16 Inflammation and Lung Cancer
Oxidative Stress, ROS, and DNA Damage

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CONTENTS

ABSTRACT

Cancer is the leading cause of death in the world, accounting for more than 25% of all deaths in developed countries, and lung cancer is the most common cause of cancer-related death in the world. The predominant risk factor for this cancer is smoking, accounting for approximately 90% of these lung cancer deaths. Furthermore, lung cancer risk is associated with several indicators of inflammation. The inflammation process is a complex response to stimuli involving the interplay of host cells and signaling molecules, such as angiogenesis factors and chemokines. Inhalation of air pollutants and microorganisms results in lung injury and generation of reactive oxygen species/reactive nitrogen species (ROS/RNS), leading to a cascade of signaling events that trigger the production of proinflammatory cytokines. Inflammation is the primary reaction of a tissue to eliminate pathogenic insult and injured tissue components in order to restore normal physiological functions or replace the irreparable tissue with scar tissue. Cancer and inflammation are closely linked, and many inflammatory conditions increase the risk of cancer development. Matrix metalloproteins are clearly important effectors in inflammation both in physiological situations, such as tissue repair, and in pathological inflammatory conditions and cancer. A better understanding of the role of ROS/RNS in lung inflammation and cancer is probable to inspire new strategies for lung cancer prevention and treatment.

16.1 INTRODUCTION

Cancer is one of the leading causes of death in the world, accounting for more than 25% of all deaths in developed countries, and lung cancer holds the top position in cancer morbidity and mortality among men worldwide (Ferlay et al. 2010). Lung cancer was found to be the most commonly diagnosed cancer and the primary cause of cancer-related mortality for males worldwide and the second leading cause of cancer-related deaths for women (Jemal et al. 2011; Siegel et al. 2012). For the year 2012, it was estimated that lung cancer would account for 26% of all female cancer deaths and 29%

of all male cancer deaths (Siegel et al. 2012). The mortality in this neoplasia, during the first year after diagnosis, is very high, which is about 67% (Grigoryeva et al. 2015). Success of surgical treatment is closely related to the opportunity for early diagnosis of lung cancer. The importance of early diagnosis is confirmed by the 5-year survival rate after radical surgery, so people diagnosed with stages I and II of lung cancer tend to have higher (5-year) survival rate (63.5% and 43.5%, respectively) than people diagnosed with stage III (22.9%) (Grigoryeva et al. 2015).

Lung cancer is rare among young adults, with the average age of occurrence and diagnosis being over 60 years. There are two major classes of lung cancer: primary lung cancer and secondary lung cancer (Azad et al. 2008). Primary lung cancer originates in the lung itself and is further classified into two subtypes: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), depending on the morphology of the malignant cells; NSCLC accounts for approximately 85% of all cases of lung cancer (Molina et al. 2008; Chen et al. 2014).

NSCLC is currently defined by pathological characteristics, and the two predominant NSCLC histological phenotypes are adenocarcinoma (ADC ≈ 50%) and squamous cell carcinoma (SCC ≈ 40%) (Chen et al. 2014). Secondary lung cancer is initiated in other organs such as breast or colon and then spreads to the lungs (Azad et al. 2008).

Recently, molecular subtyping of NSCLC has led to the approval of and use of targeted therapies in the frontline setting. Patients with activating mutations in the epidermal growth factor receptor (EGFR) domain and echinoderm microtubule–associated protein-like 4–anaplastic lymphoma kinase (EML4–ALK) translocation benefit from firstline treatment with erlotinib or crizotinib, respectively. These mutations are seen in a relatively small subset of NSCLC patients. They are common in patients with ADC, never smokers, and patients of East Asian origin. Kirsten rat sarcoma viral oncogene homolog (KRAS) is the most common mutation found in NSCLC; however, an effective targeted therapy for this subset of NSCLC does not exist. Despite the addition of new therapies, the median 5-year overall survival of patients in advanced staged disease remains a dismal 1%–2% (Aggarwal 2014).

Several researches indicate that long-term exposure to inhaled carcinogens has the greatest impact on risk of lung cancer. The predominant risk factor for lung cancer is smoking, accounting for approximately 90% of these lung cancer deaths (Azad et al. 2008; Shiels et al. 2013). Mostly, polyaromatic hydrocarbons (PAHs) and nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) are the major components of tobacco that are associated with the etiology of lung cancer (Azad et al. 2008). The lung is vulnerable to a wide range of toxicants and infectious agents with the potential to induce oxidative damage (Azad et al. 2008). An average adult inhales about 10,000 L of air per day, polluted with cigarrete smoke, automobile exhaust, diesel soot, ozone (O_3), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and varying degrees of other pollutants. Inhalation of such toxic air pollutants and microorganisms results in lung injury and generation of reactive oxygen species/reactive nitrogen species (ROS/RNS), leading to cascades of signaling events that trigger the production of proinflammatory cytokines and chemokines (Azad et al. 2008). Additionally, lung cancer risk is associated with several indicators of inflammation, including pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), and chronic pulmonary infections, even after taking the effects of smoking into consideration (Shiels et al. 2013). Overall, the pathogenesis of lung cancer involves multiple molecular abnormalities accrued over a long period. Although a large number of genetic pathways associated with lung cancer are being discovered, the basic molecular mechanisms involved in lung cancer are still unclear (Azad et al. 2008).

16.2 INFLAMMATION

Inflammation is a physiologic process in response to tissue damage resulting from microbial pathogen infection, chemical irritation, and/or wounding. At the very early stage of inflammation, neutrophils are the first cells to migrate to the inflammatory sites under the regulation of molecules, produced by rapidly responding macrophages and mast cells prestationed in tissues (Lu et al. 2006).

As the inflammation progresses, various types of leukocytes, lymphocytes, and other inflammatory cells are activated and attracted to the inflamed site by a signaling network involving a great number of growth factors, cytokines, and chemokines (Lu et al. 2006).

The most commonly recognized features of cancer-associated inflammation are also those expressed by innate immune system, normally activated in response to stress or infection. The observed chronic inflammation milieu in notable subsets of human cancers is proposed to support tumor growth, plasticity, and resistance to therapy (Grimm et al. 2013). Unluckily, dysregulated persistent inflammation contributes to the chronic phase of many diseases, including maintenance of many cancers. It is accepted that inflammation drives the development of some cancers that adapt to thrive in the oxidant-rich microenvironment as described initially by *co-opting* expression of inflammation mediators (Coussens and Werb 2002; de Visser et al. 2006).

The dynamic role of chronic inflammation in cancer is not novel. In 1863, Rudolf Virchow hypothesized that some irritants associated with tissue injury and resulting cellular inflammation may play a role in cell proliferation and neoplastic development (Balkwill and Mantovani 2001). Based on his observations that normal cellular responses might lead to cancer, he postulated that cancer may develop at sites of chronic inflammation (Balkwill and Mantovani 2001).

Over recent years, several research in this area clearly demonstrated that cell proliferation alone does not produce cancer. However, unlimited proliferation potential of cells is achieved in an environment that is rich in inflammatory cells, producing abundant ROS and RNS promoting unremitting DNA damage, inactivation of apoptosis, upregulation of growth factors and cytokines, and activation of growth-supporting genes (Azad et al. 2008). In recent years, increased understanding of the basic mechanisms involved in inflammation and its physiological systems supported Virchow's hypothesis, establishing an important relationship between cancer and inflammation (Azad et al. 2008).

Inflammation is the primary reaction of a tissue to eliminate pathogenic insult and injured tissue components in order to restore normal physiological functions or replace the irreparable tissue with scar tissue (Azad et al. 2008). The inflammation process is a complex response to stimuli involving the interplay between host cells and signaling molecules, such as proinflammatory and anti-inflammatory cytokines, growth and angiogenesis factors, and chemokines (Shiels et al. 2013).

Inflammation is classified as acute or chronic inflammation, depending on a variety of factors including clinical symptoms and the nature of injury. Acute inflammation is the immediate response, usually of short duration, and results in the release of polymorphonuclear leukocytes (PMNs) so as to eliminate the pathogenic or cytotoxic insult. On the other hand, chronic inflammation is characterized by persistent inflammation, tissue injury, and tissue repair, occurring simultaneously (Azad et al. 2008).

Chronic inflammation induced by various agents including viruses and bacteria is associated with an increased cancer risk due to tissue damage and genetic instability (Linhart et al. 2014). Thereby, repeated tissue damage and regeneration produce increased ROS/RNS from inflammatory cells and then interact with DNA in proliferating epithelium, resulting in permanent genomic alteration such as point mutations, deletions, or rearrangements (Coussens and Werb 2002). Cells respond to DNA damage by activating p53-controlled genes associated with cell cycle and DNA repair, and when the rate of ROS/RNS-mediated DNA damage is extensive, it leads to chronic inflammation (Azad et al. 2008). Chronic inflammation provides a microenvironment rich in inflammatory cells, ROS/RNS, recurring DNA damage, cell-proliferating growth factors, and other growth-supporting stimuli, which increases the frequency of mutations. In pulmonary pathologies such as COPD, fibrosis, and lung carcinogenesis, inflammation is considered as a major precursor or the *hallmark* for cancer development (Azad et al. 2008; Hanahan and Weinberg 2011).

By upregulating key inflammatory molecules, including inducible nitric oxide synthetase (iNOS), cyclooxygenase (COX2), and proinflammatory cytokines and chemokines, tumor cells invoke a chronic inflammatory state that also induces tumor-supporting myeloid cells such as

tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) and drives their infiltration of the tumor microenvironment (TME) (Grimm et al. 2013). While many host cell types including T cells are involved in creating an inflammatory pro-TME, inflammation-directed recruitment of MDSC and macrophage polarization are also important (Grimm et al. 2013).

Actually, tumors are considered as complex tissues with a dynamic and reactive TME. The TME is populated by different nonplastic cells (inflammatory leukocytes, activated fibroblast, and endothelial cells) that actively communicate with cancer cells via chemokines or cytokines (D'Incalci et al. 2014). Recently, it is established that the persistence of inflammatory pathways in the TME is linked with tumor promotion (Diakos et al. 2014; D'Incalci et al. 2014). Among stromal cells, TAMs derived from blood circulating monocytes can functionally be *educated* by tumor cells, through the activity of different cell types of the TME. These cells can promote basically all phases of tumorigenesis and tumor progression, including tumor cell proliferation, invasion, angiogenesis, metastasis formation, and immune suppression (Allavena and Mantovani 2012; Reinartz et al. 2014). Indeed, TAMs play a major role in the production of growth factors (epidermal growth factor, chemokines, interleukins, metalloproteinase, and vascular endothelial growth factor), which promote tumor cell survival and metastatic phenotype (Galmarini et al. 2014).

16.2.1 Inflammation, Oxidative Stress, and DNA Damage

ROS additionally are involved in regulating certain normal cellular processes. When excessive ROS stimulation occurs, it may trigger DNA repair responses in normal cells to remove ROS-mediated DNA damage. For highly active metabolism, cancer cells commonly have higher levels of ROS than normal cells, leading to carcinogenesis by oxidative DNA damage and DNA repair impairment. This nature of high ROS level in cancer cells also provides an opportunity for drug therapy to generate overloading ROS level and induce oxidative stress–induced cell death (Farooqi et al. 2014).

Oxidative stress is an important mechanism in the pathogenesis of many diseases including cancer. The generation of ROS with a consecutive DNA damage is an initial step in carcinogenesis induced by inflammatory processes (Aggarwal 2014). Chronic inflammation induced by various agents including viruses and bacteria is associated with an increased cancer risk due to tissue damage and genetic instability. Oxidative stress with the generation of ROS may occur in chronic infection and inflammation primarily due to the generation of nitric oxide (NO), superoxide anion ($O2^{-\bullet}$), and other ROS by macrophages and neutrophils that infiltrate the inflamed tissue (Aggarwal 2014). Activated inflammatory cells in various tissues including the liver in turn induce oxidant-generating enzymes such as NADPH oxidase, iNOS, xanthine oxidase (XO), and myeloperoxidase (MPO). In such conditions, ROS and RNS are generated. As a consequence, ROS and RNS can damage DNA, RNA, lipids, and proteins through nitration and oxidation, resulting in an increased mutation load (Aggarwal 2014). Furthermore, cytokines are released in inflammatory tissues, which activate not only the aforementioned enzymes to create ROS and RNS but also NF-κB, a nuclear transcription factor, which among others stimulates COX2, lipoxygenase (LOX), and iNOS, and upregulating these molecules (COX2, LOX, and iNOS) results in an overproduction of ROS and RNS (Aggarwal 2014).

Another process that can influence tumor progression by ROS formation is autophagy (Farooqi et al. 2014). This is a multistep process that maintains cellular homeostasis via the degradation and recycling of long-lived proteins, intracellular aggregates, and damaged organelles (Coussens and Werb 2002). The autophagy may be induced for survival and induction of apoptotic pathways in response to cellular oxidative stress (Farooqi et al. 2014). Recent studies have described a complex role of the autophagy pathway during tumor initiation. On one hand, autophagy protects against the production of ROS in the cells and therefore inhibits their deleterious effect on DNA damage and resulting mutation, which have been extensively described to induce tumorigenesis, defined as the transformation of a normal cell into a cancer cell (de Visser et al. 2006). Autophagy is also described as a tumor suppressor mechanism mainly by preventing ROS accumulation through the

elimination of damaged mitochondria that are known to be the major source of ROS production (Coussens and Werb 2002). During in vivo tumor formation, autophagy has been shown to play a major role for the cancer cells to survive under hypoxic stress before the vascularization of the tumor occurs (Coussens and Werb 2002). However, the mechanism is still unclear although several studies suggest a role of autophagy in the regulation of cancer cell metabolism allowing them to meet requirements for rapid proliferation (Coussens and Werb 2002).

High levels of autophagy are indeed observed in hypoxic regions of tumors, and autophagy has been described to be activated by hypoxia and ischemia (glucose deprivation and hypoxia) to promote the survival of cancer cells. Hypoxia induces ROS production leading to the stabilization of hypoxia-inducible factor 1-α (HIF-1α). This factor, a key regulator of oxygen homeostasis, induces mitophagy through the expression of Bcl-2/adenovirus E1B 19-kDa-interacting protein 3 (BNIP3), allowing the cells to survive during prolonged hypoxia by preventing increased levels of ROS production (Balkwill and Mantovani 2001). On the other hand, tumor progression and aggressiveness are characterized by metastasis, epithelial–mesenchymal transition (EMT), and angiogenesis.

Metastasis is a multistep process that allows cancer cells to migrate to distant organ sites (Linhart et al. 2014). EMT is the first step of metastasis and is characterized by the loss of epithelial properties and the acquirement of mesenchymal properties leading to increased cell mobility. Several studies have described a prometastasis role of autophagy. For example, inhibition of autophagy by FIP200 deletion leads to a decrease in metastatic potential associated with an accumulation of damaged mitochondria, which could lead to increased level of ROS. Moreover, increased autophagy in human cancer is associated with metastasis and poor prognosis in patients with melanoma and breast cancer (Coussens and Werb 2002).

16.2.2 Role of Inflammation in Lung Cancer

Inflammation is recognized both as a condition that can lead to cancer development and as a condition that can arise due to oncogenic changes in cancer cells (Jafri et al. 2013). The hallmarks of cancer are distinctive and complementary capabilities that enable tumor growth and metastatic dissemination sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis (Hanahan and Weinberg 2011). Inflammation has been described as the underlying or enabling characteristic that promotes these hallmarks of cancer (Hanahan and Weinberg 2011).

Cancer and inflammation are closely linked, and many inflammatory conditions increase the risk of cancer development (Jafri et al. 2013). In the NSCLC microenvironment, there is a complex interaction between immune cells and tumor cells as well as other stromal cell types and tissue components. The distribution of these cells and the expression of different inflammatory molecules throughout the TME are to some extents related to tumor progression and survival (Gomes et al. 2014).

The concept of tumor heterogeneity applies not only to tumor epithelial cells but also to the diverse microenvironment with the tumor cells' interaction. Carcinoma cells, in the lung (and others), are closely associated with the extracellular matrix (ECM) and mesenchymal cells such as fibroblasts, infiltrating immune cells, and vasculature (Chen et al. 2014).

Lung tumors develop through a complex process involving many stages such as initiation, promotion, and progression (Hanahan and Weinberg 2011). In lung tumorigenesis, the genesis of new blood and lymphatic vessels supplies necessary nutrients for tumor growth and allows for an influx of immune cells of the myeloid and lymphoid lineages (Chen et al. 2014). In the lung, depending on the type of inflammation, there may be direct effects such as DNA damage, mutation, or an indirect effect or induced effect, induced by activated enzymes such as cytochrome P-450 oxidase or flavin monoxides that produce ROS in the cells, resulting in protein and DNA damage (Azad et al. 2008). The second stage in cancer development is the promotion, which involves clonal expansion of the initiated cells. These initiated cells may undergo promotion under persistent oxidative

stress conditions, forming focal lesions from which invasive cancers may originate. Progression is the final stage involving the formation of fully malignant cells from an early neoplastic clone via both genetic and epigenetic mechanisms (Azad et al. 2008). Tumor cells undergo autonomous uncontrolled proliferation with the aid of suitable promoting factors such as EGFR. This factor, a transmembrane receptor with intrinsic tyrosine kinase activity, triggers many transcription factors and is activated in lung tumors (Azad et al. 2008). A very important fact of cancer initiation and progression is genome instability. It was reported that the lack of mismatch in DNA at certain nucleotide level may lead to microsatellite instability in many forms of lung cancers (Massion and Carbone 2003). Despite this endogenous sources of inflammation-induced oxidative stress, exogenous sources such as hyperoxia, radiation, exposure to particulates, and chemical carcinogens are also critical in lung carcinogenesis (Azad et al. 2008). ROS/RNS produced by inflammatory cells also stimulate oncogenes such as c-Jun and c-Fos, and the overexpression of c-Jun was reported to be associated with lung cancer (Azad et al. 2008).

In lung cancers associated with nondestructive agents, such as asbestos and silica, the chronic inflammation in the lung is persistent because of the inability of the immune system to remove these substances. Many of these agents are reported to modulate and activate various transcription factors, producing changes in cell proliferation, differentiation, apoptosis, and inflammation (Azad et al. 2008). Such inflammatory responses increase the incidence of epithelial cancers, including mesothelioma and lung cancer. Cigarrete smoke is a complex preneoplastic agent that may act, in part, by inducing a chronic inflammatory condition by delivering an array of genotoxic carcinogens such as nitrosamines, peroxides, and many potent oxidants into the lungs (Azad et al. 2008). Therefore, inflammatory cells influence the whole organ in tumor development, regulating the growth, migration, and differentiation of all cell types, including neoplastic cells, fibroblasts, and endothelial cells (Azad et al. 2008). Tumors can evade immune surveillance by expressing molecules that maintain tolerance to normal peripheral tissues, including the interaction of the tumor-associated programmed cell death-1 ligand 1 (PDL1) with the immune receptor programmed cell death-1 (PD1, also known as PDCD1). PDL1 is a distal modulator of the immune response whose expression occurs in 40%–50% of NSCLC patients (Guibert et al. 2015). Recently, the use of antibodies targeting the PD1-PDL1 checkpoint has resulted in some marked responses in early-stage clinical trial for a large panel of therapy refractory cancer subtypes, including advanced melanoma, NSCLC, and renal cell cancer, with a proportion of responding patients showing persistent long-term benefit (Chen et al. 2014; Guibert et al. 2015).

16.2.3 MMPs, Lung Cancer, and Inflammation

In inflammation, matrix metalloproteins (MMPs) recruit inflammatory cells during tissue injury, which involves a series of complex morphological changes in cell barrier, cell–cell interaction, and cell–matrix interaction. MMPs also exhibit a wide functional diversity in modulating NSCLC due to their interaction with growth factor receptors, cytokines, chemokines, cell adhesion molecules, apoptotic ligands, and angiogenic factors. MMPs are involved at all junctures of inflammation as well as tumor progression, including proliferation, adhesion, migration, angiogenesis, senescence, apoptosis, cytokine and chemokine bioactivity, and evasion of the immune system (Lopez-Otin and Bond 2008). In lung cancer, the expression of a number of MMPs and their inhibitors is exaggerated and may be causally linked to enhanced tumor progression and metastasis (Sorokin 2010).

MMPs were primarily thought solely to be involved in homeostasis and turnover of the ECM, but recent observations provide evidence suggesting that MMPs act on cytokines, chemokines, and protein mediators to regulate various aspects of inflammation and immunity (Parks et al. 2004). Cancer-associated EMT is known to contribute to tumor progression, increased invasiveness and metastasis, resistance to therapies, and generation of cell populations with stem cell–like characteristics and has been implicated in progression and metastasis of cancer specifically.

EMT is characterized by the loss of cell–cell junctions, polarity, and epithelial markers, and in turn, acquisition of mesenchymal features and motility. Changes associated with this developmental process have been extensively implicated in cancer progression and metastasis. MMP-3 induces EMT associated with malignant transformation via a pathway dependent upon the production of ROS. While the process by which exposure to MMP-3 leads to induction of ROS has been extensively studied, exactly how the MMP-3-induced ROS stimulate EMT remains unknown (Cichon and Radisky 2014).

MMPs have been speculated to play a critical role in various inflammatory diseases, such as acute lung injury, COPD, and cancer. They can regulate the integrity of physical barriers and transmigration of leukocytes from vasculature to tissue. They also regulate the availability and activity of inflammatory mediators, such as cytokines and chemokines. MMPs also generate chemokine gradients in tissue to recruit inflammatory cells to the site of injury or inflammation and can also regulate the survival of inflammatory cells (Parks et al. 2004; Nissinen and Kahari 2014). Immune system plays an important role in cancer cell surveillance by recognizing and attacking cancer cells *in vivo*. However, cancer cells can escape the immune attack in various ways. On the other hand, chronic inflammation is associated with the progression of several types of cancer (Nissinen and Kahari 2014). Inflammation is necessary to promote cancer initiation and progression via vascularization and remodeling of TME, which are important for tumor cell survival. MMPs may also exert immune regulatory function in TME, and they may also help cancer cells escape immunosurveillance (Nissinen and Kahari 2014). Recent findings indicate that MMPs play an important role in the regulation of cytokine and chemokine release and their activation, which are key steps in the immune response (Sorokin 2010). For example, MMP-1, -2, -3, -7, -9, and -12 are able to process pro–tumor necrosis factor-α (TNF-α) into soluble active TNF-α. MMP-2, -3, and -9 also have the ability to cleave IL-1β, generating a more active form. MMP-9 controls the IL-12-dependent proliferation of T lymphocytes. MMP-8, -13, and -14 can cleave IL-8 to generate truncated forms with increased activity. Therefore, inflammatory cytokines and MMPs are interconnected (Sorokin 2010).

The role of MMPs in cancer progression has been extensively studied in various animal models. In addition to tumor cells, stromal cells play an important role in cancer progression, for example, by producing MMPs (Nissinen and Kahari 2014). The association between MMPs and inflammation in cancer progression has also been emphasized. A good example of this association is that the transplantation of wild-type mouse MMP-9 expression bone marrow cells to MMP-9-deficient mice effectively restores the development of cutaneous SCC (Nissinen and Kahari 2014). Cancer progression is regulated by growth factors, chemokines, and cytokines either directly via their angiogenic or angiostatic activity or indirectly by attracting anti- or precancerous inflammatory cells. As discussed earlier, several studies have revealed the proteolytic activation or inhibition of growth factors, cytokines, and chemokines by various MMPs (Nissinen and Kahari 2014).

MMPs are clearly important effectors in inflammation both in physiological situations, such as tissue repair, and in pathological inflammatory conditions and cancer. The association of MMPs with cancer has obviously suggested them as potential therapeutic target (Nissinen and Kahari 2014).

16.3 CONCLUSION

Inflammation can affect every hallmark of tumor development and prognosis as well as the response to therapy. In the NSCLC microenvironment, there is a complex interaction between immune cells and tumor cells as well as other stromal cell types and tissue components. The production of ROS/RNS is critical for normal aerobic metabolism and functioning of several events essential for the organism. Overpowered generation of ROS/RNS is likely to induce chronic inflammatory conditions that may lead to several deleterious effects in the cells. The increased levels of ROS are extensively involved in the mechanisms of chronic lung inflammation and thus contribute

to the development of lung cancer. A better understanding of the role of ROS/RNS in lung inflammation and cancer is probable to inspire new strategies for lung cancer prevention and treatment.

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