CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) AND LUNG CANCER: IS THE INFLAMMASOME AT THE CROSS-TALK?

C. Colarusso

Department of Pharmacy (DIFARMA), University of Salerno, Fisciano, Salerno, Italy

E-mail: ccolarusso@unisa.it

SUMMARY

COPD and lung cancer (herein, non-small cell lung cancer, NSCLC) are worldwide health concerns. Epidemiological evidence highlight that COPD patients are 6.35 times more likely to develop lung cancer compared to the normal population, supporting the concept that COPD is one of the driving factors of lung cancer establishment. Because these two diseases share common etiological insults, *i.e.* cigarette smoke (CS) and environmental pollution, and common threatening lung-associated chronic inflammation, the main goal of this review is to describe what so-far identified as molecular/cellular mechanism/s that link COPD to lung cancer. Our data support the role of the inflammasome in both COPD and lung cancer establishment. In particular, we found that absent in melanoma 2 (AIM2) inflammasome paves the way for chronic inflammatory conditions at the basis of both COPD and NSCLC, standing at the crossroad for lung carcinogenesis. We believe that tracking down pathways and molecular interactions related to the inflammasome could open new prospective for therapeutic strategies for both COPD and NSCLC.

Key words
COPD; lung cancer; inflammasome; air pollution; cigarette smoke.

Impact statement
Four out of ten COPD patients develop NSCLC, implying that COPD-related inflammatory patterns can pave the way for lung cancer, which represents the first-in-class tumor-derived death. We found that AIM2 inflammasome is highly expressed in smoker subjects who develop COPD leading to NSCLC, opening new perspective for a potential therapeutic target.

Acronyms, abbreviations, units of measurements
COPD: Chronic obstructive pulmonary disease; NSCLC: non-small cell lung cancer; CS: cigarette smoke; ASC: apoptosis-associated speck-like protein; NLRP3: nucleotide-binding domain-like receptor protein 3; PAMPs: pathogen-associated molecular patterns; DAMPs: damage-associated molecular patterns; ROS: reactive oxygen species; PM: particulate matter; CANTOS: Canakinumab Anti-inflammatory Thrombosis Outcomes Study; SCLC: small cell lung cancer; EMT: epithelial to mesenchymal transition; MMP9: matrix metalloproteinase 9; pDCs: plasmacytoid dendritic cells; PBMCs: peripheral blood mononuclear cells; IARC: International Agency for Research on Cancer; MDSCs: myeloid-derived suppressor cells; HMGB1: high mobility group box 1 protein; TLRs: Toll-like receptors; BAL: broncho-alveolar lavage; AIM2: absent in melanoma 2.

edra

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) causes progressive and irreversible decline of lung function. Nowadays it is considered as a risk factor for non-small cell lung cancer (NSCLC) establishment (1). Epidemiological studies indicate that the incidence of NSCLC among COPD patients ranges from 40 up to 70% (2). Based on the fact that COPD and NS-CLC share common etiological insults, such as cigarette smoke (CS) and environmental pollutant exposure, and common threatening lung-associated chronic inflammation, studying molecular mechanisms that could underlie the development of lung cancer in COPD patients could pave the way for a new scientific window to improve therapeutical strategies.

The impact of chronic inflammation in both diseases is widely described and further proved by the detection of pro-inflammatory cytokines and immune infiltrates in samples collected from COPD and lung cancer patients. In particular, IL-1 like cytokines, which expression is tightly regulated by the multiprotein complex referred to as "inflammasome", are highly present in biological samples obtained from COPD patients (3), and are detected in the plasma and tissues of lung cancer patients (4). The inflammasome is a multimeric complex which comprises an upstream receptor, that once triggered by its ligand, assembles to an adaptor protein (ASC, apoptosis-associated speck-like protein) which leads to the binding and then to the auto-cleavage of caspase-1, responsible for IL-1-like cytokines activation and release. An alternative, non-canonical pathway, of the inflammasome involves caspase-11 that acts upstream of caspase-1 (5). The most characterized inflammasome is NLRP3 (nucleotide-binding domain-like receptor protein 3) which is activated, exogenously and/or endogenously, by various pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), reactive oxygen species (ROS), potassium efflux, changes in cell volume, calcium signaling, and lysosomal disruption (**figure 1**) (5).

The genetic ablation and pharmacological inhibition of caspase-1 in experimental mouse models of CS and particulate matter (PM) exposure prevented the release of inflammasome-dependent cytokines (IL-1α, IL-1β, IL-33, IL-18) (6), suggesting that the inflammasome may be involved in COPD pathogenesis after (7, 8). On the other side, several preclinical (9-12) and clinical studies identified the inflammasome as pro-carcinogenic. Several studies have focused on the pro-carcinogenic activity of NLRP3 (5). It was found that NLRP3 polymorphism is associated to higher susceptibility to melanoma (5), and to lower survival rate for colorectal cancer (13) and myeloma (14) patients. Moreover, altered NLRP3 and/or NLRP1 expression/activity is correlated to high serum and tissue levels of IL-1β and IL-18 which are as bad prognostic biomarkers in cancer patients (15). Although $Casp1^{-/-}Casp-11^{129mt/129mt}$ mice showed enhanced tumorigenesis during colitis-associated cancer development (16-18), the absence of caspase-1/-11 significantly reduced the establishment of lung adenocarcinoma (9, 12). In support, data from CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study, phase III) trial demonstrated that the neutralization of IL-1β by means of canakinumab, a monoclonal antibody that selectively blocks IL-1β, prevented lung cancer incidence and lung cancer-associated mortality in atherosclerosis patients (19). Moreover, two ongoing Phase III clinical trials launched by Novartis pharmaceuticals (CANOPY-1 and CANOPY-2) are currently investigating pembrolizumab plus chemotherapy with or without canakinumab, or docetaxel with canakinumab in NSCLC (ClinicalTrials.gov Identifier: NCT03626545, NCT03631199) (https://clinicaltrials.gov/ct2/show/NCT03626545; https://clinicaltrials.gov/ct2/show/NCT03631199), further underlying the relevance of the inflammasome in lung cancer.

Nevertheless, many controversies are still present in literature about the role of this complex in both COPD and lung cancer establishment. The scope of this review is to highlight the *yin*
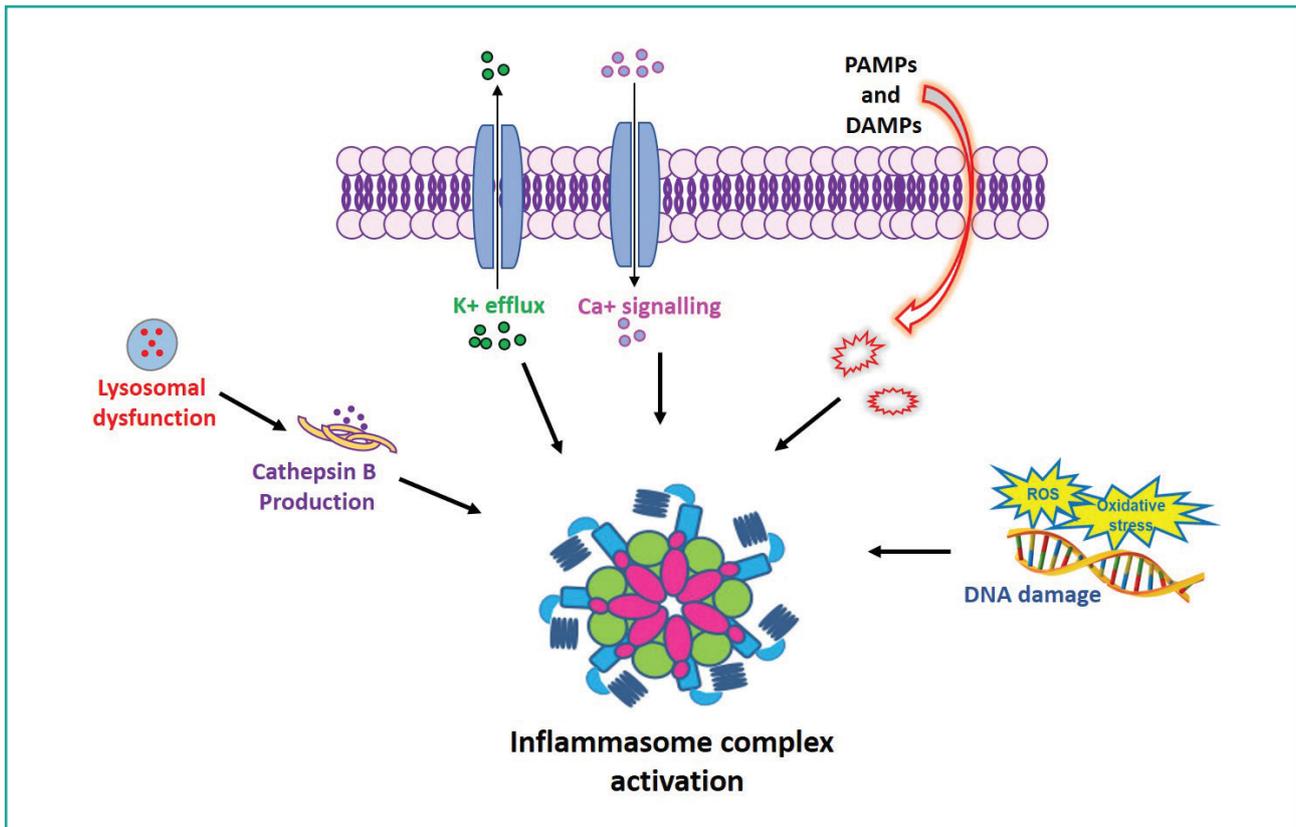
Figure 1. Signals for inflammasome activation.
It is postulated that two signals are required for the canonical activation of the inflammasome. The first signal for inflammasome activation in involves the recognition of PAMPs or DAMPs by specific pattern recognition receptors (PRR). The second signal leads to the assembly of the components into the inflammasome structure and provides the intracellular recognition of DAMPs or PAMPs. Inflammasome is turned on by ROS production and the release of mitochondrial DNA in oxidized form, potassium (K+) efflux, alterations in calcium (Ca+) concentration, change in cell volume and lysosome-mediated cathepsin B release.

and yang of the inflammasome involvement in the establishment of NSCLC starting by COPD, a pathological condition that in most cases establishes after cigarette exposure.

COPD AND LUNG CANCER: TWO LINKED DISEASES?

COPD is currently the fourth-leading causes of death worldwide after cancer, heart disease and stroke, and it is estimated to become the third leading cause of death in the world by 2030 as predicted by World Health Organization (https://www.who.int/gard/news_events/World_Health_Statistics_2008/en/). COPD leads to progressive and irreversible decline of lung function (20) and is characterized by cough,

shortness of breath, mucus hypersecretion, chronic bronchitis, airway remodeling, emphysema and airway limitation due to alveolar abnormalities (3).

Lung cancer is the most common solid tumor, accounting for an estimated 2.09 million of cases in 2018 and the leading cause of cancer-related death worldwide (cancer.org/cancer/non-small-cell-lung-cancer/about/key-statistics.html). Lung cancers are broadly classified into 3 major types: NSCLC, small cell lung cancer (SCLC) and lung carcinoid tumor. In particular, NSCLC is the most frequent (about 85% of cases) classified into three major histopathological subtypes: squamous cell carcinoma, adenocarcinoma and large cell carcinoma; SCLC and lung carcinoid tumor, that

represent, respectively, about 10-15% and fewer than 5% cases of lung cancer.

COPD and NSCLC may represent two sides of the same coin: cigarette exposure (21). The relationship between COPD and NSCLC has been studied since 1986 when Skillrud and colleagues demonstrated that lung cancer incidence increased in individuals with COPD and was correlated to decrease in respiratory airflow and chronic inflammation in these patients (22). Since then, a huge number of epidemiological studies were performed. A recent meta-analysis has showed that the prevalence of lung cancer in COPD is greater than in other patient population, and that COPD patients are 6.35 times more likely to

develop lung cancer compared to the normal population (23). Although, conflicting results over the time have not been able to define any crosstalk between the two pathologies, several mechanisms were associated to both COPD and lung cancer such us DNA damage caused by aging and/or telomere shortening, familial predisposition, genetic and epigenetic alterations, epithelial to mesenchymal transition (EMT), chronic inflammation and oxidative stress (1) (**figure 2**).

To date, tobacco smoke and air pollution represent the main risk factors for COPD and NSCLC (who.int/gard/publications/Risk%20factors.pdf). Every year tobacco kills 8 million of people, among which 1 million of deaths
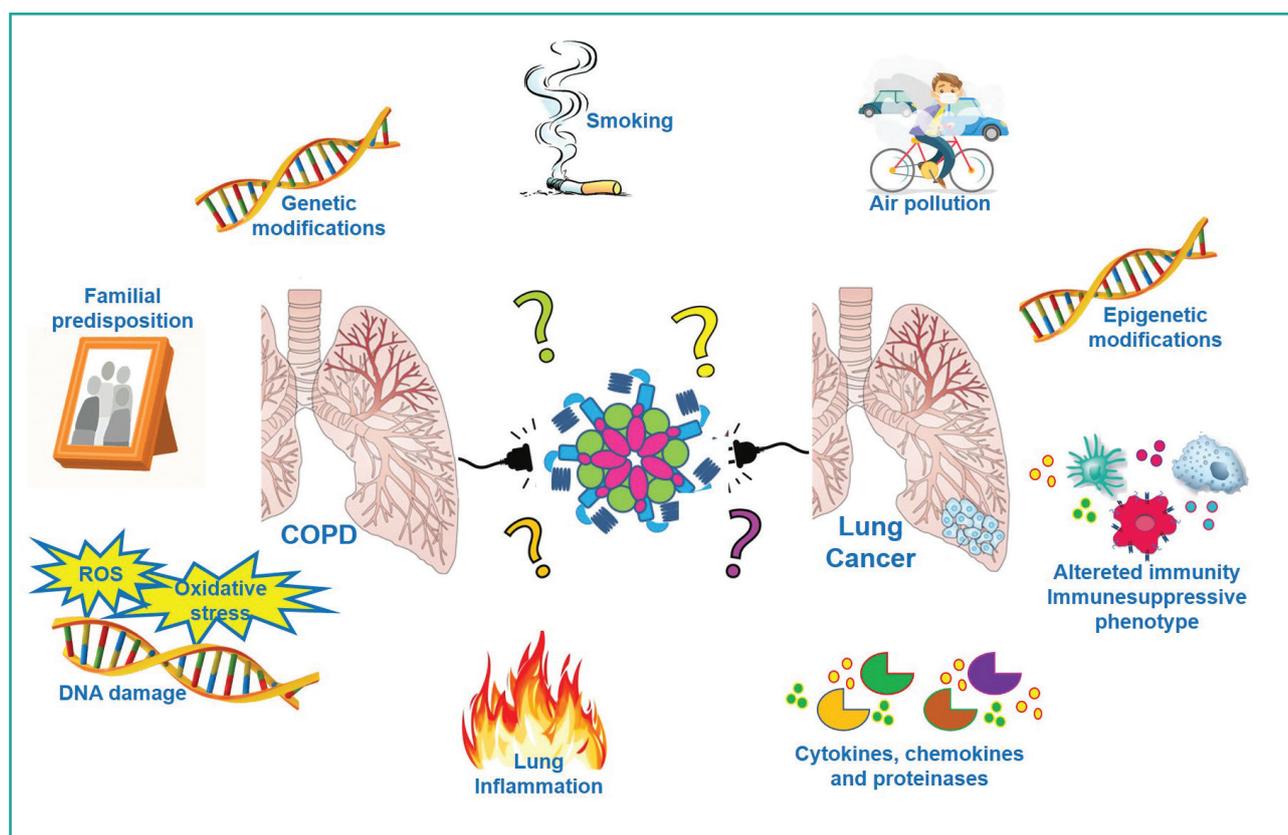

Figure 2. Putative mechanisms at the interface between COPD and Lung Cancer.
COPD and lung cancer share smoke and air pollution exposure, which are strongly associated to oxidative stress and chronic lung inflammation. Although familial predisposition is involved, both COPD and lung cancer are correlated to genetic and epigenetic alterations, DNA damage, and following recruitment of immunesuppressive immune cells and pro-inflammatory mediators (cytokines, chemokines, proteinases) leading to lung structural damage and functional impairment. Based on the concept that the inflammasome may play a critical role in COPD onset and lung cancer establishment, the activation of this multimeric complex may be at the crosstalk between COPD and lung carcinogenesis.

among COPD patients and 0.85 million of subjects affected by lung cancer (24). So far, it is known that both cigarette smoking and air pollution alter the physiological cellular oxidative state, the epigenetic and genomic signature (25, 26), which have been found in tissues of lung cancer patients (27); Moreover, both PM and CS induce epithelial inflammation via oxidative stress induction and release of pro-inflammatory mediators (28). In response to toxic particles derived by CS and air pollution the respiratory tract releases chemoattractant mediators and proteases, such as matrix metalloproteinase 9 (MMP9) (29), which induce the recruitment of neutrophils, monocytes and T cells. The recruitment of monocytes in inflamed tissues turns them into macrophages, that in both COPD and NSCLC are in their M2 phenotype, which is correlated to an immunosuppressive environment, that in NSCLC is associated to poor survival rate (30) and in COPD to an increased severity of the disease (31). Therefore, it is likely to speculate that macrophage polarization in COPD could play a pro-tumorigenic role, favoring the onset of lung cancer. In this regard, we found that M2 cells and plasmacytoid dendritic cells (pDCs) populated lung tumor masses which were induced to proliferate in an IL-1α and IL-1β-dependent manner (9, 10). Similarly, we found that smoker-derived or COPD-derived peripheral blood mononuclear cells (PBMCs) released IL-1-like cytokines in a canonical (caspase-1) and non-canonical (caspase-4) inflammasome dependent manner (7, 32). These data well correlated to the immunosuppressive environment in both experimental conditions, strengthening the hypothesis that the inflammasome is involved in both COPD and lung cancer following chronic carcinogen (CS- or PM-derived) exposure. In support, our research group and others (3) demonstrated that both the underlying inflammasome-dependent IL-1-like cytokines and caspase-1 and caspase-11 (caspase-4 in humans) are involved in lung cancer establishment (9-11).

CROSSTALK BETWEEN COPD AND LUNG CANCER: INSIGHTS INTO AIR POLLUTION- AND TOBACCO SMOKE-INDUCED INFLAMMASOME ACTIVATION

In the following paragraphs we will focus on air pollution and tobacco smoke as inflammasome triggers at the basis of lung cancer establishment in COPD condition.

Air pollution as inflammasome activator in COPD and lung cancer

The association between noxious particles in the air and the activation of the inflammasome was firstly found by Li *et al.*, 2016 (30). The authors found that the exposure to biomass fuel smoke led to the release of DAMPs and the following activation of NLRP3 inflammasome and caspase-1 (33). In our lab we demonstrated that PBMCs obtained by healthy smoker subjects and treated with ultrafine particles derived from combustion processes typical of modern engines (80-120 nm diameter particles), were more susceptible to IL-1-like cytokines release in a canonical, caspase-1-dependent, NLRP3 inflammasome (7). Instead, PBMCs from non-smokers had an immunesuppressive behavior (7). According to the sterile inflammation theory, sterile and non-infectious exogenous insults can induce chronic inflammation (5). Therefore, it is possible to speculate that the immune system recognizes combustion-derived particles and other noxious pollutants in the air as dangerous stimuli, which in turn may be sensed by the inflammasome amplifying the inflammatory pattern (34) (**figure 3**). Because inflammation plays a key role in cancer establishment and air pollution was defined by the International Agency for Research on Cancer (IARC) as a cancer-causing agent (28), based on these latter results, we could hypothesize that smoker subjects, a high-risk population, exposed to ultrafine particles may be more susceptible to the inflammatory processes involved in lung cancer development than non-smokers. It has to be pointed out though, that the precise mechanism/s involved

edra

in the pulmonary effects of air pollution are still not clear, and the role of the inflammasome in the establishment and progression of COPD is not fully known due to controversial data in literature (3). However, based on the strict relationship between air pollution and the pathogenesis of COPD, it is possible to speculate that the oxidative stress induced by exposure to noxious particles in the air mediates inflammatory pathways which may trigger activation/alteration of immune cells functions and may lead to the inflammasome activation in COPD conditions. Indeed, while several clinical studies have demonstrated that the levels of IL-1-like cytokines are elevated in the lungs of patients with COPD (8), Di Stefano et al found no correlation between NLRP3, caspase-1, and IL-1β responses when comparing a cohort of stable COPD patients to healthy smoker subjects (35), but the same authors suggested a key role of the inflammasome in the exacerbated stage of COPD (34). In accordance to this latter study, we found that that the exposure to very small pollutant air-derived particles (2-40 nm diameter) induced the release of IL-1-like cytokines (IL-18 and IL-33) from the sole exacerbated COPD-derived circulating cells (36). Indeed, PBMCs isolated from stable COPD patients, who are patients receiving corticosteroids after an exacerbation event, were not responsive/reactive against combustion-generated particles. These data could explain the inefficacy of Canakinumab and other drugs targeting inflammasome-related effectors in clinical trial on stable COPD patients (3) in that corticosteroid-based therapy should be able to inhibit inflammasome components and effectors (37). However, we found that neither the canonical, caspase-1-, nor the non-canonical, caspase-8-dependent, NLRP3 inflammasome pathways were involved in the inflammatory response typical of exacerbated COPD patients. The exposure of unstable/exacerbated COPD-derived PBMCs to combustion-derived particles induced IL-18 and IL-33 release, which was not abrogated by the pharmacological inhibition of caspase-1, NLRP3

and caspase-8 (36). It is to point out that, besides their immunological activity, IL-18 and IL-33 released in response to air pollutants, play a critical role in lung structural cells (lung alveolar type II pneumocytes and bronchial epithelial cells) where they could influence the development of chronic airway inflammation and tissue remodeling (38, 39), events that could be at the basis of lung carcinogenesis.

Along with these data, which were limited to COPD-derived circulating cells, to better understand lung alteration/s during air pollutant exposure we took advantage of a mouse model (40). We found that the lung of mice exposed to noxious particles was characterized by an immunosuppressive environment, populated by Arginase I positive macrophages and myeloid-derived suppressor cells (MDSCs) (40), which are well-known to facilitate the tolerogenic arm of the adaptive immune system (10), making the lung more susceptible to latent chronic inflammation, which could pave the way for cancer. In the attempt to understand the role of the inflammasome, we found that the pharmacological inhibition of caspase-1 by means of Ac-YVAD did not alter M2 macrophages and MDSCs recruitment (40), leading to the postulation that the non-canonical inflammasome could be responsible for the IL-1-like cytokines released in the lung of air pollutant-exposed mice. In this regard, unpublished studies are ongoing.

Cigarette smoke as inflammasome activator in COPD and lung cancer

The activation of the inflammasome by CS could be explained by several mechanisms (3):

1. CS increases the levels of ATP, endogenous alarmin (3), which leads to NLRP3 activation via purine-receptor P2X7 binding, which allows potassium efflux increasing cytosolic calcium, responsible for NLRP3 activation (3);

2. CS increases ROS levels which, directly or indirectly can activate the inflammasome, especially NLRP3, leading to the secretion of high mobility group box 1 protein
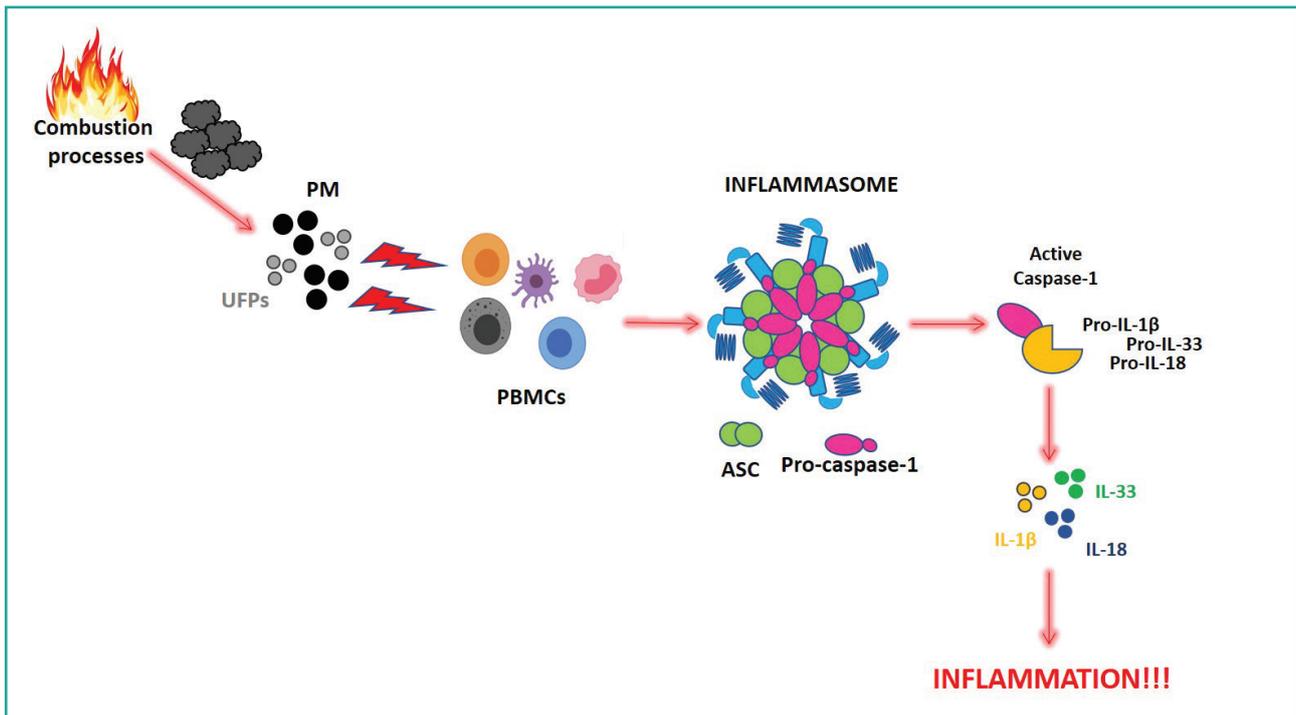
Figure 3. The recognition of ultrafine particles by the immune system could amply the inflammation through the inflammasome activation.
Combustion-derived ultrafine particles and other environmental pollutants (such as PM) could be recognized as dangerous stimuli by the immune system leading to the inflammasome activation which in turn boost the inflammation processes. Indeed, our data demonstrated that the exposure to combustion-derived ultrafine particles led to the release of pro-inflammatory IL-1-like cytokines from smoker subjects-derived PBMCs through the activation of the canonical, caspase-1-dependent, inflammasome pathway.

(HMGB1) that amplifies inflammasome-dependent response via Tool-like receptors (TLRs) signaling (3).

To note, most of the literature is exclusively focused on the role of NLRP3 inflammasome. In support, ATP is highly present in the broncho-alveolar lavage (BAL) fluid of patients with COPD compared to healthy subjects (3), and its concentration is associated to a decline of lung function (41). Moreover, NLRP3 is overexpressed in the lung of stable COPD patients rather than non-smoker and smoker subjects, implying an inverse correlation between NLRP3 mRNA and the severity of airflow obstruction (42). In contrast, the same authors found that NLRP3 is not responsible for caspase-1-dependent increase of IL-1β and IL-18 levels (42). We found that the stimulation of NLRP3 by means of LPS ± ATP did not induce neither non-smoker-, nor smoker-, nor-COPD-derived PBMCs to release IL-1-like cytokines (35), but high levels of IL-1β and IL-18 were found in the lungs of COPD patients after CS exposure (43, 44). These latter data imply that other inflammasome receptors could be involved. Indeed, for the first time to our knowledge, we demonstrated that absent in melanoma 2 (AIM2) inflammasome plays a key role in the exacerbation stage of COPD (32). AIM2 stimulation via Poly dA:dT led to the release of IL-1α in a canonical, caspase-1-dependent, and non-canonical, caspase-4-dependent manner, which in turn, was responsible for the release of the immunosuppressive and pro-fibrotic cytokine TGF-β (32, 45). In contrast to these data, Eltom *et al.*, 2014 reported that AIM2 inflammasome is not involved in IL-1α/caspase-1/11 axis in a CS-induced neutrophil inflammation in mice (46). However, this discrepancy prob-

ably stands on the difference between studies performed on humans and mice.

An important aspect deserving attention and that limits the study of the inflammasome in COPD and possible relationship with lung cancer is due firstly to the difficulties to obtain human samples from COPD patients at different status, exacerbated or stable disease, and realize an animal model that perfectly mimics what happens in humans during COPD exacerbation (47). Nowadays, the best methods to circumvent the difficulty to obtain lung samples from COPD patients, is to take advantage of a mouse model of CS-induced COPD or non-cancerous lung tissues from NSCLC patients undergoing surgical resection (3). In our laboratory, we demonstrated that smoke-exposed mice have emphysema-like features, bronchial tone impairment and release of IL-1-like cytokines (IL-1α, IL-1β, IL-33, IL-18) in a caspase-1 independent manner (48). Rather, a dysfunctional caspase-11 in 129Sv smoking mice, who lack a functional caspase-11, showed that both bronchial inflammation, collagen deposition and IL-1-like inflammation were significantly reduced (48). In addition, for the first time, we found that AIM2 inflammasome is involved in lung inflammation in smoking and COPD, in that its expression was higher in smoke-exposed C57Bl/6 compared to 129Sv smoking mice, who instead did not show any alteration of AIM2 in both macrophages and DCs. These latter data were of crucial importance to point at IL-1-like cytokines, caspase-11/-4 and AIM2 inflammasome as critical players in both COPD-derived PBMCs during the exacerbation stage of the disease and in a mouse model of COPD induced by smoke inhalation. Looking at the role of caspase-11, as well as of the human analogue of caspase-11, caspase-4, it has been already demonstrated as involved in lung inflammation (50, 51). In addition, caspase-4 was identified as a novel diagnostic tool to predict lung cancer establishment in that its levels are highly present in the blood samples collected from both smokers and COPD patients up to lung cancer patients (12, 51, 52). Although the poor data in literature regarding the role of AIM2 in cancer, it was demonstrated that its activation in tumor-associated pDCs leads to high IL-1α levels which favor lung tumor cell proliferation (10). In accordance to this latter study, the role of AIM2 in lung cancer was further supported by Zhang *et al.*, 2019 whose results revealed that AIM2 functioned as an oncogene in NSCLC in an inflammasome-dependent manner (53). Moreover, the inhibition of AIM2 in DCs was suggested as an innovative therapeutic tool for melanoma patients (54). However, we demonstrated that the expression of AIM2 in tumoral tissue from lung adenocarcinoma patients was affected by COPD and particularly by the smoking status, supporting our murine data (48). Indeed, according to the expression of AIM2, lung adenocarcinoma patients with COPD had lower survival rate than non-COPD adenocarcinoma patients.

CONCLUSIONS

The release of pro-inflammatory cytokines could result in lung structural damage and functional impairment (3), all events that link COPD to lung carcinogenesis. Data reported by the literature suggest that both air pollution and CS, two common risk factors for COPD and lung cancer (https://www.who.int/gard/publications/Risk%20factors.pdf), can lead to the activation of the inflammasome complex in both circulating cells and structural cells. Although data in literature are still discordant, our studies demonstrated that air pollution and CS stimulate the canonical, caspase-1-dependent, inflammasome pathway in circulating cells, but induce the activation of the non-canonical, caspase-1-independent, caspase-11/4-dependent inflammasome pathway in structural cells (**figure 4**) (7, 32, 36, 40, 48). On the other side, we found that AIM2 is highly expressed in the lung of both COPD and lung adenocarcinoma patients (458). Therefore, it is plausible to speculate that AIM2 is at the crossroad between COPD and lung cancer. Further studies
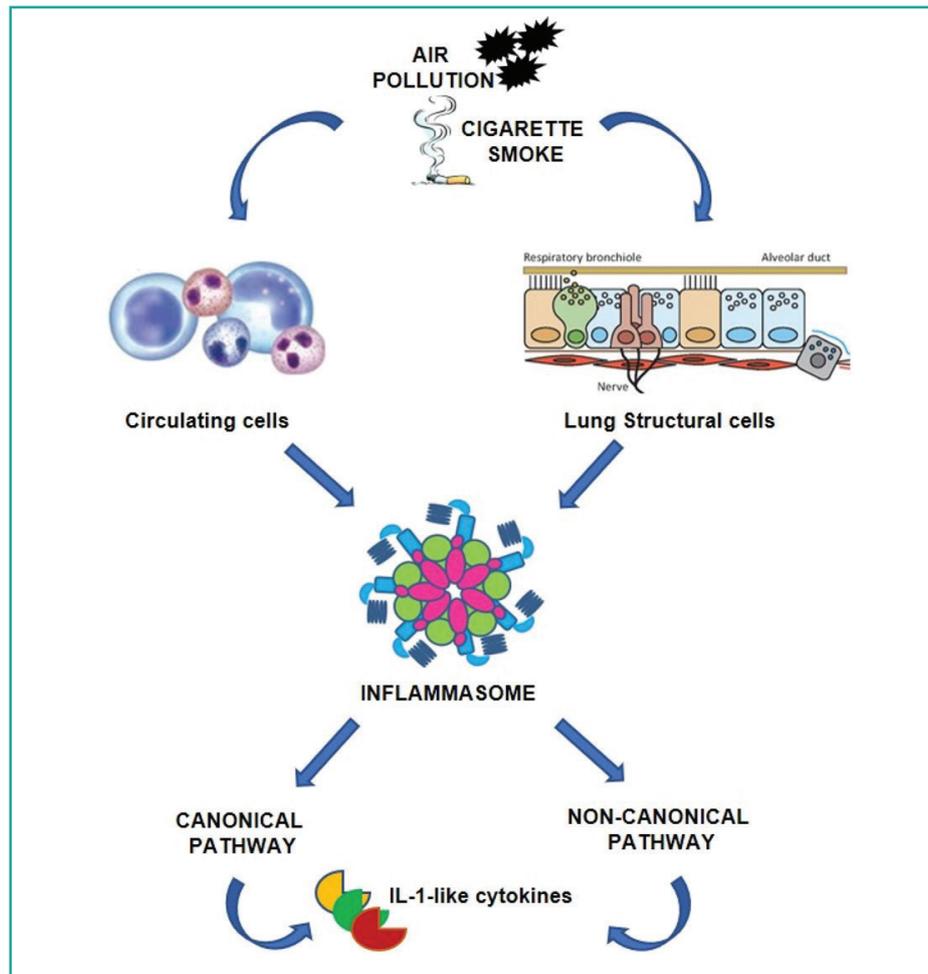
Figure 4. Air pollution and cigarette smoke lead to inflammasome activation. Literature suggests that noxious particles in the air and CS, risk factors for COPD and lung cancer, could induce the release of IL-1-like cytokines in a canonical, caspase-1-dependent, inflammasome pathway in circulating cells. In sharp contrast, caspase-1 is not involved in air pollution- and smoke-induced inflammasome activation in lung structural cells, suggesting that the ensuing IL-1-like cytokines release could be dependent on a non-canonical pathway.

are needed, but according to the published and unpublished data, we could suggest that the biology of the AIM2 inflammasome could pave the way for innovative pharmacological target/s.

ETHICS

Conflict of interests

The authors have declared no conflict of interests.

Authors' contribution

CC prepared and edited the manuscript, which was an overview of the literature and of the

experimental data obtained during the PhD training (2017-2020).

Availability of data and material
No new data were generated or analysed in this research.

Ethical approval
N/A.

REFERENCES
1. Durham AI, Adcock IM. The relationship between COPD and lung cancer. Lung Cancer 2015;90: 121-7. Doi:10.1016/j.lungcan.2015.08.017.
2. Young RP, Hopkins RJ, Christmas T, Black PN, Metcalf P, Gamble GD. COPD prevalence is increased in lung cancer, independent of age, sex and smoking history. Eur Respir J 2009;34(2):380-6. Doi: 10.1183/09031936.00144208.
3. Colarusso C, Terlizzi M, Molino A, Pinto A, Sorrentino R. Role of the inflammasome in chronic obstructive pulmonary disease (COPD). Oncotarget 2017;8(47):81813-24. Doi: 10.18632/oncotarget.17850.
4. McLoed AG, Sherrill TP, Cheng DS, et al. Neutrophil-Derived IL-1β Impairs the Efficacy of NF-κB Inhibitors against Lung Cancer. Cell Rep 2016;16(1):120-32. Doi: 10.1016/j.celrep.2016.05.085.
5. Terlizzi M, Casolaro V, Pinto A, Sorrentino R. Inflammasome: Cancer's friend or foe? Pharmacology & Therapeutics 2014;143:24-33. Doi: 10.1016/j.pharmthera.2014.02.002.
6. Hirota JA, Hirota SA, Warner SM, et al. The airway epithelium nucleotide-binding domain and leucine-rich repeat protein 3 inflammasome is activated by urban particulate matter. J Allergy Clin Immunol 2012;129:1116-25.e6. Doi: 10.1016/j.jaci.2011.11.033.
7. De Falco G, Terlizzi M, Sirignano M, et al. Human peripheral blood mononuclear cells (PBMCs) from smokers release higher levels of IL-1-like cytokines after exposure to combustion-generated ultrafine particles. Sci Rep 2017;7:43016. Doi: 10.1038/srep43016.
8. Lee S, Suh GY, Ryter SW, Choi AMK. Regulation and Function of the Nucleotide Binding Domain Leucine-Rich Repeat-Containing Receptor, Pyrin Domain-Containing-3 Inflammasome in Lung Disease. Am J Respir Cell Mol Biol 2016;54(2):151-60. Doi: 10.1165/rcmb.2015-0231TR.
9. Terlizzi M, Colarusso C, Popolo A, Pinto A, Sorrentino R. IL-1α and IL-1β-producing macrophages populate lung tumor lesions in mice. Oncotarget 2016;7(36):58181-92. Doi: 10.18632/oncotarget.11276.
10. Sorrentino R, Terlizzi M, Di Crescenzo VG, et al. Human lung cancer-derived immunosuppressive plasmacytoid dendritic cells release IL-1α in an AIM2 inflammasome-dependent manner. Am J Pathol 2015;185(11):3115-24. Doi: 10.1016/j.ajpath.2015.07.009.
11. Terlizzi M, Di Crescenzo VG, Perillo G, Galderisi A, Pinto A, Sorrentino R. Pharmacological inhibition of caspase-8 limits lung tumour outgrowth. Br J Pharmacol 2015;172(15):3917-28. Doi: 10.1111/bph.13176.
12. Terlizzi M, Colarusso C, De Rosa I, et al. Identification of a novel subpopulation of Caspase-4 positive non-small cell lung Cancer patients. J Exp Clin Cancer Res 2020;39:242. Doi: 10.1186/s13046-020-01754-0.
13. Ungerbäck J, Belenki D, Jawad ul-Hassan A, et al. Genetic variation and alterations of genes involved in NFκB/TNFAIP3- and NLRP3-inflammasome signaling affect susceptibility and outcome of colorectal cancer. Carcinogenesis 2012;33:2126-34.
14. Voronov E, Dotan S, Krelin Y, et al. Unique Versus Redundant Functions of IL-1α and IL-1β in the Tumor Microenvironment. Front. Immunol 2013;4:177. Doi: 10.3389/fimmu.2013.00177

15. Dinarello CA. Interleukin-1beta and the autoinflammatory diseases. N Engl J Med 2009;360:2467-70.

16. Allen IC, TeKippe EM, Woodford RMT, et al. The NLRP3 inflammasome functions as a negative regulator of tumorigenesis during colitis-associated cancer. J Exp Med 2010;207:1045-56. Doi: 10.1084/jem.20100050.

17. Hu B, Elinav E, Huber S, et al. Inflammation-induced tumorigenesis in the colon is regulated by caspase-1 and NLRC4. Proc Natl Acad Sci, USA 2010;107:21635-40. Doi: 10.1073/pnas.1016814108.

18. Zaki MH, Vogel P, Body-Malapel M, Lamkanfi M, Kanneganti TD. IL-18 production downstream of the Nlrp3 inflammasome confers protection against colorectal tumor formation. J Immunol 2010;185: 4912-20. Doi: 10.4049/jimmunol.1002046.

19. Ridker PM, MacFadyen JG, Thuren T, et al. CANTOS Trial Group. Effect of interleukin-1beta inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. Lancet 2017;390(10105):1833-42.

20. Sugimoto MA, Sousa LP, Pinho V, Perretti M, Teixeira MM. Resolution of Inflammation: What Controls Its Onset? Frontiers of Immunology 2016;7:160. Doi: 10.3389/fimmu.2016.00160.

21. Punturieri A, Szabo E, Croxton TL, Shapiro SD, Dubinett SM. Lung cancer and chronic obstructive pulmonary disease: needs and opportunities for integrated research. J Natl Cancer Inst 2009;101(8): 554-9. Doi: 10.1093/jnci/djp023.

22. Skillrud DM, Offord KP, Miller RD. Higher risk of lung cancer in chronic obstructive pulmonary disease. A prospective, matched, controlled study. Ann Intern Med 1986;105(4):503-7. Doi: 10.7326/0003-4819-105-4-503.

23. Butler SJ, Ellerton L, Goldstein RS, Brooks D. Prevalence of lung cancer in chronic obstructive pulmonary disease: A systematic review. Respiratory Medicine: X 2019;1:100003. Doi: 10.1016/j.yrmex.2019.100003

24. U.S. Department of Health and Human Services (Eds). The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General, Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Atlanta, GA, 2014.

25. Talikka M, Sierro N, Ivanov NV, et alC. Genomic impact of cigarette smoke, with application to three smoking-related diseases. Crit Rev Toxicol 2012;42(10):877-89. Doi: 10.3109/10408444.2012.725244.

26. Li J, Li WX, Bai C, Song Y. Particulate matter-induced epigenetic changes and lung cancer. Clin Respir J 2017;11(5):539-46. Doi: 10.1111/crj.12389.

27. Jiang XQ, Mei XD, Feng D. Air pollution and chronic airway diseases: what should people know and do? J Thorac Dis 2016;8(1):E31-40. Doi: 10.3978/j.issn.2072-1439.2015.11.50.

28. Loomis D, Grosse Y, Lauby-Secretan B, et al. The carcinogenicity of outdoor air pollution. Lancet Oncol 2013;14 (13):1262-3. Doi: 10.1016/s1470-2045(13)70487-x.

29. Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. Nature Reviews Immunology 2008;8:183-92. Doi: 10.1038/nri2254.

30. Quatromoni JG, Eruslanov E. Tumor-associated macrophages: function, phenotype, and link to prognosis in human lung cancer Am J Transl Res 2012;4 (4):376-89.

31. Ma J, Liu L, Che G, Yu N, Dai F, You Z. The M1 form of tumor-associated macrophages in non-small cell lung cancer is positively associated with survival time. BMC Cancer 2010;10(1):112. Doi: 10.1186/1471-2407-10-112.

32. Colarusso C, Terlizzi M, Molino A, et al. AIM2 Inflammasome Activation Leads to IL-1α and TGF-β Release From Exacerbated Chronic Obstructive Pulmonary Dis-

ease-Derived Peripheral Blood Mononuclear Cells. Front Pharmacol 2019;10:257. Doi: 10.3389/fphar.2019.00257.

33. Li C, Zhihong H, Wenlong L, et al. The Nucleotide-Binding Oligomerization Domain-Like Receptor Family Pyrin Domain-Containing 3 Inflammasome Regulates Bronchial Epithelial Cell Injury and Proapoptosis after Exposure to Biomass Fuel Smoke. Am J Respir Cell Mol Biol 2016;55(6):815-24. Doi: 10.1165/rcmb.2016-0051OC.

34. Gross O, Thomas CJ, Guarda G, Tschopp J. The inflammasome: an integrated view. Immunological Reviews 2011:243;136-51. Doi: 10.1111/j.1600-065X.2011.01046.x.

35. Di Stefano A, Caramori G, Barczyk A, et al. Innate immunity but not NLRP3 inflammasome activation correlates with severity of stable COPD. Thorax 2014;69:516-24. Doi: 10.1136/thoraxjnl-2012-203062.

36. De Falco G, Colarusso C, Terlizzi M, et al. Chronic Obstructive Pulmonary Disease-Derived Circulating Cells Release IL-18 and IL-33 under Ultrafine Particulate Matter Exposure in a Caspase-1/8-Independent Manner. Front Immunol 2017;26(8):1415. Doi: 10.3389/fimmu.2017.01415.

37. Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol 2016;138(1):16-27. Doi: 10.1016/j.jaci.2016.05.011.

38. Yasuda K, Muto T, Kawagoe T, et al. Contribution of IL-33-activated type II innate lymphoid cells to pulmonary eosinophilia in intestinal nematode-infected mice. Proc Natl Acad Sci, USA, 2012;109: 3451-6.

39. Kearley J, Silver JS, Sanden C, et al. Humbles AA. Cigarette smoke silences innate lymphoid cell function and facilitates an exacerbated type I interleukin-33-dependent response to infection. Immunity 2015;42:566-79.

40. Colarusso C, De Falco G, Terlizzi M, et al. The Inhibition of Caspase-1- Does Not Revert Particulate Matter (PM)-Induced Lung Immunesuppression in Mice. Front Immunol 2019;10:1329. Doi: 10.3389/fimmu.2019.01329.

41. Lommatzsch M, Cicko S, Muller T, et al. Extracellular adenosine triphosphate and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010;181(9):928-34. Doi: 10.1164/rccm.200910-1506OC.

42. Faner R, Sobradillo P, Noguera A, et al. The inflammasome pathway in stable COPD and acute exacerbations. ERJ Open Res 2016;2(3):00002-2016. Doi:10.1183/23120541.0000-2016.

43. Kim RY, Pinkerton JW, Gibson PG, Cooper MA, Horvat JC, Hansbro PM. Inflammasomes in COPD and neutrophilic asthma. Thorax 2015;70:1199-201. Doi: 10.1136/thoraxjnl-2014-206736.

44. Wang J, Liu X, Xie M, Xie J, Xiong W, Xu Y. Increased expression of interleukin-18 and its receptor in peripheral blood of patients with chronic obstructive pulmonary disease. COPD 2012;9:375-81. Doi: 10.3109/15412555.2012.670330.

45. Terlizzi M, Molino A, Colarusso C, et al. Activation of the absent in melanoma 2 inflammasome in peripheral blood mononuclear cells from idiopathic pulmonary fibrosis patients leads to the release of pro-fibrotic mediators. Front. Immunol 2018;9:670. Doi: 10. 3389/fimmu.2018.00670.

46. Eltom S, Belvisi MG, Stevenson CS, et al. Role of the inflammasome caspase1/11-IL-1/18 axis in cigarette smoke driven airway inflammation: an insight into the pathogenesis of COPD. PLoS One 2014:9(11):e112829. Doi: 10.1371/journal.pone.0112829.

47. Franklin BS, Bossaller L, De Nardo D, et al. The adaptor ASC has extracellular and 'prionoid' activities that propagate inflammation. Nat Immunol 2014;15:727-37. Doi: 10.1038/ni.2913.

48. Colarusso C, Terlizzi M, Lamort AS, et al. Caspase-11 and AIM2 inflammasome are involved in smoking induced COPD and

lung adenocarcinoma. Oncotarget 2021. Doi: 10.18632/oncotarget.27964.

49. Man SM, Karki R, Kanneganti TD. Molecular mechanisms and functions of pyroptosis, inflammatory caspases and inflammasomes in infectious diseases. Immunol Rev 2017;277:61-75. Doi: 10.1111/imr.12534.

50. Oh C, Verma A, Aachoui Y. Caspase-11 Non-canonical Inflammasomes in the Lung. Front Immunol 2020. 11:1895. Doi. org/10.3389/fimmu.2020.01895.

51. Terlizzi M, Colarusso C, De Rosa I, et al. Circulating and tumor-associated caspase-4: a novel diagnostic and prognostic biomarker for non-small cell lung cancer. Oncotarget 2018;9:19356-67. Doi.org/10.18632/oncotarget.25049.

52. Terlizzi M, Molino A, Colarusso C, et al. Altered lung tissue lipidomic profile in caspase-4 positive nonsmall cell lung cancer (NSCLC) patients. Oncotarget 2020;11:3515-25. Doi: 10.18632/oncotarget.27724.

53. Zhang M, Jin C, Yang Y, et al. AIM2 promotes non-small-cell lung cancer cell growth through inflammasome-dependent pathway. J Cell Physiol 2019;234(11):20161-273. Doi: 10.1002/jcp.28617.

54. Fukada K, Okamura K, Riding RL,et al. AIM2 regulates anti-t umor immunity and is a viable therapeutic target for melanoma. J Exp Med 2021;218(9):e20200962. Doi: 10.1084/jem.20200962.