modulatory roles in autocrine and paracrine fashion in regulating ECM in different lung compartments, and in giving rise to pathological changes in the ECM of lung cancers, such as increased collagen expression, altered collagen cross-linking and subsequent increase in tissue stiffness [144].

SCLC is encircled by an extensive stroma of ECM and tumorigenicity has been shown to be enhanced by SCLC cells binding to the ECM, creating a highly specific microenvironment [147]. Activated fibroblasts, known as cancer-associated fibroblasts (CAFs), play an essential role in tumour progression by substantially remodelling tumour ECM, suppressing immune response and releasing tumour growth-promoting factors [148]. Thus, the tumour ECM provides a specialised microenvironment, favouring proliferation and metastasis and inhibiting apoptosis of tumour cells. Encapsulating tumour stroma can confer resistance to chemotherapy [147]. In COPD, there are processes ongoing in parallel with excessive ECM being produced and manifested as both peribronchial fibrosis and degraded ECM in the alveoli resulting in emphysema [145]. Alterations in elastic fibres, fibronectin, collagens, tenascin-C and versican have been identified throughout all lung compartments in patients with moderate COPD [149] and there are pronounced alterations in proteoglycan synthesis from central and distally-derived lung fibroblasts from patients with severe COPD [150]. Importantly, distal lung fibroblasts from patients with severe COPD appeared to have altered fibroblast function and defective repair mechanisms in the ECM structure of the collagen network assembly in response to the prostacyclin analogue iloprost, perhaps thereby affecting emphysema progression [151].

The homeostasis of ECM is tightly regulated by matrix metalloproteinases (MMPs) and specific tissue inhibitors of metalloproteinases (TIMPs) [152] [153]. These proteases target the ECM for degradation, which alters tissue architecture and causes the release of ECM derived chemoattractant signals known as matrikines, which can propagate inflammation [154]. MMPs, especially MMP-2 and MMP-9, are implicated in the degradation of ECM in basement membranes, which facilitates tumour invasion and metastasis. MMP-2 is expressed in both normal and tumour tissues, whereas MMP-9 is largely induced during tissue remodelling [153].

In cancer, MMP-9 overexpression may contribute to stimulating tumour vascularisation and tumour cell proliferation [155]. An overproduction of MMPs in intratumoral stromal cells is associated with poor prognosis of NSCLC [153, 155]. Interestingly, the proteoglycan decorin, which is essential for collagen fibrillogenesis, interacts with MMPs and can act as a tumour suppressor by attenuating tumour growth, migration and angiogenesis [156]. In COPD, there is an imbalance between MMPs and TIMPs, which causes an overproduction of MMPs. Increased MMP activity and neutrophil elastase correlate with COPD pathology and MMP-9, in particular, has a major role in the development of emphysema [157]. The degrading of ECM by MMPs may also increase the bioavailability of growth factors, cytokines and receptors stored in the ECM. MMP-9 also increases as part of the EMT process in smokers and people with COPD [158].

8.5 Angiogenesis

Smoking, a key factor in the development of both COPD and lung cancer, results in hypoxia, which is an important driver of angiogenesis [159]. Nicotine may increase hypoxia-inducible factor (HIF)-1 in NSCLC and promote tumour angiogenesis [160, 161]. Vascular endothelial growth factor (VEGF) is one of the most important factors promoting angiogenesis and vascular remodeling processes [162]. In cancer, tumour progression from a benign to a malignant stage is often related to an angiogenic switch – which involves triggering and development of a vascular network that is actively growing and infiltrative [163]. As tumours increase in size their microenvironment becomes hypoxic and HIF is activated, which induces expression of MMPs and VEGF, leading to progression and invasion. VEGF correlates with progression, metastasis and poorer prognosis [164]. Proteinases induce the release of growth factors such as TGF- β and VEGF, which play a pivotal role in tumorigenesis and metastasis of lung cancer. Cancer associated fibroblasts have well-established pro-angiogenic functions in tumours and are, together with other hypoxic cancer cells, major sources of secreted VEGF-A, which initiates tumour angiogenesis through vascular endothelial growth factor receptor-2 (VEGFR-2), expressed on endothelial cells [165]. During hypoxic conditions, prostacyclin synthase expression was up-regulated in human lung fibroblasts, promoting VEGF synthesis in tumours [166].

Pulmonary vascular remodeling is common in COPD [162] and comorbidities including cardiovascular disease have negative impacts on COPD prognosis [167]. In COPD, airflow obstructions in small airways and destruction of alveolar capillaries result in decreased oxygen

transport and alveolar hypoxia. This causes an activation of HIF, which promotes angiogenesis via VEGF [168]. Interestingly, VEGF is synthesised in high amounts by distally derived lung fibroblasts and induced by both prostacyclin and TGF- β . In a recent study, synthesised VEGF acted in an autocrine fashion by increasing ECM synthesis, migration and proliferation of human lung fibroblasts [169]. However, in this study there were no significant differences in synthesised VEGF levels between fibroblasts from non-smoking control subjects and those from patients with severe COPD. In line with these findings, expression of VEGF in pulmonary arteries did not differ between patients with severe COPD with emphysema and non-smoking control subjects, whereas patients with mild-moderate COPD showed an increased expression of VEGF [170]. Patients with chronic bronchitis phenotype COPD had increased levels of VEGF in sputum in contrast to COPD patients with more emphysema who showed lower levels of VEGF [171]. Patients with acute exacerbations had higher levels of VEGF in the circulation compared to patients with stable COPD and healthy individuals [172]. Increased VEGF expression is associated with bronchial angiogenesis that correlated inversely with lung function in patients with COPD [173, 174]. In contrast, a decreased expression of VEGFR-2 in parenchymal regions in patients with severe COPD correlated with increased endothelial cell death [175]. Inhibition of VEGFR-2 in an animal model resulted in emphysematous lung structure and cell apoptosis [176]. VEGF may act both as a promoter of endothelial cell function and a negative regulator of vascular smooth muscle cells and vessel maturation in combination with platelet derived growth factor [177], highlighting the complex role of VEGF in vascular remodelling and its capacity to play different roles depending on disease progression and disease severity. VEGF has the ability to bind to multiple proteins and proteoglycans present in the ECM [178, 179]. The proteoglycan biglycan is important for migration of cells [180] and may up-regulate VEGF expression [181]. Endothelial cells that form vasculature play an important role in providing nutrients and oxygen to the tumour.

We have previously reported an increase in vessels in general, and VEGF and TGF- β 1 positive vessels, in particular, in the reticular basement membrane (Rbm) of smokers and patients with COPD, they were also seen encroaching into the epithelium [182-186]. It is quite possible that these two growth factors actively promote neoangiogenesis of both the Rbm and the epithelium itself, supporting formation of a pro-cancer stroma with associated active EMT [183, 187]. In a separate study, we also reported effects of inhaled fluticasone propionate on vascular remodelling in patients with COPD [187]. In that study, we observed that lamina propria vascularity returned to normal after six months of corticosteroid treatment but that Rbm vessels

did not decrease significantly. This suggests that six months of corticosteroid therapy may be inadequate for complete depletion of Rbm vessels, and angiogenic sustainability might be the reason for continued cancer growth in both smokers and patients with COPD [188]. We believe these are important clinical observations, which warrant further investigation.

In NSCLC the degree of tumour associated angiogenesis correlates with disease progression and predicts unfavourable outcomes. High vascularity at tumour periphery has been correlated with tumour progression [189]. Perlecan is a major ECM protein located in pulmonary vessels essential for the structure of vascular basement membranes [178, 150] and a crucial co-factor for VEGF binding and storage [178]. A study on endothelial cell function showed that interaction between perlecan and VEGF-A promotes VEGFR-2 signalling [190]. Down-regulation of perlecan caused reduced angiogenesis in an animal model [191]. Interestingly, perlecan and biglycan synthesis are reduced in fibroblasts from patients with severe COPD [150]. Furthermore, endothelial-derived angiocrine signals were shown to induce regenerative lung alveolarization. Activation of VEGF2 and fibroblast growth factor receptor-1 (FGFR1) in pulmonary capillary endothelial cells induced MMP14 expression that unmasked epidermal growth factor (EGF) receptor ligands to enhance alveologenesis [192]. Perlecan, from endothelial cells, blocked proliferation and invasiveness of lung cancer by acting in a paracrine way to impact pro-inflammatory pathways [193].

Cyclooxygenase-2 (COX-2) is expressed in many tumours, especially adenocarcinoma, and is associated with carcinogenesis and tumour resistance to anti-cancer drugs. COX-2 and prostaglandins (PGs) may play a role in the pathogenesis of lung cancer via effects on angiogenesis, cell proliferation and apoptosis [194]. EGF-induced angiogenesis via the COX-2 pathway involves p38 and JNK kinase activation pathways in endothelial cells [195]. COX-2 is increased in the distal lung of patients with COPD and also in the sputum of smokers together with MMP-2, which correlated with severity of airflow limitation in patients with stable COPD [196]. COX-2 is also constitutively expressed in different lung cancers including NSCLC [194, 197]. COX-2 via mPGES-1 and PGE₂ receptor EP₁ promote cancer growth in a chronic inflammatory environment [198]. Activation of PPAR-receptors by nicotine also induces expression of PGE₂ receptor EP₄ through PI3-K signals and increased human lung carcinoma cell proliferation in NSCLC [199]. Interestingly, matrix stiffening and fibrosis appear to be linked through COX-2 suppression and reduced PGE₂ levels in an autocrine feedback loop [200]. Preclinical and clinical studies have shown that COX-2 inhibitor has some

efficacy in treatment of NSCLC [201], however further studies are warranted.

8.6 Genetic predisposition

A role for familial or genetic susceptibility has been suggested in both COPD and lung cancer. Genome-wide association studies (GWASs) have identified the same risk loci on chromosome 15q that map to CHRNA3 and CHRNA5 – both of which are nicotinic acetyl-choline receptors associated with nicotine dependence and cigarette smoke consumption [202, 203]. The linkage of COPD, lung cancer and peripheral vascular disease, with these genes, points out their possible role as surrogates for tobacco exposure [202]. Single nucleotide polymorphisms of other genes such as FAM13A (at 4q24) that encode for a RhoGTPase-activating protein binding domain have been associated with both COPD and lung cancer [203]. Although their functional contribution to lung cancer and/or COPD remains yet to be elucidated, the involvement of Rho GTPases in the pulmonary endothelial barrier in lung suggests a potential mode of involvement for FAM13A [204]. Direct effects of nicotine have also been reported on endothelial and fibroblast cell populations. In a Swedish study, authors reported that pure nicotine has the potential to alter gene expression, cellular morphology and cell growth of normal human endothelial and fibroblast cells [205]. They suggested that it would potentially promote tumorigenesis and various diseases in cigarette smokers [205]. Nicotine has also been suggested to induce EMT in human airway epithelial cells via the Wnt/ β -catenin signalling pathway and thereby to increase the risk of lung cancer [206].

8.7 Epigenetics in lung cancer and COPD

Besides genetic susceptibility, epigenetic factors such as DNA methylation and covalent histone modifications have been reported to be important in developing COPD and lung cancer. A common methylation link between COPD and lung cancer is CDKN2A which encodes for tumour suppressors p16 (INK4A) and p14 (ARF) [202], an observation consistent with both COPD and lung cancer being viewed as diseases of ageing [207]. Similarly, DNA methylation of the genes CCDC37 and MAP1B was observed in patients with COPD and lung cancer, with the greatest degree of methylation observed in patients with both diseases [207]. In cancer patients with COPD [208], immune genes expressed by either tumour cells or by tumour-infiltrating immune cells were highly methylated as compared to those from patients without COPD [209]. Thus, COPD may epigenetically alter the immune repertoire.

8.8 Epithelial-Mesenchymal Transition (EMT)

Epithelial-mesenchymal transition is a biological process by which epithelial cells lose cell-cell adhesion, gain mesenchymal traits of migration and invasion and produce components of extracellular matrix. EMT is a manifestation of airway basal reprogramming in smokers and patients with COPD [210]. EMT need not be a binary process, rather cells can display a spectrum of phenotypes ranging from fully epithelial to fully mesenchymal [211-213]. Hallmarks of EMT have been observed in airways of patients with COPD and smokers, and NSCLC cells can attain either partial EMT – i.e. a hybrid epithelial/mesenchymal (E/M) phenotype – or a complete EMT phenotype [213]. Thus, EMT has been proposed as a potential link between COPD and lung cancer [104].

We have previously reported that EMT is an active process in both small and large airways of patients with COPD [214-219]. EMT associated with organ fibrosis (termed Type-2 EMT) is deprived of angiogenesis. When EMT leads to the formation of pro-cancer stroma, it is termed Type-3 EMT, and is strongly associated with neo-angiogenesis [220, 104, 221]. We have shown that Type-2 EMT is active in small airways, leading to small airway fibrosis/obliteration and Type-3 EMT is active in large airways, where cancer formation (especially SqCC) is quite common, [222, 223]. We also reported that inhaled fluticasone propionate has the potential to ameliorate airway EMT in COPD patients, suggesting EMT as a novel therapeutic target in this condition [183, 224, 225]. EMT may be the mechanism through which inhaled corticosteroids could provide protection against lung cancer in COPD. Statins might have similar effects but further studies are needed to explore their effect [188]. In a cigarette smoke exposed mouse model of COPD, we recently reported that apoptosis signal-regulating kinase 1 (ASK1) inhibition reduced migration of airway smooth muscle cells [226]. These could have implications for EMT as well, as cell migration is one of key hallmarks of epithelial plasticity.

EMT in COPD may be activated by interactions among epithelial cells and fibroblasts [227], reminiscent of non-cell autonomous regulation of EMT in lung cancer [228]. A recent report showed that the acute effects of cigarette smoke and associated infection, together play an important role in driving complete EMT; thus an extra insult, such as an infection can further exaggerate EMT [76] leading to chronically remodelled airways as observed in COPD [229]. SLUG and ZEB1 – transcription factors often associated with a partial EMT[227, 230] – were activated in COPD bronchial epithelial cells, potentially enabling cell survival [231]. We also

recently reported increased expressions of β -catenin, Twist and Snail in airways of smokers with and without COPD [219]. These transcriptional regulators of EMT correlated with markers of EMT and were associated with decreased lung function in both smokers and patients with COPD [219]. A partial EMT phenotype can be maintained by adenosine receptor A2BAR that can activate both EMT-inducing (ERK/MAPK) and EMT-inhibiting (cAMP/PKA) pathways[232], similar to the transcription factor NP63 α that can both activate and inhibit ZEB1[233, 234]. Intriguingly, a hybrid E/M phenotype has been identified to possess enriched stem-like abilities as well as resistance to the epidermal growth factor receptor inhibitor erlotinib [235]. The emerging notion about the highly aggressive behaviour of a hybrid E/M phenotype in cancer [236, 237] [238] argues for its potential role in driving COPD, in addition to that of complete EMT.

8.9 Endothelial-to-mesenchymal transition (EndoMT)

Similar to epithelial plasticity in EMT, endothelial cells can also lose markers such as vascular endothelial cadherin (VE-cadherin), can attain a motile phenotype and can express fibroblast associated markers such as vimentin, type I collagen, and α -smooth muscle actin (SMA) [239]. EndoMT is a critical process during embryogenesis, playing an important role in embryonic cardiac development [240]. However, when challenged by persistent damage and inflammation during pathological conditions, EndoMT is initiated and can contribute to organ fibrosis [241] as well as to cancer promotion [242-244, 241, 245]. As with EMT, EndoMT can also be a non-binary process, with cells apparently co-expressing both endothelial and mesenchymal markers, suggesting a dual role in disease manifestation [246]. EndoMT, like EMT, may be active in both COPD [247] [248] and lung cancer [249, 250]. In cancer, it is suggested that activated myofibroblasts and cancer-associated fibroblasts produced by EndoMT can facilitate tumour growth and cancer progression. This fits with the underlying cancer pathology wherein tumours are heavily associated with increased angiogenesis, thus, it is possible that endothelial cells are contributing to the pool of CAFs [242, 251, 245]. EndoMT can also initiate the formation of pro-cancer stroma quite similar to Type-3 EMT, with the potential to both initiate cancer and help the tumour to thrive [245].

We and others have reported vascular remodelling in COPD, notably structural changes involving intimal and medial thickening, leading to reduction of lumen diameter and muscularization of arterioles [252]. The other changes involve hypo-vascular lamina propria and hyper-vascular Rbm in large airways of smokers and patients with COPD [253-255, 186,

256]. Both loss of vessels and vascular remodelling give rise to pulmonary hypertension in COPD [252, 257]. Interestingly, these vascular remodelling changes are also observed in early COPD and in current smokers with normal lung function [252, 258, 168, 253-255, 186]. Increased expression of fibroblast specific protein-1 (FSP-1) has been reported in arteries and small vessels [258]. Abnormal deposition of mesenchymal like cells has been considered as a key pathological feature of arterial remodelling, possibly through endothelium as source of these cells through EndoMT [259]. These cells lead to increased production of ECM proteins, with deposition of collagen and elastin proteins contributing to narrowing of the arterial lumen and the development of pulmonary hypertension. But the origin of these smooth muscle like cells and the underlying mechanisms involved in vascular remodelling are poorly understood [259].

EndoMT has been suggested to be involved in angiogenesis, where, during angiogenic sprouting, endothelial cells may compromise their basement membrane and migrate together as a ‘train’ of cells, indicating a partial EndoMT phenotype [246]. Similar collective migration has been observed in cells that are maintained in a partial EMT phenotype by molecular brakes such as OVOL2 or GRHL2 that can prevent a complete EMT [260-262][26–28]. ‘Phenotypic stability factors’ for a partial EndoMT state remain to be identified. Computational approaches to calculate the rates and trajectories of EndoMT may be valuable in better characterizing the dynamics and phenotypic spectrum of EndoMT [263]. Recent studies have highlighted that ‘molecular EMT’ and ‘morphological EMT’ does not need to always occur simultaneously, that is, cells expressing markers of EMT need not always migrate/invade, and cells that can invade/migrate need not show molecular markers of EMT [264, 265]. Similar criteria can be used to distinguish between ‘molecular EndoMT’ and ‘morphological EndoMT’ as well. Thus, further investigations into the functional and morphological aspects of EndoMT should yield greater insights into the contribution of EndoMT in COPD and cancer progression.

9. Insights from mouse models of COPD

Animal models of cigarette smoke (CS)-induced disease using guinea pigs, rats and mice have been developed [266, 267]. Mice are the most popular because of cost, ease of housing, and the availability of a plethora of molecular and immunological reagents and genetically modified strains [267-269]. Mouse models can be used to assess the impact of short-term CS exposure (1 day to 4 weeks) or the mechanisms involved in the development of COPD (up to

6 months). Many of the characteristic features of human COPD, such as chronic lung inflammation, pulmonary hypertension, airway remodelling, emphysema, and impaired lung function, can be generated in CS exposed mice [270-273, 267-269, 274-279]. The effects of CS also predispose to EMT that contributes to the progression of lung cancer [222, 280].

Current treatments for COPD such as corticosteroids and bronchodilators are ineffective at inhibiting chronic inflammation, and do not reverse pathology. Thus, it is clear that there is an urgent need to develop new therapies to prevent the initiation and progression of COPD, and an effective option is using animal models that accurately reflect the physiopathology of the disease. Indeed, many potential future COPD therapeutics currently in clinical development, such as inhibitors of inflammatory mediators, oxidative stress, kinases, phosphodiesterases (PDE) and proteinases were originally identified in studies using animal models.

Various inhibitors of inflammatory mediators are being developed and tested for the treatment of COPD. Inhibitors of TRAIL, leukotriene B4 (LTB₄), TNF- α , IL-1, IL-8, and epidermal growth factor have shown strong beneficial effects when used in animal models, however translation into the clinic has been slow [281]. Studies exposing TNF- α receptor deficient mice to CS resulted in reduced inflammatory cells in lavage fluid and attenuated alveolar enlargement compared to wild-type mice [282]. These findings were supported by another knockout mouse study where both TNF- α receptors were shown to contribute to the pathogenesis of murine COPD, with TNF- α receptor-2 being the most active in the development of systemic weight loss, inflammation and emphysema [283]. However, as occurred with asthma, where mouse studies were not interpreted properly or transferred effectively into clinical studies, it is likely that selected groups or phenotypes of patients may respond better to specific treatments [284].

Anti-oxidants, particularly those that target specific processes in COPD have shown some promise. Resveratrol and the antioxidant enzyme Gpx-1 have been shown to protect against lung inflammation and CS-induced emphysema in mice, and a Gpx mimetic also reduced lung inflammation when administered both prophylactically and therapeutically [285, 286]. Resveratrol is a plant originated polyphenol that suppresses lung inflammation through upregulating MyD88s which is a negative regulator of inflammation [286].

Studies of animal models of CS-induced airway inflammation support the potential therapeutic

use of kinase inhibitors, such as those that inhibit p38 mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K), in COPD [287]. MAPKs play key roles in chronic inflammation [288]. The p38 MAPK pathway is activated by cellular stress and regulates the expression of various inflammatory cytokines and remodeling factors including IL-8, TNF- α and MMPs [289]. PI3Ks play roles in controlling a several intracellular signaling pathways in asthma and COPD [290, 274]. Recent studies suggest that numerous components of the PI3K pathway contribute to the expression and activation of inflammatory mediators, inflammatory cell recruitment, immune cell function and airway remodelling as well as corticosteroid insensitivity in chronic inflammatory respiratory diseases such as asthma [291, 290, 274]. We recently discovered that PI3K also plays a pivotal role in the pathogenesis of COPD. Its activity increases and is utilised by influenza virus during infections to suppress anti-viral responses [292, 274].

The PDE4 inhibitor roflumilast, a licensed treatment for severe COPD, was originally identified as a potential therapeutic in acute and chronic murine models of CS-exposure [293]. PDE4 degrades the anti-inflammatory cyclic adenosine monophosphate and its inhibition in mice has been shown to have protective effects including reversing the loss of lung desmosine, (a breakdown product of elastin), reducing neutrophil and macrophage influx, increasing the anti-inflammatory cytokine IL-10, and improving emphysema [293]. Other murine studies showed that another PDE4 inhibitor – rolipram, had little effect on airway inflammation and remodeling or emphysema whereas a semicarbazide-sensitive mono-amine oxidase inhibitor did [279].

Serine-, metallo- and cysteine proteinases are the primary proteinases implicated in the development of COPD [294]. In studies aimed at preventing the destruction of alveolar walls by proteolysis, and ultimately the development of emphysema, inhibitors of various proteinases have been trialed in animal models with varying levels of success. Emerging studies are also using mouse models to elucidate the roles of other new areas such as inflammasomes, microbiomes and the gut lung axis [295-299]. Collectively, the use of murine models of COPD and infective exacerbations is valuable in furthering our understanding of the pathogenic aspects of the disease with the aim of identifying novel therapeutic targets and developing and testing new therapies [300]. The inherent heterogeneity of the disease can also be reproduced and studied in animal models using different combinations or doses of induction agents.

10. Insights from mouse models of lung cancer

Numerous different mouse models have been developed to study the etiology, transformation, invasion and metastasis of lung cancer. These models have been used to elucidate the mechanisms of cancer initiation, progression and metastasis, and to discover biomarkers, as well as in testing preventives and treatments. Different types of mouse models of lung cancer have been developed, with the vast majority using immunodeficient or genetically modified mice.

Xenograft models are induced by injecting human lung cancer cells subcutaneously, orthotopically or systemically into immunocompromised mice. These models are mainly used to assess the efficacy of drugs before proceeding to clinical trials. Cell lines commonly used in xenograft mouse models are HCC4006, HCC827, H1975 and A549 for adenocarcinomas [301-303]; NCI-H1299 for carcinomas [304]; NCI-H460 for large cell carcinomas [305]; and NCI-H226 for SqCC [306]. Another type is termed the patient derived xenograft (PDX) mouse model where surgically removed human primary tumour tissues are grafted into mice subcutaneously or orthotopically. These models are used to develop and test personalised therapies [307]. Although xenograft models are relatively poor in predicting clinical efficacy of drugs, these models have been successfully used for developing personalised therapy [308]. Hodgkinson and colleagues demonstrated that circulating tumour cells (CTCs) molecular analysis via serial blood sampling could facilitate delivery of personalized medicine for SCLC. CTC-derived explants are readily passaged, and these unique mouse models provide tractable systems for therapy testing and understanding drug resistance mechanisms. [309]. Apart from this, xenograft models also showed accuracy in testing the efficacy of a number of drugs such as gefitinib, erlotinib and crizotinib, which showed similar results in clinical trials as seen in mouse models [310-315].

Transgenic mouse models are generated by microinjecting modified DNA into zygotes, and are used to explore the functional activity of the gene of interest- particularly their impact on the initiation, progression and metastasis of lung cancer [316]. A lung specific promoter is added to the coding region of the target gene in modified DNA to enable its expression only in the lung, and not in other organs or tissues [316]. A transgenic mouse model was developed to test the dependency of EGFR signalling in tumour development and progression. This model also showed that inhibiting EGFR through small molecular inhibitors (erlotinib or HKI-272)

and humanized anti-hEGFR antibody (cetuximab) was effective in inducing tumour regression [317].

Syngeneic mouse models are generated by injecting immunologically compatible cancer cells into immunocompetent mice. The use of these models in the study of lung cancer is rare and the only mouse model developed so far is the Lewis lung carcinoma model [318]. This model is valuable for investigating the tumour microenvironment and exploring the immune and toxicological responses of potential drugs. Spontaneous models are induced using oral, intraperitoneal or topical application of carcinogens to genetically susceptible but wild-type mouse strains like A/J and SWR. Carcinogens used are cigarette smoke, 4-methylnitrosamino-3-pyridyl-1-butanone (NNK), benzo(a)pyrene for adenocarcinomas [319, 320], and N-nitroso-tris-chloroethyl urea (NTCU) for SqCC [321]. Small cell lung cancer is induced through inactivation of both Rb and p53 genes. These models are valuable for exploring carcinogenesis, disease pathology, biomarker discovery, tumour microenvironment and roles of immune cells in cancer initiation development and progression, immune responses and the efficacy and toxicology of drug treatment [322].

Carcinogens such as cigarette smoke and NNK, can be combined to induce adenomas and after many months, adenocarcinomas. Published models are long term at 5-9 months [323, 320, 324]. Initially, hyperplastic foci are seen in the bronchioles and alveoli that develop as adenomas and then progress to adenocarcinomas [325]. It is often difficult to distinguish adenomas, premalignant adenomas and malignant adenocarcinomas. Adenocarcinomas are mostly distinguished from other tumours based on characteristics such as the presence of large pleiomorphic cells with vesicular nuclei, prominent nucleoli, undifferentiated cytoplasm and high mitotic index [326]. Morphologically, they have both solid and papillary characteristics [327]. Tumours that develop in mice have low vascularization and metastatic potential [323]. Club cells (originally known as Clara cells), alveolar type II cells, multipotent stem cells or derivative lineages of these cells are usually the cells of origin of tumours [327, 328]. The origin of papillary tumours is unclear, however, solid tumours usually originate from alveolar type II cells [327]. The histopathological and molecular characteristics of spontaneous mouse lung adenocarcinoma models are similar to the tumours that develop in humans [326].

Squamous cell carcinoma (SqCC), mouse models can be induced using N-nitroso-tris-chloroethylurea (NTCU) administration and initially show premalignant lesions which

progress to frank lung SqCC similar to those that develop in humans [329]. SCLCs in mice are histologically similar to those seen in humans with a similar pattern of metastatic disease [330]. Neuroendocrine cells are believed to be the origin of SCLC [331].

Further characterisation of lung cancer mouse models and the development of novel models that accurately recapitulate the histological, immunological and molecular characteristics of human tumours are needed to advance our understanding of lung cancer and to discover more effective early diagnostics and treatment.

11. Conclusions

Currently, there is a lack of strong evidence to suggest that medical management for COPD should be modified in patients with concomitant lung cancer. Given both COPD and lung cancer are heterogeneous conditions, individualised treatment strategies are needed for patient management. Optimisation of care for patients with COPD prior to, during and after definitive treatment for lung cancer should be part of the multidisciplinary management of patients with these dual pathologies. The use of long-acting bronchodilators and pulmonary rehabilitation is the mainstay management for these patients. Addition of inhaled corticosteroids is appropriate for patients with moderate-to-severe COPD and recurrent exacerbations. Inhaled corticosteroids may have the potential to ameliorate EMT in patients with COPD, thus potentially protecting against the development of lung cancer. However, at this stage, there is no prospective data linking corticosteroid therapy to cancer protection, and ICS continue to be reserved for those with more severe COPD and either or both of poorly controlled symptoms and exacerbations. There is an urgent need for the development of new therapeutics, which could be given in early COPD, given that the incidence of lung cancer is even higher in patients with mild-moderate COPD (GOLD 1 and 2) than in those with more severe disease [332]. Therapeutic options available for patients with lung cancer and concomitant COPD have improved with advances in radiotherapy such as IMRT and SABR, as well as systemic therapies such as TKI and immunotherapy. However, pneumonitis secondary to radiotherapy or systemic therapies is a potential significant side effect in patients with pre-existing lung disease. At present, it is unknown whether COPD or its therapies may impact on the development or clinical course of therapy-related lung toxicity. Well-controlled clinical trials are needed to explore the efficacy of various strategies for reducing lung cancer risk in patients with COPD and improving clinical outcomes for patients with both diseases. There is a need

for the development of pre-clinical animal models, which more faithfully represent human disease. With increasing understanding of the molecular pathogenesis underlying both lung cancer and COPD, new strategies using molecularly targeted therapies may be developed in future for prevention of lung cancer and treatment of COPD in this population.

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Compliance with Ethical Standards

Conflict of interest

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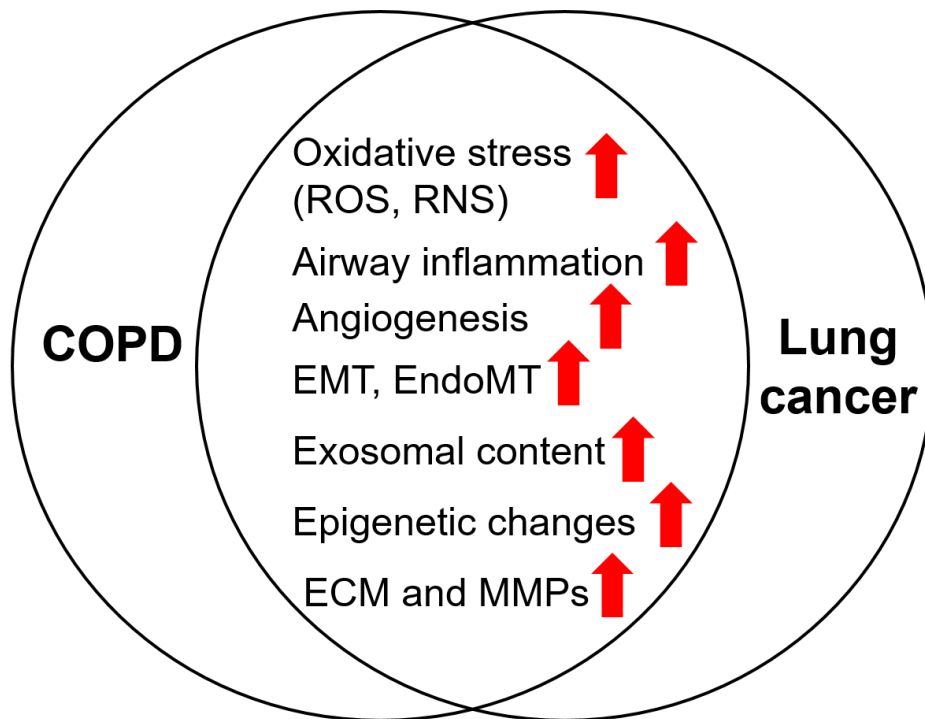
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Table 1: Observational studies of inhaled corticosteroids (ICS), statins and risk of lung cancers in patients with COPD

Reference	Design (duration)	Number of participants	Type of drug	Hazard ratio [95% CI]
Parimon 2007 [23]	Retrospective cohort study (median 3.8 years)	ICS = 517 No ICS = 9957	Triamcinolone, beclomethasone, flunisolide and fluticasone	Adjusted: ICS < 1200µg = 1.3 (0.67-1.90) ICS ≥ 1200µg = 0.39 (0.16-0.96)
Kiri 2009 [24]	Retrospective nested case-control study (1989-2003 to June 2005)	ICS = 127 No ICS = 1470	Any ICS	Overall = 0.64 (0.42-0.98) 1-2 prescriptions/year = 0.88 (0.51-1.52) 3+ prescriptions/year = 0.51 (0.30-0.84)
Liu 2017 [25]	Retrospective cohort study (median 9.8 years)	ICS = 1290 No ICS = 12396	Fluticasone and budesonide	Overall = 0.70 (0.46-1.09) Cumulative ICS dose > 39.48mg = 0.45 (0.21-0.96)
Liu 2016 [30]	Retrospective cohort study (between January 1, 2001 and December 31, 2012)	Simvastatin = 3418 Lovastatin = 2109 Atorvastatin = 5484 Fluvastatin = 1510 Pravastatin = 1501 Rosuvastatin = 2741	Statins	Overall lung cancer risk in the statin users was lower than that in the statin nonusers (adjusted hazard ratio [aHR] = 0.37) Of the individual statins, lovastatin and fluvastatin did not reduce lung cancer risk significantly Lung cancer risk in patients using rosuvastatin, simvastatin, atorvastatin, and pravastatin was significantly lower than that in statin nonusers (aHRs = 0.41, 0.44, 0.52, and 0.58, respectively)

ICS inhaled corticosteroids; *COPD* chronic obstructive pulmonary disease

Figure 1: Showing shared mechanisms between COPD and lung cancer. *ROS* reactive oxygen species; *RNS* reactive nitrogen species; *EMT* epithelial mesenchymal transition; *EndoMT*; endothelial to mesenchymal transition; *ECM* extracellular matrix; *MMPs* matrix metalloproteinases.



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