**Title:** The role of COPD in lung cancer pathogenesis

**Authorship:**Clara E. Green1, Alice M. Turner1,2

**Institution:**1University of Birmingham, Centre for Translational Inflammation research, Mindelsohn Way, Edgbaston, Birmingham, United Kingdom, B152WB.2Heart of England NHS Foundation Trust, Birmingham, United Kingdom, B9 5SS

**Author contributions:** CEG conducted literature searches; CEG and AMT contributed to writing the article.

**Supportive foundations**: CEG is supported by the National Health Service (UK); AMT is supported by research grants from the National Institute of Health Research (UK), Alpha 1 Foundation, MRC, Linde Real Fund, Healthcare Infection Society (UK) and by a contract for research services to Mologic. She has also received fees for educational talks or advisory boards from Boehringer, GSK, Novartis and Almirall.

**Correspondence to:**Alice Turner , Clinician Scientist and Honorary Consultant Physician, University of Birmingham, Mindelsohn Way, Birmingham, UK, B15 2WB. Email: a.m.wood@bham.ac.uk

**Telephone and fax:** Tel: +44 (0) 121 3713886, Fax: +44 (0) 121 3713887

**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 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.

Abstract word count: 149

Total word count: 3274 (excluding tables, figure legend and references)

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

**Core tip:**

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.

**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](#_ENREF_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](#_ENREF_1), [2](#_ENREF_2)]. Damage in both the airways and lung parenchyma contribute to the airway obstruction [[1](#_ENREF_1), [3](#_ENREF_3)]. COPD is common. One study found a 10.1% prevalence of COPD (with Forced expiratory volume in one second (FEV1) <80%) in adults over 40 years in 12 different countries worldwide [[4](#_ENREF_4)].COPD is an important cause of morbidity and mortality and resulted in over 3 million deaths in 2005 globally[[5](#_ENREF_5)].

Lung cancer is the leading cause of cancer morbidity in North America, and is amongst the top 5 cancers ranked by disability adjusted life years lost (DALYs) in all regions of the world, except Sub-Saharan Africa[[6](#_ENREF_6)]. It causes 626 DALYs/100000 heads of population worldwide [[6](#_ENREF_6)] and is the most common cause of cancer death accounting for 1.18 million deaths in 2002 [[7](#_ENREF_7)]. 90% of lung cancers are caused by smoking, although other environmental factors such as asbestos exposure also play a role [[8](#_ENREF_8)]. Lung cancers are classified by histology into small cell and non-small cell cancers (NSCLC); the latter are the more common and include squamous and adenocarcinomas. Generally small cell tumours have the poorest prognosis, with overall survival being 9 months when managed by chemotherapy [[9](#_ENREF_9)]. Even in NSCLC prognosis is generally poor unless surgery can be offered, and a recent systematic review reported mean survival of just over 7 months if left untreated[[10](#_ENREF_10)].

The relative risk of lung cancer in COPD is over twice that of the general population[[11](#_ENREF_11)]. Longitudinal studies have shown that after approximately 15 years up to 33% of patients with COPD will develop lung cancer[[12-14](#_ENREF_12)]. COPD is also a common co-morbidity in lung cancer patients occurring in 40-70% of lung cancer cases [[15](#_ENREF_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](#_ENREF_15)]. One study demonstrated that patients with COPD were six times more likely to develop lung cancer when compared to matched smokers without COPD [[15](#_ENREF_15)]. Furthermore increased severity of airway obstruction is associated with a correspondingly elevated risk of lung cancer [[18](#_ENREF_18)]. Emphysema in non-smokers is also a risk for lung cancer further reinforcing that smoking, alone, cannot explain the relationship between COPD and lung cancer [[19](#_ENREF_19), [20](#_ENREF_20)]. In addition stopping smoking does not completely reduce the risk of lung cancer in patients with COPD [[12](#_ENREF_12)]. Taken together this evidence suggests that there is a link between COPD and lung cancer other than smoking; this article will review the current evidence for common pathogenesis of the two conditions. The key concepts are summarized in Figure 1.

**Shared genetic and genomic mechanisms**

Genetic epidemiology

Only 20-30% of smokers develop COPD and 10-15% develop lung cancer [[21](#_ENREF_21)]. This epidemiological evidence, together with familial patterns of disease, and many subsequent genetic association studies have demonstrated that for both diseases a proportion of the risk of developing them is due to genetic factors. In fact, there is evidence that COPD has a heritability of 40-77% and lung cancer a heritability of 15-25% [[21](#_ENREF_21)]. Familial linkage studies and genome-wide association studies (GWAS) have been performed for COPD, lung function and lung cancer and there is overlap in the chromosome areas identified, which demonstrates shared genetic risk[[21](#_ENREF_21), [22](#_ENREF_22)].Most of the primary studies have been in patients with either COPD or lung cancer and others have then sought areas of commonality. Key regions of shared susceptibility are shown in Table 1.

|  |  |  |
| --- | --- | --- |
| **Chromosomal region** | **Possible gene(s)** | **Reference** |
| 2q | *GSS* | [[23](#_ENREF_23)] |
| 4q31 | *HHIP, GYPA* | [[21](#_ENREF_21)] |
| 5q33 | *HTR4, ADAM19* | [[21](#_ENREF_21)] |
| 6p | *GCLCL* | [[23](#_ENREF_23)] |
| 6q | *SMOC2* | [[22](#_ENREF_22), [24](#_ENREF_24), [25](#_ENREF_25)] |
| 10q | *GSTO2* | [[23](#_ENREF_23)] |
| 11p | *MMP1, MMP12, RRM1* | [[23](#_ENREF_23), [26](#_ENREF_26)] |
| 12p | *GSTM1* | [[27](#_ENREF_27), [28](#_ENREF_28)] |
| 15q25 | *CHRNA3-5, IREB2* | [[21](#_ENREF_21)] |
| 19q | *ERCC1* | [[23](#_ENREF_23)] |

Table 1: Examples of genetic regions relevant to increased susceptibility to both COPD and lung cancer

Gene expression studies

In common with genetic epidemiology work, most of 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* 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[[29](#_ENREF_29)]. It was also shown that urokinase plasminogen activator, its receptor and thrombospondin were expressed which are involved in transforming growth factor- β1 (*TGFB*) and matrix metalloprotease (*MMP*) activation[[29](#_ENREF_29)]. Growth factors and MMPs may be responsible for promoting malignant transformation of the bronchial epithelium[[30-32](#_ENREF_30)]. 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](#_ENREF_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](#_ENREF_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](#_ENREF_35), [36](#_ENREF_36)]. Some of these genetic changes reverse on smoking cessation, but others including changes in oncogenes and tumor suppressor genes do not [[35](#_ENREF_35)]. Wistuba *et al* also demonstrated genetic alterations in the form of microsatellite deletions and loss of heterozygosity in normal epithelium of both current and ex-smokers [[37](#_ENREF_37)]. 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](#_ENREF_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](#_ENREF_19)]. Cigarette smoke contains many carcinogens which can be activated by cytochrome P450 enzymes(CYPs); inhalation of these, pollutants and micro-organisms can cause damage directly or due to oxidative stress[[19](#_ENREF_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](#_ENREF_39)]. Commonly these mutations are in oncogenes, but they may also affect inflammatory pathways [[40](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_43)]. Deacetylation of *H3K56* is controlled by histone deactylases (HDACs) 1 and 2 and sirtuin (SIRT) 1[[44](#_ENREF_44)].As there are low levels of HDAC2 and SIRT1 in COPD [[45](#_ENREF_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](#_ENREF_19)]. The degree of histone acetylation in promoters of pro-inflammatory genes in COPD is related to disease severity and reversed by HDACs[[46](#_ENREF_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](#_ENREF_47), [48](#_ENREF_48)]. Mouse models suggest this is a relevant pathway leading to lung tumors[[48](#_ENREF_48)].

Genome-wide demethylation with site-specific hypermethylation is seen in lung cancer[[19](#_ENREF_19)]. DNA methylation is usually associated with gene silencing[[49](#_ENREF_49)]and is associated with tumorigenesis and recurrence of NSCLC[[50](#_ENREF_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 shared mechanism of disease[[51](#_ENREF_51)]. Hypermethylation of p16, *CDH13, RASSF1A* and *APC* have been associated with recurrence in lung cancer[[50](#_ENREF_50)], but have not yet been reported in COPD.

Micro-RNA (miRNA)

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](#_ENREF_52)]. The function of miRNAs may be altered by single nucleotide polymorphisms (SNPs), some of which are associated with poor survival in NSCLC [[52](#_ENREF_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-κB pathway were down-regulated [[53](#_ENREF_53)] (see table 3.) Other studies have also demonstrated unique miRNA profiles in COPD[[54](#_ENREF_54)] and lung cancer[[55](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_56)]. Smoking can cause inflammation, but the degree seen in COPD is higher than in smokers alone and persists despite smoking cessation [[57](#_ENREF_57)]. Inflammation in COPD also appears to be greater in severe disease[[58](#_ENREF_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](#_ENREF_59)]. Interleukin-6 (IL-6), C-reactive protein (CRP), IL-8 and surfactant protein D (SP-D)[[60](#_ENREF_60), [61](#_ENREF_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](#_ENREF_56), [59](#_ENREF_59)].Fibrinogen levels are associated with increased exacerbation rates and poorer outcomes [[62](#_ENREF_62), [63](#_ENREF_63)], however it is a non-specific marker and as such has inherent weaknesses. More specific related markers, such as AaVal360 may prove more useful in the future [[64](#_ENREF_64)].

There is an accumulation of inflammatory cells in COPD lungs, including macrophages, neutrophils, B cells and CD4+ and CD8+ T cells [[65](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_68)] although whether they are cause or effect is a matter of debate[[69](#_ENREF_69)].

There is evidence that carcinogenesis occurs at sites of chronic inflammation [[70](#_ENREF_70)]. For example, hepatocellular carcinoma can occur in patients with chronic hepatitis and colon cancer in the setting of colitis [[71](#_ENREF_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 >3mg/dl [[72](#_ENREF_72)]. Furthermore, a mouse model of chronic inflammation showed increased lung tumorigenesis[[73](#_ENREF_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](#_ENREF_74)], whilst a randomized controlled trial (RCT) did not [[75](#_ENREF_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 (EGFR) cascade. (Please refer to figure 1.) This is activated in response to oxidative stress, neutrophil elastase and other proteases[[76](#_ENREF_76)], thus might be expected to be overactive in COPD; recent evidence suggests this may be the case [[77](#_ENREF_77)].Overexpression of EGFR has been associated with a high risk of developing lung cancer and can occur years after smoking cessation[[78](#_ENREF_78)].The arachidonic acid metabolic pathway may also be related to COPD and lung cancer development. Inflammatory cells release arachidonic acid metabolites including prostaglandins - this is mediated by cyclooxygenase enzymes (COX) including COX-2. Prostaglandin E2 (PGE2), the product of COX-2, regulates the inflammatory response, but also has effects on cell proliferation, apoptosis and angiogenesis[[70](#_ENREF_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](#_ENREF_79)]. Raised COX-2 levels relate to survival in NSCLC[[80](#_ENREF_80)], inhibition of COX-2 reduces lung cancer in animal models[[81](#_ENREF_81)] and patients who regularly take COX-2 inhibitors have reduced rates of lung cancer[[82](#_ENREF_82)]. Finally, carriers of a polymorphism of the COX-2 gene have an increased risk of lung cancer [[83](#_ENREF_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](#_ENREF_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](#_ENREF_84)]. Oxidative stress is well recognized in COPD and is particularly elevated during exacerbations [[85](#_ENREF_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](#_ENREF_86), [87](#_ENREF_87)].An example of a metabolic enzyme involved in both diseases is Microsomal epoxide hydrolase (EPHX1)[[88](#_ENREF_88), [89](#_ENREF_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.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Gene** | **Polymorphism** | **COPD risk** | **Lung cancer risk** | **Refs** |
| *EPHX1* | Rs2234922 (A139G)  & haplotypes | ↑Asians  ↔ Caucasians | ↑ | [[88](#_ENREF_88), [89](#_ENREF_89)] |
| *GSTM1* | Null genotype | ↑ | ↑ | [[28](#_ENREF_28), [90](#_ENREF_90)] |
| *SOD3* | Rs1799896 | ↑ | In vitro evidence of SOD3 ↑risk | [[90-92](#_ENREF_90)] |

Table 2: Oxidative stress genes with good evidence that they contribute to both COPD and lung cancer

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](#_ENREF_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](#_ENREF_94), [95](#_ENREF_95)]. Defective Nrf2 occurs in COPD and this may also predispose patients with COPD to lung cancer due to increased oxidative stress [[96](#_ENREF_96)].Oxidative stress also increases p21 expression. p21is acyclin-dependent kinase inhibitor whose levels are raised in alveolar epithelial cells and macrophages exposed to smoke[[97](#_ENREF_97)], and in patients with COPD and lung cancer[[98](#_ENREF_98)].Elevation of p21 promotes the cell cycle to move from G1 to G2/M phase resulting in hyperproliferation and carcinogenesis[[99](#_ENREF_99)].

Proteinase-antiproteinase imbalance

The balance between anti-proteinases and proteinases is an important determinant of emphysema that occurs in COPD[[100](#_ENREF_100)]. Proteinases are also important in lung cancer development as they release growth factors TGF-β and VEGF, which can lead to tumorigenesis[[19](#_ENREF_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](#_ENREF_101)]. Patients who are AATD carriers also have a 70% increased risk of developing lung cancer compared to healthy controls [[102](#_ENREF_102)]. Drugs targeting matrix-metalloproteinases (MMPs), which are recognized in the pathogenesis of both COPD and lung cancer have been tested in early phase trials in COPD [[103](#_ENREF_103)] and are at a more advanced stage of development in NSCLC [[104](#_ENREF_104)].

Fibrotic pathways

Fibrotic processes are recognized in the small airway in COPD and are thought to be driven by theTGFβ1/MMP12 pathway, asTGFβ1 levels are raised in relation to the severity of airway obstruction [[105](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_107)]. (Please refer to figure 1.) Fibrosis due to integrins and TGFβ is regulated by galectin 3. There are raised levels of galectin 3 in COPD lung [[108](#_ENREF_108)] and increased levels are also associated with poor prognosis in NSCLC [[109](#_ENREF_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-κB 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](#_ENREF_110)] and lung cancer patients.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Signal pathway** | **Downstream effects** | **Role in COPD** | **Role in lung cancer** | **References** |
| NFκβ | ↑MMPs, ↑TNFα, ↓apoptosis, ↑angiogenesis | ↑inflammation | ↑cell proliferation, ↓cell death, metastasis | [[111](#_ENREF_111)] |
| PI3K | Activation and migration of leukocytes | ↑inflammation | ↑cell proliferation, ↓cell death | [[112](#_ENREF_112), [113](#_ENREF_113)] |
| P38 MAPK | Block JNK/c-Jun, ↑TNFα | ↑inflammation | Metastasis, ↓cell death | [[114](#_ENREF_114)] |
| PPARγ | ↓MMP9, ↓TNFα, ↓TGFβ | ↓inflammation | ↑cell differentiation, ↓cell proliferation | [[115](#_ENREF_115), [116](#_ENREF_116)] |

Table 3: Signalling pathways common to COPD and lung cancer

**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](#_ENREF_117)]. (Please refer to figure 1.)This leads to hypoxia-inducible factor (HIF) release, VEGF expression and angiogenesis[[118](#_ENREF_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](#_ENREF_119)]. Low VEGF levels can also cause apoptosis and airspace enlargement[[120](#_ENREF_120)].Conversely VEGF can be increased in chronic bronchitis[[118](#_ENREF_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](#_ENREF_121)]. Circulating VEGF is associated with a poor prognosis in operated lung cancer patients as it predicts recurrence [[122](#_ENREF_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](#_ENREF_123)]. Physical inactivity is associated with lung cancer incidence [[124](#_ENREF_124)] and appears to remain so even after adjustment for smoking and other lifestyle factors[[125](#_ENREF_125)]. The mechanism behind this association is not yet clear.

**Conclusions**

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.

**Figure legend**

Figure 1: Pathogenic processes linking COPD and lung cancer

The figure shows some of the key pathways leading to both COPD and cancer, and demonstrates the complexity of the interactions between the diseases. Cigarette smoke causes oxidative stress which can both drive inflammation and occur due to inflammation; both processes lead to COPD. Inflammation may in turn lead to activation of MMPs and the TGFB pathway, which by way of epithelial mesenchymal transition (EMT) can promote lung cancer growth. Oxidative stress may also directly activate the EGFR pathway which is involved in lung cancer growth. Cigarette smoke also interacts with pre-existing genetic predisposition and causes changes in DNA and miRNA which lead to processes relevant to cancer growth, such as cell proliferation and apoptosis, as well as to COPD. Finally, COPD may cause hypoxia which may augment angiogenesis, thereby interacting with prostaglandin based pathways to influence cell proliferation further, with the potential to influence cancer risk.

**References**

1. Global Initiative for Obstructive Lung Disease. [Accessed 21st September 2012]; Available from: [www.goldcopd.com](http://www.goldcopd.com).

2. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Lancet. 2009;374:733-43. PMID: 19716966

3. Kim WJ, Silverman EK, Hoffman E, Criner GJ, Mosenifar Z, Sciurba FC, Make BJ, Carey V, San Jose Estepar R, Diaz A, Reilly JJ, Martinez FJ, Washko GR. CT Metrics of Airway Disease and Emphysema in Severe COPD. Chest. 2009;136:396-44. Epub 2009/05/05. PMID: 19411295

4. Buist AS, Vollmer WM, Sullivan SD, Weiss KB, Lee TA, Menezes AM, Crapo RO, Jensen RL, Burney PG. The Burden of Obstructive Lung Disease Initiative (BOLD): rationale and design. COPD. 2005;2(2):277-83. Epub 2006/12/02. PMID: 17136954

5. World Health Organisation Statistics [database on the Internet]. WHO. 2013 [cited 28th June 2013]. Available from: <http://www.who.int/respiratory/copd/burden/en/index.html>.

6. Soerjomataram I, Lortet-Tieulent J, Parkin DM, Ferlay J, Mathers C, Forman D, Bray F. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. Lancet. 2012;380(9856):1840-50. Epub 2012/10/20. PMID: 23079588

7. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55(2):74-108. Epub 2005/03/12. PMID: 15761078

8. Tyczynski JE, Bray F, Parkin DM. Lung cancer in Europe in 2000: epidemiology, prevention, and early detection. Lancet Oncol. 2003;4(1):45-55. Epub 2003/01/09. PMID: 12517539

9. Rossi A, Di Maio M, Chiodini P, Rudd RM, Okamoto H, Skarlos DV, Fruh M, Qian W, Tamura T, Samantas E, Shibata T, Perrone F, Gallo C, Gridelli C, Martelli O, Lee SM. Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(14):1692-8. Epub 2012/04/05. PMID: 22473169

10. Wao H, Mhaskar R, Kumar A, Miladinovic B, Djulbegovic B. Survival of patients with non-small cell lung cancer without treatment: a systematic review and meta-analysis. Systematic reviews. 2013;2:10. Epub 2013/02/06. PMID: 23379753

11. Brenner DR, McLaughlin JR, Hung RJ. Previous lung diseases and lung cancer risk: a systematic review and meta-analysis. PloS one. 2011;6(3):e17479. Epub 2011/04/13. PMID: 21483846

12. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Annals of internal medicine. 2005;142(4):233-9. Epub 2005/02/16. PMID: 15710956

13. de Torres JP, Marin JM, Casanova C, Cote C, Carrizo S, Cordoba-Lanus E, Baz-Davila R, Zulueta JJ, Aguirre-Jaime A, Saetta M, Cosio MG, Celli BR. Lung cancer in patients with chronic obstructive pulmonary disease-- incidence and predicting factors. American journal of respiratory and critical care medicine. 2011;184(8):913-9. Epub 2011/07/30. PMID: 21799072

14. Kornum JB, Svaerke C, Thomsen RW, Lange P, Sorensen HT. Chronic obstructive pulmonary disease and cancer risk: a Danish nationwide cohort study. Respiratory medicine. 2012;106(6):845-52. Epub 2012/01/05. PMID: 22214771

15. Young RP, Hopkins RJ, Christmas T, Black PN, Metcalf P, Gamble GD. COPD prevalence is increased in lung cancer, independent of age, sex and smoking history. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2009;34(2):380-6. Epub 2009/02/07. PMID: 19196816

16. Koshiol J, Rotunno M, Consonni D, Pesatori AC, De Matteis S, Goldstein AM, Chaturvedi AK, Wacholder S, Landi MT, Lubin JH, Caporaso NE. Chronic obstructive pulmonary disease and altered risk of lung cancer in a population-based case-control study. PloS one. 2009;4(10):e7380. Epub 2009/10/09. PMID: 19812684

17. de Torres JP, Bastarrika G, Wisnivesky JP, Alcaide AB, Campo A, Seijo LM, Pueyo JC, Villanueva A, Lozano MD, Montes U, Montuenga L, Zulueta JJ. Assessing the relationship between lung cancer risk and emphysema detected on low-dose CT of the chest. Chest. 2007;132(6):1932-8. Epub 2007/12/15. PMID: 18079226

18. Wasswa-Kintu S, Gan WQ, Man SF, Pare PD, Sin DD. Relationship between reduced forced expiratory volume in one second and the risk of lung cancer: a systematic review and meta-analysis. Thorax. 2005;60(7):570-5. Epub 2005/07/05. PMID: 15994265

19. Rooney C, Sethi T. The epithelial cell and lung cancer: the link between chronic obstructive pulmonary disease and lung cancer. Respiration; international review of thoracic diseases. 2011;81(2):89-104. Epub 2011/02/12. PMID: 21311210

20. Brenner DR, Boffetta P, Duell EJ, Bickeboller H, Rosenberger A, McCormack V, Muscat JE, Yang P, Wichmann HE, Brueske-Hohlfeld I, Schwartz AG, Cote ML, Tjonneland A, Friis S, Le Marchand L, Zhang ZF, Morgenstern H, Szeszenia-Dabrowska N, Lissowska J, Zaridze D, Rudnai P, Fabianova E, Foretova L, Janout V, Bencko V, Schejbalova M, Brennan P, Mates IN, Lazarus P, Field JK, Raji O, McLaughlin JR, Liu G, Wiencke J, Neri M, Ugolini D, Andrew AS, Lan Q, Hu W, Orlow I, Park BJ, Hung RJ. Previous lung diseases and lung cancer risk: a pooled analysis from the International Lung Cancer Consortium. American journal of epidemiology. 2012;176(7):573-85. Epub 2012/09/19. PMID: 22986146

21. Young RP, Hopkins RJ, Whittington CF, Hay BA, Epton MJ, Gamble GD. Individual and cumulative effects of GWAS susceptibility loci in lung cancer: associations after sub-phenotyping for COPD. PloS one. 2011;6(2):e16476. Epub 2011/02/10. PMID: 21304900

22. Schwartz AG, Ruckdeschel JC. Familial lung cancer: genetic susceptibility and relationship to chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine. 2006;173(1):16-22. Epub 2005/09/06. PMID: 16141445

23. de Andrade M, Li Y, Marks RS, Deschamps C, Scanlon PD, Olswold CL, Jiang R, Swensen SJ, Sun Z, Cunningham JM, Wampfler JA, Limper AH, Midthun DE, Yang P. Genetic variants associated with the risk of chronic obstructive pulmonary disease with and without lung cancer. Cancer Prev Res (Phila). 2012;5(3):365-73. Epub 2011/11/03. PMID: 22044695

24. Bailey-Wilson JE, Amos CI, Pinney SM, Petersen GM, de Andrade M, Wiest JS, Fain P, Schwartz AG, You M, Franklin W, Klein C, Gazdar A, Rothschild H, Mandal D, Coons T, Slusser J, Lee J, Gaba C, Kupert E, Perez A, Zhou X, Zeng D, Liu Q, Zhang Q, Seminara D, Minna J, Anderson MW. A major lung cancer susceptibility locus maps to chromosome 6q23-25. American journal of human genetics. 2004;75(3):460-74. Epub 2004/07/24. PMID: 15272417

25. Joost O, Wilk JB, Cupples LA, Harmon M, Shearman AM, Baldwin CT, O'Connor GT, Myers RH, Gottlieb DJ. Genetic loci influencing lung function: a genome-wide scan in the Framingham Study. American journal of respiratory and critical care medicine. 2002;165(6):795-9. Epub 2002/03/19. PMID: 11897646

26. Hunninghake GM, Cho MH, Tesfaigzi Y, Soto-Quiros ME, Avila L, Lasky-Su J, Stidley C, Melen E, Soderhall C, Hallberg J, Kull I, Kere J, Svartengren M, Pershagen G, Wickman M, Lange C, Demeo DL, Hersh CP, Klanderman BJ, Raby BA, Sparrow D, Shapiro SD, Silverman EK, Litonjua AA, Weiss ST, Celedon JC. MMP12, lung function, and COPD in high-risk populations. N Engl J Med. 2009;361(27):2599-608. Epub 2009/12/19. PMID: 20018959

27. DeMeo DL, Celedon JC, Lange C, Reilly JJ, Chapman HA, Sylvia JS, Speizer FE, Weiss ST, Silverman EK. Genome-wide linkage of forced mid-expiratory flow in chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine. 2004;170(12):1294-301. Epub 2004/09/07. PMID: 15347563

28. Carlsten C, Sagoo GS, Frodsham AJ, Burke W, Higgins JP. Glutathione S-transferase M1 (GSTM1) polymorphisms and lung cancer: a literature-based systematic HuGE review and meta-analysis. American journal of epidemiology. 2008;167(7):759-74. Epub 2008/02/14. PMID: 18270371

29. Wang IM, Stepaniants S, Boie Y, Mortimer JR, Kennedy B, Elliott M, Hayashi S, Loy L, Coulter S, Cervino S, Harris J, Thornton M, Raubertas R, Roberts C, Hogg JC, Crackower M, O'Neill G, Pare PD. Gene expression profiling in patients with chronic obstructive pulmonary disease and lung cancer. American journal of respiratory and critical care medicine. 2008;177(4):402-11. Epub 2007/11/03. PMID: 17975202

30. Wang RD, Wright JL, Churg A. Transforming growth factor-beta1 drives airway remodeling in cigarette smoke-exposed tracheal explants. American journal of respiratory cell and molecular biology. 2005;33(4):387-93. Epub 2005/07/05. PMID: 15994428

31. Shintani Y, Maeda M, Chaika N, Johnson KR, Wheelock MJ. Collagen I promotes epithelial-to-mesenchymal transition in lung cancer cells via transforming growth factor-beta signaling. American journal of respiratory cell and molecular biology. 2008;38(1):95-104. Epub 2007/08/04. PMID: 17673689

32. Lechapt-Zalcman E, Pruliere-Escabasse V, Advenier D, Galiacy S, Charriere-Bertrand C, Coste A, Harf A, d'Ortho MP, Escudier E. Transforming growth factor-beta1 increases airway wound repair via MMP-2 upregulation: a new pathway for epithelial wound repair? American journal of physiology Lung cellular and molecular physiology. 2006;290(6):L1277-82. Epub 2006/01/18. PMID: 16414983

33. Boelens MC, Gustafson AM, Postma DS, Kok K, van der Vries G, van der Vlies P, Spira A, Lenburg ME, Geerlings M, Sietsma H, Timens W, van den Berg A, Groen HJ. A chronic obstructive pulmonary disease related signature in squamous cell lung cancer. Lung Cancer. 2011;72(2):177-83. Epub 2010/09/14. PMID: 20832896

34. Butler MW, Fukui T, Salit J, Shaykhiev R, Mezey JG, Hackett NR, Crystal RG. Modulation of cystatin A expression in human airway epithelium related to genotype, smoking, COPD, and lung cancer. Cancer research. 2011;71(7):2572-81. Epub 2011/02/18. PMID: 21325429

35. Spira A, Beane J, Shah V, Liu G, Schembri F, Yang X, Palma J, Brody JS. Effects of cigarette smoke on the human airway epithelial cell transcriptome. Proceedings of the National Academy of Sciences of the United States of America. 2004;101(27):10143-8. Epub 2004/06/24. PMID: 15210990

36. Beane J, Sebastiani P, Liu G, Brody JS, Lenburg ME, Spira A. Reversible and permanent effects of tobacco smoke exposure on airway epithelial gene expression. Genome biology. 2007;8(9):R201. Epub 2007/09/27. PMID: 17894889

37. Wistuba, II, Lam S, Behrens C, Virmani AK, Fong KM, LeRiche J, Samet JM, Srivastava S, Minna JD, Gazdar AF. Molecular damage in the bronchial epithelium of current and former smokers. Journal of the National Cancer Institute. 1997;89(18):1366-73. Epub 1997/10/06. PMID: 9308707

38. Steiling K, Kadar AY, Bergerat A, Flanigon J, Sridhar S, Shah V, Ahmad QR, Brody JS, Lenburg ME, Steffen M, Spira A. Comparison of proteomic and transcriptomic profiles in the bronchial airway epithelium of current and never smokers. PloS one. 2009;4(4):e5043. Epub 2009/04/10. PMID: 19357784

39. Tuder RM, Yun JH, Graham BB. Cigarette smoke triggers code red: p21CIP1/WAF1/SDI1 switches on danger responses in the lung. American journal of respiratory cell and molecular biology. 2008;39(1):1-6. Epub 2008/04/29. PMID: 18441278

40. Sancar A, Lindsey-Boltz LA, Unsal-Kacmaz K, Linn S. Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints. Annual review of biochemistry. 2004;73:39-85. Epub 2004/06/11. PMID: 15189136

41. Caramori G, Adcock IM, Casolari P, Ito K, Jazrawi E, Tsaprouni L, Villetti G, Civelli M, Carnini C, Chung KF, Barnes PJ, Papi A. Unbalanced oxidant-induced DNA damage and repair in COPD: a link towards lung cancer. Thorax. 2011;66(6):521-7. Epub 2011/04/05. PMID: 21460372

42. Popanda O, Schattenberg T, Phong CT, Butkiewicz D, Risch A, Edler L, Kayser K, Dienemann H, Schulz V, Drings P, Bartsch H, Schmezer P. Specific combinations of DNA repair gene variants and increased risk for non-small cell lung cancer. Carcinogenesis. 2004;25(12):2433-41. Epub 2004/08/31. PMID:

15333465

43. Miller KM, Tjeertes JV, Coates J, Legube G, Polo SE, Britton S, Jackson SP. Human HDAC1 and HDAC2 function in the DNA-damage response to promote DNA nonhomologous end-joining. Nature structural & molecular biology. 2010;17(9):1144-51. Epub 2010/08/31. PMID: 20802485

44. Vempati RK, Jayani RS, Notani D, Sengupta A, Galande S, Haldar D. p300-mediated acetylation of histone H3 lysine 56 functions in DNA damage response in mammals. The Journal of biological chemistry. 2010;285(37):28553-64. Epub 2010/07/01. PMID: 20587414

45. Nakamaru Y, Vuppusetty C, Wada H, Milne JC, Ito M, Rossios C, Elliot M, Hogg J, Kharitonov S, Goto H, Bemis JE, Elliott P, Barnes PJ, Ito K. A protein deacetylase SIRT1 is a negative regulator of metalloproteinase-9. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2009;23(9):2810-9. Epub 2009/04/21. PMID: 19376817

46. Ito K, Ito M, Elliott WM, Cosio B, Caramori G, Kon OM, Barczyk A, Hayashi S, Adcock IM, Hogg JC, Barnes PJ. Decreased histone deacetylase activity in chronic obstructive pulmonary disease. The New England journal of medicine. 2005;352(19):1967-76. Epub 2005/05/13. PMID: 15888697

47. Tseng RC, Lee CC, Hsu HS, Tzao C, Wang YC. Distinct HIC1-SIRT1-p53 loop deregulation in lung squamous carcinoma and adenocarcinoma patients. Neoplasia. 2009;11(8):763-70. Epub 2009/08/04. PMID: 19649206

48. Iskandar AR, Liu C, Smith DE, Hu KQ, Choi SW, Ausman LM, Wang XD. beta-cryptoxanthin restores nicotine-reduced lung SIRT1 to normal levels and inhibits nicotine-promoted lung tumorigenesis and emphysema in A/J mice. Cancer Prev Res (Phila). 2013;6(4):309-20. Epub 2013/01/01. PMID: 23275008

49. Esteller M. Epigenetics in cancer. The New England journal of medicine. 2008;358(11):1148-59. Epub 2008/03/14. PMID: 18337604

50. Brock MV, Hooker CM, Ota-Machida E, Han Y, Guo M, Ames S, Glockner S, Piantadosi S, Gabrielson E, Pridham G, Pelosky K, Belinsky SA, Yang SC, Baylin SB, Herman JG. DNA methylation markers and early recurrence in stage I lung cancer. The New England journal of medicine. 2008;358(11):1118-28. Epub 2008/03/14. PMID: 18337602

51. Palmisano WA, Divine KK, Saccomanno G, Gilliland FD, Baylin SB, Herman JG, Belinsky SA. Predicting lung cancer by detecting aberrant promoter methylation in sputum. Cancer research. 2000;60(21):5954-8. Epub 2000/11/21. PMID: 11085511

52. Hu Z, Chen J, Tian T, Zhou X, Gu H, Xu L, Zeng Y, Miao R, Jin G, Ma H, Chen Y, Shen H. Genetic variants of miRNA sequences and non-small cell lung cancer survival. The Journal of clinical investigation. 2008;118(7):2600-8. Epub 2008/06/04. PMID: 18521189

53. Izzotti A, Calin GA, Arrigo P, Steele VE, Croce CM, De Flora S. Downregulation of microRNA expression in the lungs of rats exposed to cigarette smoke. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2009;23(3):806-12. Epub 2008/10/28. PMID: 18952709

54. Ezzie ME, Crawford M, Cho JH, Orellana R, Zhang S, Gelinas R, Batte K, Yu L, Nuovo G, Galas D, Diaz P, Wang K, Nana-Sinkam SP. Gene expression networks in COPD: microRNA and mRNA regulation. Thorax. 2012;67:122-31. Epub 2011/09/24. PMID: 21940491

55. Markou A, Sourvinou I, Vorkas PA, Yousef GM, Lianidou E. Clinical evaluation of microRNA expression profiling in non small cell lung cancer. Lung Cancer. 2013. Epub 2013/06/13. PMID: 23756108

56. Agusti A, Edwards LD, Rennard SI, MacNee W, Tal-Singer R, Miller BE, Vestbo J, Lomas DA, Calverley PM, Wouters E, Crim C, Yates JC, Silverman EK, Coxson HO, Bakke P, Mayer RJ, Celli B. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. PloS one. 2012;7(5):e37483. Epub 2012/05/25. PMID: 22624038

57. Babusyte A, Stravinskaite K, Jeroch J, Lotvall J, Sakalauskas R, Sitkauskiene B. Patterns of airway inflammation and MMP-12 expression in smokers and ex-smokers with COPD. Respir Res. 2007;8:81. Epub 2007/11/16. PMID: 18001475

58. Thorleifsson SJ, Margretardottir OB, Gudmundsson G, Olafsson I, Benediktsdottir B, Janson C, Buist AS, Gislason T. Chronic airflow obstruction and markers of systemic inflammation: results from the BOLD study in Iceland. Respir Med. 2009;103(10):1548-53. Epub 2009/05/12. PMID: 19427181

59. Dickens JA, Miller BE, Edwards LD, Silverman EK, Lomas DA, Tal-Singer R. COPD association and repeatability of blood biomarkers in the ECLIPSE cohort. Respir Res. 2011;12:146. Epub 2011/11/08. PMID: 22054035

60. Sin DD, Leung R, Gan WQ, Man SF. Serum surfactant protein D as a potential lung specific biomarker in COPD: a pilot study. BMC Pulm Med. 2007;7:13. PMID: 17922919

61. Lomas DA, Silverman EK, Edwards L, Locantre NW, Miller BE, Horstman DH, Tal-Singer R. Serum surfactant protein D is steroid sensitive and associated with exacerbations of COPD. European Respiratory Journal. 2009;34:95-102. PMID: 19164344

62. Celli BR, Locantore N, Yates J, Tal-Singer R, Miller BE, Bakke P, Calverley P, Coxson H, Crim C, Edwards LD, Lomas DA, Duvoix A, Macnee W, Rennard S, Silverman E, Vestbo J, Wouters E, Agusti A. Inflammatory Biomarkers Improve Clinical Prediction of Mortality in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2012;185(10):1065-72. Epub 2012/03/20. PMID: 22427534

63. Thomsen M, Ingebrigtsen TS, Marott JL, Dahl M, Lange P, Vestbo J, Nordestgaard BG. Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease. JAMA : the journal of the American Medical Association. 2013;309(22):2353-61. Epub 2013/06/13. PMID: 23757083

64. Carter RI, Mumford RA, Treonze KM, Finke PE, Davies P, Si Q, Humes JL, Dirksen A, Piitulainen E, Ahmad A, Stockley RA. The fibrinogen cleavage product Aalpha-Val360, a specific marker of neutrophil elastase activity in vivo. Thorax. 2011;66(8):686-91. Epub 2011/05/28. PMID: 21617168

65. Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L, Cherniack RM, Rogers RM, Sciurba FC, Coxson HO, Pare PD. The nature of small-airway obstruction in chronic obstructive pulmonary disease. The New England journal of medicine. 2004;350(26):2645-53. Epub 2004/06/25. PMID: 15215480

66. Taylor AE, Finney-Hayward TK, Quint JK, Thomas CM, Tudhope SJ, Wedzicha JA, Barnes PJ, Donnelly LE. Defective macrophage phagocytosis of bacteria in COPD. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2010;35(5):1039-47. Epub 2009/11/10. PMID: 19897561

67. van der Strate BW, Postma DS, Brandsma CA, Melgert BN, Luinge MA, Geerlings M, Hylkema MN, van den DA, Timens W, Kerstjens HA, . Cigarette smoke induced emphysema: a role for the B cell? Am J Respir Crit Care Med. 2006;173:751 - 8. PMID: 16399994

68. Lee SH, Goswami S, Grudo A, Song LZ, Bandi V, Goodnight-White S, Green L, Hacken-Bitar J, Huh J, Bakaeen F, Coxson HO, Cogswell S, Storness-Bliss C, Corry DB, Kheradmand F. Antielastin autoimmunity in tobacco smoking-induced emphysema. Nature medicine. 2007;13(5):567-9. Epub 2007/04/24. PMID: 17450149

69. Sapey E, Wood AM. Auto-antibodies and inflammation. A case of the chicken and the egg? American journal of respiratory and critical care medicine. 2011;183(8):959-60. Epub 2011/04/19. PMID: 21498815

70. Vendramini-Costa DB, Carvalho JE. Molecular link mechanisms between inflammation and cancer. Current pharmaceutical design. 2012;18(26):3831-52. Epub 2012/05/29. PMID: 22632748

71. Chiba T, Marusawa H, Ushijima T. Inflammation-associated cancer development in digestive organs: mechanisms and roles for genetic and epigenetic modulation. Gastroenterology. 2012;143(3):550-63. Epub 2012/07/17. PMID: 22796521

72. Siemes C, Visser LE, Coebergh JW, Splinter TA, Witteman JC, Uitterlinden AG, Hofman A, Pols HA, Stricker BH. C-reactive protein levels, variation in the C-reactive protein gene, and cancer risk: the Rotterdam Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2006;24(33):5216-22. Epub 2006/11/23. PMID: 17114654

73. Moghaddam SJ, Li H, Cho SN, Dishop MK, Wistuba, II, Ji L, Kurie JM, Dickey BF, Demayo FJ. Promotion of lung carcinogenesis by chronic obstructive pulmonary disease-like airway inflammation in a K-ras-induced mouse model. American journal of respiratory cell and molecular biology. 2009;40(4):443-53. Epub 2008/10/18. PMID: 18927348

74. Parimon T, Chien JW, Bryson CL, McDonell MB, Udris EM, Au DH. Inhaled corticosteroids and risk of lung cancer among patients with chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine. 2007;175(7):712-9. Epub 2006/12/23. PMID: 17185647

75. van den Berg RM, van Tinteren H, van Zandwijk N, Visser C, Pasic A, Kooi C, Sutedja TG, Baas P, Grunberg K, Mooi WJ, Snijders PJ, Postmus PE, Smit EF. The influence of fluticasone inhalation on markers of carcinogenesis in bronchial epithelium. American journal of respiratory and critical care medicine. 2007;175(10):1061-5. Epub 2007/02/10. PMID: 17290039

76. Bergin DA, Greene CM, Sterchi EE, Kenna C, Geraghty P, Belaaouaj A, Taggart CC, O'Neill SJ, McElvaney NG. Activation of the epidermal growth factor receptor (EGFR) by a novel metalloprotease pathway. The Journal of biological chemistry. 2008;283(46):31736-44. Epub 2008/09/06. PMID: 18772136

77. Ganesan S, Unger BL, Comstock AT, Angel KA, Mancuso P, Martinez FJ, Sajjan US. Aberrantly activated EGFR contributes to enhanced IL-8 expression in COPD airways epithelial cells via regulation of nuclear FoxO3A. Thorax. 2013;68(2):131-41. Epub 2012/10/27. PMID: 23099361

78. Lapperre TS, Sont JK, van Schadewijk A, Gosman MM, Postma DS, Bajema IM, Timens W, Mauad T, Hiemstra PS. Smoking cessation and bronchial epithelial remodelling in COPD: a cross-sectional study. Respiratory research. 2007;8:85. Epub 2007/11/28. PMID: 18039368

79. Chen Y, Chen P, Hanaoka M, Droma Y, Kubo K. Enhanced levels of prostaglandin E2 and matrix metalloproteinase-2 correlate with the severity of airflow limitation in stable COPD. Respirology. 2008;13(7):1014-21. Epub 2008/08/14. PMID: 18699805

80. Cathcart MC, Gray SG, Baird AM, Boyle E, Gately K, Kay E, Cummins R, Pidgeon GP, O'Byrne KJ. Prostacyclin synthase expression and epigenetic regulation in nonsmall cell lung cancer. Cancer. 2011;117(22):5121-32. Epub 2011/04/28. PMID: 21523772

81. Setia S, Vaish V, Sanyal SN. Chemopreventive effects of NSAIDs as inhibitors of cyclooxygenase-2 and inducers of apoptosis in experimental lung carcinogenesis. Molecular and cellular biochemistry. 2012;366(1-2):89-99. Epub 2012/03/14. PMID: 22411738

82. Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet. 2011;377(9759):31-41. Epub 2010/12/15. PMID: 21144578

83. Campa D, Zienolddiny S, Maggini V, Skaug V, Haugen A, Canzian F. Association of a common polymorphism in the cyclooxygenase 2 gene with risk of non-small cell lung cancer. Carcinogenesis. 2004;25(2):229-35. Epub 2003/11/08. PMID: 14604894

84. Lawless MW, O'Byrne KJ, Gray SG. Oxidative stress induced lung cancer and COPD: opportunities for epigenetic therapy. Journal of cellular and molecular medicine. 2009;13(9A):2800-21. Epub 2009/07/16. PMID: 19602054

85. Rahman I, Morrison D, Donaldson K, MacNee W. Systemic oxidative stress in asthma, COPD, and smokers. American journal of respiratory and critical care medicine. 1996;154(4 Pt 1):1055-60. Epub 1996/10/01. PMID: 8887607

86. DeMeo DL, Hersh CP, Hoffman EA, Litonjua AA, Lazarus R, Sparrow D, Benditt JO, Criner G, Make B, Martinez FJ, Scanlon PD, Sciurba FC, Utz JP, Reilly JJ, Silverman EK. Genetic determinants of emphysema distribution in the national emphysema treatment trial. Am J Respir Crit Care Med. 2007;176(1):42-8. Epub 2007/03/17. PMID: 17363767

87. Gresner P, Gromadzinska J, Wasowicz W. Polymorphism of selected enzymes involved in detoxification and biotransformation in relation to lung cancer. Lung Cancer. 2007;57(1):1-25. Epub 2007/03/06. PMID: 17337085

88. Hu G, Shi Z, Hu J, Zou G, Peng G, Ran P. Association between polymorphisms of microsomal epoxide hydrolase and COPD: results from meta-analyses. Respirology. 2008;13(6):837-50. Epub 2008/09/25. PMID: 18811882

89. Liu H, Li HY, Chen HJ, Huang YJ, Zhang S, Wang J. EPHX1 A139G polymorphism and lung cancer risk: a meta-analysis. Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine. 2013;34(1):155-63. Epub 2012/10/12. PMID: 23055191

90. Castaldi PJ, Cho MH, Cohn M, Langerman F, Moran S, Tarragona N, Moukhachen H, Venugopal R, Hasimja D, Kao E, Wallace B, Hersh CP, Bagade S, Bertram L, Silverman EK, Trikalinos TA. The COPD genetic association compendium: a comprehensive online database of COPD genetic associations. Human molecular genetics. 2010;19(3):526-34. Epub 2009/11/26. PMID: 19933216

91. Svensk AM, Soini Y, Paakko P, Hiravikoski P, Kinnula VL. Differential expression of superoxide dismutases in lung cancer. American journal of clinical pathology. 2004;122(3):395-404. Epub 2004/09/15. PMID: 15362370

92. Teoh-Fitzgerald ML, Fitzgerald MP, Jensen TJ, Futscher BW, Domann FE. Genetic and epigenetic inactivation of extracellular superoxide dismutase promotes an invasive phenotype in human lung cancer by disrupting ECM homeostasis. Molecular cancer research : MCR. 2012;10(1):40-51. Epub 2011/11/09. PMID: 22064654

93. Kosmider B, Messier EM, Janssen WJ, Nahreini P, Wang J, Hartshorn KL, Mason RJ. Nrf2 protects human alveolar epithelial cells against injury induced by influenza A virus. Respiratory research. 2012;13:43. Epub 2012/06/08. PMID: 22672594

94. Singh A, Misra V, Thimmulappa RK, Lee H, Ames S, Hoque MO, Herman JG, Baylin SB, Sidransky D, Gabrielson E, Brock MV, Biswal S. Dysfunctional KEAP1-NRF2 interaction in non-small-cell lung cancer. PLoS medicine. 2006;3(10):e420. Epub 2006/10/06. PMID: 17020408

95. Shibata T, Ohta T, Tong KI, Kokubu A, Odogawa R, Tsuta K, Asamura H, Yamamoto M, Hirohashi S. Cancer related mutations in NRF2 impair its recognition by Keap1-Cul3 E3 ligase and promote malignancy. Proceedings of the National Academy of Sciences of the United States of America. 2008;105(36):13568-73. Epub 2008/09/02. PMID: 18757741

96. Malhotra D, Thimmulappa R, Navas-Acien A, Sandford A, Elliott M, Singh A, Chen L, Zhuang X, Hogg J, Pare P, Tuder RM, Biswal S. Decline in NRF2-regulated antioxidants in chronic obstructive pulmonary disease lungs due to loss of its positive regulator, DJ-1. American journal of respiratory and critical care medicine. 2008;178(6):592-604. Epub 2008/06/17. PMID: 18556627

97. Marwick JA, Kirkham P, Gilmour PS, Donaldson K, Mac NW, Rahman I. Cigarette smoke-induced oxidative stress and TGF-beta1 increase p21waf1/cip1 expression in alveolar epithelial cells. Annals of the New York Academy of Sciences. 2002;973:278-83. Epub 2002/12/18. PMID: 12485877

98. Cebulska-Wasilewska A, Wierzewska A, Nizankowska E, Graca B, Hughes JA, Anderson D. Cytogenetic damage and ras p21 oncoprotein levels from patients with chronic obstructive pulmonary disease (COPD), untreated lung cancer and healthy controls. Mutation research. 1999;431(1):123-31. Epub 2000/02/03. PMID: 10656491

99. Vermeulen K, Van Bockstaele DR, Berneman ZN. The cell cycle: a review of regulation, deregulation and therapeutic targets in cancer. Cell proliferation. 2003;36(3):131-49. Epub 2003/06/20. PMID: 12814430

100. Stockley RA. Neutrophils and protease/antiprotease imbalance. American journal of respiratory and critical care medicine. 1999;160(5 Pt 2):S49-52. Epub 1999/11/11. PMID: 10556170

101. Wood AM, Stockley RA. Alpha one antitrypsin deficiency: from gene to treatment. Respiration. 2007;74(5):481-92. Epub 2007/08/03. PMID: 17671403

102. Yang P, Sun Z, Krowka MJ, Aubry MC, Bamlet WR, Wampfler JA, Thibodeau SN, Katzmann JA, Allen MS, Midthun DE, Marks RS, de Andrade M. Alpha1-antitrypsin deficiency carriers, tobacco smoke, chronic obstructive pulmonary disease, and lung cancer risk. Archives of internal medicine. 2008;168(10):1097-103. Epub 2008/05/28. PMID: 18504338

103. Dahl R, Titlestad I, Lindqvist A, Wielders P, Wray H, Wang M, Samuelsson V, Mo J, Holt A. Effects of an oral MMP-9 and -12 inhibitor, AZD1236, on biomarkers in moderate/severe COPD: a randomised controlled trial. Pulmonary pharmacology & therapeutics. 2012;25(2):169-77. Epub 2012/02/07. PMID: 22306193

104. Douillard JY, Peschel C, Shepherd F, Paz-Ares L, Arnold A, Davis M, Tonato M, Smylie M, Tu D, Voi M, Humphrey J, Ottaway J, Young K, Vreckem AV, Seymour L. Randomized phase II feasibility study of combining the matrix metalloproteinase inhibitor BMS-275291 with paclitaxel plus carboplatin in advanced non-small cell lung cancer. Lung Cancer. 2004;46(3):361-8. Epub 2004/11/16. PMID: 15541822

105. Takizawa H, Tanaka M, Takami K, Ohtoshi T, Ito K, Satoh M, Okada Y, Yamasawa F, Nakahara K, Umeda A. Increased expression of transforming growth factor-beta1 in small airway epithelium from tobacco smokers and patients with chronic obstructive pulmonary disease (COPD). American journal of respiratory and critical care medicine. 2001;163(6):1476-83. Epub 2001/05/24. PMID: 11371421

106. Morris DG, Huang X, Kaminski N, Wang Y, Shapiro SD, Dolganov G, Glick A, Sheppard D. Loss of integrin alpha(v)beta6-mediated TGF-beta activation causes Mmp12-dependent emphysema. Nature. 2003;422(6928):169-73. Epub 2003/03/14. PMID: 12634787

107. Katsuno Y, Lamouille S, Derynck R. TGF-beta signaling and epithelial-mesenchymal transition in cancer progression. Current opinion in oncology. 2013;25(1):76-84. Epub 2012/12/01. PMID: 23197193

108. Pilette C, Colinet B, Kiss R, Andre S, Kaltner H, Gabius HJ, Delos M, Vaerman JP, Decramer M, Sibille Y. Increased galectin-3 expression and intra-epithelial neutrophils in small airways in severe COPD. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2007;29(5):914-22. Epub 2007/01/26. PMID: 17251233

109. Szoke T, Kayser K, Baumhakel JD, Trojan I, Furak J, Tiszlavicz L, Horvath A, Szluha K, Gabius HJ, Andre S. Prognostic significance of endogenous adhesion/growth-regulatory lectins in lung cancer. Oncology. 2005;69(2):167-74. Epub 2005/08/30. PMID: 16127288

110. Di Stefano A, Caramori G, Oates T, Capelli A, Lusuardi M, Gnemmi I, Ioli F, Chung KF, Donner CF, Barnes PJ, Adcock IM. Increased expression of nuclear factor-kappaB in bronchial biopsies from smokers and patients with COPD. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2002;20(3):556-63. Epub 2002/10/03. PMID: 12358328

111. Karin M. NF-kappaB as a critical link between inflammation and cancer. Cold Spring Harbor perspectives in biology. 2009;1(5):a000141. Epub 2010/01/13. PMID: 20066113

112. Gustafson AM, Soldi R, Anderlind C, Scholand MB, Qian J, Zhang X, Cooper K, Walker D, McWilliams A, Liu G, Szabo E, Brody J, Massion PP, Lenburg ME, Lam S, Bild AH, Spira A. Airway PI3K pathway activation is an early and reversible event in lung cancer development. Science translational medicine. 2010;2(26):26ra5. Epub 2010/04/09. PMID: 20375364

113. Popkie AP, Zeidner LC, Albrecht AM, D'Ippolito A, Eckardt S, Newsom DE, Groden J, Doble BW, Aronow B, McLaughlin KJ, White P, Phiel CJ. Phosphatidylinositol 3-kinase (PI3K) signaling via glycogen synthase kinase-3 (Gsk-3) regulates DNA methylation of imprinted loci. The Journal of biological chemistry. 2010;285(53):41337-47. Epub 2010/11/05. PMID: 21047779

114. Matsuo Y, Amano S, Furuya M, Namiki K, Sakurai K, Nishiyama M, Sudo T, Tatsumi K, Kuriyama T, Kimura S, Kasuya Y. Involvement of p38alpha mitogen-activated protein kinase in lung metastasis of tumor cells. The Journal of biological chemistry. 2006;281(48):36767-75. Epub 2006/10/10. PMID: 17028194

115. Li MY, Yuan H, Ma LT, Kong AW, Hsin MK, Yip JH, Underwood MJ, Chen GG. Roles of peroxisome proliferator-activated receptor-alpha and -gamma in the development of non-small cell lung cancer. American journal of respiratory cell and molecular biology. 2010;43(6):674-83. Epub 2010/01/19. PMID: 20081051

116. Huang TH, Razmovski-Naumovski V, Kota BP, Lin DS, Roufogalis BD. The pathophysiological function of peroxisome proliferator-activated receptor-gamma in lung-related diseases. Respiratory research. 2005;6:102. Epub 2005/09/13. PMID: 16153299

117. Kent BD, Mitchell PD, McNicholas WT. Hypoxemia in patients with COPD: cause, effects, and disease progression. Int J Chron Obstruct Pulmon Dis. 2011;6:199-208. Epub 2011/06/11. PMID: 21660297

118. Siafakas NM, Antoniou KM, Tzortzaki EG. Role of angiogenesis and vascular remodeling in chronic obstructive pulmonary disease. International journal of chronic obstructive pulmonary disease. 2007;2(4):453-62. Epub 2008/02/14. PMID: 18268919

119. Michaud SE, Menard C, Guy LG, Gennaro G, Rivard A. Inhibition of hypoxia-induced angiogenesis by cigarette smoke exposure: impairment of the HIF-1alpha/VEGF pathway. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2003;17(9):1150-2. Epub 2003/04/24. PMID: 12709416

120. Edirisinghe I, Yang SR, Yao H, Rajendrasozhan S, Caito S, Adenuga D, Wong C, Rahman A, Phipps RP, Jin ZG, Rahman I. VEGFR-2 inhibition augments cigarette smoke-induced oxidative stress and inflammatory responses leading to endothelial dysfunction. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2008;22(7):2297-310. Epub 2008/02/12. PMID: 18263699

121. Karoor V, Le M, Merrick D, Fagan KA, Dempsey EC, Miller YE. Alveolar hypoxia promotes murine lung tumor growth through a VEGFR-2/EGFR-dependent mechanism. Cancer Prev Res (Phila). 2012;5(8):1061-71. Epub 2012/06/16. PMID: 22700853

122. Tang XP, Li J, Yu LC, Chen YC, Shi SB, Zhu LR, Chen P. Clinical significance of survivin and VEGF mRNA detection in the cell fraction of the peripheral blood in non-small cell lung cancer patients before and after surgery. Lung Cancer. 2013. Epub 2013/06/13. PMID: 23756092

123. Watz H, Waschki B, Meyer T, Magnussen H. Physical activity in patients with COPD. Eur Respir J. 2009;33(2):262-72. Epub 2008/11/18. PMID: 19010994

124. Friedenreich CM, Neilson HK, Lynch BM. State of the epidemiological evidence on physical activity and cancer prevention. Eur J Cancer. 2010;46(14):2593-604. Epub 2010/09/17. PMID: 20843488

125. Albanes D, Blair A, Taylor PR. Physical activity and risk of cancer in the NHANES I population. American journal of public health. 1989;79(6):744-50. Epub 1989/06/01. PMID: 2729471