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Abstract

Chronic obstructive pulmonary disease (COPD) and lung cancer are leading cause of death, and both are associated with cigarette smoke exposure. It has been shown that 50–70% of patients diagnosed with lung cancer suffer from COPD, and reduced lung function is an important event in lung cancer suggesting an association between COPD and lung cancer. However, a causal relationship between COPD and lung tumorigenesis is not yet fully understood. Recent studies have suggested a central role of chronic inflammation in pathogenesis of both the diseases. For example, immune dysfunction, abnormal activation of NF-κB, epithelial-to-mesenchymal transition, altered adhesion signaling pathways, and extracellular matrix degradation/altered signaling are the key underlying mechanisms in both COPD and lung cancer. These parameters along with other processes, such as chromatin modifications/epigenetic changes, angiogenesis, and autophagy/apoptosis are altered by cigarette smoke, are crucial in the development of COPD and lung cancer. Understanding the cellular and molecular mechanisms underlying these processes will provide novel avenues for halting the chronic inflammation in COPD and devising therapeutic strategies against lung cancer.

Keywords

Cigarette smoke; angiogenesis; oxidants; epigenetics; growth factors

Introduction

Both chronic obstructive pulmonary disease (COPD) and lung cancer are associated with cigarette smoking and/or various environmental pollutants exposure. They represent the fourth- and second-leading causes of death in USA/worldwide respectively. COPD is shown to increase the risk for developing lung cancer [1]. Hence, there are shared mechanisms (e.g. chronic inflammation) in both COPD and lung cancer, or in the progression of COPD which increase the susceptibility for lung tumorigenesis up to 4.5-fold (Figure 1). This review focuses on current knowledge of specific processes/molecules that drive chronic inflammation which are important in the pathogenesis of both COPD and lung cancer, and identify the potential therapeutic targets for these chronic diseases (Figure 2).

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Chronic inflammation in COPD and lung cancer

Cigarette smoke contains more than 10^{14} oxidants/free radicals and 4700 reactive chemical compounds including aldehydes, quinones, semiquinones, nitrosamines, benzo(*a*)pyrene, and other carcinogens, and it is a risk factor in the development of COPD/emphysema and lung cancer by inducing chronic inflammation. Macrophages, neutrophils, and lymphocytes, the main orchestrators and amplifiers in the progression of COPD, are thought to fight against cancers by eradicating dysplastic and neoplastic cells. However, these inflammatory cells can be manipulated to induce immune escape of cancer cells especially in a tumor-promoting microenvironment which is created by chronic inflammation seen in lungs of patients with COPD [2]. For example, it has been shown that COPD-like airway inflammation induced by nontypeable *Haemophilus influenza* promotes lung carcinogenesis in mice [3]. Furthermore, repeated lung injury and repair triggered by chronic inflammation enhance cell turnover and potential genetic error, epithelial-to-mesenchymal transition and ultimately lead to lung tumorigenesis. Interestingly, patients with COPD who are treated with inhaled corticosteroids have reduced incidence of lung cancer and death suggesting inhibition of inflammation can halt lung tumorigenicity [4]. These studies highlight the key role of inflammation in both the diseases.

NF-κB pathway in COPD and lung cancer

It is well known that canonical and non-canonical NF-κB pathways play crucial role in pathogenesis/development of COPD by increasing the release of pro-inflammatory mediators leading to chronic inflammation in the lung. Indeed, NF-κB-regulated genes including cytokines, adhesion molecules, angiogenic factors, anti-apoptotic factors, and matrix metalloproteinases (MMPs) that all have shown to be associated with tumor progression and metastasis. Furthermore, NF-κB in lung epithelium functions as an extrinsic promoter by inducing the influx of inflammatory cells, thus potentiating lung adenocarcinoma metastasis. Treatment with NF-κB inhibitors (e.g. pyrrolidine dithiocarbamate, PDTC) and IκB protease inhibitor (tosylphenylalanylchloromethane, TPCK) repress TGF-β1-induced cell migration in human lung cancer cells [5]. Therefore, downregulation of NF-κB activation may improve the efficacy of first-line therapy in both COPD and lung cancer.

Adaptive immune response and immunosculpting in COPD and lung cancer

Chronic inflammation of COPD is characterized by accumulation of neutrophils, macrophages, B cells, CD4^{+}-, CD8^{+}-T cells, dendritic cells, and eosinophils, particularly in the smaller airways, and the severity of COPD is associated with the infiltration of these inflammatory-immune cells. The role of inflammatory cells in COPD has focused on oxidants, proteinases, perforin and granzymes released from these cells leading to alveolar wall destruction and mucus hypersecretion. Recently, it has been shown that adaptive immune response also participates in the pathogenesis of COPD since mature lymphoid follicles with a germinal center and separated T and B cells zone occur in lungs of patients with COPD [6–8]. These lymphoid follicles are rarely found in the lungs of nonsmokers, but they are present in airways and are correlated with the severity of COPD [6]. This may be due to the large antigen load associated with bacterial and viral infections in lower respiratory tract during severe stages of COPD [6]. Another possibility underlying these findings may attribute to increased exposure to neoantigens from degraded extracellular matrix (ECM) or carbonyl modifying proteins by cigarette smoke leading to autoimmune impairment in advanced stages of COPD [8–10].

As aforementioned, host immune cells mediate antitumor effects by eradicating aberrant cells which is termed as immunosurveillance. However, these cells including macrophages, neutrophils, and T lymphocytes (CD4^{+} and CD8^{+}) can communicate with cancer cells through a reciprocal and self-perpetuating interaction resulting in increased growth and resistance to

immune destruction by sculpting/mounting tumor immunogenicity or attenuating anti-tumor immune response in local milieu [2,11,12]. Indeed, the ability of alveolar macrophages to induce T cell and anti-tumor immune responses is significantly compromised in many patients with lung cancer. Hence, the studies on ligands and signaling pathways of communication between cancer and immune/inflammatory cells may provide therapeutic options for not only augmenting antitumor immune response but also blocking or overcoming immunosculpting at the same time.

Adhesion molecules: integrins and TGF-β pathways in COPD and lung cancer

Integrins are heterodimeric transmembrane receptors, and are involved in a variety of cellular functions as well as in lung inflammation. Integrin αvβ6 is one of the integrins which is located in epithelial cells, and its expression is increased during lung inflammation or injury. Interestingly, integrin αvβ6 plays an important role in maintaining normal lung homeostasis and preventing lung destruction since ablation of integrin αvβ6 leads to airspace enlargement in mice by regulating TGF-β/MMP-12 pathway [13]. The inhibition of MMP-12 by integrin αvβ6 is dependent on its ability to bind and activate latent TGF-β [13]. In addition, inhibition of mucus hypersecretion (goblet cells) by TGF-β also contributes to its protective effect in COPD through its type II receptor (TβRII). However, the levels of TGF-β 1 mRNA and protein are up-regulated in the airway and alveolar epithelial cells in patients with COPD, and the levels of TGF-β1 mRNA are positively correlated with the smoking history and degree of small airway obstruction suggesting the pro-fibrogenic, pro-remodeling, and a cell-specific role of TGF-β in COPD [14]. Given that a potential role as an inhibitor of normal epithelial cell proliferation and repair, TGF-β activation may prevent proliferative response to environmental carcinogens, such as cigarette smoke, under normal conditions. However, it is interesting to note that human lung cancer cells can escape from autocrine growth inhibitory effect of TGF-β due to the loss/deficiency of TβRII. Restoration of TGF-β signaling through expression of TβRII may be a potential strategy for chemotherapeutic intervention of lung cancer since the majority of non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) show weak or no expression of TβRII. However, at the late stages of lung cancer, TGF-β promotes tumor spreading by enhancing invasion and angiogenesis [5]. Not much information is currently available regarding TGF- β pathways as a potential therapeutic target in clinic for lung cancer.

Recent studies showed that integrin-induced cell adhesion and TGF-β-mediated fibrogenesis are regulated by galectin-3, a galactose-binding protein. Furthermore, galectin-3 is involved in cell cycle, apoptosis, angiogenesis, as well as airway inflammation. In addition, galectin-3 has also described as a receptor for advanced glycation end products which is increased in the lenses and blood vessels of cigarette smokers. Interestingly, increased expression of galectin-3 occurs in small airway epithelial cells of patients with COPD as compared to non-smokers, as well as in cigarette smoke-exposed rat lung suggesting a role of galectin-3 in pathogenesis of COPD [15,16]. In lung cancers, differential expression of galectin-3 between different histological cell types suggested an important role of galectin-3 in tumor cell adhesion, apoptosis, and response to chemotherapy. Nuclear expression of galectin-3 is considered as a significant prognostic predictor for recurrence in lung adenocarcinoma and squamous cell carcinoma. Most importantly, the susceptibility to tobacco carcinogen [4-(methylnitrosamino)-1-(3-pyridle)-1-butanone]-induced lung tumorigenesis is decreased in galectin-3 deficient mice suggesting an important role of galectin-3 in progression of lung cancer [17]. Further studies on the role of galectin-3 are needed to discern its potential involvement in abnormal cell adhesion, apoptosis and angiogenesis in COPD and lung cancer.

Hypoxia/angiogenesis in COPD and lung cancer

Hypoxia is shown to induce pulmonary inflammation by inducing activation of transcription factor and triggering the expression of pro-inflammatory genes. In COPD, progressive airflow limitation and destruction of the alveolar capillary may lead to decreased oxygen transport and alveolar hypoxia. In this context, hypoxia-inducible factor (HIF) is activated leading to enhancement of VEGF transcription and increased angiogenesis. Interestingly, the levels of VEGF and its receptors are decreased in emphysematous lungs and in cigarette smoke exposed lung epithelial cells, and cigarette smoke-induced emphysematous alveolar septa are almost avascular (limited angiogenesis). This is due to the abnormality in induction of HIF and other signaling molecules involved in hypoxia sensing in emphysema [18]. Therefore, oxygen therapy will offer significant short-term benefits in hypoxemic patients with COPD. However, chronic oxygen therapy results in oxidative cellular injury leading to aggravation of lung inflammation and cell death. Apart from altered angiogenesis, VEGF pathway is also involved in apoptosis since inhibition of VEGF receptor 2 increased the alveolar septal cell apoptosis resulting in airspace enlargement (emphysema) [19,20]. It is interesting to note that the expression/level of VEGF is increased in patients with chronic bronchitis [21] implicating a paradoxical role of VEGF in the bronchi and airspaces of patients with COPD.

As tumor grow their microenvironment becomes hypoxic, and HIF is activated to induce MMPs, urokinase-type plasminogen activator receptor, and VEGF leading to progression, invasion, and metastasis of lung cancer. VEGF is shown to be positively correlated with progression, metastasis, and poor prognosis in NSCLC (increased angiogenesis). Intravenous injection of siRNA directed against HIF-1α and HIF-2α reduced angiogenesis and prolonged the survival in a Lewis lung carcinoma cancer model [22]. Bevacizumab, a monoclonal antibody against VEGF, has shown to be effective in phase II and III trials in combination with standard first-line chemotherapy for NSCLC. Alternative anti-angiogenic approaches such as VEGF-trap (Aflibercept) are currently being investigated in the treatment of NSCLC with or without others chemotherapies.

MMPs in COPD and lung cancer

Emphysema is a consequence of an imbalance between antiproteinases and proteinases (balance shifted towards proteinases) including elastase and MMPs from activated inflammatory cells and epithelial cells in lungs. Lung structural cell death occurs when they lose the attachment due to ECM degradation by MMPs as well as defective tissue repair. Furthermore, ECM fragments have chemotactic activity to attract inflammatory cells into the lung which aggravates the progression of emphysema in mice [23,24]. Hence, antagonism of ECM fragments will ameliorate the progression of COPD/emphysema. Indeed, intratracheal administration of L-arginine-threonine-arginine, a complementary peptide to elastin fragment N-acetyl-proline-glycine-proline (PGP), attenuated LPS- and elastin/PGP-induced neutrophilic inflammation and emphysema in mice [24]. Therefore, the development of new compounds similar to L-arginine-threonine-arginine may represent a novel class of anti-inflammatory therapy to intervene COPD.

Proteinases are also shown to induce the release of growth and other factors, such as TGF-β and VEGF, which play a pivotal role in tumorigenesis and metastasis of lung cancer. Several MMP inhibitors including batimastat (BB-94), marimastat (BB-2516), prinomastat (AG-3340), BMS-275291 and ONO-4817, are currently being investigated to evaluate the efficacy in maintenance and remission after other treatments or in combination with standard chemotherapy in NSCLC [25–27]. However, these inhibitors act against all MMPs, and will result in side-effects because some MMPs play a beneficial role in host defense during

tumorigenesis. Hence, tumor-specific MMP inhibitors need to be developed for intervening lung tumorigenesis, invasion and metastasis.

Cell cycle regulator in COPD and lung cancer

Cigarette smoke is a potent genotoxic stimulus of DNA damage through oxidant stress/carcinogens, thereby arrests cell cycle. It has been shown that the expression of p21$^{CIP1/WAF1/SDI1}$ (p21), a cyclin-dependent kinase (CDK) inhibitor, is increased in alveolar epithelial cells exposed to cigarette smoke extract, and in alveolar macrophages and biopsies isolated from smokers [28,29]. Furthermore, the anti-apoptotic protein Bcl-X$_L$ is increased in alveolar macrophages from smokers suggesting that p21 may play an important role in cigarette smoke-mediated lung inflammation by inhibiting alveolar macrophages apoptosis. Indeed, genetic ablation of p21 attenuated lung inflammation which is associated with decreased number of macrophages in lungs of mice exposed to cigarette smoke [30]. Chimeric experiments also demonstrated that p21-expressing hematopoietic cells are required for cigarette smoke-mediated lung inflammation (Yao *et al*, unpublished data). The mechanism for pro-inflammatory effect of p21 is associated with activation of NF-κB pathway, p21-activated kinase and galectin-3 which are crucial in cigarette smoke-mediated chronic lung diseases including COPD. Interestingly, p21 expression is also increased in lung epithelial cells *in vitro*, and in lungs of mouse exposed to cigarette smoke, and from smokers [28,29,31]. It is well known that p21 is necessary and sufficient to trigger replicative senescence. Therefore, cigarette smoke-mediated p21 activation may cause senescence in lung epithelial cells leading to increased release of pro-inflammatory mediators since senescent cells are more prone to produce pro-inflammatory mediators [31,32]. Oxidative stress increases cytoplasmic expression of p21, and promotes transition from the G1 to the G2/M phase of the cell cycle resulting in imbalance of apoptosis/proliferation towards hyperproliferation in lung epithelial cells [29]. This may enhance the epithelial transition from normal to hyperplastic to carcinomatous in smokers and patients with COPD. However, some CDK inhibitors (e.g. R-roscovitine) are shown to enhance the resolution of neutrophil-dependent inflammation in carrageenan-elicited acute pleurisy and bleomycin-induced lung injury in mice, which are used to treat NSCLC with encouraging results suggested the differential role of CDK inhibitors in lung inflammation and tumorigenesis [33,34].

Autophagy/apoptosis in COPD and lung cancer

Autophagy is a dynamic process responsible for the turnover of cellular organelles and proteins, which are essential for maintaining cell homeostasis and conferring adaption to adverse environmental stimuli. However, excessive autophagy will lead to cell death. Recently, it has been shown that autophagy regulated the inflammatory immune response via controlling inflammasome activation [35]. Interestingly, increased autophagy and apoptosis of epithelial/endothelial cells are shown to occur in lungs of patients with COPD, in lungs of mouse exposed to cigarette smoke, and in cells treated with cigarette smoke extract suggesting a critical role of autophagy and apoptosis in pathogenesis of COPD [36]. The mechanism underlying these observations is not known but it may be associated with increased oxidative stress in response to cigarette smoke since reactive oxygen species are known to induce autophagy [37]. This is confirmed by the study showing overexpression of extracellular superoxide dismutase attenuated hypoxia-induced increase of early growth response protein-1 (Egr-1) which is an important transcription factor for autophagy in lungs [38]. Interestingly, inhibition of HDACs (in particular HDAC6) activity results in the complex formation of Egr-1 with E2F-4, enhancing expression of microtubule-associated protein light chain 3 (LC3), the best characterized autophagy protein [36]. Therefore, cigarette smoke-mediated decrease in deacetylases, such as HDACs and SIRT1, regulates autophagy by acetylating autophagic

proteins or enhancing transcriptional activation of autophagic genes through chromatin modifications.

It has been shown that lung cancer is resistant to pro-apoptotic effect of anti-neoplastic agents due to defective apoptotic pathway in lung cancer cells. Autophagy is also known as type II programmed cell death, and prolonged autophagy results in cancer cell death implying that autophagy can be exploited as a therapeutic target for cancer [39,40]. Indeed, induction of autophagy by mTOR inhibitor (Rad001) enhances radiosensitization in the presence of caspase-3 inhibitor in a mouse model of lung cancer. Furthermore, knockdown of ATG5 and Beclin-1, two essential pro-autophagic proteins, increases the survival of H460 lung cancer cells under irradiation, and Beclin-1 haploinsufficiency in mice increases the incidence of lymphomas and carcinomas in lungs [41]. These results suggest a clinical therapeutic potential of autophagy inducers on lung cancer, particularly the cells which are defective in apoptosis pathway or resistant to pro-apoptotic agents.

Chromatin remodeling/epigenetics in COPD and lung cancer

Chromatin remodeling includes post-translational modifications of core histone proteins and DNA methylation which is shown to regulate pro-inflammatory gene expression during the development of COPD and lung carcinogenesis. Increased histone acetylation is observed on the promoters of pro-inflammatory genes in airway epithelial cells and alveolar macrophages in patients with COPD, and the degree of acetylation is positively correlated with disease severity [42]. The mechanism that underlies hyperacetylation of histones/non-histone proteins in lungs of patients with COPD is associated with reduced histone deacetylase (HDAC) 2 level/ activity [42,43]. This is also observed in lungs of rodents exposed to cigarette smoke [43,44]. Therapeutic strategies aimed to elevate HDAC2 activity/level, such as by phenolic antioxidants and theophylline, are being investigated to reduce the lung inflammatory response and attenuate corticosteroid resistance in patients with COPD [45]. Methylation of p16 promoter is frequent in sputum of patients with COPD, and this methylation is positively correlated with heavy cigarette smoking suggesting the involvement of DNA methylation in COPD. Further studies on specific histone/DNA modifications and signaling mechanisms that govern chromatin remodeling will provide the prospects of new biomarkers and/or therapeutic targets for inflammatory airways diseases, such as COPD.

Similar to COPD, lung cancer also exhibits profound alteration in chromatin structure. Genome-wide DNA demethylation with site-specific hypermethylation occurs in lung cancer cells leading to silencing of a variety of tumor-suppressor genes by recruitment of HDACs. The mechanisms underlying these observations may be due to aberrant expression/activity of DNA methyltransferases (DNMTs) and demethylases in cancer cells. Methylation in the promoters of multiple genes is shown in adenocarcinomas and NSCLC, and this methylation is associated with tumor progression and recurrence [46]. Therefore, determination of DNA methylation on specific gene may provide the useful biomarkers for early detection and/or chemoprotective intervention in lung cancer. Modifications of core histone proteins increase the complex of epigenetic alterations mediated by aberrant DNA methylation in cancer cells. Increased HDAC1, and decreased HDAC5 and HDAC10 are correlated with advanced stage of disease and adverse outcome in lung cancer patients. DNA demethylating agents and HDAC inhibitors synergistically induce apoptosis in lung cancer cells, and prevent lung cancer development in animals exposed to tobacco carcinogens. To date, there are several clinical data available for HDAC inhibitors (e.g. vorinostat and N-acetyldinaline) in treatment of advanced NSCLC [47], and these agents are being investigated in randomized phase III trails. However, the specificity on a particular isoform of HDAC, optional therapeutic doses, timing, and mode of administration are still under evaluation for these agents.

SIRT1 in COPD and lung cancer

SIRT1, a class III HDAC, is shown to regulate inflammation, senescence, autophagy/apoptosis, and aging by deacetylating histones/non-histone proteins including transcription factors, co-activators and other signaling molecules, such as NF-κB FOXO, and p53. Anti-inflammatory property of SIRT1 is associated with decreased NF-κB transcriptional activity by deacetylating RelA/p65 at lys310 residue [48]. Given that a significant reduction of SIRT1 in rodent lungs exposed to cigarette smoke and in lungs of patients with COPD [48,49], activation of SIRT1 may be a potential pharmacotherapy for COPD. Indeed, inhibition of SIRT1 enhanced NF-κB activation whereas up-regulation of SIRT1 by SRT1720 and resveratrol attenuated proinflammatory mediators release in response to cigarette smoke exposure [49]. However, it is not known whether SIRT1 activators protect lung against cigarette smoke-induced immune-inflammatory and injurious responses, senescence, and endothelial dysfunction (acetylation of eNOS, adiponection, and caveolins). The ability of SIRT1 to affect cell survival and cell cycle progression suggests that SIRT1 might be directly involved in tumorigenesis. It has been shown that SIRT1 is up-regulated in a number of different types of cancers including mouse lung carcinomas and human lung cancer. Down-regulation of SIRT1 by antisense oligonucleotides induces apoptosis in lung cancer cells suggesting its therapeutic use in lung cancer [50]. The tumorigenic role of SIRT1 may be due to deacetylation and inactivation of the anti-apoptotic/tumor suppressor genes p53 and p73 as well as deacetylation of histone H4 (lys16) on the promoters of these genes. Therefore, further studies on SIRT1 regulation (and possibly SIRT6) and its role in various cell processes would differentiate its involvement in the development of COPD or lung cancer in response to toxicants/pollutants, and provide the potential therapeutic targets for these diseases.

Conclusions and future directions

Both COPD and lung cancer are tobacco smoking-associated chronic diseases that cluster in families and aggravate with age, and 50–70% of patients diagnosed with lung cancer have declined spirometric evidence of COPD. Furthermore, reduced lung function (FEV_1) is the important event for lung cancer indicating an association between COPD and lung cancer. Nevertheless, a causal relationship between COPD and lung tumorigenesis is not yet known. It is generally accepted that chronic inflammation plays a central role in pathogenesis of COPD and lung tumorigenesis. Further investigations on the mechanisms of chronic inflammation, such as immune dysfunction and immunosculpting, abnormal activation of transcription factors (e.g. NF-κB), altered adhesion signaling pathways, epithelial-to-mesenchymal transition, and oxidants/inflammation-driven ECM degradation will facilitate the understanding of how lung cancer is associated with COPD. Cigarette smoke is known to influence the inflammation-related processes, such as angiogenesis, autophagy/apoptosis, and chromatin remodeling, which are critical in the development of COPD and cancer. Thus, understanding the cellular and molecular mechanisms underlying these processes and multiple pathways will provide novel avenues in the treatment of cigarette smoke-induced lung chronic inflammatory diseases including COPD and lung cancer.

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• of special interest

•• of outstanding interest

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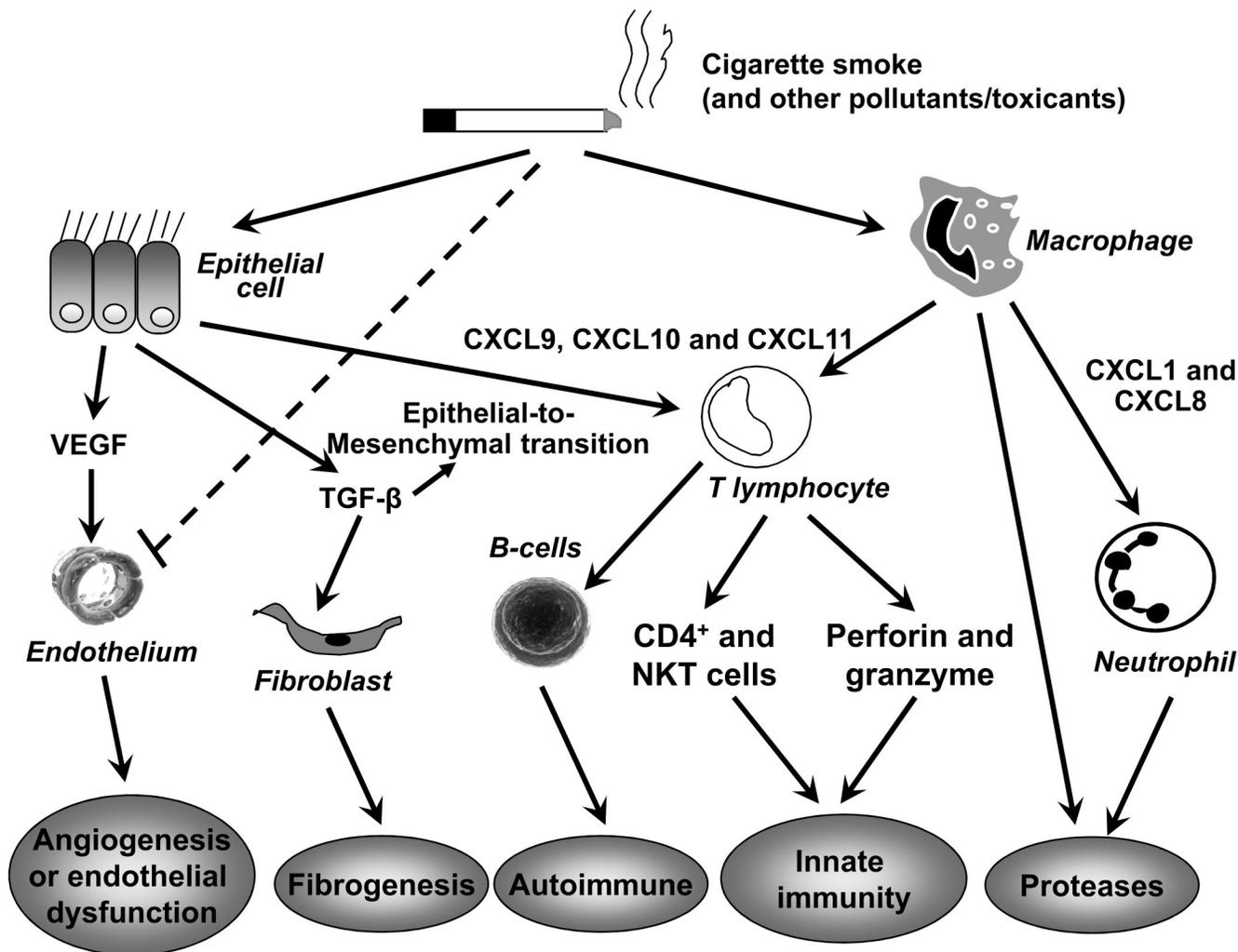
Figure 1. Cells and mediators involved in the pathogenesis of COPD and lung cancer
Exposure to cigarette smoke or other pollutants/toxicants induces the release of chemokines from macrophages and epithelial cells which further attract other inflammatory and immune cells including neutrophils, T-cells, and B-cells into the lungs. As a result of influx of these inflammatory cells, proteases, perforin, and granzyme are released leading to alveolar wall destruction and mucus hypersecretion. Furthermore, activated B-cells produce autoantibodies against elastin, epithelium, and endothelium leading to autoimmune impairment in lungs. Epithelial cells and macrophages also release TGF-β leading to small airway remodeling through activation/differentiation of fibroblasts to myofibroblasts. Cigarette smoke is shown to induce the release of VEGF from epithelial cells leading to angiogenesis which plays an important role in progression, invasion, and metastasis of lung cancer. Interestingly, VEGF receptor 2 in endothelial cells is downregulated by cigarette smoke leading to endothelial dysfunction which occurs in emphysema.
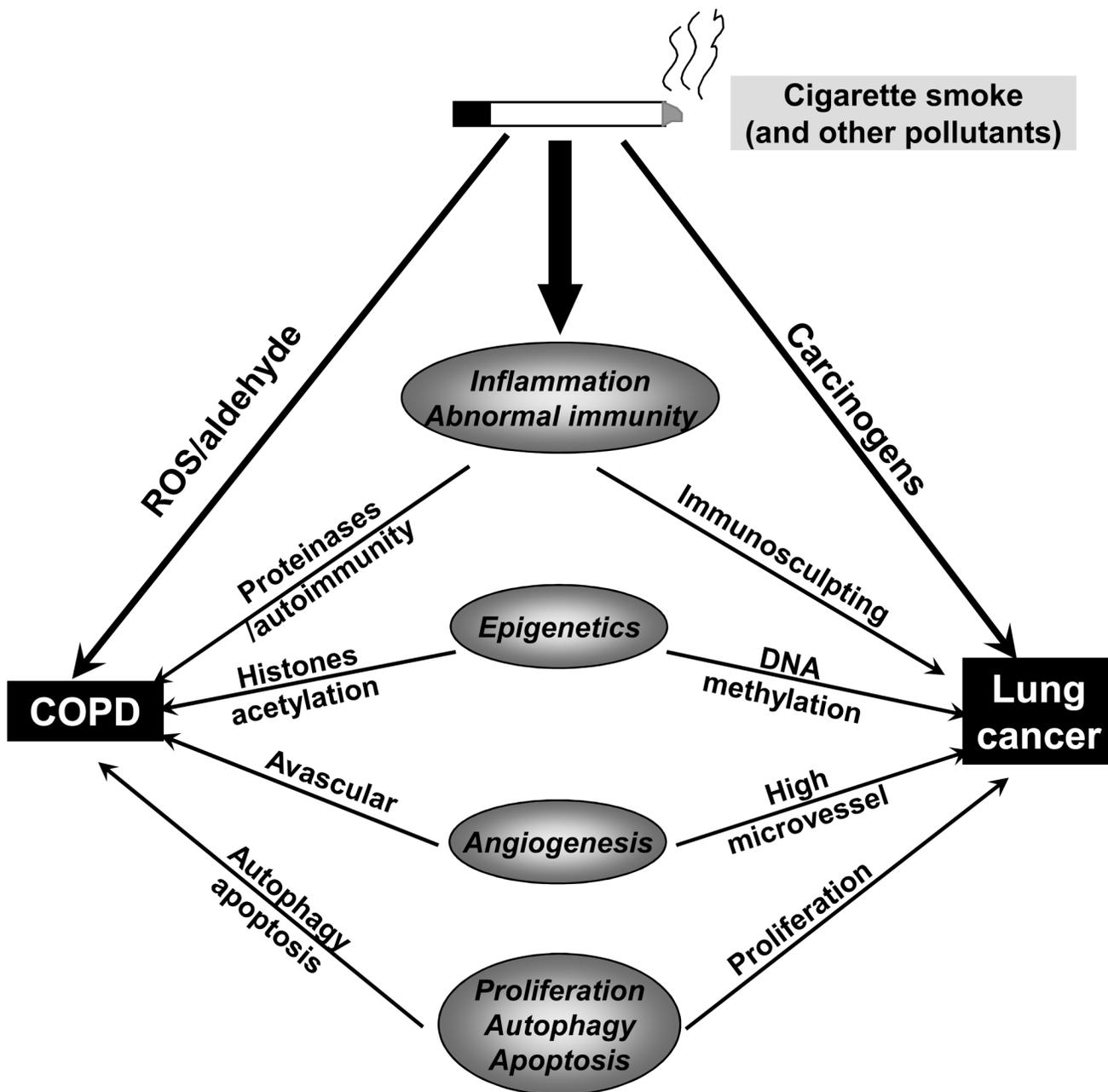
Figure 2. Inflammation and its related pathways in COPD and lung cancer
Cigarette smoke is an important risk factor for COPD and lung cancer by inducing
inflammation and oxidative stress in the lung. Furthermore, a number of proven and suspected
carcinogens contained in cigarette smoke can induce gene mutations/epigenetic changes,
ultimately leading to lung tumorigenesis. In addition, cigarette smoked-mediated processes,
such as abnormal immunity, angiogenesis, cell proliferation/autophagy/apoptosis, and
chromatin modifications, would differentiate and contribute to the development of COPD and
lung cancer.