

Role of chronic obstructive pulmonary disease in lung cancer pathogenesis

Clara E Green, Alice M Turner

Clara E Green, Alice M Turner, Centre for Translational Inflammation Research, University of Birmingham, B152WB Birmingham, United Kingdom

Alice M Turner, Heart of England NHS Foundation Trust, B9 5SS Birmingham, United Kingdom

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Correspondence to: Alice M Turner, Clinician Scientist, Honorary Consultant Physician, Centre for Translational Inflammation Research, University of Birmingham, Mindelsohn Way, B15 2WB Birmingham, United Kingdom. a.m.wood@bham.ac.uk
Telephone: +44-121-3713886 Fax: +44-121-3713887

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and lung cancer in detail it is possible that new treatments may be developed and the risk of lung cancer in COPD may be reduced.

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Key words: Chronic obstructive pulmonary disease; Non-small cell lung carcinoma; Smoking; Oxidative stress; Inflammation

Core tip: Chronic obstructive pulmonary disease (COPD) has been shown to be an independent risk factor for lung cancer regardless of smoking history, suggesting that COPD and lung cancer may share a common pathogenesis. Chronic inflammation and oxidative stress are the most likely mechanistic links between COPD and lung cancer. Further analysis and elucidation of the molecular mechanisms involved in the pathogenesis of COPD and lung cancer should provide us with new treatment modalities and perhaps a key to understanding how the risk of lung cancer in COPD patients may be reduced.

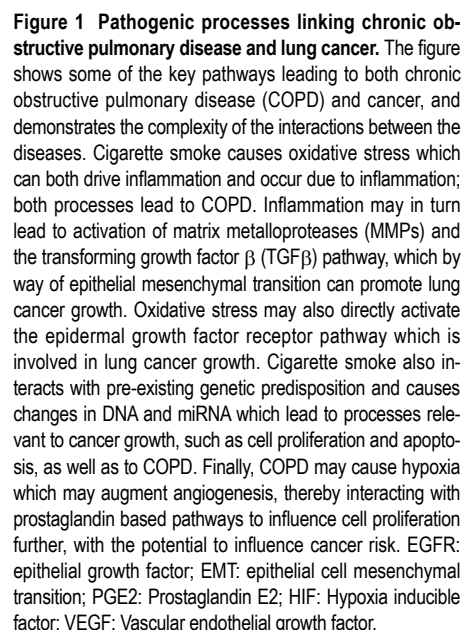
Abstract

Chronic obstructive pulmonary disease (COPD) and lung cancer are two important smoking related conditions. However, COPD has been shown to be an independent risk factor for lung cancer regardless of smoking history, suggesting that COPD and lung cancer may share a common pathogenesis. This review summarizes the epidemiology of lung cancer and COPD briefly, as well as discussing the potential for shared genetic risk, and shared genomic mechanisms, such as epigenetic changes or DNA damage induced by smoking. How key areas of COPD pathogenesis, such as inflammation, oxidative stress and protease imbalance may contribute to subsequent development of cancer will also be covered. Finally the possibility that consequences of COPD, such as hypoxia, influence carcinogenesis will be reviewed. By understanding the pathogenesis of COPD

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a condition characterized by airflow obstruction which is not normally fully reversible with the use of bronchodilators and is progressive over time^[1]. The airflow obstruction usually occurs as a result of smoking but genetic factors (e.g., alpha 1 antitrypsin deficiency), the burning of biomass fuels in developing countries and occupational factors also play a role^[1,2]. Damage in both the airways and



The relative risk of lung cancer in COPD is over twice that of the general population^[11]. Longitudinal studies have shown that after approximately 15 years up to 33% of patients with COPD will develop lung cancer^[12-14]. COPD is also a common co-morbidity in lung cancer patients occurring in 40%-70% of lung cancer cases^[15]. As both diseases are related to smoking it could be assumed that the relationship between COPD and lung cancer might be related to smoking alone. However, in recent years it has been shown that patients with COPD, or CT diagnosed emphysema, have a higher risk for lung cancer even when adjusting for smoking history^[15-18]. One study demonstrated that patients with COPD were six

In common with genetic epidemiology work, most of

Table 1 Examples of genetic regions relevant to increased susceptibility to both chronic obstructive pulmonary disease and lung cancer

Chromosomal region	Possible gene(s)	Ref.
2q	GSS	[23]
4q31	HHIP, GYPA	[21]
5q33	HTR4, ADAM19	[21]
6p	GCLCL	[23]
6q	SMOC2	[22,24,25]
10q	GSTO2	[23]
11p	MMP1, MMP12, RRM1	[23,26]
12p	GSTM1	[27,28]
15q25	CHRNA3-5, IREB2	[21]
19q	ERCC1	[23]

the studies that have linked COPD and lung cancer at a genomic level have been in one disease or the other, and similarities or common themes have been noted later. Some studies have taken advantage of resections performed for lung cancer in patients who have COPD to get data on both diseases. For example, Wang *et al*^[29] looked at the gene expression pattern in lung samples from COPD patients and demonstrated that genes involved in extracellular membrane synthesis and apoptosis were up-regulated, whilst genes involved in the anti-inflammatory response were down-regulated. It was also shown that urokinase plasminogen activator, its receptor and thrombospondin were expressed which are involved in transforming growth factor- β 1 (TGF- β) and matrix metalloprotease (MMP) activation^[29]. Growth factors and MMPs may be responsible for promoting malignant transformation of the bronchial epithelium^[30-32]. Another study looking at gene expression in squamous cell carcinoma found that in patients with co-existing COPD there was a more frequent loss of 5q or a low expression of genes on 5q than in patients without co-existing COPD^[33]. Cystatin A (*CSTA*), an intracellular protease inhibitor, has been shown to be up-regulated in NSCLC. *CSTA* is also expressed to a greater level in patients with COPD compared to smokers with normal lung function^[34]. This suggests that pathways leading to lung tumorigenesis may vary between COPD patients and smokers with normal lung function.

Smoking has also been shown to alter gene expression - specifically it increases expression of xenobiotic genes, antioxidants, electron transport and oncogenes. Reduced levels of inflammatory regulator genes and tumor suppressor genes have also been seen in smokers^[35,36]. Some of these genetic changes reverse on smoking cessation, but others including changes in oncogenes and tumor suppressor genes do not^[35]. Wistuba *et al*^[37] also demonstrated genetic alterations in the form of microsatellite deletions and loss of heterozygosity in normal epithelium of both current and ex-smokers. Irreversibility of genetic alterations or gene expression may explain why ex-smokers remain at an increased risk of developing lung cancer. It has also been shown that these changes in gene expression are associated with changes in protein expression^[38].

DNA damage and repair

Smoking, occupational toxins and air pollution may result in damaging mutations which have potential to induce dysplastic and neoplastic changes in the lung parenchyma due to alterations in cell differentiation, growth and death^[19]. Cigarette smoke contains many carcinogens which can be activated by cytochrome P450 enzymes; inhalation of these, pollutants and micro-organisms can cause damage directly or due to oxidative stress^[19]. Repeated insults such as in COPD results in increased amounts of reactive oxygen species (ROS) which interact with DNA in the epithelium causing mutations. This results in DNA adducts which in turn may cause mutations if they are not repaired^[39]. Commonly these mutations are in oncogenes, but they may also affect inflammatory pathways^[40]. Mostly these mutations are repaired, but when there is a high rate of damage due to ROS cells are likely to be transformed to a malignant phenotype^[40]. Studies have shown that there is impairment in DNA repair in COPD due to low levels of Ku 86, a protein involved in DNA repair^[41]. This suggests that oxidant induced damage in COPD patients is more likely to result in carcinogenesis.

It is also possible that processes which control DNA repair may influence a patient's risk of developing lung cancer^[42] and that such processes may be altered in COPD. For example, there is evidence that acetylation of histone H3 on lysine 56 (*H3K56*) is important in DNA repair^[43]. Deacetylation of *H3K56* is controlled by histone deacetylases (HDACs) 1 and 2 and sirtuin (SIRT) 1^[44]. As there are low levels of HDAC2 and SIRT1 in COPD^[45] this may reduce the protection against DNA breakage caused by environmental factors further increasing lung cancer risk.

Epigenetics

Epigenetics is the regulation of gene expression by heritable mechanisms that do not make direct changes to DNA itself. Examples of epigenetic mechanisms include histone acetylation and methylation; these may silence genes without changing their coding sequence and regulate pro-inflammatory gene expression in COPD and lung cancer^[19]. The degree of histone acetylation in promoters of pro-inflammatory genes in COPD is related to disease severity and reversed by HDACs^[46]. Since HDAC2 levels are low in COPD this could result in hyperacetylation of histones. SIRT1 acts similarly to HDACs and there are variable SIRT1 levels in lung cancer. However tumor suppressor genes, including *p53* may be rendered inactive in patients with low SIRT1 levels, including COPD patients^[47,48]. Mouse models suggest this is a relevant pathway leading to lung tumors^[48].

Genome-wide demethylation with site-specific hypermethylation is seen in lung cancer^[19]. NA methylation is usually associated with gene silencing^[49] and is associated with tumorigenesis and recurrence of NSCLC^[50]. Methylation of the promoter of *p16* (a tumor suppressor gene) is seen in the sputum of COPD patients and aberrant methylation of *p16* can be also seen in the sputum of patients with NSCLC suggesting this too may be a

Table 2 Oxidative stress genes with good evidence that they contribute to both chronic obstructive pulmonary disease and lung cancer

Gene	Polymorphism	COPD risk	Lung cancer risk	Ref.
EPHX1	Rs2234922 (A139G) and haplotypes	↑Asians ↔ Caucasians	↑	[88,89]
GSTM1	Null genotype	↑	↑	[28,90]
SOD3	Rs1799896	↑	<i>In vitro</i> evidence of SOD3 ↑risk [90-92]	

COPD: Chronic obstructive pulmonary disease; EPHX1: Epoxide hydrolase; GSTM1: Glutathione S-transferase M1; SOD3: Superoxide dismutase 3.

shared mechanism of disease^[51]. Hypermethylation of *p16*, *CDH13*, *RASSF1A* and *APC* have been associated with recurrence in lung cancer^[50], but have not yet been reported in COPD.

Micro-RNA

These are small non-coding RNAs which act to regulate protein expression and immune response by acting on mRNA synthesis or translation. They can act as oncogenes or tumor suppressor genes and promote a range of functions including cell proliferation and apoptosis, both of which are relevant to tumor growth^[52]. The function of micro-RNA (miRNA) may be altered by single nucleotide polymorphisms (SNPs), some of which are associated with poor survival in NSCLC^[52].

miRNA expression is down-regulated with smoke exposure in both animal lungs and bronchial epithelium in man. In the rat model it was seen that many of the miRNAs involved in the activation of the NF- κ B pathway were down-regulated^[53]. Other studies have also demonstrated unique miRNA profiles in COPD^[54] and lung cancer^[55]. In COPD miR-223 and miR-1274a were the most markedly different from healthy smokers, and there were smaller changes in some of the miRNA associated with cancer, such as miR-10a and miR-451^[54]. In NSCLC miR-21, miR-30d, miR-451, miR-10a, miR-30e-5p, miR-126*, miR-126 and miR-145 were differentially regulated and it was possible for some of their signatures to be picked up in the circulating blood^[55]. These signatures could be used to aid prognostication in lung cancer or potentially to diagnose cancer earlier in high risk groups, although such strategies have not yet been evaluated in clinical studies.

COPD MECHANISMS WHICH INCREASE THE RISK OF CANCER

Inflammation

There is a wealth of evidence of systemic inflammation in COPD, as shown by increased levels of chemokines, cytokines and acute phase reactants^[56]. Smoking can cause inflammation, but the degree seen in COPD is higher than in smokers alone and persists despite smoking cessation^[57]. Inflammation in COPD also appears to be greater in se-

vere disease^[58], although its variability over time and with exacerbations has thwarted attempts to find biomarkers in the blood that relate consistently to clinical features^[59]. Interleukin-6 (IL-6), C-reactive protein (CRP), IL-8 and surfactant protein D (SP-D)^[60,61] levels are typically high in COPD and are important in the recruitment of inflammatory cells, although fibrinogen seems the most reliable biomarker to date^[56,59]. Fibrinogen levels are associated with increased exacerbation rates and poorer outcomes^[62,63], however it is a non-specific marker and as such has inherent weaknesses. More specific related markers, such as Aa-Val360 may prove more useful in the future^[64].

There is an accumulation of inflammatory cells in COPD lungs, including macrophages, neutrophils, B cells and CD4+ and CD8+ T cells^[65]. Macrophages release multiple inflammatory mediators including reactive oxygen species, cytokines, chemokines, extracellular matrix proteins and matrix metalloproteinases (MMPs). In COPD their function may be impaired, for instance they show impaired phagocytosis of bacteria, which may result in an increased inflammatory response to bacteria in the lower airways^[66]. Neutrophils also produce reactive oxygen species, elastase and cytokines which play a role in emphysema and COPD development. Lymphocytes, including both B and T cells, are also found in high numbers in COPD lung^[67] and may be involved in immune activation, leading to perpetuation of inflammation and ongoing parenchymal destruction. Such a reaction is typical of autoimmune disease, and characteristics of autoimmunity have been reported in COPD^[68] although whether they are cause or effect is a matter of debate^[69].

There is evidence that carcinogenesis occurs at sites of chronic inflammation^[70]. For example, hepatocellular carcinoma can occur in patients with chronic hepatitis and colon cancer in the setting of colitis^[71]. There is some evidence that increased inflammation may also be associated with the development of lung cancer. Epidemiologically, a cohort study of 7081 patients showed an increased risk of lung cancer in patients with a CRP of > 3 mg/dL^[72]. Furthermore, a mouse model of chronic inflammation showed increased lung tumorigenesis^[73]. However clinical studies of anti-inflammatory drugs, such as inhaled corticosteroids, have shown inconsistent results. A cohort study has shown lower rates of lung cancer compared to patients not taking inhaled corticosteroids^[74], whilst a randomized controlled trial (RCT) did not^[75]. Whether targeting pulmonary inflammation to prevent lung cancer will be beneficial therefore remains uncertain.

One way inflammation may lead to the development of lung cancer is by activation of the epithelial growth factor receptor (EGFR) cascade (Figure 1). This is activated in response to oxidative stress, neutrophil elastase and other proteases^[76], thus might be expected to be overactive in COPD; recent evidence suggests this may be the case^[77]. Overexpression of EGFR has been associated with a high risk of developing lung cancer and can occur years after smoking cessation^[78]. The arachidonic acid metabolic pathway may also be related to COPD and lung cancer development. Inflammatory cells release ara-

Table 3 Signalling pathways common to chronic obstructive pulmonary disease and lung cancer

Signal pathway	Downstream effects	Role in COPD	Role in lung cancer	Ref.
NFκB	↑MMPs, ↑TNFα, ↓apoptosis, ↑angiogenesis	↑inflammation	↑cell proliferation, ↓cell death, metastasis	[111]
PI3K	Activation and migration of leukocytes	↑inflammation	↑cell proliferation, ↓cell death	[112,113]
P38 MAPK	Block JNK/c-Jun, ↑TNFα	↑inflammation	Metastasis, ↓cell death	[114]
PPARγ	↓MMP9, ↓TNFα, ↓TGFβ	↓inflammation	↑cell differentiation, ↓cell proliferation	[115,116]

COPD: Chronic obstructive pulmonary disease; MMPs: Matrix-metalloproteinases; JNK: c-Jun N-terminal kinases; TNFα: Tumour necrosis factor alpha; TGFβ: Tissue growth factor beta.

chidonic acid metabolites including prostaglandins - this is mediated by cyclooxygenase enzymes (COX) including COX-2. Prostaglandin E₂, the product of COX-2, regulates the inflammatory response, but also has effects on cell proliferation, apoptosis and angiogenesis^[70] and therefore may have a role in cancer development. Whilst this concept has been focused on far more in other cancers than in the lung there is some evidence it is relevant to cancer risk in COPD. Increased levels of COX-2 occur in COPD and are inversely proportional to FEV₁^[79]. Raised COX-2 levels relate to survival in NSCLC^[80], inhibition of COX-2 reduces lung cancer in animal models^[81] and patients who regularly take COX-2 inhibitors have reduced rates of lung cancer^[82]. Finally, carriers of a polymorphism of the COX-2 gene have an increased risk of lung cancer^[83].

Oxidative stress

The normal metabolism of oxygen results in the development of ROS - these are usually removed from the cell by enzymes or anti-oxidants^[84]. If the balance between the formation and removal of ROS is disturbed oxidative stress can occur; this may activate intracellular pathways which modulate the inflammatory response, as well as causing DNA damage (discussed above), and therefore have a role in the development of COPD and lung cancer^[84]. Oxidative stress is well recognized in COPD and is particularly elevated during exacerbations^[85].

Cigarette smoke is a key driver of oxidative stress. It contains noxious chemicals which are metabolized to benign and/or toxic metabolites, the latter of which can damage tissue and predispose to disease. Differences in metabolism between individuals can contribute to the risk of developing COPD or lung cancer^[86,87]. An example of a metabolic enzyme involved in both diseases is Microsomal epoxide hydrolase (EPHX1)^[88,89]. Many of the early studies of antioxidant genes such as this were hampered by low power; and most have not been borne out by GWAS, but there is other biological evidence (*e.g.*, *in vitro* work) delineating their role in pathogenesis, which is covered in the primary genetic papers referenced in Table 2.

Nuclear factor erythroid 2-related factor 2 (Nrf2) is the main transcription factor that regulates phase II detoxifying antioxidant enzymes and therefore plays an important role in defence against carcinogens in smoke^[93]. Nrf2 is negatively regulated by Kelch-like ECH-associated protein 1 (Keap1); mutations in either of these genes can predispose to malignancy including NSCLC^[94,95]. Defec-

tive Nrf2 occurs in COPD and this may also predispose patients with COPD to lung cancer due to increased oxidative stress^[96]. Oxidative stress also increases p21 expression. p21 is acyclin-dependent kinase inhibitor whose levels are raised in alveolar epithelial cells and macrophages exposed to smoke^[97], and in patients with COPD and lung cancer^[98]. Elevation of p21 promotes the cell cycle to move from G₁ to G₂/M phase resulting in hyperproliferation and carcinogenesis^[99].

Proteinase-antiproteinase imbalance

The balance between anti-proteinases and proteinases is an important determinant of emphysema that occurs in COPD^[100]. Proteinases are also important in lung cancer development as they release growth factors TGFβ and VEGF, which can lead to tumorigenesis^[19]. Proteinases common to both diseases are summarized in Table 3. A good clinical example of the importance of proteinase balance is alpha1-antitrypsin deficiency (AATD); this is a genetically determined anti-proteinase deficiency which predisposes to COPD^[101]. Patients who are AATD carriers also have a 70% increased risk of developing lung cancer compared to healthy controls^[102]. Drugs targeting MMPs, which are recognized in the pathogenesis of both COPD and lung cancer have been tested in early phase trials in COPD^[103] and are at a more advanced stage of development in NSCLC^[104].

Fibrotic pathways

Fibrotic processes are recognized in the small airway in COPD and are thought to be driven by the TGFβ1/MMP12 pathway, as TGFβ1 levels are raised in relation to the severity of airway obstruction^[105]. MMP12 is normally inhibited by the binding of αvβ6 to TGFβ resulting in TGFβ activation. αvβ6 is a transmembrane receptor of the integrin family which is present on the surface of epithelial cells and is up-regulated in lung inflammation^[19]. Loss of αvβ6 helps to preserve normal lung architecture and homeostasis and if it is removed in mice airspace enlargement results, suggesting it is important in the development of emphysema as well as fibrosis^[106]. TGFβ also drives epithelial cell mesenchymal transition (EMT) which is a recognized pre-malignant change capable of enhancing invasion and thus predisposing to cancer development and progression^[107] (Figure 1). Fibrosis due to integrins and TGFβ is regulated by galectin 3. There are raised levels of galectin 3 in COPD lung^[108] and increased levels are also associated with poor prognosis in NSCLC^[109].

Intracellular signaling

A number of intracellular signaling pathways, often directing processes such as inflammation, oxidative stress and protease balance, are dysregulated in both COPD and lung cancer. They are summarized in Table 3. NF- κ B is particularly important due to its role in chronic inflammation. It is a transcription factor activated in inflammatory cells and in the lower airways of COPD^[110] and lung cancer patients.

COPD CONSEQUENCES WHICH MAY INCREASE THE RISK OF CANCER

Hypoxia

Parenchymal destruction in COPD may ultimately result in hypoxaemia, which may activate transcription factors and result in the expression of pro-inflammatory genes^[117] (Figure 1). This leads to hypoxia-inducible factor (HIF) release, VEGF expression and angiogenesis^[118]. The induction of HIF is reduced in emphysema and levels of VEGF are low in emphysematous lungs which results in low levels of angiogenesis^[119]. Low VEGF levels can also cause apoptosis and airspace enlargement^[120]. Conversely VEGF can be increased in chronic bronchitis^[118] such that the consequences in airway predominant compared to emphysema predominant COPD might differ. Hypoxia and HIF activation can also occur in lung tumors that are increasing in size and can result in progression and metastasis of lung cancer through induction of VEGF and MMPs in an animal model^[121]. Circulating VEGF is associated with a poor prognosis in operated lung cancer patients as it predicts recurrence^[122].

Physical inactivity

Patients with COPD often reduce their physical activity levels due to breathlessness, and have markedly reduced activity levels compared to those without airflow obstruction^[123]. Physical inactivity is associated with lung cancer incidence^[124] and appears to remain so even after adjustment for smoking and other lifestyle factors^[125]. The mechanism behind this association is not yet clear.

CONCLUSION

Chronic inflammation and oxidative stress are the most likely mechanistic links between COPD and lung cancer. Further analysis and elucidation of the molecular mechanisms involved in the pathogenesis of COPD and lung cancer should provide us with new treatment modalities and perhaps a key to understanding how the risk of lung cancer in COPD patients may be reduced.

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