The Epithelial Cell and Lung Cancer: The Link between Chronic Obstructive Pulmonary Disease and Lung Cancer

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Key Words

Chronic obstructive pulmonary disease • Non-small cell lung cancer • Epithelial cell

Abstract

Chronic obstructive pulmonary disease (COPD) and lung cancer currently form the basis for an enormous disease burden in the developed world. As a result of changing smoking trends and tobacco use, regrettably, a similar picture is arising rapidly within the developing world. COPD is a recognised risk factor for lung cancer, and a significant proportion of patients diagnosed with lung cancer have COPD. An association between both conditions has long been suspected but has proven difficult to demonstrate thus far. However, the common factors between both conditions are now becoming apparent thanks to recent clinical and molecular advances. Abnormal regulation of the immune system and the establishment of chronic inflammation appear to be key events in this process. In addition, the complex interplay between genes and environment and the possibility of a genetic basis to lung cancer susceptibility in the context of COPD are becoming clearer concepts. As we begin to unravel the common pathways and molecules in the pathogenesis of both conditions, we may be able to not only iden-

tify novel strategies to prevent and treat COPD and lung cancer, but also recognise molecular markers to identify patients at high risk of developing lung cancer.

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Introduction

Lung cancer and chronic obstructive pulmonary disease (COPD) are significant causes of morbidity and mortality worldwide. One shared risk factor is found in exposure to cigarette smoke and a presumed genetic predisposition illustrated by the incidence of these diseases in only a small proportion of smokers.

Worldwide, 1.35 million people are diagnosed with lung cancer per year [1]. It is the most prevalent fatal malignancy in the western world, causing approximately 35,000 deaths per year in the UK in particular [2]. Limitations in current treatment in combination with a high relapse rate and usually late diagnosis mean that prognosis is poor and 5-year survival rates are around 6.3% for men and 7.5% for women [3]. Similarly, the morbidity and mortality burden of COPD is high and is expected to increase with the rising incidence of cigarette smoking in developing countries, such as China and India. It is

thought that by 2020, COPD will become the third leading cause of death worldwide [4]. Clearly, a key element in tackling this burgeoning health problem will be smoking cessation.

Tobacco smoke is associated with 90% of lung cancers [5], the majority of which arise from epithelial cells. We know that exposure to tobacco smoke leads to progressive histological changes: from metaplasia, dysplasia, carcinoma in situ and adenomatous hyperplasia to eventually invasive carcinoma. However, only 15% of lifetime smokers develop lung carcinoma and 10% of lung cancers occur in never-smokers [6]. Interestingly, never-smokers make up 10% of new non-small cell lung cancer (NSCLC) cases in men and 20% of cases in females [7].

Additionally, we know that between 50 and 70% of patients with lung cancer have COPD and that COPD is a major independent risk factor for lung cancer, in fact more so than smoking alone [8]. Therefore, it is evident that there are diverse and complex mechanisms governing the individual risk of developing lung cancer, COPD or indeed both. What therefore is the common pathway linking these disparate disease processes?

Firstly, the role of genetic risk and lung cancer is becoming a clearer concept. This encompasses familial risk and also individual susceptibility traits, including loci for nicotine dependence and carcinogenesis which have recently been described. Secondly, it has long been hypothesised that chronic inflammation is a significant player in this progression of disease by virtue of the process of injury, inflammation, cellular proliferation and subsequent cancer development.

This review will illustrate the links between COPD and lung cancer from both a clinical and molecular angle and begin to unravel shared biological threads implicated in the pathogenesis of both. This will be extrapolated to comment on future directions for investigation and treatment of lung cancer.

Association between COPD and Lung Cancer

The relationship between COPD and lung cancer is well established, with an association recognised as early on as 1939. A 1950s survey of hospitals in London managed to identify and characterise 709 patients with lung cancer [9]. The conclusion was drawn from this commentary that there was a tangible association between smoking and lung cancer.

Clinical studies clarifying this assumption took place later on with Davis et al. [10] in New York who followed

up 835 patients between 1955 and 1974 and found an incidence of lung cancer in smokers which was 4–5 times higher than that previously reported. A matched study by Skillrud et al. [11] from the Mayo Clinic in Rochester showed a risk 4.4 times greater in smokers than in non-smokers but, importantly, did not control for the effects of cigarette smoking due to small sampling size.

Tockman et al. [12] later showed that COPD was a greater risk factor for lung cancer than either age or quantity of smoking. Lung cancer risk was also shown to be increased in proportion to the degree of COPD. The Lung Health Study results, published in 1994, showed that in 6,000 smokers with mild to moderate airways obstruction on pulmonary function tests, lung cancer was the most common cause of death at 5-year follow-up [13]. In COPD, we generally see one of two pathophysiological profiles: either alveolar obliteration resulting in airway dilatation/emphysema, or narrowing of the bronchi leading to obstructive airways disease. Other studies have taken the characterisation of this link further, showing that extent of airflow obstruction and also radiological degree of emphysematous change are independently associated with an increased risk of lung cancer [14], and that this effect is independent of smoking. Kishi and colleagues [15] studied 1,520 patients over the age of 50 with a >20 pack-year smoking history and demonstrated that the likelihood of developing lung carcinoma increased if the forced expiratory volume in 1 s was <40% of predicted. This has been further illustrated by Wilson et al. [16] who carried out a study of 3,638 patients, evaluated by visually graded emphysema on CT and airflow obstruction on spirometry.

Interestingly, there are studies which have sought to determine whether the same link exists in non-smokers. As far back as 1980, there has been evidence suggesting the increased incidence of lung cancer in never-smokers with emphysema [17]. Turner et al. [18] in 2007 published results of a 20-year follow-up study of 1.2 million participants in the USA. They showed that lung cancer mortality was significantly associated with emphysema and the combined end point of emphysema/bronchitis. No association was seen with chronic bronchitis alone in the overall analysis.

Genetic Susceptibility to COPD and Lung Cancer

Clearly, lung cancer and COPD are complex diseases in which environmental factors and multiple polymorphic genes interact to influence disease susceptibility.

Given the similarities and association between COPD and lung cancer, an obvious question is whether there is a common underlying genetic susceptibility acting in addition to the known shared risk associated with cigarette smoking. However, only a small percentage of smokers go on to develop lung cancer and/or COPD in their lifetime. This suggests an individual variation in the degree of susceptibility and risk – but could there be in addition a genetic predisposition?

α 1-Antitrypsin deficiency (α 1ATD) is a genetic disorder common in the European population which leads to early-onset emphysema in homozygous individuals. A potential link between lung cancer and α 1ATD was first postulated in 1974 by Harris et al. [19]. This group found an increased serum α 1AT in 73 patients with lung cancer not amenable to resection. A further study by Yang et al. [20] looked at three risk factors (α 1ATD, COPD and smoking) and the impact thereof in the development of lung cancer. They characterised 1,856 patients between the years 1997 and 2003, matched to unrelated and sibling controls. In never-smokers, it was found that carriers of the Z and the S alleles of the α 1AT gene were at a 2.2-fold increased risk of lung cancer when adjusted for age, gender and COPD history.

In smokers of >20 pack-years, the α 1ATD allele-associated lung cancer risk was 2.3-fold, and in light smokers (<20 pack-years), the α 1ATD risk was 2-fold. A history of COPD increased lung cancer risk significantly for all three groups of smokers (2.5- increasing to 9-fold) with the biggest effect on never-smokers. Interestingly, in never-smokers, there was a predilection for tumours of the adenocarcinoma and squamous cell subtype.

As far back as the mid-1970s, Cohen and colleagues [17] demonstrated a common familial component to lung function, COPD and lung cancer not completely explained by smoking or α 1AT genotype. A family history of lung cancer has since been reliably shown to increase the risk of development of lung cancer in smokers and non-smokers [21, 22]. We now have clear evidence linking a hereditary component to lung carcinoma, based on animal models [23], family studies [24], linkage analysis [25] and candidate gene association/genome-wide association studies [26].

More recently, via genome association studies, several specific susceptibility loci have been described which are thought to impact on both smoking behaviour and carcinogenesis [27, 28]. There are two single nucleotide polymorphisms which are particularly significant, located on the long arm of chromosome 15 (15q25.1) which contains genes including nicotinic α receptor subunit 3 and 5

(CHRNA3 and CHRNA5) and the β nicotinic ACh receptor subunit amongst others. One variant of CHRNA5, which substitutes aspartic acid for asparagine, is strongly associated with disease. Similarly, a variant in exon 5 of CHRNA3 (rs1051730) confers a similar disease risk. Overall, this region may potentially be involved in up to 14% of all lung cancers.

Interestingly, these variants are thought to not only play a direct role in carcinogenesis, but also in smoking behaviour. Several studies have shown that CHRNA5 single nucleotide polymorphism (rs16969968) is significantly associated with nicotine dependence in African Americans and European Americans. The CHRNA3 single nucleotide polymorphism rs578776 is associated with nicotine dependence in European Americans but not in African Americans [29]. This is an ongoing area of active investigation and would clearly be an important target for intervention.

Nicotine stimulates ACh secretion and activity of ACh receptor and has been shown to stimulate growth of NSCLC cell lines [30]. In vitro, by its action on nicotinic receptors, nicotine stimulates mitogen-activated protein kinase (MAPK) and nuclear factor (NF)- κ B-dependent survival of NSCLC cell lines [31]. Of note, in the same model, blockage of the M3 mAChR by darifenacin prevented nicotinic and muscarinic receptor-induced growth of squamous cell cancer (SCC) lines via MAPK initiation. In addition, via activation of peroxisome proliferator-activated receptors β/δ , nicotine has been shown to stimulate NSCLC growth [32]. It is also seen to increase hypoxia-inducible factor (HIF)-1 α and vascular endothelial growth factor (VEGF) in NSCLC and promote tumour angiogenesis [33]. Therefore, the case is made for the chronic effects of nicotine inhalation and the effect of local acetylcholine release being important mediators in carcinogenesis.

Therefore, a natural progression is the assumption that risk reduction ought to be achieved via smoking cessation. Indeed, the effect of sustained smoking cessation on mortality was assessed in patients with fixed airflow obstruction in a study by Anthonisen et al. [13]. This was achieved via a randomised smoking cessation trial which analysed all cause mortality over a period of 14.5 years. They found that death from lung cancer was 2.2 times more likely in ongoing smokers than in sustained quitters. This suggests that the impact of smoking cessation is substantial and may prevent further damage and reduce the subsequent risk of developing lung cancer.

Individual Variation in Carcinogen Metabolism

It is also known that there are specific genetic abnormalities possible in the carcinogen-metabolising enzymes which may impact on the pathogenesis of both COPD and lung cancer. Although metabolism of foreign compounds occurs in order to allow detoxification and removal from the system, it is often the case that substances may be transformed into toxins via metabolic bioactivation. Individual differences in the *in situ* activation and inactivation of xenobiotics are thought to contribute to the risk of developing COPD and squamous cell lung cancer [34]. The major metabolising enzymes include phase I enzymes [cytochrome P450 enzymes (CYPs), microsomal epoxide hydrolases, flavin monooxygenases and myeloperoxidase] and phase II enzymes (transferases including glutathione S-transferases and arylamine N-acetyltransferases) and are found in human lung tissue. Foreign compounds are initially activated by phase I metabolism and, thereafter, transformed into inactivated hydrophilic compounds by phase II enzymes for excretion.

One example lies within the CYP family, where the homozygous *2A allele of CYP1A1 is known to be an independent risk factor for severe COPD. Contrastingly, CYP1A1m1 homogenous genotype is a risk factor for lung cancer [35]. Interestingly, this is not the case with CYP1B1*3 and CYP1B1*4 genotypes, which confer no increased risk of lung cancer or COPD [36]. However, there is an association with CYP2E1 gene polymorphism and increasing lung cancer risk. COPD patients have a greater frequency of -1053T and 1293C alleles in the promoter of CYP2E1 which is associated with higher transcription, increased protein levels and increased enzymatic activity [37, 38].

There are two haplotypes in the EPHX1 gene which are implicated in the development of lung cancer and COPD. EPHX1 139 and 113 are both significantly associated with lung cancer risk. Interestingly, the EPHX1 139 heterozygote has been found to be protective in Asian populations against the development of COPD. This is not the case in Caucasians. Other gene types of EPHX1 113 and 139 have not been shown to confer an increased risk of COPD. The slow phenotype of EPHX1 is associated with an increased risk of COPD, in contrast to the fast phenotype which is protective of developing COPD in Asian but not in Caucasian populations. Finally, the very slow activity phenotype of EPHX1 is a risk factor for developing COPD in Caucasian but not in Asian populations [39].

It is clear that genetic variation in enzymes that influence metabolism of tobacco smoke carcinogens impacts on the risk of chronic smokers subsequently developing lung cancer or COPD, or both.

Genetics and Carcinogenesis Risk

As mentioned previously, there is a progressive sequence of histological change seen in the bronchial epithelium of smokers which is the precursor to invasive disease [40]. This phenomenon, known as field carcinogenesis, is frequently seen in pre-neoplastic lesions. One study showed widespread dysplasia in the whole of the bronchial tree without evidence of carcinoma. Molecular investigation revealed a widespread point mutation in the protein TP53, suggesting that a single epithelial clone could have expanded to populate large areas of bronchial mucosa. However, it is felt that the overall process of carcinogenesis is more intricate, and recent theories have suggested that the effect of lower airways inflammation and chronic damage, perhaps related to impaired clearance of toxic substances in airflow obstruction, could be the key [41].

Bronchioalveolar stem cells (BASCs) may potentially be involved in this process. BASCs are a population of pulmonary stem cells found in the mouse small airway. They are progenitors of bronchiolar Clara cells and alveolar type I and II cells. They are crucial for the renewal of bronchial, bronchiolar and alveolar epithelium [42, 43]. Epithelial stem cell populations are thought to exist in anatomically and functionally distinct locations within the lung, as suggested by earlier observations of lung injury models [44]. One study looked at murine models to support the hypotheses that stem cell populations exist in the distal lung, that these stem cells act to maintain bronchiolar Clara and alveolar cells, and that their transformation may give rise to lung adenocarcinomas. In this particular study [42], the effects of specific ablation of Clara cells and specific alveolar damage were observed. Proliferation of the BASC population was felt to directly mirror the increase in epithelial repair required secondary to the ablated Clara and alveolar cell populations. Clara and alveolar type II cells are widely thought to be the precursor cells in lung adenocarcinomas. In previous studies [45], a K-ras mouse model showed that BASC numbers were increased, even in the earliest lesions, and increased further during tumour progression. These findings support the existence of stem cell populations within the distal lung. The observed proliferation of

BASC during epithelial repair in vivo, linkage to lung tumours and properties of self-renewal and multipotent differentiation in culture are all important features of stem cell populations that were observed in the proposed BASC population.

Airways homeostasis and repair involving proliferation of BASCs in the context of smoking-related genetic damage and processes such as epithelial to mesenchymal transition (EMT) may then lead to cancerous transformation of lung epithelial cells. Could these cells be important in the linking process between COPD and lung cancer? Identification of BASCs in future work may permit directed differentiation of these cells, allowing regeneration of defective epithelium in chronic lung diseases. It may also allow more effective early identification of lung carcinomas with the opportunity to direct treatment against proliferating BASCs. Further work is required to clarify the role of BASCs in adenocarcinomas of the human lung.

Carcinogenesis is often the product of multiple and cumulative independent genetic alterations which may involve the overexpression of oncogenes or the inhibition of tumour suppressor genes. This leads to disruption of normal signalling pathways and variable abnormalities in cell differentiation, growth and death. To use the scenario of SCC of the lung as an example, we know that molecular genetic studies have identified multiple genetic and epigenetic abnormalities in invasive SCC including DNA sequence alterations, copy number changes and aberrant promoter hypermethylation [46]. These cumulatively activate oncogenes and inhibit tumour suppressor genes. Interestingly, these changes are found in both pre-malignant lesions and in the epithelium of histologically normal lung cells and will be explored in more detail below.

DNA Repair Mechanisms

Cigarette smoke contains multiple carcinogens, in particular polycyclic aromatic hydrocarbons and nitrosamine. These are activated by CYPs and bind to DNA, causing DNA adduct formation. Glutathione S-transferases protect against adduct formation by detoxifying carcinogen intermediates. On the whole, these DNA adducts are repaired; however, on a chronic basis, they may lead to gene mutations such as in p53 which is central to lung cancer formation [47].

Inhalation of toxic pollutants and microorganisms cause lung injury. This comes about through the generation of reactive oxygen species and reactive nitrogen species including superoxide, hydrogen peroxide and nitric

oxide. These trigger a signal cascade leading to the production of pro-inflammatory cytokines and chemokines [48]. Ordinarily, this would assist in neutralising the offending agent and subside once repair is complete. However, in the context of repeated insult and tissue damage, increased amounts of reactive oxygen species and reactive nitrogen species are produced which interact with DNA in proliferating epithelium producing permanent genomic alterations such as deletions, rearrangements and point mutations. Although protective mechanisms are in place via p53 pathways to control cell cycle and DNA repair, when the rate of damage via reactive oxygen species/reactive nitrogen species is high then it leads to chronic inflammation and transformation of cells to a malignant phenotype, thereby increasing the risk of lung cancer [49].

Damage to DNA initiates a process of cell protection by specific repair mechanisms including direct repair, base excision repair, nucleotide excision repair, double-strand break repair and cross-link repair [50]. It has been hypothesised that defective processes in DNA repair efficacy and quality may link COPD and lung cancer. Popanda et al. [51] have reported the polymorphisms in DNA repair genes that are associated with SCC risk. Indeed, one interesting paper has reported on the finding that females have a 10–15% lower capacity for tobacco-induced DNA damage repair than males [50].

The mismatch repair pathway is an important protective mechanism and plays a role in repairing mismatches or small insertions and deletions which occur during DNA replication. If this process fails, a type of genetic instability occurs, known as microsatellite instability, which manifests as increased rates of DNA replication errors throughout the genome. It is known that inflammation down-regulates the process of mismatch repair in several ways.

In a landmark clinical and molecular study, it was shown that the transcriptome profile of normal bronchial epithelium is distinct from that of the lung parenchyma, that this profile differs again between SCLC and NSCLC, and that there is in each individual an association between cumulative tobacco exposure and gene transcription [52, 53]. In addition, the expression of a number of presumed oncogenes and tumour suppressor genes in the airway epithelial cells of smokers did not return to normal for decades after smoking cessation [54], although many others (especially the antioxidant and drug-metabolising genes) did so within 2 years. This may in part explain why 50% of all lung cancer cases occur in ex-smokers.

Epigenetics

Gene expression is regulated by acetylation of core histones that open up the chromatin structure to allow transcription factors and RNA polymerase to bind to DNA, thus initiating gene transcription. Therefore, epigenetic mechanisms involving DNA and histone modifications result in the silencing of genes without a change in their coding sequence. Chromatin remodelling induces post-translational alteration of core histone proteins and DNA methylation, which are known to regulate pro-inflammatory gene expression during the development of COPD and lung cancer.

It is known that increased histone acetylation occurs on the promoters of pro-inflammatory genes in alveolar macrophages and airway epithelial cells in COPD patients. The amount of acetylation is positively correlated with disease severity [55]. Histone acetylation is reversed by histone deacetylases (HDACs). There are 11 HDAC isoenzymes that deacetylate histones and other proteins within the nucleus, and specific HDACs appear to be differentially regulated and to regulate different groups of genes. HDACs play a critical role in the suppression of gene expression by reversing the hyperacetylation of core histones. It is known that for the regulation of inflammatory genes, HDAC2 is of critical importance. The expression of inflammatory genes is determined by a balance between histone acetylation and deacetylation (activating and arresting transcription, respectively).

The pathways that result in hyperacetylation of histones and non-histone proteins in patients with COPD are seen in association with reduced levels and reduced activity of HDAC2 [56]. Similarly, this has been seen in the lungs of rodents exposed to cigarette smoke [57]. Investigations are ongoing as to whether increasing levels and activity of HDAC2 using phenolic antioxidants or theophyllines can modulate the lung inflammatory response and whether or not this may impact on corticosteroid resistance [58].

Methylation of the p16 promoter is seen in the sputum of COPD patients and is positively correlated with cigarette smoking, which implicates DNA methylation in the evolution of COPD. Key alterations are seen of chromatin structure in lung cancer. Genome-wide DNA demethylation with site-specific hypermethylation is known to occur in lung cancer cells. The result is silencing of diverse tumour-suppressing genes by the recruitment of HDACs. Theories on the mechanisms as to how these events may occur include aberrant expression or activity of DNA methyltransferases and histone demethylases in cancer cells.

Methylation in the promoters of several genes is reported in adenocarcinoma and other NSCLC and is associated with tumorigenesis and recurrence [59]. Therefore, it is possible to surmise that identification of specific gene DNA demethylation could be used as a surrogate or biomarker for detection or chemoprotective intervention in lung cancer.

Alteration of core histone proteins increases the amount of epigenetic modifications mediated by aberrant DNA methylation in cancer cells. Increased HDAC1, decreased HDAC5 and HDAC10 are associated with stage of disease and adverse outcome in patients with lung cancer [60]. HDAC inhibitors and DNA-demethylating agents may synergistically cause apoptosis of lung cancer cells and, therefore, potentially prevent lung cancer genesis in animals exposed to tobacco carcinogens. HDAC inhibitors such as N-acetyldinaline and vorinostat already have evidence for their use in advanced-stage NSCLC, and randomised phase III trials are in progress [61].

How can this increased knowledge of the genetic basis of lung cancer be utilised? Recent research has shown that lung cancers can be classified by microarray gene expression, looking at their unique genetic, epigenetic and molecular fingerprint. This has been shown to match current histological classifications and correlate with survival. It is known that combining cytopathology and gene expression profiles to classify lung cancer improves diagnostic sensitivity to almost 95%, with a 95% negative predictive value. This will allow us the ability to predict prognosis and also gauge response to specific treatment.

Additionally, one recent gene microarray study of histologically normal bronchial epithelium has identified an 80-gene biomarker which can distinguish between smokers with and without lung cancer, with an accuracy of 83% in stage I lung cancer [62]. Therefore, it follows that if we can build up an individualised risk profile for patients based on family history, smoking and COPD status, we can implement multi-faceted and targeted screening programs.

miRNA

More recent research has focused on the role of miRNAs, a class of regulatory RNAs which play a role in the pathogenesis of several disease states. miRNA is involved in the development and fate of immune cells, as well as in innate and adaptive immune responses. It is also involved in signalling pathways and receptors with critical roles in manipulation mediators of the inflammatory response, such as NF- κ B and the Toll-like receptors (TLRs). Recent

studies illustrate that unique miRNA expression profiles exist in inflammatory lung diseases such as COPD and lung cancer.

Izzotti et al. [63] studied the expression of miRNA in mouse and rat lungs following exposure to cigarette smoke and concluded that down-regulation of miRNA occurred. This concurs with results from miRNA expression profiling studies in human bronchial epithelium comparing smokers and non-smokers. Analysis of miRNA altered in mice exposed to cigarette smoke linked their roles to a variety of functions including development of airway epithelium, formation of pulmonary surfactant and inflammation. Many miRNAs involved in the activation of the NF- κ B pathway, such as miR-30, miR-146, miR-132 and miR-155, were down-regulated by cigarette smoke in rodents [63].

The role of miRNA in lung cancer has been investigated extensively. Two miRNA clusters of particular interest comprise the let-7 family and the miR-126 cluster, respectively. Reduced expression of let-7 family members in human lung cancer correlates with poor survival [64], and delivery of exogenous let-7 to a mouse model of NSCLC resulted in the reduction in tumour burden, suggesting a role for this miRNA as a tumour suppressor [65]. Down-regulation of miR-126, a proposed tumour suppressor, correlated with reciprocal expression of VEGF in eight lung cancer cell lines and was shown to reduce tumour growth in a xenograft mouse model [66].

miRNA is detectable in blood, serum and sputum and, on this basis, is a potential diagnostic and prognostic tool in the management of lung cancer. One study of individuals with NSCLC identified a signature of 5 miRNAs (consisting of 2 protective miRNAs – miR-221 and let-7a – and 3 associated with poor prognosis – miR-137, miR-372 and miR-182) which aids in the prediction of treatment outcome [67]. Similarly, miRNAs are stable in sputum, and one particular grouping (miR-21, miR-486, miR-375 and miR-200b) has been shown to distinguish lung adenocarcinoma from normal subjects with >80 and 90% sensitivity and specificity, respectively [68]. The ability to classify SCC versus adenocarcinoma has also been reported based on the detection of high levels of miR-205 which are found only in SCC [69].

The Role of Inflammation

As early as 1836, it was hypothesised that the origin of cancer was at sites of chronic inflammation [70]. Two recent large studies have identified that chronic inflamma-

tion appears to be associated with lung cancer: the first is an observational cohort study which followed 7,081 patients without known malignancy for approximately 10 years. 6,273 patients had inflammation as measured by C-reactive protein level, and the likelihood of developing lung cancer was shown to be increased if the C-reactive protein level was >3 mg/dl. Patients whose C-reactive protein level was >10 mg/dl were excluded from the trial [71]. An interesting retrospective cohort study of 10,474 patients with COPD found that the risk of lung cancer was decreased among patients taking inhaled corticosteroids at a dose $\geq 1,200$ μ g/day, compared to patients not taking inhaled corticosteroids or taking lower doses [72]. Similarly, a prior meta-analysis of 5,085 patients with COPD demonstrated lower mortality due to lung cancer among patients taking inhaled corticosteroids, although this did not achieve statistical significance. This suggests that inhibiting inflammation impacts on tumorigenesis. However, the exact mechanism remains unclear. It is worthwhile mentioning that a randomised controlled trial looking at fluticasone did not show any chemoprotective effect on premalignant lesions [73].

It is well established that chronic infection and therefore chronic inflammation may serve as a precursor to carcinoma. One example is the association between hepatitis B and C virus and the incidence of hepatocellular carcinoma [74]. In smokers, the establishment of chronic microbial colonisation in the lungs is seen, even in the absence of airway obstruction, and this persists in ex-smokers with COPD [75]. Unlike the sterile lungs of a healthy individual, we know that there is a failure of the innate immune system in COPD. This allows chronic infection to take hold with further disruption of the immune defences, and a vicious cycle of infection, inflammation and COPD progression begins. Mouse studies of infection with non-typeable *Haemophilus influenza* showed evidence of bronchial inflammation similar to COPD and a subsequent predisposition to lung carcinogenesis [76].

The coexistence and well-established link between tuberculosis (TB) and lung cancer has been described in the literature since 1810 and is yet another example of chronic inflammation increasing lung cancer risk. This is illustrated by two large population-based studies based in China and Taiwan, respectively, which have recently published results showing that a diagnosis of TB significantly increases lung cancer risk. The first study, which looked retrospectively at 42,422 patients in Xuanwei, showed increased lung cancer mortality in subjects with TB (25 vs. 3.1 per 1,000 person/years). Adjustment for demographic

characteristics, lung disease and tobacco use did not affect results. Interestingly, the association was especially pronounced in the first 5 years after TB diagnosis but remained strong 5–9.9 years and 10+ years after TB [77]. This was validated by the second study, recruiting in total 5,657 TB patients and 23,984 controls matched for age and sex between 1997 and 2008 [78]. This increased lung cancer risk, persisting years after a TB diagnosis, most likely reflects the effects of chronic pulmonary inflammation and scarring.

Indeed, Zheng et al. [79] reported that not only are TB patients at an increased risk of lung cancer but that the lesions may arise on the same side of the chest as the original focus of TB. One study by Nalbandien et al. [80] has taken this further and illustrates a step by step transformation from squamous cell dysplasia to malignant SCC. In addition, they found that macrophages infected with TB produce DNA-damaging reactive oxygen and nitrogen species and also a member of the epidermal growth factor (EGF) family called 'epiregulin'. This has been implicated as a growth factor in the initial stages of tumorigenesis. Another important facet of their work is the identification of the genetic locus *sstl*. It controls tissue damage and TB progression and, in their model, served as a modifier of TB-induced lung tumorigenesis.

Thus far, we have discussed the evolution of lung cancer as a result of a series of genetic insults and mutational events. However, the exact molecular pathogenesis and the role of inflammation in this process remain incompletely understood.

COPD is characterised by profound abnormalities in inflammatory pathways. Tobacco-induced changes in the bronchial epithelium and lung microenvironment provide a unique milieu in which carcinogenesis proceeds in conjunction with surrounding lung inflammatory, structural and stromal cells. The tumour microenvironment becomes an important mediator in this context by promoting and perpetuating the action of cytokines, growth factors and mediators released in these lung diseases, including among others, VEGF, prostaglandin E_2 and transforming growth factor (TGF)- β . These exert damaging effects that simultaneously pave the way for both EMT and inhibition of specific host cell-mediated immune responses against tumour antigens via specific signalling pathways. These mechanisms will be discussed in more detail below.

Hypoxia and Angiogenesis

Hypoxia is known to activate transcription factors and trigger the expression of pro-inflammatory genes, thus

leading to pulmonary inflammation. In COPD, progressive airflow obstruction and destruction of alveolar capillaries lead to decreased oxygen transport and alveolar hypoxia. This leads to activation of HIF which in turn promotes angiogenesis via VEGF [81]. In the short term, the benefits of oxygen are clear. However, in the long term, chronic oxygen use causes oxidative cellular injury and aggravation of lung inflammation and cell death, which theoretically may predispose to lung cancer.

Interestingly, levels of VEGF and its receptors are reduced in emphysematous lungs. Kasahara et al. [82] have shown that loss of alveolar walls is a consequence of loss of capillaries from reduced VEGF. This is due to altered induction of HIF and other signalling molecules involved in oxygen sensing in emphysema, although the mechanistic process is not entirely clear. It is postulated that as capillaries from the pulmonary vascular bed are lost due to accelerated apoptosis, so too are alveolar walls.

Paradoxically, an increase in VEGF expression is seen in the bronchi of patients with chronic bronchitis – this may suggest a differing role in bronchi as opposed to alveoli in COPD/emphysema.

As tumours increase in size, their microenvironment becomes hypoxic and HIF is activated, which in turn induces expression of matrix metalloproteinases (MMPs), urokinase-type plasminogen activator receptor and VEGF, leading to progression and invasion. VEGF correlates with progression, metastasis and poorer prognosis. Injection of siRNA against HIF-1 α and HIF-2 α was shown to reduce angiogenesis and prolong survival in a Lewis lung carcinoma model [83]. Bevacizumab, a targeted monoclonal antibody against VEGF, has shown to be effective in stage II and I trials in combination with standard chemotherapy and, thus, is now part of standard first-line treatment for stage IV NSCLC. Newer anti-angiogenesis agents such as VEGF-Trap (aflibercept) are currently under investigation.

TGF- β and Integrins Impacting on Extracellular Matrix Structure and Function

Integrins are well-known mediators in the attachment of cells to each other and to their surrounding extracellular matrix (ECM). Owing to their cell membrane localisation and their dual function, integrins not only preserve tissue integrity by connecting the intracellular actin cytoskeleton with the ECM but also mediate signals for the control of diverse cell functions, including survival, proliferation, differentiation, adhesion and migration. Integrins are heterodimeric transmembrane receptors which are involved in the above cellular mechanisms but

also in lung inflammation. The integrin $\alpha\text{v}\beta 6$ is expressed on epithelial cells and is increased during lung inflammation. It has been shown to play an important role in the preservation of normal lung architecture and homeostasis. Removal of integrin $\alpha\text{v}\beta 6$ leads to airspace enlargement in mice via the TGF- β /MMP-12 pathway [84]. The inhibition of MMP-12 is dependent on the ability of integrin $\alpha\text{v}\beta 6$ to bind and activate latent TGF- β [85].

Levels of TGF- β mRNA and protein are up-regulated in the airways and alveolar epithelial cells of patients with COPD and are positively associated with smoking history and the degree of small airways obstruction, suggesting a pro-fibrotic and pro-remodelling role for TGF- β in COPD [85]. Human lung cancer cells are thought to avoid the autocrine growth-inhibitory effect of TGF- β because of loss of TGF- β RII. Most NSCLC and SCLC show minimal or no expression of TGF- β RII – it is therefore thought that restoration of this path may be a potential target for therapeutic involvement [86, 87].

It has been more recently shown that integrin and TGF- β -mediated fibrosis are regulated by a galactose-binding protein called 'galectin 3'. It appears to be ubiquitous in pathways relating to the pathogenesis of COPD and lung cancer. It has been shown to have a role in the promulgation of the cell cycle, apoptosis, angiogenesis and airway inflammation.

Increased expression of galectin 3 is seen in small airway epithelial cells of patients with COPD (when compared to non-smokers) and cigarette-exposed rat lung, which suggests a role for galectin 3 in the pathogenesis of COPD [88]. Differential expression of galectin 3 between particular cell types of lung cancer implies a role for galectin 3 in tumour cell adhesion, apoptosis and response to chemotherapy. Nuclear expression of galectin 3 is thought to be a predictor for disease recurrence in squamous and adenocarcinoma of the lung. Importantly, susceptibility of particular tobacco carcinogens in mouse models of galectin-3-deficient mice are reduced, suggesting a significant role in the evolution of lung cancer [89].

Epithelial to Mesenchymal Transition

EMT is the process whereby cells undergo an alteration in development from a particular epithelial phenotype to a fibroblastoid or mesenchymal phenotype. This has been shown to be central in the process of not only embryonic development but also in that of chronic inflammation and fibrosis [90]. Dysregulated inflammation allows the bronchial epithelial cells to undergo EMT,

which is pivotal in the promotion of not only COPD but also carcinogenesis [91].

Turning an epithelial cell into a mesenchymal cell requires alterations in morphology, cellular architecture, adhesion and migration capacity. Commonly used molecular markers for EMT include increased expression of N-cadherin and vimentin, nuclear localization of β -catenin and increased production of the transcription factors that inhibit E-cadherin production. Phenotypic markers for an EMT include an increased capacity for migration and 3-dimensional invasion, as well as resistance to apoptosis. Importantly, these developmental regulators can induce EMT in a non-developmental context and thereby have an important role in cancer and fibrosis.

Aberrant activation of embryonic signalling pathways that are necessary for stem cell function and development provide a major driving force for EMT and tumour growth. Examples of such pathways include Wnt/ β -catenin, Hedgehog (Hh) and Notch signalling. The overall function of each pathway in EMT has been studied extensively; however, the specific role of each in lung cancer is less clear [92].

Originally identified as a mediator of segment polarity in *Drosophila*, the Hh pathway is essential for normal embryonic development in mammals and the early period of lung formation [93]. The importance of Hh signalling in cancer lies in the transcription targets of Gli, including Gli itself, and other genes known to control cell proliferation: cyclin D1, cyclin E1 and Myc. Gli also activates genes known to control angiogenesis including components of VEGF and platelet-derived growth factor signalling pathways. We know that both SCLC and NSCLC require an active Hh signalling pathway. Furthermore, it has been shown that an antagonist of the Hh pathway inhibits proliferation of NSCLC cell lines with a Hh autocrine loop [94].

Wnt signalling has been demonstrated in many cancers and has recently emerged as a critical pathway in lung carcinogenesis. Wnt-1 was found first from retroviral integration in mammary tumours in mice and was thereafter found to be up-regulated in human cancers. Cells expressing Wnt-1 are resistant to therapies that mediate apoptosis. Wnt-1 and Wnt-2 have been found to be over-expressed in NSCLC lines and other primary tumour tissues. In addition, the monoclonal antibody, anti-Wnt-1, has been shown to suppress tumour growth [95].

Notch signalling is also required for lung development, as illustrated by studies on knockout mice. Notch receptor and ligand are shown to be elevated in NSCLC lines. Blockade of Notch pathway activation, using a γ -

secretase inhibitor shows increased apoptosis and serum dependence and reduced in vivo and in vitro NSCLC tumour growth [96]. More recently, it has been shown that the M2-like tumour-associated macrophages (TAMs) have a lower level of Notch pathway activation in mouse tumour models. Forced activation of Notch signalling increased M1 macrophages which produce interleukin (IL)-12, no matter whether M1 or M2 inducers were applied. When Notch signalling was blocked, the M1 inducers induced M2 response on the expense of M1. Macrophages deficient in canonical Notch signalling showed TAM phenotypes. Forced activation of Notch signalling in macrophages enhanced their anti-tumour capacity [97]. Therefore, Notch signalling plays critical roles in the determination of M1 versus M2 polarisation of macrophages, and compromised Notch pathway activation will lead to the M2-like TAMs. The role of TAMs will be further explored below.

To further elucidate the role of EMT in tumorigenesis, there are studies looking at tissue culture models of epithelial cells and mouse tumour models [98]. It has been shown that EMT requires the cooperation of oncogenic Ras or receptor tyrosine kinases, which both induce hyperactive downstream signalling of Raf/MAPK with endogenous TGF- β signalling. Sustained TGF- β signalling (for example by an autocrine TGF- β loop) can be required for the maintenance of EMT in epithelial cells and also for metastasis in several mouse models [84, 99].

Adaptive Immune Responses and the Extracellular Matrix

Chronic inflammation in COPD is associated with the infiltration and accumulation of neutrophils, macrophages, B cells, CD4⁺ T cells, CD8⁺ T cells, dendritic cells and eosinophils, particularly in the smaller airways. The severity of COPD is associated with the degree of infiltration of these inflammatory mediators. Macrophages, neutrophils and lymphocytes play the largest role in progression of COPD and emphysema. The role of these cells in COPD has previously focused on the release of oxidants, proteinases, perforin and granzymes which, when released, lead to alveolar wall destruction and mucous hypersecretion.

However, we now know that the adaptive immune system plays a role in the pathogenesis of COPD since mature lymphoid follicles with fully separated T and B zones and a germinal centre occur in the lungs of COPD patients [100]. These follicles are rare in the lungs, and their presence correlates with the severity of COPD. The exact reason for their presence is not well understood but may

relate to the large antigen load associated with viral or bacterial infections, or to increased exposure to neoantigens from degraded ECM. Another possibility may relate to carbonyl-modifying proteins in cigarette smoke leading to autoimmune impairment in advanced COPD [101]. These cells can be hijacked by lung cancer cells to engender a tumour-promoting environment.

Most tumours have an associated inflammatory cell infiltrate. This includes TAMs and other similar cell types, as well as mast cells and T cells. It is thought that these bone marrow-derived components are involved in tumorigenesis [102, 103].

The interaction between the tumour cells and stromal cells in the tumour microenvironment plays an important role in tumour growth and metastasis. Macrophages are prominent stromal cells in this interaction. They secrete a variety of growth factors, cytokines, chemokines and enzymes that regulate tumour growth, angiogenesis, invasion and metastasis.

Recently, it has been recognised that TAMs are not homogenous [104]. 'Microlocalisation', i.e. where macrophages are seen under a microscope, is an important factor for prognosis. An increased number of macrophages within the tumour islets confers a marked survival advantage, whereas an increased number of macrophages in the tumour stroma is associated with poor prognosis in NSCLC [105]. In addition, macrophages are 'polarised' into two distinct forms with differing functions: M1 and M2, much like the Th1 and Th2 classification of T cells [106]. Differentiation of the M1 macrophages is induced by interferon- γ , lipopolysaccharides, TNF- α and granulocyte-monocyte colony-stimulating factor. The M1 macrophages produce high levels of IL-12, IL-23, TNF- α , IL-1, IL-6, CXCL ligand 10, inducible nitric oxide synthase, human leukocyte antigen-DR, and reactive oxygen and nitrogen intermediates. Differentiation of the M2 macrophages is induced by IL-4, IL-10, IL-13, IL-21, activin A, immune complexes, and glucocorticoid. M2 macrophages express high levels of IL-10, IL-1 receptor antagonist, CC ligand 22, scavenger, mannose receptor, galactose receptor, arginase I, and CD163 antigen.

It has been demonstrated in previous studies that the number of TAMs in the tumour islets and the ratio of TAMs in the tumour islets versus stroma are positively associated with survival time in patients with NSCLC [105, 107]. Subsequent studies have illustrated that the M1 form of TAMs is an independent prognostic factor in patients with NSCLC [108].

In addition to the processes described above it is clear that the ECM is important in the propagation of cancer-

related inflammation. The importance of the ECM in the protection of SCLC cells from apoptosis is already clear [109].

The balance between anti-proteinases and proteinases, including elastase and MMPs from inflammatory and epithelial cells in the lung, dictates the degree of emphysema that occurs. Structural cells of the lung are irreparably damaged when they lose attachments because of defective tissue repair and ECM degradation by MMPs. In addition, ECM remnants provide a chemotactic target for inflammatory cells, recruiting them into the lung, leading to an increase in emphysematous progression as seen in mouse models [110]. Therefore, antagonism of ECM fragments may somewhat ameliorate the progression of COPD.

Proteinases too have been shown to induce the release of TGF- β and VEGF, which both play a key role in tumorigenesis and metastasis. These MMP inhibitors – marimastat (BB_2516), batimastat (BB-94) and prinomastat (AG-3340), ONO-4817 and BMS-275291 – are under current investigation to determine their effectiveness in maintenance and remission after treatment, or as an adjunct to standard chemotherapy in NSCLC [111, 112].

More recently, the role of the ECM in promotion of metastasis via inflammation has been illustrated by Kim et al. [127]. They showed that Lewis lung carcinoma cells were significant macrophage activators leading to the production of IL-6 and TNF- α through activation of the TLR family members TLR2 and TLR6. Further analysis of these cells identified versican which is an ECM proteoglycan known to be up-regulated in many human cancers, including lung cancer [112]. Versican has since been found to activate macrophages through TLR2 and its co-receptors TLR6 and CD14. This reinforces the theory that advanced cancer cells generate the inflammatory micro-environment that allows metastatic cells to flourish and propagate.

As the link between inflammation and cancer continues to be deciphered, several signalling molecules have been identified as important mediators in this complex process.

Signal Transducer and Activator of Transcription

Signal transducer and activator of transcription (STAT3) is another molecule which has become of interest in recent times. Its role is to transduce signals from various oncogenic proteins and pathways [89]. It is an effective negative of Th1 cell-mediated inflammation and an activator of genes which are responsible for immunosuppression [113].

In the beginning, STAT3 was found to be constitutively active in cells transformed by an oncoprotein steroid receptor coactivator, which is a non-receptor tyrosine kinase. Thereafter, it became evident that STAT3 signalling blocks fibroblast transformation by steroid receptor coactivator [114]. Additionally, a role has been found for STAT3 in the prevention of human tumour cell apoptosis, and it has also been shown to be important in angiogenesis [115].

It has been shown to be constitutively active in many human cancer cell lines and tumour tissues. In models comparable to (onco-)gene amplification, forced transgenic expression of constitutively active STAT3C conferred tumorigenic capacity in a 3T3 xenograph model. Increased expression of STAT3C in vivo also induced bronchoalveolar adenocarcinomas and the formation of SCC in situ when expressed in type II alveolar epithelial cells and keratinocytes [116].

STAT3, in other tumour models including melanoma, has been shown to have a role in the immune evasion by tumour through inhibition of expression of pro-inflammatory cytokines and chemokines. In lung cancer cell lines, STAT3 up-regulates the expression of MUC1, a gene important in lung cancer cell survival and metastasis in vivo and in vitro [117]. Notably, bronchoalveolar adenocarcinomas in STAT3C transgenic mice were preceded by inflammatory cell infiltrates, and tumour development was associated with excessive secretion of inflammatory cytokines, including IL-6 [118].

Targeting the EGF receptor (EGFR) is by now a well-recognised method of NSCLC treatment. In NSCLC lines with constitutively active mutant EGFR, STAT3 is phosphorylated and is necessary for the proliferative events associated with mutant EGFR [119]. Inhibition of STAT3 activity halts the transforming effects of EGFR-activating mutations. In vitro studies show that EGFR blockade decreases STAT activation. Equally, cell lines resistant to EGFR inhibitors demonstrate persistent activation of STAT3 [120]. It follows that STAT3 becomes a target of interest for drug development in the treatment of lung cancer. For example, it is known that blockade of STAT3 results in extensive NSCLC cell apoptosis. In addition, it has been demonstrated that combined inhibition of EGFR and STAT3 using small molecules has synergistic effects in a variety of NSCLC cell lines.

It seems clear that STAT3 is a key target for investigation for new drug development. Multiple roles in the processes of inflammation and carcinogenesis only highlight again the link between conditions characterised by inflammation such as COPD and lung cancer.

NF- κ B Pathway in Lung Cancer and COPD

The transcription factor NF- κ B plays a significant role in the pathogenesis of COPD by promoting the release of inflammatory mediators leading to chronic inflammation. Although they are often activated simultaneously, the two NF- κ B activation pathways have individual regulatory functions [121]. The classical pathway is usually triggered by ligand binding to TNF type 1/2 receptors, T-cell receptors, B-cell receptors, or the TLR-IL-1R family members. This pathway ends in the increased transcription of target genes encoding chemokines, cytokines and adhesion molecules, perpetuating inflammatory responses and promoting cell survival. Contrastingly, the alternative pathway is triggered by the activation of certain TNF receptor family members, including lymphotoxin- β receptor, B-cell-activating factor belonging to the TNF family receptor, CD40 and CD30, and regulates the adaptive immune system.

There is evidence that NF- κ B is involved in tumorigenesis and progression in the genitourinary tract and liver [86], two typical organs where inflammation-driven cancer is known to occur. Furthermore, there is burgeoning evidence that NF- κ B may be implicated in lung carcinogenesis. It is activated in premalignant lesions of the bronchial epithelium and neoplastic cells of squamous cell lung cancer [87]. It is also thought to play a role in tumour initiation as evidenced by studies which show that NF- κ B-activated macrophages can release oxidants in the proximity of bronchial epithelial cells to cause damage. Studies with NF- κ B inhibitors such as pyrrolidine dithiocarbamate and N-tosyl-L-phenylalanyl-chloromethyl ketone repress TGF- β_1 -induced cell migration in human lung cancer lines. Inhibition of NF- κ B activation may improve efficacy of first-line therapy in COPD and lung cancer.

TRAIL and the Role of Mesenchymal Stem Cells

TRAIL is a protein which causes apoptosis and death of cancer cells, without harming normal cells. This occurs by binding to specific TRAIL death receptors (DR4 and DR5) leading to activation of the extrinsic apoptosis pathways. In vivo studies have proven that these cells are able to target multiple tumours and reduce both primary and metastatic disease. TRAIL receptors 1, 2 and 3 have been shown to be up-regulated in the alveolar epithelial cells of smokers with emphysema and also in ex-smokers. Additionally, their expression was closely related to the levels of tumour suppressor p53 present in emphysematous lung parenchyma. Interestingly, a lung adenocarcinoma cell line exposed in vitro to oxidative stress and TNF had higher expression of TRAIL receptors 1, 2 and

3 but also higher levels of p53, suggesting that the adaptation of the TRAIL system seen in the emphysematous lung may be resultant from oxidative stress and inflammatory cytokines. TRAIL itself is released from activated inflammatory cells and, therefore, oxidative stress and inflammation in the emphysematous lung may sensitise alveolar cells to its apoptotic effects. Specific inflammatory mediators, like TNF, and oxidative stress can also alter the elements involved in alveolar cell sensitivity to TRAIL-mediated apoptosis (TRAIL receptors, p53 and Bax levels) and switch alveolar cells from a TRAIL-mediated apoptosis-resistant state to a responsive state and lead to increased alveolar cell apoptosis [122].

Triggering of tumour cell apoptosis is the cornerstone of many cancer therapies. There is much interest in work done recently which revolves around mesenchymal stem cells expressing TRAIL which migrate to tumours and reduce the growth of primary cancers and metastases. Mesenchymal stem cells have been used as delivery agents for targeted, anti-mitotic therapies. These cells are derived from bone marrow and have the ability to directly reach tumours throughout the body. In addition, they are 'immunoprivileged', enabling their use without rejection or requiring prior immunosuppression. Work by Loebinger et al. [123] demonstrates that these cells cause apoptosis, death and reduced colony formation of the side populations of squamous and adenocarcinoma lung cancer cells, and that this effect is synergistic when united with standard chemotherapy in the induction of apoptosis.

Arachidonic Acid Pathway

Inflammatory cells release metabolites of arachidonic acid, or eicosanoids, including prostaglandins and leukotrienes. Cyclooxygenases are enzymes that control rate-limiting steps in prostaglandin synthesis.

COX-2 and its product prostaglandin E_2 not only modulate the inflammatory response, but are additionally thought to play a role in the pathogenesis of lung cancer via effects on cell proliferation, apoptosis and angiogenesis. COX-2 is increased in the peripheral lung of COPD patients and is also found to be increased in the sputum of smokers in conjunction with MMP-2 [124]. Levels of both correlate inversely with forced expiratory volume in 1 s percent predicted in COPD patients. COX-2 is also shown to be constitutively active in both premalignant adenocarcinoma and more established lung cancers. Both adenocarcinoma and SCC stain positive for COX-2. Interestingly, one study has recently demonstrated that carriers of the C allele of a polymorphism in the 3' UTR of COX-2 have a significantly increased risk of lung cancer [125].

Patients who regularly use COX-2 inhibitors such as aspirin are found to have a decreased risk of lung, colorectal and breast cancer, as evidenced by a recent meta-analysis of eight trials investigating the impact of aspirin on cancer death over a period of treatment >4 years [126]. The study concluded that daily aspirin reduced deaths both during and after the trial durations. In the case of lung cancer in particular, the latent period before an effect on deaths was approximately 5 years, and the benefit confined to adenocarcinoma, with the overall effect on 20-year risk, was also greatest in adenocarcinomas.

Conclusion

The investigative field of lung cancer and COPD has been a hotbed of interest over recent years. As a result, our understanding of the links between lung cancer and COPD has advanced exponentially. It is becoming increasingly obvious that the role of inflammation in promoting and perpetuating lung carcinogenesis is critically important. However, despite advances in the treatment of lung cancer over this time, survival rates tell a different story, suggesting that an entire rethink of our management of lung cancer as an entity is required. Increasing education and prevention of cigarette smoking are clearly important. Additionally, we know now that there are high-risk populations as illustrated by the work done in smokers with COPD and familial/genetic susceptibility studies – therefore, should screening now be instigated in order to identify these individuals early and permit early intervention? With the knowledge of susceptibility loci impacting on both nicotine dependence and the process of carcinogenesis, this concept of screening to permit

timely intervention and education becomes ever more crucial. It is hoped that as our understanding of the chronic inflammatory pathways predisposing to COPD and potentially lung cancer improve at a molecular level, specific biomarkers of risk may be identified which would allow us to further hone this screening strategy.

It becomes increasingly evident that a 'one size fits all' approach to lung cancer treatment is no longer good enough. Recent research makes amply clear that cancers have their own individual genetic and molecular fingerprint. As our ability to further define this process and identify specific subsets of lung cancer improves, we will then be able to offer targeted and individual treatment regimes with the aim of providing more efficacious treatment and improving survival.

A fuller understanding of the mechanisms of this picture of chronic inflammation, such as immune dysfunction and immunosculpting, abnormal activation of transcription factors, altered adhesion signalling paths, EMT and inflammation-driven ECM degradation will help us decipher the link between COPD and lung cancer. Selective blockade of these pathways and specific molecular targets will hopefully afford novel avenues for therapeutic intervention.

Stem cells and their relationship to cancer progression is a new and expanding area of research. Recent studies suggest that endogenous stem cell signalling and differentiation paths are maintained within cancer types, and that disruption of this signalling mechanism may initiate specific lung cancers. A better understanding of this relationship among stem cell regulation and carcinogenesis will allow the manipulation of these cells and targeted treatment.

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