Chronic obstructive pulmonary disease (COPD) 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 especially at a higher risk of developing lung cancer 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 and susceptibility to DNA damage and cellular mutagenesis. In fact, COPD could indeed be the driving factor for lung cancer, providing a conducive environment that propagates its evolution. In the early stages of smoking, the body's 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 radio and chemotherapy. Vital to the development of new-targeted therapies is an in-depth understanding of the various molecular mechanisms that are associated with both pathologies. Thus in this comprehensive review, we shall provide a detailed overview of the possible underlying factors that link COPD and lung cancer and current therapeutic advances both 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 but more understanding is needed. Only by understanding what is happening new therapeutic targets may emerge.

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

Inhaled corticosteroids suppress EMT in COPD patients and decrease lung cancer risk as shown in epidemiological studies. EMT might be the process through which inhaled corticosteroids are showing anti-cancer effects. This suggests EMT as a novel therapeutic target for management of both COPD and lung cancer.

Majority of the lung cancer and obliteration of small airways occurs quite early in COPD. Therefore, it is important to understand mechanism that gets switched on early in the disease, to have more personalised early intervention.

Exercise training should be 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. Compared to smokers without COPD, people with COPD are twice as likely to develop lung cancer, a common cause of death in COPD [1]. Further, patients with lung cancer and concomitant COPD have a worse survival than patients with lung cancer without COPD [2-4]. Although 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 now considered 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 [5]. The current average survival rate for lung cancer patients is 5 years in population that varies from 4-17% depending on regional differences and this has been attributed to the poor advances in treatment and diagnostics [5, 6]. 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 (US) and France [7], 61% in Asia, and 40% in sub-Saharan Africa. Other causes of lung cancer also includes second hand tobacco smoking, and with over 21,400 lung cancer deaths in non-smokers annually [8]. In lower and middle-income countries the risks for lung cancer are also associated with indoor air pollution mostly due to combustion of wood or coal used for cooking and heating purpose [9]. A recent estimate by Australian Institute of Health and Welfare (AIHW) [10] found that lung cancer was the leading cause of death for both male and female Australians followed by colorectal, breast, prostrate, and pancreatic cancer. In 2017, nearly 12,500 Australians were diagnosed with lung cancer, which is 34 people every day [10]. Lung cancer also remained the highest in overall burden among different cancers [10].

Lung cancer are broadly classified into two major types; non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) [11, 12]. NSCLC constitute 85% of all lung cancers, and is further characterised into squamous cell carcinoma (SqCC), adenocarcinoma, and large cell carcinoma. SqCC is the most common form of NSCLC, and accounts for up to 30% of all lung cancers [13]. While SqCC typically arises from large airway bronchial squamous epithelium, adenocarcinoma arises from the secretory (glandular) cells that are located in the distal epithelium lining of the lung bronchi [14]. 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 [15]. In addition to these common subtypes of NSCLC, there are also other variants, including bronchoalveolar carcinoma, mixed and undifferentiated pulmonary carcinomas.

Small-cell lung cancer (SCLC) usually arises centrally in the chest (large airways or lymph nodes) [16]. It is associated with paraneoplastic syndromes at presentation such as inappropriate secretion in antidiuretic hormone as small-cell tumours contain dense neurosecretory granules that can then give this tumour endocrine/paraneoplastic syndrome components. SCLCs have traditionally been staged into limited and extensive stage disease [17]. They are divided into typical and atypical and can grow either in the airways or in the lung periphery [16, 17]. Like SCLC, carcinoid tumours are characterised as neuroendocrine tumours, which are commonly located in the gastrointestinal tract, and occasionally in the lung [18].

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 [19-21]. In view of potential shared mechanism of chronic inflammation in both diseases, 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 [22-24]; **Table 1**), with a negative dose-response relationship between the dose of inhaled corticosteroids and the risk of developing lung cancer [22-24]. 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 [25]. In contrast, inhaled corticosteroids have not been shown to exert significant chemopreventive effects in smokers with premalignant lung lesions [26, 27]. The exact mechanisms through which inhaled corticosteroids exert these 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 [28]. A retrospective cohort study of more than 40,000 patients with COPD reported that the use of statins reduced lung cancer risk by 63% [29]. 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 [30]. However, randomised controlled trials on lung cancer prevention using antioxidant supplements in ever-smokers have been disappointing. Neither individual or combination supplementation of alpha-tocopherol, beta-carotene and retinol was found to reduce lung cancer risk in major randomised controlled trials, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study (ATBC) [31] and Beta-Carotene and Retinol Efficacy trial (CARET)[32]. Indeed, the ATBC and CARET studies, which include over 47,000 ever-smokers in total, have consistently shown an increased risk of lung cancer with beta-carotene supplementation in ever-smokers [31, 32]. 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 [33]. The mechanism of increased lung cancer risk with micronutrient supplementations is unclear.

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 [34]. 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 [34]. 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 [35].

Exercise capacity of patients with COPD and/or lung cancer can be measured using either laboratory-based (such as maximal incremental cardiopulmonary exercise test [CPET]) or field-based exercise tests (e.g. 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 (VO_2peak) measured during a CPET has been shown to be a strong predictor of mortality [36, 37]. Furthermore, VO_2peak measured before surgery is a strong predictor of postoperative pulmonary complications for patients undergoing lung resection for NSCLC [36] Of note, the performance during field-based walking tests have also demonstrated important prognostic value. A systematic review of 13 studies reported the association between six-minute walk distance and mortality in patients with COPD [38]. In patients undergoing lung resection for NSCLC, poor performance in the 6MWT or the ISWT (i.e. < 400 m) before surgery is associated with an increased risk of postoperative pulmonary complications [39, 40].

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. [41] When compared to COPD, research on exercise training in patients with lung cancer is on its infancy. However, recent studies have demonstrated its value across the whole lung cancer continuum, especially in patients with NSCLC [42-45].

Pulmonary rehabilitation, including exercise training, should be offered to patients with stable COPD or following an exacerbation of their disease [34, 46]. A Cochrane review of 65 randomised controlled trials (RCT's) concluded that pulmonary rehabilitation significantly improves exercise capacity, health related quality of life (HRQoL), and symptom control in patients with COPD [47]. Of note, there was no difference between exercise training only and more complex pulmonary rehabilitation programmes [47]. Pulmonary rehabilitation following an exacerbation of COPD has been shown to reduce hospital readmissions [48]. In patients with early stage NSCLC, both preoperative and postoperative exercise training programmes have demonstrated to be effective at improving health outcomes [49, 43]. However, despite the growing evidence of the benefits of exercise training in this population, referral of such patients to exercise training programmes is still low [50]. A standard pulmonary rehabilitation exercise program runs between 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 is mainly comprised of aerobic training and usually conducted whilst patients are waiting for surgery. In most studies to date, this timeframe ranged between 1 to 4 weeks [43]. In both cohort studies and a systematic review of randomized controlled trials (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 [51, 52, 43]. In addition, pre-operative exercise training was associated with improved lung function recovery after surgery and reduced post-operative pulmonary complications (51, 73).

A decline in exercise capacity and lung function, which is an important prognostic factor, is commonly observed following lung resection for NSCLC [53, 54, 36]. 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; sessions are performed 2 to 3 times/week and include both aerobic and resistance training. Postoperative exercise training has been shown to improve exercise capacity (VO_2peak and six-minute walk distance),[49, 42, 44] total muscle mass[44] and HRQoL [44].

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 RCT's being conducted to investigate effectiveness of exercise training in this population [55-57]. To date, exercise training has been shown to be feasible and safe in patients with advanced lung cancer [58].

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 [59-62]. 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 perioperative period are important for optimisation of baseline lung function and fitness in order to minimise potential surgical morbidities. The evidence on short-term effects of these approaches for improving perioperative outcomes is limited.

Long-acting bronchodilators, including long-acting muscarinic antagonists (LAMAs) and long-acting beta$_2$-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 [63, 64]. Perioperative commencement of long-acting bronchodilators, within 1 to 2 weeks prior to thoracic surgery significantly improved pre-operative lung function [65, 66]. Initiation of LAMAs or LABAs prior to surgery has also been shown to reduce post-operative cardiorespiratory complications in patients with lung cancer [67, 68]. 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 [69]. Cardiovascular complications are common following thoracic surgery, particularly in those with COPD who are at high risk of cardiovascular events [61, 70]. Concerns have been raised that cardiovascular adverse events could be associated with the use of long-acting bronchodilators. Activation of beta2-agonists with LAMAs can precipitate arrhythmias, myocardial ischaemia and congestive heart failure. Muscarinic receptor antagonists have been associated with cardiovascular events in observational and clinical trials [67, 71]. However, increased incidence of post-operative cardiac complications, including arrhythmias, with the use of LABAs and LAMAs has not been reported in retrospective studies [67, 71].

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 [72-74] [75-78]. A retrospective study by Yamanashi et al revealed no association between perioperative use of inhaled corticosteroids and post-operative respiratory complications [79]. 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 [66].

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. 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 as lungs are exquisitely sensitive to ionizing radiation. The incidence of radiation pneumonitis in lung cancer varies depending upon irradiation techniques and regimen. The reported incidence of clinically symptomatic radiation pneumonitis is up to 17% among patients undergoing radical radiotherapy [80, 81]. 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 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%) [82]. Clinically significant radiation pneumonitis develops in less than 10% of patients receiving SBRT for lung cancer [83, 84].

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 [85, 86]. 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 [87, 88]. 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 [89].

7. Systemic therapies

While systemic chemotherapy is the standard of care for patients with advanced lung cancer, recent development of tyrosine kinase inhibitors (TKIs) and immunotherapy has revolutionised the 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 [90]. Current approach of 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 for 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 [91-93]. 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 [94]. Interstitial lung disease, another risk factor for drug-induced pneumonitis, not uncommonly co-exists in patients with COPD [95]. In addition, long-term 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 [96, 97]. 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.

Given that 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 [98]. 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. COPD has been shown to be a risk factor for lung cancer [99]; COPD patients are at five-fold higher risk to develop lung cancer as compared to those with normal pulmonary function [100]. 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 the 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 are 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 efficient immune response to infections as well as obliterating cancer cells. In smokers and COPD patients Morlá et al [101] 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. [102] 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 (MDA) and TBA-reactive substances (TBARS). Thus, decreasing life span and DNA damage in

lymphocytes in smoker and COPD patients 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 current findings, where we recently reported that early COPD is associated with decrease in key inflammatory cell populations and making patients more susceptible to respiratory infections as well [103-105, 77, 78].

In lung cancer, elevated levels of ROS induce single or double-stranded DNA breaks and abnormal DNA crosslinking [106]. 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 irreversibly damage to the DNA by forming DNA adducts through covalent binding or oxidation. BPDE–DNA adducts formation, if left unrepaired by nucleotide excision repair mechanisms, can block the transcription of essential genes, leading to unwarranted cellular effects [107]. Genome-Wide Association Study (GWAS) studies have also revealed that suboptimal DNA repair capacity (DRC) as a major determinant for genetic susceptibility to lung cancer although there have been considerable inter-individual variation in DRC partly due to the variability in DNA repair genes [108].

ROS also induces cellular senescence via DNA damage, arrests cellular growth and alters their function. Senesced immune cells have activated protein complexes leading to a condition termed senescence-associated secretory phenotype (SASP) which produce phlogogenic substances such as IL-1, IL-6, and IL-8 [109]. 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 there [110]. In lung cancer, cytokines that are enhanced in SASP complex are also known to be a prognostic marker for NSCLC. Interestingly, among them IL-6 is known to initiate growth and spread of lung cancer in mouse models, and has been attributed to the IL-6/STAT3 pathways [111].

The impact of ROS and their association to smoking and lung cancer and COPD are of paramount importance and further understanding the underlying mechanisms could possible provide new therapeutic opportunity for early interventions.

8.2 Inflammation

Airway inflammation is known to play a critical role in COPD and cancer [112]. 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 [113, 114]. However, evidence suggests substantial contradiction about the actual picture of the type of inflammation in the airway wall wherein hypo-cellularity or cellular dysfunctionality/abnormalities are observed [114].

In lung cancer, it remains to be deciphered whether there is casual role of inflammation in enhancing mutations in cancer. However, inflammatory factors can enhance the progressive capacity of cancer cells. For examples, increased activation of NF-κB activity results in lung inflammation and substantial pro-tumorigenic effect. The effector cell population that mediates tumorigenicity are macrophages, which could be recruited to the lungs because of the epithelial cell induced NF-κB activation [115]. A number of studies have reported increase in alveolar and luminal macrophages in normal lung function smokers and COPD current smokers when compared to non-smoker controls [116]. Further, sub-phenotyping the macrophages in these

patients groups also revealed predominantly M2 macrophages, with increased expression of phagocytic receptor CD163/CD206 [117, 114]. 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 [114]. Interestingly, in tumour microenvironment itself, tumour-associated macrophages (TAMs) were shown to be predominantly M2 as well, which suggest that polarization of macrophages observed in mild-moderate COPD patients could be pro-tumorigenic [118]. A recent meta-analysis with over 2500 NSCLC patients [119], observed that M2 macrophages were indeed the dominant macrophage phenotype and specifically the increase in survival of NSCLC patients was attributed to the sub-type of macrophages that dominated the tumour microenvironment [119, 118]. They concluded that patients with larger numbers of M2 macrophages had lesser chances of survival than those with M1 macrophage phenotype. 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 mild-moderate COPD patients over CD4 T cells and this dominance may be partly due to increased susceptibility of COPD patients to viral infections [113]. Recently, McKendry et al [120] provided evidence of increased expression of PD-1 in CD8+ T cells and the ligands PD-L1 on macrophages in ex-vivo samples from mild-moderate COPD patients. The interaction between PD-1 and its ligand PD-L1 induce 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 [120]. Similar, increased expression of PD-1 on CD8+ T cells was found to be especially 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 advance stages of cancer [121, 122].

These studies are suggestive indicators that orientation of immune cell expression patterns in lung cancer are observed quite early in smokers and COPD patients than previously thought and that detecting these changes could help to design more effective future diagnosis and therapies that can address this more efficiently.

8.3 Role of extracellular vesicles (EVs)

Extracellular vesicles (EVs) are small membranous vesicles that are secreted or shed by cells. EVs are categorized as exosomes, ectosomes, microvesicles, or apoptotic bodies defined by the size of the particle [123]. In humans, EVs can be detected in various body fluids, including blood, urine, saliva, breast milk, ascites, and cerebrospinal fluid among others. The size of EVs vary from 30-1000 nm, depending on the type of EV, such as exosomes are the smallest (30-100 nm) and larger are apoptotic bodies that are up to 100 nm [124]. Exosomes can play a crucial role in both COPD and lung cancer. EVs in general, are known to actively regulate tumour microenvironment (TME) by altering the immune response or through modulating through epithelial transition, fibroblasts activation or regulating angiogenesis [125]. The changes to the TME could take place through selective transfer mechanisms and would ideally involve both proteins and nuclear materials such as RNA. For examples, McCready et al [126] observed that HSP90α, in tumour associated secretory exosomes increases invasiveness of cancer cells through the activation of plasmin and annexin-II. Interestingly, HSP90α protein is abundant in COPD patients and act as potent biomarkers along with HSP 27 and 70 [127]. HSP90 potentiates epithelial mesenchymal transition (EMT) in several forms of cancer [128] and this phenomenon is active in early stage COPD patients as well, pointing towards possible association. Similar to transfer of proteins, miRNA-containing exosomes can be a determining factor in both lung cancer and other chronic lung disease [129]. miRNAs are known to

selectively inhibit or silence mRNA translational process, thus acting as an important cellular modulator. For example, miR-200 family of miRNA can actively inhibit TGF-β1 induced EMT activity in airway epithelial cells [130] and forms a double negative feedback loop with a family of EMT-inducing transcription factors ZEB [131]. Observation in both lung cancer and COPD suggest a significant reduction in cellular miR-200 and an increase in extracellular exosomal miR-200 [132, 133]. The decrease in exosomal miRNA suggest 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 smoking could lead to the discovery of potential biomarkers and novel therapeutic interventions [134].

8.4 Extracellular matrix (ECM) and proteinases

Extracellular matrix (ECM) has important roles in maintaining tissue functionality and stability and 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 [135, 136]. 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 [137, 138]. One of the major producers and regulators of ECM are fibroblasts, they synthesise large amounts of matrix components, different growth factors and inflammatory mediators. Fibroblasts may thereby have important modulatory roles in autocrine and paracrine fashions 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 [136]. 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 [139]. 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 [140]. 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 [139]. In COPD, there are processes ongoing in parallel with excessive ECM being produced manifested as peribronchial fibrosis and degraded ECM in the alveoli resulting in emphysema [137]. Alterations in elastic fibres, fibronectin, collagens, tenascin-C and versican have been identified throughout all lung compartments in patients with moderate COPD [141] and there are pronounced alterations in proteoglycan synthesis from central and distally-derived lung fibroblasts from patients with severe COPD [142]. Importantly, distal lung fibroblasts from severe COPD patients appeared to have altered fibroblast function and defect repair mechanisms in the ECM structure of the collagen network assembly in response to the prostacyclin analogue iloprost, which may thereby affect emphysema progression [143].

The homeostasis of ECM is tightly regulated by matrix metalloproteinases (MMPs) and specific tissue inhibitors of metalloproteinases (TIMPs) [144] [145]. These proteases target the ECM for degradation, which alter tissue architecture and cause the release of ECM derived chemoattractant signals known as matrikines, which can propagate inflammation [146]. MMPs, especially MMP-2 and MMP-9, are implicated in the degradation of ECM in basement membranes, which facilitate tumour invasion and metastasis. MMP-2 is expressed in both

normal and tumour tissues, whereas MMP-9 mostly is induced during tissue remodelling [145]. In cancer, MMP-9 overexpression may contribute to stimulate tumor vascularisation and tumor cell proliferation [147]. An overproduction of MMPs in intratumoral stromal cells is associated with poor prognosis of NSCLC [145, 147]. 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 [148]. In COPD, there is an imbalance between MMPs and TIMPs which causes an overproduction of MMPs. Increased MMP activity and neutrophil elastases (NE) correlates with COPD pathology and especially MMP-9 has a major role in the development of emphysema [149]. The degrading of ECM by MMPs may also increase the bioavailability of growth factors, cytokines and receptors stored in the ECM.

8.5 Angiogenesis

Smoking, a key factor in both COPD and lung cancer, results in hypoxia, which is an important driver of angiogenesis. Nicotine may increase hypoxia-inducible factor (HIF)-1 in NSCLC and promote tumour angiogenesis [150, 151]. Vascular endothelial growth factor (VEGF) is one of the most important factors promoting angiogenesis and vascular remodeling processes [152]. 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 [153]. As tumors increase in size their microenvironment becomes hypoxic and HIF is activated, which induce expression of MMPs and VEGF, leading to progression and invasion. VEGF correlates with progression, metastasis and poorer prognosis [154]. Proteinases induce the release of growth factors such as TGF-B and VEGF, which play a pivotal role in tumorgenesis and metastasis of lung cancer. CAFs 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 (VEGFR) 2, expressed on endothelial cells [155]. During hypoxic conditions, prostacyclin synthase expression was up-regulated in human lung fibroblasts promoting VEGF synthesis in tumours [156].

Pulmonary vascular remodeling is common in COPD [152] and comorbidities in cardiovascular disease have negative impacts on COPD prognosis [157]. 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 [158]. Interestingly, VEGF is synthesised in high amounts by distally derived lung fibroblasts and induced by both prostacyclin and TGF-B. The synthesised VEGF acted in an autocrine fashion by increasing ECM synthesis, migration and proliferation of human lung fibroblasts [159]. However, in this study there were not any 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 [160]. COPD patients with chronic bronchitis had increased levels of VEGF in sputum in contrast to COPD patients with more emphysema that showed lower levels of VEGF [161]. Patients with acute exacerbations presented high levels of VEGF in the circulation compared to stable COPD patients and healthy individuals [162]. Increased VEGF expression is associated with bronchial angiogenesis that inversely correlated with lung function in COPD patients [163, 164]. In contrast, a decreased expression of VEGFR2 in parenchymal regions in severe COPD patients correlated with increased endothelial cell death [165]. Inhibition of

VEGFR2 in an animal model resulted in emphysematous lung structure and cell apoptosis [166]. Interestingly, VEGF may act both as a promoter of endothelial cell function and a negative regulator of vascular smooth muscle cells (VSMCs) and vessel maturation in combination with platelet derived growth factor [167], highlighting the complex role of VEGF in vascular remodelling. Altogether, VEGF may have different roles depending on disease progression and disease severity. VEGF has the ability to bind to multiple proteins and proteoglycans present in the ECM [168, 169]. The proteoglycan biglycan is important for migration of cells [170] and may up regulate VEGF expression [171]. Endothelial cells that form vasculature play an important role in providing nutrients and oxygen to the tumour. We have previously reported the VEGF and TGF-β1 positive vessels and vessels in general increase in the reticular basement membrane (Rbm) of smokers and COPD patients but also seen encroaching into the epithelium [172-176]. It is quite possible that these two growth factors actively promote neoangiogenesis of the Rbm and epithelium itself supporting formation of a pro-cancer stroma with associated active epithelial mesenchymal transition (EMT) [173, 177]. In a separate study, we also reported effects on inhaled fluticasone propionate on vascular remodelling in COPD patients [177]. In this study, we observed that lamina propria vascularity returned to normality after the steroid treatment but the Rbm vessels did not decrease significantly after the 6 months of treatment. This also suggested that may be for complete depletion of Rbm vessels 6 months of corticosteroid therapy is inadequate, and angiogenic sustainability might be the reason for continues cancer growth in smokers and COPD patients [178]. We believe these are important clinical observations and warrants further investigations.

In NSCLC the degree of tumour associated angiogenesis correlates with disease progression and predicts unfavourable survival outcome. High vascularity at tumour periphery has been correlated with tumour progression [179]. Perlecan is a major ECM protein located in pulmonary vessels, essential for the structure of vascular basement membranes [168, 142] and a crucial co-factor for VEGF binding and storage of VEGF [168]. A study on endothelial cell function showed that interaction between perlecan and VEGF-A promotes VEGFR2 signalling [180]. Down regulation of perlecan caused reduced angiogenesis in vivo [181]. Interestingly, perlecan and biglycan synthesis are reduced in fibroblasts from severe COPD patients [142]. Furthermore, endothelial-derived angiocrine signals were shown to induce regenerative lung alveolarization. Activation of VEGF2 and FGFR1 in pulmonary capillary endothelial cells induced MMP14 expression that unmasked EGF receptor ligands to enhance alveologenesis [182]. Perlecan, from endothelial cells in a paracrine way blocked proliferation and invasiveness of lung cancer by impacting pro-inflammatory pathways [183].

Cyclooxygenase-2 (COX-2) is expressed in many tumours, especially adenocarcinoma, and associated with carcinogenesis and tumour resistance to anti-cancer drugs. COX-2 and prostaglandins (PGs) may thereby play a role in the pathogenesis of lung cancer via effects on angiogenesis, cell proliferation and apoptosis [184]. EGF-induced angiogenesis via the COX-2 pathway involves p38 and JNK kinase activation pathways in endothelial cells [185]. COX-2 is increased in the distal lung of COPD patients and increased in sputum of smokers together with MMP-2, which correlated with severity of airflow limitations in stable COPD patients [186]. COX-2 is also constitutively expressed in different lung cancers including NSCLC [184, 187]. COX-2 via mPGES-1 and PGE_2 receptor EP_1 promote cancer growth in a chronic inflammatory environment [188]. Activation of PPAR-receptors by nicotine also induces expression of PGE_2 receptor EP_4 through PI3-K signals and increased human lung carcinoma cell proliferation in NSCLC [189]. Interestingly, matrix stiffening and fibrosis appear to be linked through COX-2 suppression and reduced PGE_2 levels in an autocrine feedback loop

[190]. Preclinical and clinical studies have shown that COX-2 inhibitor has some efficacy for NSCLC [191], 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 that are associated with nicotine dependence and cigarette smoke consumption [192, 193]. The linkage of COPD, lung cancer and peripheral vascular disease, with these genes point out their possible role – surrogates for tobacco exposure [192]. Single nucleotide polymorphisms (SNPs) 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 [193]. Although its functional contribution to lung cancer and/or COPD remains yet to be elucidated, the involvement of Rho GTPases in pulmonary endothelial barrier in lung suggests a potential mode of involvement for FAM13A [194].

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 mark between COPD and lung cancer is that of CDKN2A that encodes for tumor suppressors p16 (INK4A) and p14 (ARF) [192], an observation consistent with both COPD and lung cancer viewed as ageing diseases [195]. Similarly, DNA methylation of 2 genes CCDC37 and MAP1B was observed in COPD and lung cancer patients, with the greatest degree of methylation observed in patients with both diseases[195]. In cancer patients with COPD, immune genes expressed either by tumor cells or by tumor-infiltrating immune cells were highly methylated as compared to patients without COPD [196]. Thus, COPD may epigenetically alter the immune repertoire.

8.8 Epithelial-Mesenchymal Transition (EMT)

Epithelial-Mesenchymal Transition (EMT) is a biological process by which epithelial cells lose cell-cell adhesion and gain mesenchymal traits of migration, invasion, and producing components of extracellular matrix (ECM). EMT is a manifestation of airway basal reprogramming in smokers and COPD [197]. EMT need not be a binary process, rather cells can display a spectrum of phenotypes ranging from fully epithelial to fully mesenchymal [198-200]. Hallmarks of EMT have been observed in airways of COPD patients and smokers, and NSCLC cells can attain partial EMT – i.e. a hybrid epithelial/mesenchymal (E/M) phenotype – or a complete EMT phenotype [200]. Thus, EMT has been proposed as a potential link between COPD and lung cancer.

We have previously reported that EMT is an active process in both small and large airways of COPD patients [201-206]. EMT associated with organ fibrosis is deprived of angiogenesis, termed as Type-2 EMT and when it leads to the formation of pro-cancer stroma, it is termed as Type-III EMT, which is strongly associated with neo-angiogenesis [207, 99, 208]. 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 in quite common, especially squamous cell carcinomas [209, 210]. 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 [173, 211, 212]. EMT may be the mechanism through which ICS provide protection against lung cancer in COPD, statins might have similar effects but more work is needed [178].

Furthermore, EMT in COPD may be activated by interactions among epithelial cells and fibroblasts [213], reminiscent of non-cell autonomous regulation of EMT in lung cancer [214]. A recent report showed that acute cigarette smoke and associated infections, together plays an important role in driving complete EMT; thus an extra insult, such as an infections leads to more exaggerated form of EMT leading to chronically remodelled airways as observed during COPD [215]. SLUG and ZEB1 – transcription factors often associated with a partial EMT[213, 216] – were activated in COPD bronchial epithelial cells, potentially enabling cell survival [217]. We also recently reported increased expressions of β-catenin, Twist and Snail in airways of smokers and COPD [206]. These transcriptional regulators of EMT correlated with markers of EMT and were associated with decrease in lung function in both smokers and COPD [206]. 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[218], similar to the transcription factor NP63α that can both activate and inhibit ZEB1[219, 220]. Intriguingly, a hybrid E/M phenotype has been identified to possess enriched stem-like abilities as well as resistance to epidermal growth factor receptor inhibitor erlotinib [221]. The emerging notion about the highly aggressive behaviour of a hybrid E/M phenotype in cancer [222, 223] [224] argues for a potential role of a partial EMT in driving COPD, in addition to 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) and can attain motile phenotype and express fibroblast associated markers such as vimentin, type I collagen, and α-smooth muscle actin (SMA). EndoMT is a critical process during embryogenesis, and especially play an important role in embryonic cardiac development [225]. However, when challenged by persistent damage and inflammation during pathological conditions, EndoMT get initiated and can contribute to organ fibrosis [226] and promote cancer conditions as well [227-229, 226, 230]. Similar to 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 [231]. EndoMT like EMT may be active in both COPD [232] [233] and lung cancer [234, 235]. In cancer, it is suggested that activated myofibroblasts and cancer associated fibroblasts (CAFs) produced by EndoMT can facilitate tumour growth and cancer progression. This also fits in with the underlying cancer pathology wherein tumours are heavily associated with increased angiogenesis. Thus, it is very much possible that endothelial cells are contributing to the pool of CAFs [227, 236, 230]. EndoMT can also initiate the formation of pro-cancer stroma quite similar to Type-3 EMT, so again it has the potential to initiate cancer and at the same time could help the tumour to thrive [230].

Others and we have reported vascular remodelling in COPD, main structural changes involve intimal and medial thickening, leading to reduction of lumen diameter and muscularization of arterioles [237]. The other changes involve hypo-vascular lamina propria and hyper-vascular Rbm in large airways of smokers and COPD [238-240, 176, 241]. Both loss of vessels and vascular remodelling give rise to pulmonary hypertension in COPD [237, 242]. Interestingly, these vascular remodelling changes are also observed in early COPD and in normal lung function current smokers [237, 243, 158, 238-240, 176]. Increased expression of FSP-1 has

been reported in occulated arteries and small vessels [243]. Abnormal deposition of pulmonary smooth like cells has been considered as the key pathological feature of arterial remodelling [244]. These cells lead to increased production of ECM proteins, with deposition of collagen and elastin proteins contributing to narrowing of arterial lumen hence pulmonary hypertension. But the origin of these smooth muscle like cells and the underlying mechanisms involved in vascular remodelling are poorly understood [244]. It is quite possible again EndoMT is the process which actively contributing to this pathology.

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 [231]. 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 [245-247][26–28]. Similar 'phenotypic stability factors' for a partial EndoMT state remain to be identified. Computational approaches to calculate the rates and trajectories of EndoMT can be valuable in better characterizing the dynamics and phenotypic spectrum of EndoMT [248]. Recent studies have highlighted that 'molecular EMT' and 'morphological EMT' need not always occur simultaneously, i.e. cells expressing markers of EMT need not always migrate/invade, and cells that can invade/migrate need not show molecular markers of EMT[249, 250]. Similar criteria can be used to distinguish between 'molecular EndoMT' and 'morphological EndoMT'. Thus, further investigations into the functional and morphological aspects of EndoMT shall yield better insights into the contribution of EndoMT in COPD and cancer progression.

9. Insights from mouse models of COPD

Animal models of CS-induced disease have been developed and have used guinea pigs, rats and mice [251, 252]. 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 [252-254]. 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 [255-258, 252-254, 259-264]. The effects of CS also predispose to epithelial to mesenchymal transition (EMT) that contributes to the progression lung cancer [209, 265].

In one model, mice were exposed to side-stream CS for 36 weeks that induced various hallmarks of human COPD, including increased airway resistance and respiratory system elastance [266]. However, this is a long model and shorter models that have the hallmark features of disease enable rapid progression of research, our understanding of COPD pathogenesis and aid in development of new treatments. Recently we developed a short-term mouse model of CS-induced experimental COPD, using nose-only exposure that develops the major features of the human disease in 8 weeks [252, 267, 253, 259]. Mice are exposed to the smoke of 12 cigarettes for 75 minutes, twice per day for 5 days per week [268]. The CS consists of normal air interspersed with puffs of CS and is representative of a pack-a-day smoker. This regimen results in acute and chronic airway and parenchymal inflammation, goblet cell metaplasia, airway remodelling, emphysema and impaired lung function [252, 259, 267, 253, 254]. Like in humans, features are not suppressed by corticosteroid treatment and do not resolve over time, mice with experimental COPD are more susceptible to viral (influenza) and

bacterial (*Streptococcus pneumoniae*) infections, and have systemic involvement with skeletal muscle loss, and effects on the gut and reproductive tract [269, 270, 252, 263].

Current treatments for COPD such as corticosteroids and bronchodilators are poorly effective 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 the progression of COPD, and an effective option is through the use of 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 the translation into the clinic has been slow [271]. 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 [272]. 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 [273]. 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 [274].

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 [275, 276]. Resveratrol is a plant originated polyphenol that suppresses lung inflammation through upregulating MyD88s which is a negative regulator of inflammation [276].

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 [277]. MAPKs plays key roles in chronic inflammation [278], and the p38 MAPK pathway is activated by cellular stress and regulates the expression of a wide variety of inflammatory cytokines and remodeling factors including IL-8, TNF-α and MMPs [279]. PI3Ks play roles in controlling a wide variety of intracellular signaling pathways in asthma and COPD [280, 259]. 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 remodeling as well as corticosteroid insensitivity in chronic inflammatory respiratory diseases such as asthma [281, 280, 259]. We recently discovered that PI3K also plays a pivotal role in the pathogenesis of COPD as it's activity is increased and it is utilised by influenza viruses during infection and it suppresses anti-viral responses [282, 259].

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 [283]. 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 [283]. Other murine studies show that another PDE4 inhibitor rolipram had little effect on airway inflammation and remodeling or emphysema whereas a semicardazide-sensitive mono-amine oxidase inhibitor did [264].

Serine-, metallo- and cysteine proteinases are the primary proteinases implicated in the development of COPD [284]. 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 [285-289]. Collectively, the use of murine models of COPD and infectious exacerbations is valuable in furthering our understanding of the pathogenic aspects of the disease and can be used to identify novel therapeutic targets and develop and test new therapies [290]. 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, and testing preventions 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 systematically 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 [291-293]; NCI-H1299 for carcinomas [294]; NCI-H460 for large cell carcinomas [295]; and NCI-H226 for squamous cell carcinomaa [296]. 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 [297]. Although xenograft models are relatively poor in predicting clinical efficacy of drugs, these models have been successfully used for developing personalised therapy [298]. Circulating tumour cells (CTCs) derived explants (CDXs) of SCLC were used to develop personalised therapy using platinum and etoposide chemotherapy that showed similar drug response to patients [299]. Apart from this, xenografts models were also showed accuracy in testing the efficacy of a number of drugs like gefitinib, erlotinib and crizotinib which showed similar results in clinical trials [300-305].

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 [306]. 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 [306]. 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 tumor regression [307].

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 [308]. 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 [309, 310], and N-nitroso-tris-chloroethyl urea (NTCU) for squamous cell carcinomas [311]. Small cell lung cancer (SCLC) 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 toxicological of drug treatment [312].

Carcinogens such as cigarette smoke and NNK, can be combined to induce adenomas and eventually after many months adenocarcinomas and the published models are long term 5-9 months [313, 310, 314]. Initially, hyperplastic foci are seen in the bronchioles and alveoli that develop as adenomas and then progress to adenocarcinomas [315]. It is often difficult to distinguish adenomas, premalignant adenomas and malignant adenocarcinomas. Adenocarcinomas are mostly distinguished from other tumours based on certain characteristics like large pleiomorphic cells with vesicular nuclei, prominent nucleoli, undifferentiated cytoplasm and high mitotic index [316]. They are morphologically have both solid and papillary characteristics [317]. Tumours that develop in mice have low vascularization and metastatic potential [313]. Clara cells, alveolar type II cells, multipotent stem cells or derivative lineages of these cells are usually the cells of origin of tumours [317, 318]. The origin of papillary tumours is unclear, however, solid tumours usually originate from alveolar type II cells [317]. The histopathological and molecular characteristics of spontaneous mouse lung adenocarcinoma models are similar to the tumours that develop in humans [316].

Squamous cell carcinoma (SCC) mouse models can be induced using NTCU administration and initially show premalignant lesions which progress to frank lung SSC that are similar to those that develop in humans [319]. SCLCs in mice are histologically similar and also metastasize to similar organs as in humans [320]. Neuroendocrine cells are believed to be the origin of SCLC [321].

Although mice are genetically distinct and have some differences in lung physiology compared to humans, non-immunocompromised, non-genetically-modified spontaneous mouse models are more accurate in predicting clinical efficacy of investigating drugs [298]. NNK carcinogen- and CS-induced adenocarcinoma models in A/J mice were successfully used to show efficacy of different chemopreventive agents like isothiocyanates and their conjugates, glucocorticoids, green tea and non-steroidal anti-inflammatory drugs (NSAIDs) [322, 323]. 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 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 are the mainstay management for these patients. Addition of inhaled corticosteroids is appropriate for patients with moderate-to-severe COPD and recurrent exacerbations. It becomes especially important given the fact that inhaled corticosteroid has potential to ameliorate EMT in COPD patients. EMT might be the process through which steroids protect lung cancer in COPD. However, steroids have been reserved for more severe form of COPD, so there is essential need for new therapeutics, which could be given in early disease state as 70% of lung cancer occurs in earlier stages of COPD. Therapeutic options available for patients with lung cancer and concomitant COPD improve 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 essential need for development of pre-clinical animal models, which represents truly human disease. With increasing understanding of the molecular pathogenesis for 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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Table 1: Observation studies of inhaled corticosteroids and risk of lung cancers in patients with COPD

	Design (duration)	Number of participants	Type of ICS	Hazard ratio [95% CI]
Parimon 2007	Retrospective cohort study (Median 3.8 years)	ICS = 517 No ICS = 9957	Triamcinolone, beclomethasone, flunisolide, fluticasone	Adjusted: ICS < 1200μg = 1.3 (0.67-1.90) ICS ≥ 1200μg = 0.39 (0.16-0.96)
Kiri 2009	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	Retrospective cohort study (Median 9.8 years)	ICS = 1290 No ICS = 12396	Fluticasone, Budesonide	Overall = 0.70 (0.46-1.09) Cumulative ICS dose > 39.48mg = 0.45 (0.21-0.96)

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