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Themed Section: Inflammation: maladies, models, mechanisms and molecules

REVIEW

COPD and squamous cell lung cancer: aberrant inflammation and immunity is the common link

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Cigarette smoking has reached epidemic proportions within many regions of the world and remains the highest risk factor for chronic obstructive pulmonary disease (COPD) and lung cancer. Squamous cell lung cancer is commonly detected in heavy smokers, where the risk of developing lung cancer is not solely defined by tobacco consumption. Although therapies that target common driver mutations in adenocarcinomas are showing some promise, they are proving ineffective in smoking-related squamous cell lung cancer. Since COPD is characterized by an excessive inflammatory and oxidative stress response, this review details how aberrant innate, adaptive and systemic inflammatory processes can contribute to lung cancer susceptibility in COPD. Activated leukocytes release increasing levels of proteases and free radicals as COPD progresses and tertiary lymphoid aggregates accumulate with increasing severity. Reactive oxygen species promote formation of reactive carbonyls that are not only tumourigenic through initiating DNA damage, but can directly alter the function of regulatory proteins involved in host immunity and tumour suppressor functions. Systemic inflammation is also markedly increased during infective exacerbations in COPD and the interplay between tumour-promoting serum amyloid A (SAA) and IL-17A is discussed. SAA is also an endogenous allosteric modifier of FPR2 expressed on immune and epithelial cells, and the therapeutic potential of targeting this receptor is proposed as a novel strategy for COPD–lung cancer overlap.

LINKED ARTICLES

This article is part of a themed section on Inflammation: maladies, models, mechanisms and molecules. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2016.173.issue-4

Abbreviations

COPD, chronic obstructive pulmonary disease; FGFR1, fibroblast growth factor-1; FPR2, formyl peptide receptor 2; LOH, loss of heterozygosity; LXA_4, lipoxinA_4; NSCLC, non-small cell lung cancer; NFE2L2, nuclear factor, erythroid 2-like 2; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; PTEN, phosphatase and tensin homologue; SAA, serum amyloid A; SCC, squamous cell cancer; RvD1, resolvinD1

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Tables of Links

TARGETS	
GPCRs[a]	**Enzymes**[c]
FPR2	Akt (PKB)
Catalytic receptors[b]	B-Raf
ALK	Elastase (NE)
EGFR	GSK3
FGFR1	Granzyme B
IGF1R	KRAS
IL-17A receptor	MMP-9
IRS1	mTOR
PDGFR	PIK3CA
ROS1	PTEN
TLR2	TP53
VEGFR	**Other protein targets**
	PD-1 (CD274)

LIGANDS		
4-hydroxynonenal	H_2O_2	Nivolumab
Acrolein	IFN-γ	Paclitaxel
Annexin A1	IL-1β	PDGF
Arachidonic acid	IL-6	Pembrolizumab
Aspirin	IL-10	Rapamycin
Carboplatin	IL-12	Resolvin D1 (RvD1)
CXCL13	IL-17A	Serum amyloid A (SAA)
FGF-1	Ipilimumab	TGF-β
FGF-2	LXA_4	TNF-α
Gefitinib	Nitric oxide (NO)	VEGF

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2013/14 ([a,b,c]Alexander *et al.*, 2013a,b,c).

Squamous cell carcinomas are non-responsive to current therapies tailored for adenocarcinomas

Globally, lung cancer is the most commonly diagnosed form of cancer and is currently the leading cause of cancer-related deaths (Jemal *et al.*, 2011). Conventional therapy for lung cancer includes surgical resection, cytotoxic agents, radiation and in some cases targeted molecular therapies. Despite the advances in new molecular therapies, the prognosis remains poor for lung cancer, with an overall 5 year survival rate of around 15% (Jemal *et al.*, 2011). Lung cancers are broadly subdivided into histological types: small-cell lung cancers and non-small-cell lung cancers (NSCLCs), where NSCLCs represent 80–85% of all lung cancers. NSCLCs are further classified into different subtypes where squamous-cell carcinoma (SCC) and adenocarcinomas account for the majority of NSCLC cases. SCC accounts for approximately 20–30% of NSCLC cases and adenocarcinomas account for about 40–50% of NSCLC cases. As many lung cancers present in advanced stages, most patients are unresectable and the 5 year survival rates for advanced histological subtype stage IV NSCLC falls to below 2% for SCC (Cetin *et al.*, 2011). Adenocarcinomas can occur in non-smokers, particularly in Asian populations, whereas SCC is strongly associated with a history of cigarette smoking. Histological classification of tumours is increasingly being supplanted by molecular typing into subsets based upon dominant mutational drivers and the use of selective tyrosine kinase such as gefitinib, which targets EGFR mutations and improves progression-free survival (Fukuoka *et al.*, 2011). The outlook for smoking-related SCC is much less optimistic with respect to targeting of dominant mutations that drive tumour progression. This, in part, reflects a complex and differential driver mutation profile for SCC, as dominant mutations in adenocarcinomas, such as EGFR, ALK and ROS1 fusions and KRAS mutations, are relatively infrequent in SCC (<5% frequency rate) as reviewed in Pao and Girard (2011) and summarized in Table 1.

Cigarette smoking is also the predominant risk factor for chronic obstructive pulmonary disease (COPD). Globally, COPD is predicted to become the third leading cause of death in the world by 2020 (Lopez and Murray, 1998). Cigarette smoking accounts for more than 95% of cases in industrialized countries (Barnes *et al.*, 2003), although environmental pollutants are recognized as important causes in developing countries (Dennis *et al.*, 1996). COPD is characterized by progressive airflow obstruction and is associated with an abnormal and chronic inflammatory response of the lungs to noxious particles and gases (Pauwels *et al.*, 2001). The pathology of COPD is heterogeneous encompassing (i) airways disease, chronic obstructive bronchiolitis with fibrosis and obstruction of small airways and/or mucous metaplasia and mucus gland hypertrophy leading to plugging of the larger airways, and (ii) emphysema, enlargement of airspaces and destruction of lung parenchyma. Of significance, approximately 30% of patients with mild to moderate COPD have been reported to die from lung cancer (Anthonisen *et al.*, 1994), which has traditionally been linked to a common aetiological exposure, namely tobacco smoke. There are however multiple studies to show that both airways disease and emphysema are significant risk factors for lung cancer, even when adjustments for smoking history are made

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Table 1

Prevalence of abnormalities detected in NSCLC subsets and in COPD

	Adenocarcinoma	SCC	COPD
EGF receptor mutations	5–15% frequency	Infrequent	EGF receptor amplification occurs
ELM4/ALK translocations	5–15% frequency	Infrequent	Not detected
KRAS mutations	>15% frequency	Infrequent	Not detected
FGFR family amplification/ overexpression	Infrequent	20% frequency in FGFR1 amplification	Overexpression of FGF1/2 and FGFR1 detected
PI3KCA amplification	Infrequent	>30% frequency	Increased PI3K pathway activation
Loss of PTEN status	Infrequent	Mutations and methylation detected (10–40% frequency)	PTEN pathway down-regulated

(Skillrud *et al.*, 1986; Mannino *et al.*, 2003; Ueda *et al.*, 2006; Purdue *et al.*, 2007). In particular, the presence of COPD was found to increase the risk for squamous cell histological subtypes by more than fourfold (Papi *et al.*, 2004).

Cytogenetic studies have demonstrated that the lung epithelium of heavy smokers transforms into a squamous metaplasia phenotype that is correlated with the severity of airway obstruction (Cosio *et al.*, 1978). Hence, the chronic injurious state of this lung microenvironment may facilitate tumour development progressing from metaplasia, dysplasia, carcinoma *in situ* and subsequent malignant transformation. Morphological changes in the bronchial epithelium are accompanied by an increase in loss of heterozygosity (LOH) and field cancerization involving the accumulation of mutations that eventually predispose the lung to cancer (Franklin *et al.*, 1997; Minna *et al.*, 2002; Wistuba *et al.*, 2002). The widespread presence of TP53 mutations in smoker epithelium exhibiting squamous metaplasia occurs early during this transformation, which can expand from a single progenitor clone to populate broad areas of the injured bronchial mucosa (Franklin *et al.*, 1997). Microsatellite instability (MSI) is frequent in the non-malignant bronchial epithelium of COPD and is associated with EGFR amplification (Romeo *et al.*, 2003). Increased EGFR expression has been observed in COPD epithelium (de Boer *et al.*, 2006) and EGFR transactivation augments inflammatory responses initiated by viral and bacterial infection in the bronchial epithelial cells (Liu *et al.*, 2008a,b). A significant increase in severe exacerbations was observed in COPD patients exhibiting MSI (Makris *et al.*, 2008). The acquisition of early somatic mutations required for tumourigenesis may also worsen inflammation in COPD (Anderson and Bozinovski, 2003).

Smoke-mediated epithelial transformation can also drive a fibrotic response contributing to small airway wall thickening in COPD through TGFβ-dependent mechanisms (Araya *et al.*, 2007). Increased bronchial expression of fibroblast growth factors (FGF-1/2) that target FGFR1 have been implicated in the remodelling of bronchial airways in COPD (Kranenburg *et al.*, 2005). Focal FGFR1 amplification has been detected in 22% of SCC where this receptor pathway is associated with tumour growth and survival (Weiss *et al.*, 2010). Signature genes activated by the phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) pathway are also overexpressed in the bronchial airway of smokers with dysplastic lesions, suggesting that PIK3CA is activated early during carcinogenesis (Gustafson *et al.*, 2010). Dysregulated PIK3CA/PTEN/Akt/mTOR signalling coordinates tumour-promoting survival, metabolism, migration and angiogenesis. Activation of Akt leads to inhibition of downstream signalling proteins, including glycogen synthase kinase 3, forkhead box O transcription factors and BAD, thereby suppressing apoptotic signals. In addition, Akt indirectly activates mammalian target of rapamycin (mTOR), a master regulator of cell growth and metabolism, through its regulation of anabolic processes, including lipid and protein biosynthesis. This pathway is activated by multiple tyrosine kinase receptors, including EGF, IGF1, VEGF and PDGF receptors, and mutations are frequently detected along this pathway. Amplification of PIK3CA has been detected in high frequency in SCC, in contrast to gain-of-function mutations that are much less frequent (Drilon *et al.*, 2012).

Loss of PTEN protein expression has been characterized as an independent poor prognostic factor for patients with NSCLC associated with a more aggressive subset of lung tumours (Tang *et al.*, 2006; Lim *et al.*, 2007). Somatic mutation or deletion of PTEN has been reported in a variety of tumour types and genetic analysis of SCC demonstrates a mutational frequency around 10% (Drilon *et al.*, 2012). An increased frequency of PTEN promoter methylation has been proposed as an alternative method for loss of PTEN expression in NSCLC (Soria *et al.*, 2002). The microRNA miR-29b has been shown to regulate *PTEN* gene expression through inducing hypomethylation in the PTEN promoter (Li *et al.*, 2012). However, mutations of PTEN and methylation of its promoter in NSCLC are infrequent relative to PTEN protein expression, which is reported to be reduced or lost in 74% NSCLC tumours (Marsit *et al.*, 2005). In this study, neither methylation of the PTEN promoter nor loss of LOH at MSI surrounding and intragenic to the PTEN locus was a significant predictor of PTEN protein expression (Marsit *et al.*, 2005). PTEN expression is also dysregulated in COPD; however, the implications of this observation are not well characterized. Microarray analysis of primary airway epithelial cells revealed down-regulation of PTEN expression in chronic smokers that progressively decreased with development of COPD (Shaykhiev *et al.*, 2011). Cigarette smoke extract has been shown to down-regulate PTEN expression, which was associated with an increase in EGFR transactiva-

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tion required for increased mucin production (Lee *et al.*, 2006); however, the epigenetic mechanism behind reduced PTEN expression has yet to be determined.

Oxidative stress, COPD and squamous cell carcinoma

Another important pathogenic feature of COPD that can initiate lung tumourigenesis is excessive and uncompensated oxidative stress, where oxidative DNA damage has been shown to be prominent in COPD lungs (Pastukh *et al.*, 2011). Moreover, oxidative stress can induce oncogenic lipid peroxides, inactivate defensive mechanisms and permissively alter the extracellular matrix. A lifetime of cigarette smoking exposes lung cells to over 4700 different chemical compounds and more than 10^{15} oxidants/free radicals per puff (Church and Pryor, 1985; Nakayama *et al.*, 1989; Pryor and Stone, 1993; Rahman, 2012). At least 69 of these are carcinogenic compounds, including polycyclic aromatic hydrocarbons, tobacco-specific nitrosamines, aromatic amines and volatile carcinogens such as formaldehyde and benzene (Hoffmann *et al.*, 2001). In addition, free radicals in cigarette smoke are known to initiate conversion of procarcinogens into their active state to promote formation of DNA adducts (Pryor, 1997). Highly reactive molecules are also generated enzymatically by inflammatory and epithelial cells within the lung in response to repeated exposure to smoke constituents and inhaled pathogens. Activation of leukocytes by cigarette smoke generates superoxide radicals ($O_2^{\bullet-}$), which can then either react with NO to form reactive peroxynitrite ($ONOO^-$) or alternatively be rapidly converted to hydrogen peroxide (H_2O_2) under the influence of superoxide dismutase. Non-enzymatic production of the more damaging hydroxyl radical ($^{\bullet}OH$) from H_2O_2 through Fenton reactions catalysed by free iron can also proceed (Vlahos and Bozinovski, 2013). ROS activity as assessed by measuring exhaled H_2O_2 in current smokers and patients with COPD is significantly higher than non-smokers (Nowak *et al.*, 1996), and levels are further increased during exacerbations of COPD due to increased release of $O_2^{\bullet-}$ (Dekhuijzen *et al.*, 1996).

Thus, while ROS are required for host defence against invading pathogens, increased levels of ROS have been implicated in sustaining a damaging cycle of inflammation in COPD through redox-dependent activation of inflammatory transcription factors such as NF-κB and AP-1 (Rahman and Adcock, 2006; Rahman, 2012). Increased production of ROS in COPD is also confounded by the down-regulation of nuclear factor, erythroid 2-like 2 (NFE2L2 or NRF2) in COPD (Malhotra *et al.*, 2008), which is a transcription factor that promotes expression of a suite of cytoprotective and antioxidant genes that contain an antioxidant response element in their promoter. Agents that increase NFE2L2 expression have shown promise in pre-clinical models of lung cancer when administered during the initiation phase of carcinogenesis, and consequently, there has been interest in their use as cancer chemopreventative agents (reviewed in Sporn and Liby, 2012). However, emerging reports have led to safety concerns relating to the long-term use of such agents. It has been shown that oncogenes can increase NFE2L2, a master regulator of antioxidant defence levels, and this facilitates a cytoprotective advantage in the tumour microenvironment (DeNicola *et al.*, 2011), which may have significant implications during chemotherapy. Dietary supplementation with antioxidants can also increase tumour progression and reduce survival in mouse models of lung cancer (Sayin *et al.*, 2014). In this model, the oncogenic drivers KRAS or B-Raf are already introduced at initiation of antioxidant therapy and NAC provided a survival advantage in the advanced tumours. The opposing effects of antioxidants in various cancer models may suggest that timing of antioxidant therapy will be critical, where early intervention can prevent accumulation of cytotoxic DNA damage, whereas late intervention may facilitate tumour survival.

Oxidative stresses can also directly influence the activity of the tumour suppressor gene, *PTEN*. *PTEN* is reported to be very susceptible to oxidative modification, which inactivates its enzymatic activity leading to increased PIK3CA/Akt signalling (Leslie *et al.*, 2003). Smoking and COPD are associated with ROS-dependent peroxidation of polyunsaturated fatty acids and generation of reactive carbonyl species, including acrolein, 4-hydroxynonenal and malondialdehyde. Reactive carbonyls lead to the oxidation of proteins, lipids, carbohydrates and DNA and can target approximately 10% of the entire proteome during ageing, starvation or disease (Maisonneuve *et al.*, 2009). Hence, protein carbonylation represents a major pathway to protein oxidation (Stadtman, 1993) where reactive carbonyls target susceptible arginine, histidine, lysine, proline or threonine residues (Dalle-Donne *et al.*, 2006; 2009). Once proteins are carbonylated, they are rapidly ubiquinated and degraded within proteosomal complexes as a primary mechanism for removal of carbonylated proteins (Bernhard *et al.*, 2005). Reactive carbonyls are increased in COPD (Rahman *et al.*, 2002; Kirkham *et al.*, 2011) and carbonyl stress caused by cigarette smoke has been associated with impairment of macrophage function required for bacterial clearance (Bozinovski *et al.*, 2011). Reactive carbonyls also covalently modify and inactivate cellular PTEN, leading to activation of PIK3CA/Akt signalling (Covey *et al.*, 2010). Hence, loss of PTEN function by post-translational modification caused by reactive carbonyls occurs independently of genetic PTEN alterations that are typically screened for and represents an alternative pathway to maintaining tumour-promoting PIK3CA/Akt/mTOR signalling.

Inflammatory responses in COPD support tumour initiation and progression

Hanahan and Weinberg comprehensively described emerging hallmarks and enabling characteristics of cancer (Hanahan and Weinberg, 2011). Enabling characteristics that promote acquired functional capabilities allow cancer cells to survive, proliferate and disseminate. The two enabling characteristics include (i) the development of genomic instability in cancer cells and (ii) the initiation of tumour-promoting inflammation driven by cells of the immune system. They also highlighted a core hallmark involving the active evasion by cancer cells from attack and elimination by immune cells

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(Hanahan and Weinberg, 2011). Hence, inflammation and immunity play a key role in tumour initiation and progression, and as COPD is a chronic inflammatory condition, aberrant immunity in COPD will be central to increased risk of lung cancer, independently of tobacco exposure. Immunological processes in COPD are complex but involve disruption of both innate and adaptive immunity, and a greater understanding of this distinct microenvironment is needed to develop therapeutic strategies to combat tumour-promoting inflammation and tumour-evading immunity in COPD. A prominent hallmark of the tumour microenvironment is the emergence of tumour-associated macrophages (TAMs), which accumulate within hypoxic regions of tumours. TAMs promote pro-angiogenic programmes through production of angiogenic factors, such as VEGF and PDGF, and facilitate tumour progression by secreting matrix-degrading enzymes (Allavena *et al.*, 2008). In an analogous manner, neutrophils have been shown to accumulate in certain human tumours and their presence can either be associated with better or worse outcomes. Like macrophages, tumour-associated neutrophils are likely to be transformed by their microenvironment, leading to divergent phenotypes (N1 vs. N2) that can either support tumour growth through expression of pro-angiogenic factors [VEGF, matrix metalloproteinase-9 (MMP-9)] or suppress tumour growth.

Innate immunity

Macrophages and neutrophils are considered to be central in the pathophysiology of COPD, where they accumulate in the airways and lung parenchyma (Keatings *et al.*, 1996; Pesci *et al.*, 1998). In particular, macrophage numbers in the parenchyma of patients with emphysema markedly increase (Retamales *et al.*, 2001) and their selective depletion conferred protection against the development of emphysema in an experimental model of COPD (Beckett *et al.*, 2013). In response to cigarette smoke, irritants and infection, macrophages release inflammatory mediators and secrete elastolytic enzymes including MMP-9 (Barnes *et al.*, 2003). There is an increase in lung parenchymal MMP-9 activity in emphysematic patients (Ohnishi *et al.*, 1998) and proteinases released in COPD are well known for their ability to promote tumour growth and invasion (Houghton, 2013). MMP-9 has been shown to promote angiogenesis through proteolytic activation of ECM-bound VEGF (Bergers *et al.*, 2000) and tumour progression has been shown to be reduced in mice deficient in MMP-9 (Itoh *et al.*, 1998).

The molecular profiling of disease-associated macrophages in COPD demonstrates that they do not conform to the classic M1/M2 dichotomy and it is likely that the inflammatory environment of the COPD airways drives the development of both M1 and M2 macrophages (Mosser and Edwards, 2008; Hodge *et al.*, 2011). The emergence of alveolar macrophages expressing an M2 gene profile in heavy smokers with normal lung function is progressive in patients with COPD (Shaykhiev *et al.*, 2009). The accumulation of M2 airway macrophages may reflect a deficiency in processes that normally resolve inflammation and restore lung homeostasis, where oxidative stress is known to impair phagocytic and efferocytic programmes required to clear infected/damaged tissue (Vlahos and Bozinovski, 2014). In addition, impaired macrophage efferocytosis is observed in lung cancer and this deficiency is associated with tumour-derived arachidonic acid products including PGE_2 (Dehle *et al.*, 2013). The accumulation of macrophages in the tumour stroma in NSCLC is associated with a worse prognosis, in contrast to accumulation within the tumour inlet, which conferred a significant survival advantage (Welsh *et al.*, 2005). Distinct macrophage phenotypes have been characterized in NSCLC tissue, where M1 macrophages found in the tumour islet are associated with survival extension, whereas M2 macrophages that express CD163 and VEGF were not related to increased survival (Ohri *et al.*, 2009). CD163-positive macrophages are also found in ex-smokers with COPD (Kunz *et al.*, 2011). Hence, there is a need to better define the relative contribution of M1 versus M2-skewed macrophages in COPD and lung cancer overlap as both populations do concurrently exist and their relative ratio and localization will be very important in the progression of lung tumours.

Neutrophilic inflammation is also prominent in COPD, where cigarette smoke promotes the recruitment of neutrophils (Vlahos *et al.*, 2006) and smoking cessation fails to fully resolve inflammation (Stanescu *et al.*, 1996; Rutgers *et al.*, 2000; Willemse *et al.*, 2005). Since neutrophils are relatively short-lived, their persistence is indicative of continual recruitment even when the primary insult of smoke exposure is removed. Neutrophils are also a potent source of ROS in COPD, which are released in response to inhaled irritants and respiratory microbes that infect the airways. During neutrophil respiratory burst, myeloperoxidase can catalyse the formation of the potent and very damaging oxidants hypochlorous acid (HOCl) and hypobromous acid (HOBr) from H_2O_2 in the presence of chloride (Cl^-) and bromide (Br^-) ions respectively. Persistent activation of neutrophils can therefore contribute to the accumulation of DNA damage through generation of potent free radicals. The insufficiency to clear exhausted neutrophils can also lead to indiscriminate degranulation and subsequent release of proteases, including neutrophil elastase from azurophilic granules, and neutrophil elastase activity increases with COPD severity in the presence of inhaled glucocorticosteroids (Vlahos *et al.*, 2012). Colonizing pathogens and viral infections can directly cause neutrophil necrosis and release of azurophilic granular content in COPD (Naylor *et al.*, 2007; Mallia *et al.*, 2012).

Anti-proteinases such as α1-antitrypsin (α1-AT) that normally provide an anti-proteinase screen become overwhelmed in COPD. Neutrophil elastase degrades extracellular matrix components, including elastin and the degree of elastase localized to lung elastic fibres correlates with the degree of emphysema (Damiano *et al.*, 1986). Neutrophil elastase can also directly activate TLR4 signalling that promotes CXCL8 expression in the bronchial epithelial cells (Walsh *et al.*, 2001; Kuwahara *et al.*, 2006) and promote mucin production via EGFR transactivation (Shao and Nadel, 2005). α1-AT deficiency remains the only heritable genetic defect that leads to accelerated emphysematic phenotype, and of significance, carriers are also at increased risk for developing lung cancer (Yang *et al.*, 2008). In a murine KRAS mutant lung cancer model, ablation of neutrophil recruitment significantly reduced the number of lung tumours, where neutrophil elastase activity was required for tumour-promoting proliferation and angiogenesis (Gong *et al.*, 2013). Neutrophil elastase was also shown to accelerate lung tumour

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growth by regulating the activity of the PIK3CA/Akt pathway through the degradation of its binding partner, IRS1 (Houghton *et al.*, 2010). Hence, excessive neutrophil degranulation cannot only contribute to tumour initiation by facilitating DNA damage through release of ROS, but its proteolytic content can induce proliferation, angiogenesis and migration required for tumour progression.

Adaptive immunity

COPD is also characterized by the accumulation of adaptive immune cells. As COPD progresses, organized tertiary lymphoid follicles emerge with increasing disease severity (Hogg *et al.*, 2004). These organized structures consist of B-cells, T-cells and dendritic cells that are maintained by up-regulation of homeostatic chemokines, where B-cell recruitment is dependent upon CXCL13 (Bracke *et al.*, 2013). B-cells may contribute to deleterious autoantibody production against self-antigens, leading to local complement fixation and tissue damage; however, a causative role has yet to be established. Neutralizing CXCL13 activity effectively reduced B-cell tissue accumulation and partially reduced alveolar tissue destruction in a chronic smoke model but did not alter other features of emphysema, inflammation and airway wall remodelling (Bracke *et al.*, 2013). There may also be a case for a protective role for lymphoid follicles in COPD. Inducible bronchus-associated lymphoid tissues are increasingly recognized for their ability to enhance protective immunity and maintain memory cells in the lungs against respiratory pathogens (Foo and Phipps, 2010). As infectious exacerbations become more frequent with increasing severity of COPD, the emergence of lymphoid follicles may play a role in protective immunity in this setting.

The role for lymphoid follicles in lung cancer is also intriguing, where the combination of follicular B-cell and mature dendritic cell densities was predictive of longer survival in early and advanced stage NSCLC (Germain *et al.*, 2014). In addition, intra-tumoural follicles are associated with the development of antigen-specific humoral responses, with the emergence of plasma cells secreting tumour antigen-specific immunoglobulins (Germain *et al.*, 2014). Since the risk of developing lung cancer decreases in severe COPD relative to mild-moderate COPD, the potential anti-tumourigenic role for lymphoid aggregates warrants further investigation. This robust humoral response may further contribute to antigen-specific CD8 T-cell generation and expansion central to protective immunity. Dendritic cells also play a key role in tumour eradication by ingesting tumour debris, homing back to the draining lymph nodes and facilitating the development of tumour-specific CD4 and CD8 T-cells. Tumour-specific T-cells can then home to the tumour site where their cytolytic function effectively destroys the remaining antigen-bearing cancer cells. In COPD, several dendritic cell subsets are present in the respiratory mucosa and their relative abundance and activation state appear to be influenced by smoking status and severity of COPD (Brusselle *et al.*, 2011). Dendritic cells will regulate activation of cytotoxic T-cells in COPD that contribute to development of emphysema through promoting apoptosis of structural cells (Brusselle *et al.*, 2011). Further investigation into the interactions between dendritic and cytotoxic T-cell function in COPD will reveal their role in lung cancer susceptibility.

The concept of cancer immunoediting now recognizes that the immune system can play a dual role in cancer that not only suppresses tumour growth by destroying cancer cells but can also promote tumour progression by either selecting poorly immunogenic tumours or establishing a microenvironment that facilitate tumour outgrowth (Dunn *et al.*, 2002). Destruction of cancer cells by tumour infiltrating cytotoxic CD8 and NK cells recognize tumour antigen and produce mediators such as IFN-γ, TNF-α, granzymes and perforin to promote tumour control, and their levels have been shown to be decreased in lung cancer (Hodge *et al.*, 2014). Reduced granzyme B release from CD8 T-cells has been associated with increased expression of its inhibitor, PI-9, by the lung tumour cells (Soriano *et al.*, 2012). In COPD, there is an expansion of cytotoxic CD8 T-cells that increase in the airway and alveolar compartment with disease severity (Saetta *et al.*, 1998), where they are thought to promote emphysema through release of perforin and granzymes that promote apoptosis of the structural cells (Urbanowicz *et al.*, 2010). Although the emergence of cytotoxic CD8 T-cells in COPD may theoretically provide a protective role in reducing lung cancer risk, it has also been reported that cigarette smoke can induce a state of T-cell anergy that is dependent upon the degree of smoke exposure (Stampfli and Anderson, 2009). Consistent with this concept, oxidative stress has been shown to alter the survival, activation, differentiation and migration of cytotoxic effector cells directly through oxidative modification including carbonylation and nitrosylation (Klemke and Samstag, 2009). The expression of the CD3 zeta chain of T-cell receptor complex is particularly vulnerable to ROS, where circulating T-cells produce less cytokines in the presence of activated granulocytes (Schmielau and Finn, 2001). In addition to suppression of inflammatory cytokine release by epithelial cells (Laan *et al.*, 2004), ROS has also been shown to decrease cytokine production by blocking NF-κB signalling in T-cells (Malmberg *et al.*, 2001). In addition, peroxynitrite can enhance nitration of tyrosine residues on TCR and CD8 molecules on CD8 T-cells, thereby blocking their ability to bind antigen presented by MHC-I (Nagaraj *et al.*, 2007). Oxidation of the actin cytoskeleton in T-cells can also promote a state of T-cell hyporesponsiveness (Klemke *et al.*, 2008), which ultimately compromises immune surveillance required for eradication of cancer cells.

Checkpoint inhibitors are increasingly been evaluated for their ability to modulate cytotoxic T-cell function and improve immunological eradication of cancer cells, including ipilimumab, a monoclonal blocking antibody against cytotoxic T lymphocyte associated protein 4 (CTLA-4), and pembrolizumab, a monoclonal antibody against programmed cell death protein 1 (PD-1). Since immune checkpoint pathways normally prevent excessive effector activity by cytotoxic T-cells, their inhibition has shown promise in increasing T-cell activation and killing of tumour cells. An increase in CTLA-4 expression on the cell surface of lymphocytes from patients with NSCLC has been observed (Erfani *et al.*, 2012), which may contribute to an anergic phenotype that fails to eradicate tumour cells. There are multiple clinical trials that are currently evaluating the efficacy of ipilimumab in lung cancer. A phase II trial has shown that phased ipilimumab plus paclitaxel and carboplatin improved immune-related progression-free survival, and importantly, this appeared to

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be greater in patients with squamous histology then non-squamous histology (Lynch *et al.*, 2012). Like CTLA-4, PD-1 is a surface receptor that is expressed on many cell types including activated T-cells and interaction with its ligand (PD-L1) induces T-cell tolerance by reducing proliferation and cytokine production. PD-L1 has been shown to be expressed by NSCLC cells and was associated with poor survival (Mu *et al.*, 2011), which may contribute to immune evasion in this setting. The anti-tumour activity of PD-1 inhibitors such as pembrolizumab is currently being evaluated for advanced NSCLC expressing PD-1. In addition, the activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, has been assessed in patients with advanced, refractory SCC, and 14.5% subjects had an objective response with a manageable safety profile in this phase II trial (Rizvi *et al.*, 2015). The Food and Drug Administration has now approved the use of nivolumab in SCC. In COPD, circulating levels of PD-1 + exhausted effector T-cells were found to be increased (Kalathil *et al.*, 2014), which may not only mitigate deficient antiviral and antibacterial effector functions in COPD but may also compromise tumour immune surveillance.

IL-17A, COPD and lung cancer

IL-17A is increasingly recognized as a fundamentally important regulator of cellular immunity and is conventionally considered to arise predominantly from the 'Th17' specific subset of CD4 cells (Park *et al.*, 2005). IL-17A is uniquely positioned at the interface of innate and adaptive immunity (Ouyang *et al.*, 2008) and can regulate lung inflammation by promoting recruitment of leukocytes, release of myeloperoxidase, neutrophil elastase and MMP-9 (Prause *et al.*, 2004; Ivanov *et al.*, 2007). There is also evidence for an emerging role for IL-17A in COPD, where IL-17A$^+$ cells are increased in bronchial submucosa of chronic smokers and stable COPD subjects (Di Stefano *et al.*, 2009; Doe *et al.*, 2010). Genetic ablation of IL-17 receptors also prevented the development of experimental emphysema (Chen *et al.*, 2011) and inhibition of IL-17A reduced neutrophilic inflammation induced by cigarette smoke (Shen *et al.*, 2011). Of significance, IL-17A expression was induced in NOD.SCID mice, which reveals that alternate sources of IL-17A including NK cells are activated by smoke exposure (S. Bozinovski *et al.*, unpubl. data). Consistent with this concept, both IL-17A and NK cells were shown to be induced by cigarette smoke exposure and were persistently up-regulated following prolonged smoking cessation (Hansen *et al.*, 2014). NK cell function has not been extensively characterized in COPD; however, chronic cigarette smoke exposure primed NK cells to release inflammatory mediators including IL-12 and IL-18 in mice (Motz *et al.*, 2010). The NK cell group 2D (NKG2D) ligand is also elevated in CS-exposed pulmonary epithelial cells, which may sustain deleterious activation of cytotoxic T-cells including NK cells involving release of granzymes and perforin (Borchers *et al.*, 2009).

IL-17A is also increasingly recognized as a key cytokine in lung cancer where its levels are inversely correlated with patient survival and is implicated in metastasis of lung cancer by promoting lymphangiogenesis (Chen *et al.*, 2010). IL-17A transcript levels were increased in NSCLC biopsies and inhibition of IL-17A reduced tumour growth by inducing activation of tumour-infiltrating CD4 T-cells in mice injected with L1C2 tumour cells (Reppert *et al.*, 2011). Suppression of IL-17A in the KRAS^{G12D} mouse model of lung cancer also resulted in the reduction of tumour cell proliferation and angiogenesis and decreased the expression of pro-inflammatory mediators (Chang *et al.*, 2014). In this model, IL-17A promoted the recruitment of myeloid cells that were required for tumour growth (Chang *et al.*, 2014). Hence, there is a compelling case for targeting IL-17A in both COPD and lung cancer, where both conventional T_H17 and alternate innate sources will contribute to disease progression and poor prognosis.

SAA and FPR2 in lung cancer and COPD

COPD is associated with systemic inflammation as characterized by an increase in circulating cytokines, acute phase proteins and abnormalities in circulating cells, where the degree of inflammation increases with disease severity (Agusti *et al.*, 2012). Systemic inflammation also markedly rises during infectious exacerbations of COPD, and the acute phase reactant termed serum amyloid A (SAA) has been shown to be predictive of exacerbation severity (Bozinovski *et al.*, 2008). Systemically, SAA is secreted by the liver and associates with HDLs (Coetzee *et al.*, 1986), where this complex is involved in mobilizing and recycling macrophage cholesterol during tissue injury. There is also evidence of extrahepatic SAA production, as *de novo* transcript synthesis is increased in the lung tissue from mice exposed to cigarette smoke, LPS and influenza infection (Bozinovski *et al.*, 2012). In addition, SAA immunoreactvity was detected in lung resection samples obtained from COPD subjects with lung cancer (Bozinovski *et al.*, 2012). SAA is considered to be pro-inflammatory as it is a potent chemotactic factor that mediates migration of leukocytes (Su *et al.*, 1999) and can also stimulate expression of pro-inflammatory mediators under *in vitro* (He *et al.*, 2003) and *in vivo* conditions (Bozinovski *et al.*, 2012). More recently, SAA was shown to promote the differentiation of human monocyte-derived macrophages into a pro-inflammatory phenotype that expressed higher levels of the T_H17 polarizing cytokines, IL-6 and IL-1β (Anthony *et al.*, 2014). Inhibition of IL-17A signalling in this model also markedly reduced the recruitment of neutrophils into the airways in response SAA (Anthony *et al.*, 2013). Hence, increased expression of SAA in the lungs of COPD subjects with lung cancer may contribute to tumour growth by stimulating an M2-like alternative macrophage phenotype and inducing IL-17A-mediated inflammation.

Like COPD, SAA has been identified as a severity biomarker and a potential therapeutic candidate in lung cancer. Proteomic screening of sera from lung cancer patients have demonstrate that when SAA is combined with other circulating inflammatory markers, high sensitivity and specificity (>90%) are achieved with respect to differentiating healthy subjects from lung cancer (Liu *et al.*, 2011; Dowling *et al.*, 2012). Furthermore, when SCC patients are stratified on the basis of pre-surgery SAA levels into rapid recurrence group

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versus no evidence of recurrence group following resection of tumour, high SAA levels (cut-off of 17 $\mu g \cdot mL^{-1}$) were predictive of rapid recurrence and poor survival outcomes (Liu *et al.*, 2012). Hence, the application of SAA in combination with other markers are not only powerful in prognosis determination but can also inform on treatment optimization and patient-tailored therapies based upon serum signatures. Like COPD, there is also emerging literature that SAA function extends beyond its clinical utility as a disease biomarker and may transition into an important pathogenic mediator of disease progression.

There is now evidence for production of SAA within the tumour microenvironment in melanoma (De Santo *et al.*, 2010) and lung cancer (Bozinovski *et al.*, 2012) in close proximity to tumour-infiltrating macrophages. In addition, there was a positive association between the number of neutrophils and the expression of SAA in lung resection samples obtained from subjects with COPD and lung cancer (Anthony *et al.*, 2013). This is an important observation, as SAA has been shown to promote the recruitment and differentiation of an IL-10+ expressing neutrophil population that has been shown to be immunosuppressive towards cytotoxic T-cells (De Santo *et al.*, 2010). The expansion of immunosuppressive neutrophils by SAA was shown to be dependent upon the activation of MAPK and PIK3CA through its interaction with the FPR2 receptor (De Santo *et al.*, 2010). Immunosuppressive neutrophils are normally counteracted by crosstalk with invariant or CD1-restricted NKT cells, which reverse this suppressive phenotype by decreasing IL-10 and promoting IL-12 production, and restoring proliferation of antigen-specific $CD8^+$ T-cells (De Santo *et al.*, 2010). The functional capabilities of NKT cells have not been determined in COPD; however, possible defects in this mucosal cell type have been implicated in recurrent infections (Stampfli and Anderson, 2009). Furthermore, SAA has been reported to promote immune evasion of cancer cells by enhancing the suppressive capacity of myeloid-derived suppressor cells (Lee *et al.*, 2014) via TLR2-dependent mechanisms, which have been proposed as an alternative receptor for SAA. In another study, a mouse-specific isoform of SAA was shown to stimulate inflammation associated with the accelerated migration of primary tumour cells to the lungs, where blocking SAA function in the pre-metastatic phase prevented pulmonary metastasis in mice (Hiratsuka *et al.*, 2008).

SAA has also been shown to modulate the differentiation of monocyte-derived macrophages, including the induction of IL-10 and T_H17 inducing cytokines (Anthony *et al.*, 2014). In addition, SAA has been shown to promote an M2-like polarization state that exacerbated hepatocellular carcinoma cell invasion (Li *et al.*, 2011). In this study, the polarization towards a tumour-promoting phenotype was dependent upon FPR2 signalling, and alternative ligands to this receptor involved in the resolution of inflammation skewed macrophages towards an anti-tumourigenic phenotype (Li *et al.*, 2011). FPR2 is a GPCR superfamily member characterized by seven putative TM domains that display diverse ligand affinities that extend beyond its interaction with SAA to include pro-resolving mediators (PRM) such as lipoxins, series D-resolvins and annexin A1. The diverse conformation of endogenous and synthetic ligands that bind to alternate regions of the FPR2 can promote ligand-biased signalling, leading to differential biological actions (Cooray *et al.*, 2013). Lipoxin A_4 (LXA_4) is synthesized in response to cell–cell interactions (reviewed in Serhan, 2005; Chiang *et al.*, 2006), where it opposes leukocyte migration and activation (Papayianni *et al.*, 1996). LXA_4 can also suppress inflammatory cytokine production in mucosal epithelial cells (Bonnans *et al.*, 2006) and reduce lung inflammation initiated by SAA (Bozinovski *et al.*, 2012). Other important roles for LXA_4 include the stimulation of macrophage-mediated efferocytosis (Godson *et al.*, 2000; El Kebir *et al.*, 2009) and the promotion of an alternative macrophage phenotype associated with anti-tumourigenic properties (Li *et al.*, 2011). The D series resolvins (RvD1) derived from the omega-3 fatty acid, docosahexaenoic acid also engage FPR2 and have been shown to reduce neutrophilic lung inflammation, inflammatory cytokine production and promote phagocytosis in an acute cigarette smoke exposure model (Hsiao *et al.*, 2013). There are also emerging data that FPR2 and its murine homologues are critical in mediating homeostasis, inflammation and epithelial repair processes and any perturbation of this mechanism may contribute to tumour development (Bonnans *et al.*, 2006; Khau *et al.*, 2011; Chen *et al.*, 2013). Further work is needed to characterize what effect different FPR2 ligands have on lung epithelial survival and proliferation.

Conclusions

COPD is a chronic inflammatory condition where aberrant immunity not only contributes to excessive oxidative stress and deleterious lung remodelling but will also contribute to lung cancer susceptibility and progression (summarized in Figure 1). COPD is associated with persistent activation of innate immune cells including neutrophils, where the uncontrolled release of powerful free radicals and proteases will not only cause DNA damage but also promote tumour migration. Airway macrophages in COPD are skewed towards an M2 state that will release supportive factors within the tumour microenvironment. Adaptive immunity in COPD is also compromised, which is potentially associated with the development of exhausted T-cell populations that fail to effectively respond to respiratory infections. T-cell anergy in COPD may also lead to tumour evasion through suppressed cytotoxic T-cell clearance of cancer cells. The stimulation of T-cell function using CTLA-4 and PD-1 inhibitors may provide an opportunity to stimulate T-cell function in COPD in order to reduce exacerbation and lung cancer risk; however, activation of cytotoxic T-cells are also implicated in development of emphysema through apoptosis of structural cells. Non-conventional T-cells may also be important sources of IL-17A in COPD, which is a pivotal immunological cytokine that is increasingly recognized as a mediator of tumour growth. Systemic inflammation is common in COPD and lung cancer, and SAA has predictive utility in both diseases with respect to severity indices. There is also emerging evidence to suggest that SAA is actively modulating inflammation and immunity in cancer by promoting pro-tumourigenic inflammation and facilitating tumour evasion. Since the treatment of SCC remains a major therapeutic challenge, targeted inhibition of FPR2 expressed on immune cells provides a therapeutic opportunity to combat

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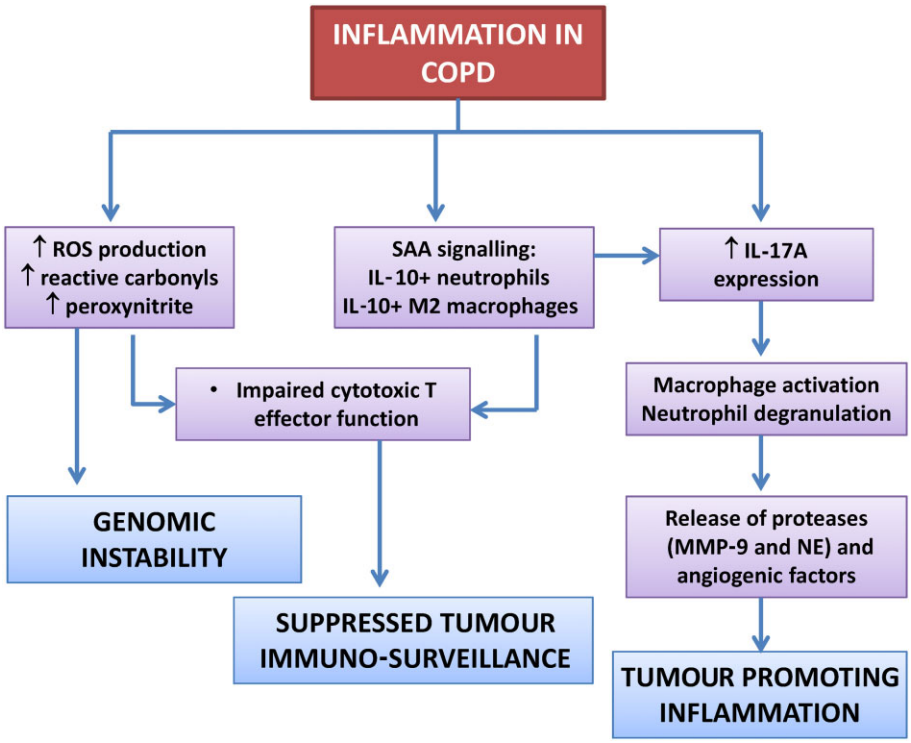

Figure 1

Inflammatory and oxidative mechanisms prominent in COPD that can promote lung cancer by causing genomic instability, suppressing tumour immuno-surveillance mechanisms and promoting inflammation that is beneficial to tumour growth and migration.

pro-tumourigenic inflammation and immunity caused by underlying COPD. Epimers of LXA_4 and RvD1 can be produced following aspirin treatment (Serhan *et al.*, 2008) and since aspirin may reduce the risk of developing lung cancer (Jonsson *et al.*, 2013), the relative contribution of these known FPR2 ligands warrants further investigation.

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