



Particulates induced lung inflammation and its consequences in the development of restrictive and obstructive lung diseases: a systematic review

Hamid Reza Shamsollahi¹ · Behnaz Jahanbin² · Shahab Rafieian³ · Masud Yunesian^{1,4,5}

Received: 4 November 2020 / Accepted: 16 March 2021 / Published online: 29 March 2021

© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2021

Abstract

Particulate matters (PMs) are significant components of air pollution in the urban environment. PMs with aerodynamic diameter less than 2.5 μm ($\text{PM}_{2.5}$) can penetrate to the alveolar area and introduce numerous compounds to the pneumocystis that can initiate inflammatory response. There are several questions about this exposure as follows: does $\text{PM}_{2.5}$ -induced inflammation lead to a specific disease? If yes, what is the form of the progressed disease? This systematic review was designed and conducted to respond to these questions. Four databases, including Web of Science, Scopus, PubMed, and Embase, were reviewed systematically to find the related articles. According to the included articles, the only available data on the inflammatory effects of $\text{PM}_{2.5}$ comes from either in vitro or animal studies. Both types of studies have shown that the induced inflammation is type I and includes secretion of proinflammatory cytokines. The exposure duration of longer than 28 weeks was not observed in any of the reviewed studies. However, as there is not a specific antigenic component in the urban particulate matters and based on the available evidence, the antigen-presenting is not a common process in the inflammatory responses to $\text{PM}_{2.5}$. Therefore, neither signaling to repair cells such as fibroblasts nor over-secretion of extracellular matrix (ECM) proteins can occur following $\text{PM}_{2.5}$ -induced inflammation. These pieces of evidence weaken the probability of the development of fibrotic diseases. On the other hand, permanent inflammation induces the destruction of ECM and alveolar walls by over-secretion of protease enzymes and therefore results in progressive obstructive effects.

Keywords Inflammation · Air pollution · $\text{PM}_{2.5}$ · COPD · Emphysema · Idiopathic pulmonary fibrosis

Introduction

Particulate matters (PMs) with an aerodynamic diameter of less than 2.5 μm ($\text{PM}_{2.5}$) are the most critical and objectionable group of pollutants in the ambient air (Wang et al. 2017).

$\text{PM}_{2.5}$ includes several components such as heavy metals, polycyclic aromatic hydrocarbons (PAHs), unburned or incompletely burned fuel, sulfur compounds, and nitric compounds (Prieto-Parra et al. 2017; Zhang et al. 2018). They can penetrate the alveolar region of the lung effectively and

Responsible Editor: Ludek Blaha

✉ Masud Yunesian
yunesian@tums.ac.ir

Hamid Reza Shamsollahi
hrshamsollahi@gmail.com

Behnaz Jahanbin
b-jahanbin@sina.tums.ac.ir

Shahab Rafieian
Shahab_rafieian@yahoo.com

¹ Department of Environmental Health Engineering, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

² Department of Pathology, Cancer Research Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

³ General Thoracic Surgery Ward, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

⁴ Center for Air Pollution Research (CAPR), Institute for Environmental Research (IER), Tehran University of Medical Sciences, Tehran, Iran

⁵ Department of Research Methodology and Data Analysis, Institute for Environmental Research (IER), Tehran University of Medical Sciences, Tehran, Iran

either deposit there or enter the bloodstream considering their size (Kulkarni et al. 2006). These characteristics allow $PM_{2.5}$ to introduce various pollutants to respiratory cells for an extended period compared to the gaseous pollutants. Smoking is the most critical risk factor in incidence or exacerbation of respiratory diseases due to induction of permanent inflammation (Cosio et al. 2002). However, according to the epidemiological studies, various lung diseases and respiratory symptoms are attributed to the exposure to the environmental $PM_{2.5}$ (Cohen et al. 2017; Dominici et al. 2006). Respiratory pathologies most commonly reported in the studies include inflammation in lung parenchyma (functional tissue of lung) or airways, oxidative stress, metabolic interruptions, and mutagenicity (Feng et al. 2016). Moreover, the relationship between exposure to particulate matters and some respiratory diseases such as exacerbation of asthma and COPD, and lung cancer has been confirmed (Raaschou-Nielsen et al. 2016). Inflammation is the most critical event in all of these diseases. Inflammation is a complicated response to exposure to pathogens or tissue injury. In normal condition, it has several steps including secretion of several cytokines as inflammatory mediators for recruitment of other immune cells, phagocytosis of damaged cells' debris or pathogens, and finally, anti-inflammatory and tissue repairing step (Medzhitov 2008). Inflammation in the respiratory system could involve different cell types and can be chronic. Depending on the cell type involved in the inflammation in the lung, induced chronic inflammation can activate different immunological pathways and lead to individual severe diseases (Abbas et al. 2019a).

Lung diseases are generally categorized as obstructive or restrictive. Interstitial lung diseases (ILD) are the dominant group of restrictive diseases. ILD are chronic diseases with the insidious but progressive onset of dyspnea and cough. Lung fibrosis is one of the main ILD (Chilosi et al. 2012). Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and usually lethal pulmonary disease; moreover, it is more prevalent among the elders (King Jr et al. 2011). IPF involves abnormal and continuous production and deposition of extracellular matrix (ECM), including collagen/elastin fibers (Wilson and Wynn 2009). Figure 1 illustrates the histopathological appearance of IPF. The fibrosis can be diagnosed by increasing the thickness of ECM because of abnormal deposition of collagen in the tissue (King Jr et al. 2011). The

regions with normal density of pneumocytes and fibrotic area are shown in Fig. 1.

Several pathogeneses have been proposed for the stimulation of fibrosis; however, the most accepted hypothesis is the chronic inflammation in epithelial cells in the lung parenchyma. Various inflammatory reaction pathways could cause fibrosis. They start from cell damage due to contact with irritant agents such as pathogens or particulates and finally lead to abnormal collagen secretion by fibroblasts/myofibroblasts. Several inflammatory mediators are involved in these pathways. Some of them are unique to a specific pathway, and the others are common between pathways (Kumar et al. 2014).

In a different scenario, inflammatory reaction cascade can activate different pathways and lead to obstructive lung diseases such as emphysema. The clinical definition of emphysema is the air space enlargement due to the alveolar wall distraction. The pathophysiological feature of emphysema is shown in Fig. 2. The healthy and enlarged alveoli are indicated by numbers 1 and 2 in this figure, respectively. Following chronic exposure to antigens, alveolar macrophages and airway epithelial cells can secrete various cytokines such as interleukin-8 (IL-8) and granulocyte-macrophage colony-stimulating factor (GM-CSF). These proinflammatory mediators can signal an increase in the recruitment of leukocytes in the lung (Ruwanpura et al. 2017). The leukocytes, especially neutrophils, secrete serine and cysteine proteinases. These enzymes are elastases and can destruct connective tissue components such as collagen and elastin (Taraseviciene-Stewart and Voelkel 2008). Consequently, alveolar attachment to the bronchioles would be decreased, and the alveoli area would be increased, followed by long-term secretion from them. Anatomically, it can lead to emphysema following hyperinflation, a significant reduction of forced vital capacity (FVC%), and other clinical symptoms (Cottin et al. 2017).

Therefore, chronic inflammation can induce both restrictive and obstructive lung diseases. Thus, numerous studies have been tried to determine the inflammatory effect of inhalable materials and further signaling pathways inducing individual lung diseases since one of the leading and frequent respiratory exposures is $PM_{2.5}$ inhalation.

Exposure to urban $PM_{2.5}$ is increasing worldwide. According to various studies, the number of cities having $PM_{2.5}$ concentrations over international guidelines is

Fig. 1 Fibrosis in lung tissue (1: normal area; 2: fibrosis area)

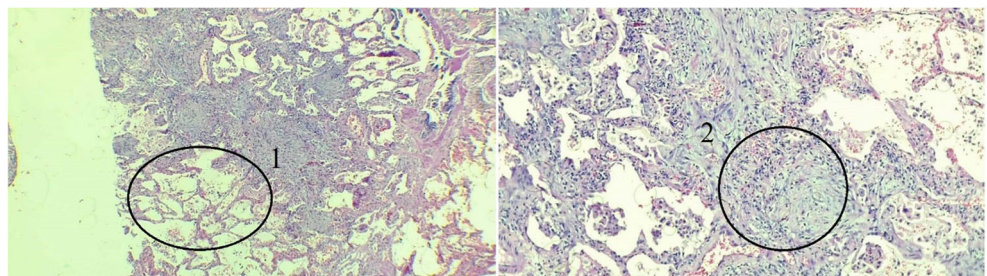
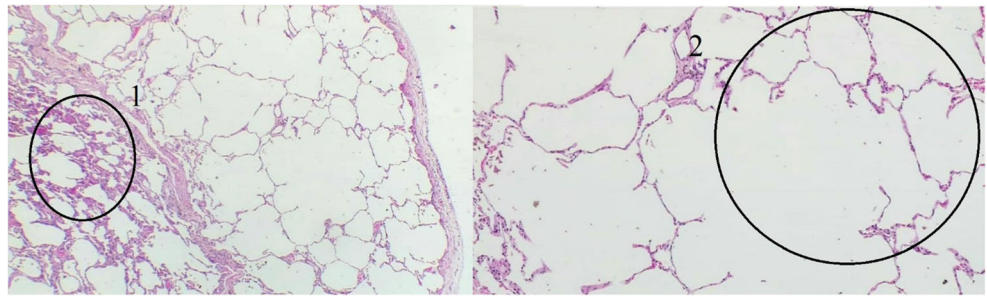


Fig. 2 Emphysema in human lung (1: normal alveoli; 2: enlarged alveoli following alveolus wall destruction)



increasing. Moreover, the incidence rate of the high level of $PM_{2.5}$ is increasing in megacities. Also, $PM_{2.5}$ has various components with confirmed health effects (Hsu et al. 2017; Kim et al. 2019; Lin et al. 2014; Zhang et al. 2018). Therefore, several studies have been tried to evaluate the inflammatory effect of $PM_{2.5}$ inhalation, and most of them confirmed these effects after exposure to this pollutant. Nevertheless, there are some differences between their experimental approaches and their results. The examples are varied in exposure doses, exposure duration, and inflammatory response levels.

Moreover, these studies measured and reported a wide range of inflammatory mediators, which were involved in different inflammation pathways and could cause different symptoms. Consequently, the possible inflammation pathways after exposure to urban $PM_{2.5}$ are unclear. However, there are many questions and controversies concerning the relation between $PM_{2.5}$ exposure and inflammation. The main questions are as follows: Can inhalation and exposure to urban $PM_{2.5}$ induce inflammation in lung parenchyma? Which inflammatory pathway will be activated after exposure to $PM_{2.5}$? What are the available procedures to evaluate the inflammatory effect of $PM_{2.5}$ inhalation? What are the possible immune response pathways that can be activated after exposure to $PM_{2.5}$?

Therefore, we reviewed available studies that specifically investigated the inflammatory effects of exposure to $PM_{2.5}$ based on defined search strategy to respond to these questions.

Methodology

Search strategy

This review was conducted in February 2019. Primarily, the main questions were formulated according to the available knowledge, as mentioned in the “Introduction.” The systematic search was carried out according to these questions among four databases: Web of Science, Scopus, PubMed, and Embase in the English language. The search keywords were the following: “lung + inflammation + $PM_{2.5}$ ” and “lung + inflammation + particulate matter.” The results were filtered using the inclusion and exclusion criteria. These criteria would be mentioned in the following sections.

Inclusion criteria

Focus on urban air $PM_{2.5}$ was the main inclusion criteria. Only original articles published in peer-reviewed journals were selected for this study. In vitro, animal, or human studies were all included. All of the selected articles reported an exposure dose, exposure period, and chemical analysis of used particulate matters. We also reviewed references within the returned review articles to find any further appropriate articles.

Exclusion criteria

We excluded all the studies conducted on natural particles such as dust. Moreover, all the studies about occupational situations, accidental exposures, polymorphism, genetic studies, and studies that reported inflammation by serum cytokine measurements were excluded. Besides, we removed studies that did not report the chemical analysis of $PM_{2.5}$. Finally, some articles were further excluded after careful study of their abstracts or the full article contents.

Data extraction

Extracted data and information from the selected articles included the type of study (in vitro, animal, or human), subjects’ characteristics, $PM_{2.5}$ source and its chemical composition, exposure procedure (dose, time, groups), type of the measured marker to determine inflammation and response level (cytokine secretion or mRNA expression), results of studies (change in marker level), and outcomes (visible histologic, anatomic, or pathologic changes and conclusion of the study). Then, extracted data/information was classified based on the similarities between studies for better visualization and semi-quantitative comparison.

Results

Included studies

The search on four databases, with inclusion and exclusion filters, returned 555 articles. After the duplication removal

($N = 366$), 189 articles remained. Finally, 21 articles were selected after screening by title, abstract, and main passage reviewing. Figure 3 is the PRISMA flow diagram presenting the study selection procedure.

Acquired data

The acquired data from 21 included studies are summarized in Table 1. The included studies could be divided into two main groups. The first group was the animal studies, which included instillation or respiration of ambient $PM_{2.5}$ by mice or rat for various periods and measurement of inflammatory mediators in serum or bronchoalveolar lavage fluid (BALF). The second group was the in vitro studies using human or animal cell lines. In these studies, $PM_{2.5}$ was filtered from ambient air, and cell lines were then exposed to them in a controlled manner, and the inflammatory mediators were measured after different exposure periods.

The $PM_{2.5}$ were collected from urban air in this study. Three articles reported using standard particles in their experiments, including urban and diesel particles. Numerous parameters were measured and reported in the included articles, which were various. Accordingly, we tried to classify

particulates' chemical composition into three categories: heavy metals (HMs); water-soluble ions (WSIs) including SO_4^{-2} , NO_3^{-} , and NH_4^{+} ; and PAHs. Besides, we tried to convert and report all concentration values in $\mu\text{g}/\text{mg}$ of particle mass. The additional extracted data from articles was exposure dose and procedures.

One of the main problems for comparison between different studies was exposure and the concentration units of inflammatory cytokines. There was no capability of converting all of the reported units to the same unit. Therefore, the exposure units were $\mu\text{g}/\text{ml}$ or $\mu\text{g}/\text{cm}^2$ of cell culture in in vitro studies and mg/kg or mg/mice for animal studies. Likewise, the concentration of the cytokine was reported as pg/ml or pg/gr of protein for in vitro studies. Various kinds of inflammatory cytokines were measured in the included studies. However, no justification was found for the selected kind of cytokines in each study. The only common mediator in all of the studies was IL-8. The exposure period and dose were different between in vitro and animal studies. Summary of exposure data, characteristics of particulates, and measured mediators are listed in Table 2.

Several diversities were observed in extracted information, including the analyzed components of $PM_{2.5}$, the analysis of

Fig. 3 PRISMA flow diagram

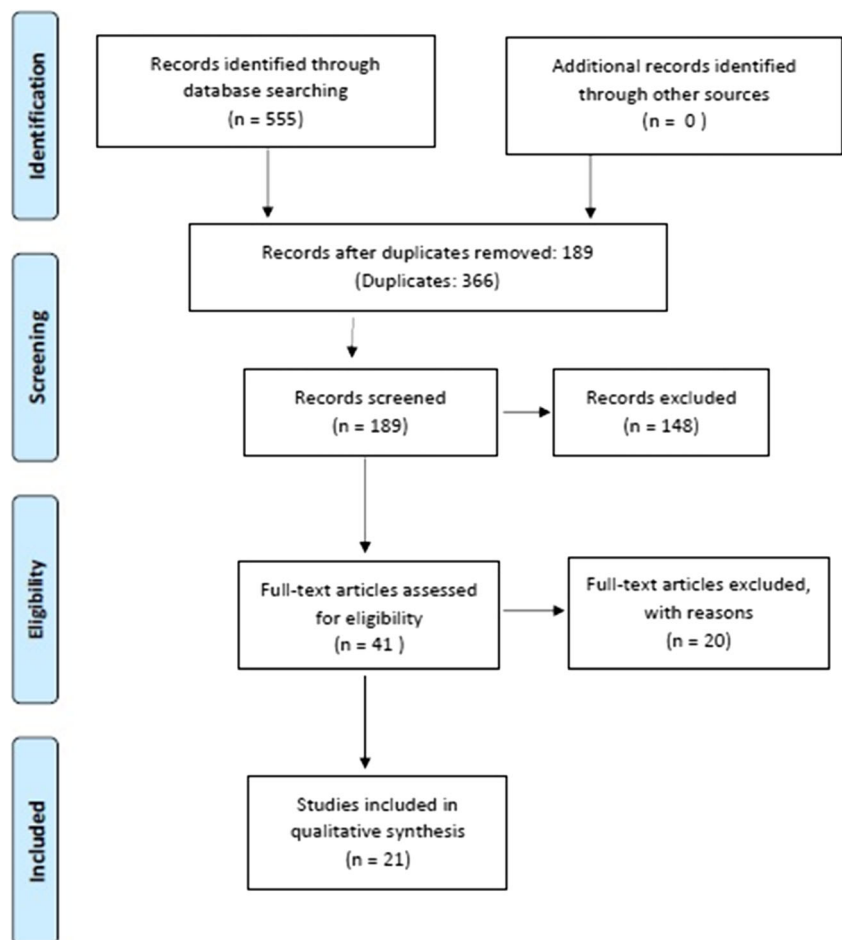


Table 1 Extracted data from included articles. ^aChemicals reported as µg/mg. HMs heavy metals, WSI water-soluble ions

Study type/subjects	PM _{2.5} source and characteristics ^a	Exposure procedure/dose	Markers, response level, and values	Result	Conclusion	Author/year
Human in-vitro study/epithelial BEAS-2B cells	Extracted organic matters from collected ambient PM _{2.5} /PAHs: 202 µg/g	-Exposing cell culture to extracted organic matters eq to 3.15 and 30 µg PM _{2.5} -Measurement of markers 6 and 24 h after exposure	Response level: protein secretion TNF-α: 0.4–0.95 IL-1β: 0.3–0.95 IL-6: 0.2–0.9 IL-8: 0.3–1.2 MCP-1: 0.5–0.85 INF-γ: 0.2–1.3	Any significant change in cytokines after 24 h in max exposure level Significant increase in INF-γ, IL-6 after exposure to B[α]P (<i>p</i> -value < 0.05)	Exposure to low level of PAHs (totally and individual) cannot induce notable inflammation in lung epithelial cells in short exposure time and just can activate inflammatory genes' transcription factors The exposure to urban and diesel PMs can induce IL-8 secretion. The particles having more heavy metals can induce more IL-8 secretion	Abbas et al. (2019b)
Human in-vitro study/epithelial A549 cells	-Urban standard reference particle (SRM1648a) HMs: 3.44 WSI: 185 -Diesel PM (SRM2975) HMs: 0.255 PAHs: 0.132 -Non-ferrous dust (PD-1) HMs: 93.3 WSI: 42.7 -Collected ambient PM _{2.5} HMs: 10.86 WSI: 624	10, 100, 300, 500, 700, 900, and 1000 µg of SRM1648a, SRM2975, PD-1, and ambient PM _{2.5} exposed to cell cultures for 24 h	Response level: protein secretion IL-8: Cultures exposed by PD-1: 6.2 ng/ml Exposed by SRM1648a: 2.3 Exposed by SRM2975: 1 Exposed by PM _{2.5} : 1.1	Significant increase in IL-8 level after exposure to all of the 4 types of particles (<i>p</i> < 0.001)	The exposure to urban and diesel PMs can induce IL-8 secretion. The particles having more heavy metals can induce more IL-8 secretion	Akhtiar et al. (2010)
Human in vitro study/lung epithelial cells (L132)	Urban-collected PM _{2.5} HMs: 9.28 PAHs: 0.04	Cell cultures were exposed to 18.84 and 76.36 µg/ml of PM _{2.5} for 24, 48, and 72 h.	Response level: protein secretion TNF-α: 2.45–45.8 IL-1β: 0.78–43.9 IL-8: 4.59–201.4 GM-CSF: 0.99–1.8 IL-6: 1415–2486 TGF-α: 48.3–258.7	Significant increase of proinflammatory cytokine secretion (4 cytokines) and anti-inflammation cytokines by increasing time and dose	Acute exposure to urban PM _{2.5} can induce inflammation and anti-inflammation response simultaneously	Dagher et al. (2005)
Animal study/male C57BL/6, CXCR3 knockout, and Foxp3-GFP knockin mice	Urban-collected PM _{2.5} HMs: 8.45	The mice were exposed to air having PM _{2.5} 6 h/day, 5 days/week for 28 weeks. PM _{2.5} concentration: 17.3 ± 2.96 µg/m ³	Response level: gene expression IL-17a: 1.5-fold vs control group	Expression of IL-17a gene was increased significantly after exposure period vs control group (<i>p</i> < 0.01)	Chronic exposure to PM _{2.5} can increase Th1 cell population in lung and induce acute inflammation.	Deiulis et al. (2012)
Human in-vitro study/human bronchial epithelial cells (BEAS-2B)	Ambient-collected PM _{2.5-0.3} in different four seasons from rural and urban area -WSI: SSR: 92.64 AWR: 137.9 SSU: 154.34	Cell cultures exposed to 3.75 and 15 µg/cm ² of collected particles for 24, 48, and 72 h	Response level: protein secretion UCS = IL-1β was after 48 exposure to 15 µg RWS = 14 Max of IL-6 was after 24 exposure to 15 µg UWS = 500 pg/mg	There were not any significant differences between IL level due to exposure to cold and warm season PM _{2.5} at the same exposure time.	The effect of long-term exposure and increasing of exposure on inflammation is not clear. The mass of exposed PM _{2.5} is not related to inflammation response and the chemical composition of PM _{2.5} needs more comprehensive	Dergham et al. (2015)

Table 1 (continued)

Study type/subjects	PM _{2.5} source and characteristics ^a	Exposure procedure/dose	Markers, response level, and values	Result	Conclusion	Author/year
	AWU: 165.73 -HMs: SSR: 29.64 AWR: 27.1 SSU: 47.59 AWU: 44.31 -PAH: SSR: 52.14 AWR: 286.31 SSU: 69.59 AWU: 139		Max of IL-8 was after 24 exposure to 15 µg UWS = 510 pg/mg	Significant differences in all IL level between first-day exposure to 15 µg PM _{2.5-0.3} vs 3.75 µg	discussion about the relation between PM _{2.5} exposure and inflammation response.	
Animal study/BALB/c mice	Collected PM _{2.5} from 2 cities (Zerbst and Hettstedt; Hettstedt is more industrial) Hettstedt PM _{2.5} -HMs: 9.733 -WSI: 278 Zerbst PM _{2.5} -HMs: 5.15 -WSI: 230.5	100 µg PM _{2.5} from 2 cities instilled into the mice's lung/BALF analyzed 48 h after exposure	Response level; protein secretion IL-5 (pg/ml): -Exposed to Z city PM _{2.5} : 16 -Exposed to H city PM _{2.5} : 15 -Control group: 15 IL-13: -Exposed to Z city PM _{2.5} : 8 -Exposed to H city PM _{2.5} : 9 -Control group: 8 TNF-α: -Exposed to Z city PM _{2.5} : 60 -Exposed to H city PM _{2.5} : 100 -Control group: 30 INF-γ: -Exposed to Z city PM _{2.5} : 10 -Exposed to H city PM _{2.5} : 55 -Control group: 10	-Any significant change in IL-5 and IL-13 level vs control group. -Significant change in TNF-α and INF-γ level in mice exposed to PM _{2.5} from Hettstedt city	Short-term exposure to PM _{2.5} can induce inflammation in lung cells. The severity of inflammation will increase following the increase of HM content.	Gravett et al. (2003)
Human in vitro study/BEAS-2B	Collected urban PM _{2.5} -Summer PM _{2.5} HMs: 29 WSI: 410 PAH: 0.036 -Winter PM _{2.5} HMs: 38 WSI: 410 PAHs: 0.312	BEAS-2B cells exposed to 1.10 and 25 and 50 µg/cm ² of summer and winter PM _{2.5} for 24 h.	Response level; protein secretion IL-8 -Summer PM _{2.5} 1 µg = 76 10 µg = 76 25 µg = 76 50 µg = 114 -Winter PM _{2.5} 1 µg = 76 10 µg = 152 25 µg = 152 50 µg = 76	Significant increase in IL-8 level by increasing PM _{2.5} dose	Increase of heavy metal and PAH content can lead to increase of inflammatory response. Also, the inflammation has a cutoff level and after that concentration, the inflammatory response will decrease.	Gualtieri et al. (2010)
Animal study/C57BL/6J mice	Urban-collected PM _{2.5} in 4 seasons -Spring PM _{2.5} WSI: 220.8	10 mg/kg PM _{2.5} was instilled to mice lung/BALF was collected, 4 and 12 h	Response level; protein secretion TNF-α (4) -Spring PM _{2.5} = 400	*Significant increase of TNF-α and IL-6 vs blank level after 4-h exposure to spring and autumn PM _{2.5}	Exposure to PM _{2.5} can induce inflammation response in very short exposure time. The inflammation decreases	Happo et al. (2010)

Table 1 (continued)

Study type/subjects	PM _{2.5} source and characteristics ^a	Exposure procedure/dose	Markers, response level, and values	Result	Conclusion	Author/year
Animal study/BALB/c mice	<p>Collected urban PM_{2.5}</p> <p>WSI: 420</p> <p>HMs: 21.51</p> <p>PAHs: 2.216</p>	<p>after exposure</p> <p>PM_{2.5} per mice, every 2 weeks (8 weeks), BALF analyzed 24 h after last instillation</p>	<p>-Summer PM_{2.5} = 180</p> <p>-Autumn PM_{2.5} = 400</p> <p>-Winter PM_{2.5} = 100</p> <p>TNF-α (12 h)</p> <p>-Spring PM_{2.5} = 30</p> <p>-Summer PM_{2.5} = 20</p> <p>-Autumn PM_{2.5} = 35</p> <p>-Winter PM_{2.5} = 20</p> <p>IL-6 (4 h)</p> <p>-Spring PM_{2.5} = 900</p> <p>-Summer PM_{2.5} = 450</p> <p>-Autumn PM_{2.5} = 950</p> <p>-Winter PM_{2.5} = 450</p> <p>IL-6 (12 h)</p> <p>-Spring PM_{2.5} = 380</p> <p>-Summer PM_{2.5} = 150</p> <p>-Autumn PM_{2.5} = 390</p> <p>-Winter PM_{2.5} = 100</p> <p>Response level: protein</p>	<p>*Significant decrease in TNF-α and IL-6 levels after 12 h</p>	<p>during a few hours after induction. The inflammatory cytokine level is directly related to heavy metal content of PM_{2.5}.</p>	He et al. (2016)
Animal and in vitro study	<p>Collected urban PM_{2.5}</p> <p>WSI = 407</p> <p>HMs: 29.97</p> <p>PAHs: 0.95</p> <p>MyD88-deficient and WT mice</p> <p>-Cell line: RAW264.7 cells</p>	<p>Animal procedure: 0.2 mg PM_{2.5} instilled to each mouse. BALF analyzed 24 h after instillation.</p> <p>In-vitro procedure: 30 μg PM_{2.5}/ml of cell culture. Inflammatory gene expression was measured after 3 h.</p>	<p>Animal test:</p> <p>-*WT mice: IL-6: 600</p> <p>IL-12: 700</p> <p>TNF-α: 79</p> <p>-*MyD88 mice</p> <p>IL-6: 40</p> <p>IL-12: 100</p> <p>TNF-α: 11</p> <p>In vitro test:</p> <p>TNF-α = 810</p> <p>IL-6 = 1</p> <p>Response level: protein secretion</p> <p>TNF-α: 1.1</p> <p>IL-6: 1.3</p> <p>IL-8: 1.3</p> <p>Control: 1</p> <p>Response level: protein secretion</p>	<p>*Significant increase of inflammatory cytokine level in mice after exposure period vs control group ($p < 0.05$)</p> <p>*Significant increase of TNF-α vs control group in the in vitro test ($p < 0.05$); increasing of IL-6 level was not significant.</p>	<p>Short-term in vitro exposure to PM_{2.5} cannot show inflammation effect of PM_{2.5}; hence, more long exposure period in animal test can show this effect and introduce quantity of inflammatory potential of PM_{2.5}.</p>	He et al. (2017)
Human in vitro study/human bronchial epithelial (16HBE) cells	<p>HMs: 16.33</p>	<p>Cell culture was exposed to 160 μg/ml PM_{0.25} for 4 h. The cytokines were measured after 20-h recovery.</p>	<p>Response level: protein secretion</p> <p>TNF-α: 1.1</p> <p>IL-6: 1.3</p> <p>IL-8: 1.3</p> <p>Control: 1</p> <p>Response level: protein secretion</p>	<p>Significant increase in IL-6 and IL-8 vs control ($p < 0.05$), any significant change in TNF-α level vs control.</p>	<p>Short-term exposure to urban PM can induce inflammation but the relationship between PM component concentration and inflammatory response level is unclear.</p>	He et al. (2018)
Human in vitro study/RPMI	<p>Collected urban PM_{2.5}</p>	<p>Cell lines exposed to 100, 400, and</p>	<p>Response level: protein secretion</p>	<p>Significant increase in all of cytokines after</p>	<p>Exposure to PM_{2.5} can induce inflammation in lung cells.</p>	Hong et al. (2016)

Table 1 (continued)

Study type/subjects	PM _{2.5} source and characteristics ^a	Exposure procedure/dose	Markers, response level, and values	Result	Conclusion	Author/year
2650 cell line	WSI: 794.8 PAHs: 1.72 HMs: 14.24	800 µg/ml of PM _{2.5} for 24 h/cytokines ^b mRNA measurement after 24 h.	*100 µg/ml exposure: -TNF-α: 480 -IL-6: 600 -IL-8: 1100 -IL-13: 170 *400 µg/ml exposure: -TNF-α: 550 -IL-6: 700 -IL-8: 1700 -IL-13: 190 *800µg/ml exposure: -TNF-α: 800 -IL-6: 1100 -IL-8: 2100 -IL-13: 195	exposure to PM _{2.5} ($p < 0.05$)		
Animal study/BALB/c mice	HMs: 6.3 µg/mg	Instillation of mice by 2.5, 10, and 20 mg/kg PM _{2.5} /cytokines ^b mRNA measurement 1, 7, and 14 days after exposure	Response: gene expression IL-4 (2.5 mg/kg) -1 day = 50 -7 days = 60 -14 days = 30 IL-4 (10 mg/kg) -1 day = 40 -7 days = 58 -14 days = 30 IL-4 (20 mg/kg) -1 day = 40 -7 days = 60 -14 days = 30 INF-γ (2.5 mg/kg) -1 day = 40 -7 days = 32 -14 days = 38 INF-γ (10 mg/kg) -1 day = 60 -7 days = 35 -14 days = 38 INF-γ (20mg/kg) -1 day = 120 -7 days = 32 -14 days = 41	Significant increase in inflammation cytokines ^b gene expression by increasing of exposure dose ($p < 0.05$)	Exposure to PM _{2.5} can induce inflammation. Max effect following a single-dose exposure was observed at 7 days after exposure and the effects cannot persist for long time. The anti-inflammatory response activates almost immediately after inflammation and decreases following inflammation declining.	Hou et al. (2018)
Animal study/BALB/c mice	Collected urban PM _{2.5} WSI: 526.5 (µg/mg)	Mice instilled twice by 1.75, 5, and 12.5 mg/kg PM _{2.5} at 0 and 7 days (2 treatments)/BALF	*1.75 mg/kg exposure dose -IL-5: 0.8 -IL-6: 1.2 -IL-13: 0.2	Significant increase in cytokines ^b level after exposure ($p < 0.05$)	Exposure to PM _{2.5} can induce lung inflammation. There is a reverse relation between exposure dose and inflammatory	Huang et al. (2017a)

Table 1 (continued)

Study type/subjects	PM _{2.5} source and characteristics ^a	Exposure procedure/dose	Markers, response level, and values	Result	Conclusion	Author/year
Human in vitro study/human bronchial epithelial cell lines (BEAS-2B and A549)	Extracted PAHs from urban PM _{2.5} PAHs: 15.69 ng/m ³	collection and analysis at 10th day.	-IL-17a: 0.75 -TNF-α: 3 *5 mg/kg exposure dose -IL-5: 0.4 -IL-6: 0.75 -IL-13: 0.2 -IL-17a: 0.5 -TNF-α: 3 *12.5 mg/kg exposure dose -IL-5: 0.5 -IL-6: 0.8 -IL-13: 0.2 -IL-17a: 0.6 -TNF-α: 10	Significant increase of inflammation cytokines by exposure to PAH extracted from PM _{2.5} (<i>p</i> < 0.05)	PAH in composition of PM _{2.5} can induce inflammation in lung epithelial cells.	Huang et al. (2017b)
Human in vitro study/bronchial epithelial cell line, BEAS-2B	Collected urban PM _{2.5} PAHs: 0.1 μg/mg (mean of PAHs in collected PM _{2.5} from 7 sites approximately)	Cell culture exposed to 50 μg/ml PM _{2.5} for 18 h	Response level: gene expression IL-6: expressed below onefold of control group IL-8: expressed below onefold of control group	Increasing in expression of IL-6 and IL-8 gene by exposure to PAHs extracted from PM _{2.5}	Exposure to low concentration of PAH (low PM _{2.5} dose) cannot induce significant inflammation in lung cells.	Lauer et al. (2009)
Human in vitro study/bronchial epithelial cell line, BEAS2B	Collected urban PM _{2.5} HMs: 58.9	Cell culture exposed to 2 μg/cm ² PM _{2.5} fractions (soluble and insoluble) for 72 h	IL-6 - *2-fold change (soluble fraction) - *4-fold change (insoluble fraction) IL-8 - *1.5-fold change (soluble fraction) - * < 1.5-fold change (soluble fraction)	Significant increase in inflammation cytokines after exposure to PM _{2.5} components.	Insoluble fractions of PM _{2.5} including metals and heavy metals have significant effect for inflammation induction in epithelial lung cell in short-term exposure.	Leclercq et al. (2017)
Animal study/transgenic C57Bl/6 mice	Standard diesel particles (SRM-2975) PAHs: 0.26	Ten nasal exposure during 2 weeks. Exposure dose = 15 ng/exposure	Response level: protein secretion TNF-α: 270 ng/ml IL-1β: 180 ng/ml	Significant increasing in inflammation cytokines after exposure to diesel particles	Midterm exposure to diesel particles (DPM) can induce inflammation in mice.	Lewis et al. (2018)
Animal study/male C57BL/6J mice	Collected urban PM _{2.5} PAHs: 0.91 (μg/mg) WSI: 244 (μg/mg)	12-week exposure to PM _{2.5} in chamber (87.87 μg/m ³)/IL	Response level: gene expression IL-1β (relative mRNA level)	There is not any significant difference between control and exposure	Exposure to PM _{2.5} cannot induce significant	Li et al. (2019)

Table 1 (continued)

Study type/subjects	PM _{2.5} source and characteristics ^a	Exposure procedure/dose	Markers, response level, and values	Result	Conclusion	Author/year
	HMs: 1.6 (µg/mg)	measurement at 3-, 6-, and 12-week exposure.	-3w: control = 1.2; exposure = 1.2 -6w: control = 1; exposure=0.8 -12w: control = 1.4; exposure=1.1 TNF-α -3w: control = 1; exposure = 1.1 -6w: control = 1.5 exposure = 4 -12w: control = 1.1; exposure = 1.1 IL-6 -3w: control = 0.8; exposure = 1.2 -6w: control = 1; exposure = 8 -12w: control = 5; exposure = 6 Response level: cytokine secretion TNF-α -24 h: 7.8 ng/µg -48 h: 9.9 ng/µg IL-6 -24 h: 9.9 ng/µg -48 h: 11.3 ng/µg	groups for inflammation response to exposure to PM _{2.5} .	inflammation in epithelial cells in mice.	
Human in vitro study/lung epithelial cell lines (A549)	Collected urban PM _{2.5} WSI: 108.61 PAHs: 14.6	100 µl water-soluble components of PM _{2.5} was added to cell culture/cytokine measurement 24 and 48 h after exposure		Significant increase in inflammation cytokine level after exposure. Response level increasing during time	Water-soluble components of PM _{2.5} can induce inflammation in lung epithelial cells.	Liu et al. (2016)
Animal study/male C57BL/6 mice	Urban-collected PM _{2.5} HMs: 11.88 WSI: 395.8	Inhalation of filtered and urban air in 2 distinguished chambers for 82 days/PM _{2.5} concentration: 64 µg/m ³	Response level: cytokine secretion TNF-α: 3 pg/ml IL-6: 30 pg/ml	Significant increase of IL-6 level after exposure. The increase of TNF-α was not significant.	Midterm exposure to PM _{2.5} can increase some of inflammatory cytokines' level.	Liu et al. (2019)

Table 2 Summarized characteristics of included articles

Exposure data	In vitro studies (<i>n</i> = 11/21)		Animal studies (<i>n</i> = 10/21)	
	Min	Max	Min	Max
Exposure dose (µg/ml or cm ²)	3	1000	1.75	10
Exposure time	3 h	72 h	4 h	12 weeks
Measured inflammatory mediators	IL-1β, IL-6, IL-8, IL-13, TNF-α, INF-γ, GM-CSF, TGF-α, MCP-1		IL-1β, IL-4, IL-5, IL-6, IL-12, IL-13, IL-17a, TNF-α, INF-γ	
PAH concentration (µg/mg)	0.036	139	0.26	8.45
WSI concentration (µg/mg)	42.7	794.8	220.8	526.5
HM concentration (µg/mg)	0.255	93.3	1.6	29.97

more components of PM_{2.5}, and the response to exposure to intact PM_{2.5} or its components. Therefore, it was impossible to illustrate the data using the plot. Hence, the results were classified based on the observed response, PM_{2.5} components, and exposure period in Tables 3 and 4. According to these tables, the number of available studies reporting responses to each component is mentioned (*N*). Besides, the number of direct (D), reverse (R), and non-significant (NS) studies have been mentioned in these tables. The symbols, including +, −, and ±, indicate the effect of exposure period at constant dose.

Discussion

We investigated PM_{2.5}-induced inflammation in lung epithelial cells in this systematic review. The articles included in this

review were in vitro and animal studies. There are several human studies on measuring inflammatory cytokines in bronchoalveolar lavage fluid (BALF). However, they cannot be interpreted to determine the inflammatory effects of inhaled PMs because the patients who need bronchoscopy and BALF collection have serious diseases with inflammation as a common complication (El-Bayoumi and Silvestri 2008; Jin and Wang 2019; Sato et al. 2017).

As shown in Table 1, all the included articles have reported the concentration of at least one of the main groups of PM_{2.5} components. Table 2 shows that the exposure duration in animal studies is significantly longer than the in vitro studies. Reversely, the applied dose of PM_{2.5} is significantly higher in the in vitro studies.

WSIs are the most frequently measured component. WSIs can dissolve in bronchiolar or alveolar fluids, leave the

Table 3 Number of studies dealt with each inflammatory mediator in relation to total PM_{2.5} and its constituents in in vitro studies

	IL-1β	IL-6	IL-8	IL-13	TNF-α	INF-γ	GM-CSF	TGF-α	MCP-1
Total PM _{2.5}	N: 3	N: 9	N: 9	N: 1	N: 6	N: 1	N: 1	N: 1	N: 1
	D: 1+	D: 3+	D: 4±	D: 1+	D: 4±	D: 1+	D: 0	D: 0	D: 0
	R: 0	R: 1−	R: 0	R: 0	R: 0	R: 0	R: 0	R: 1+	R: 0
	NS: 2±	NS: 1+	NS: 2+	NS: 0	NS: 1+	NS: 0	NS: 1+	NS: 0	NS: 1−
PAHs	N: 3	N: 6	N: 6	N: 1	N: 6	N: 1	N: 1	N: 1	N: 1
	D: 1+	D: 2+	D: 4±	D: 1+	D: 4±	D: 1+	D: 0	D: 0	D: 0
	R: 0	R: 1−	R: 1	R: 0	R: 0	R: 0	R: 0	R: 1+	R: 0
	NS: 2±	NS: 1+	NS: 1+	NS: 0	NS: 1+	NS: 0	NS: 1+	NS: 0	NS: 1−
WSI	N: 1	N: 4	N: 4	N: 1	N: 4	−	−	−	−
	D: 1±	D: 3−	D: 3−	D: 1+	D: 2±				
	R: 0	R: 0	R: 0	R: 0	R: 0				
	NS: 0	NS: 0	NS: 1	NS: 0	NS: 1				
HMs	N: 2	N: 4	N: 5	N: 1	N: 4	−	N: 1	N: 1	−
	D: 0	D: 3±	D: 4±	D: 1+	D: 2±		D: 0	D: 0	
	R: 0	R: 0	R: 0	R: 0	R: 0		R: 0	R: 1+	
	NS: 2±	NS: 0	NS: 1	NS: 0	NS: 0		NS: 1+	NS: 0	

N, number of found studies; *D*, number of studies who reported direct significant relationship between pollutant and mediator concentration; *R*, number of studies who reported reverse significant relationship between pollutant and mediator concentration; *NS*, number of studies who reported non-significant relationship between pollutant and mediator concentration; (+, −, ±), effect of time on relation between pollutant and mediator

Table 4 Number of studies dealt with each inflammatory mediator in relation to total PM_{2.5} and its constituents in animal studies

	IL-1 β	IL-4	IL-5	IL-6	IL-12	IL-13	IL-17a	TNF- α	INF- γ
Total PM _{2.5}	N: 3 D: 1+ R: 0 NS: 0	N: 2 D: 0 R: 0 NS: 2	N: 3 D: 0 R: 1 NS: 2	N: 6 D: 1+ R: 1 \pm NS: 2 \pm	N: 2 D: 2 R: 0 NS: 0	N: 2 D: 0 R: 0 NS: 2	N: 3 D: 0 R: 1 NS: 2	N: 8 D: 1 R: 0 NS: 4	N: 2 D: 1– R: 0 NS: 1
PAHs	N: 3 D: 1+ R: 0 NS: 0	N: 1 D: 0 R: 0 NS: 1 \pm	N: 1 D: 0 R: 0 NS: 1 \pm	N: 4 D: 1 R: 0 NS: 3 \pm	N: 2 D: 2 R: 0 NS: 0	– D: 0 R: 0 NS: 2	N: 2 D: 0 R: 0 NS: 2	N: 4 D: 0 R: 1– NS: 1	– D: 1 R: 0 NS: 0
WSI	N: 3 D: 1+ R: 0 NS: 0	N: 1 D: 0 R: 0 NS: 1 \pm	N: 3 D: 0 R: 2 NS: 1	N: 6 D: 1 R: 0 NS: 4 \pm	N: 2 D: 2 R: 0 NS: 0	N: 2 D: 0 R: 0 NS: 2	N: 2 D: 0 R: 0 NS: 2	N: 6 D: 1 R: 1 NS: 1	N: 1 D: 1 R: 0 NS: 0
HMs	2 D: 1+ R: 0 NS: 0	2 D: 0 R: 0 NS: 2 \pm	2 D: 0 R: 1 NS: 1	5 D: 2 \pm R: 0 NS: 2	2 D: 2 R: 0 NS: 0	1 D: 0 R: 0 NS: 2	1 D: 0 R: 0 NS: 1	6 D: 3+ R: 0 NS: 2	2 D: 2– R: 0 NS: 0

N, number of found studies; *D*, number of studies who reported direct significant relationship between pollutant and mediator concentration; *R*, number of studies who reported reverse significant relationship between pollutant and mediator concentration; *NS*, number of studies who reported non-significant relationship between pollutant and mediator concentration; (+, –, \pm), effect of time on relation between pollutant and mediator

particulate structure, and change airway surface liquid (ASL) osmolarity and pH (Miller et al. 2009). Dissolved WSIs can cause osmotic stress and induce inflammation. As mentioned in Table 3, the number of in vitro studies that reported a direct relationship between WSIs and cytokine concentration is significantly more than animal studies. The concentration of chemicals is constant in the in vitro studies, while in the animal body, the hemostatic effect moderates the concentration of pollutants.

PM_{2.5} also contains heavy metals, including Cu, Zn, and Fe, which serve as micronutrients for cells. Nevertheless, other heavy metals such as mercury, lead, cadmium, vanadium, and arsenic do not have any biological function (Gao et al. 2016). All of these toxic metals were detected in the included studies. These metals are water-soluble and can activate the oxidative stress pathway and induce inflammation (Radan et al. 2019). The PAHs are another group of measured components in urban PM_{2.5}. They can be recognized by the aryl hydrocarbon receptor (AHR) in the cytoplasm, transferred to the nucleus, and induce DNA damage (Pieterse et al. 2013). However, their entrance from the surface of the cell into the cytoplasm is unclear. Like WSI, the number of in vitro studies that reported a direct relationship between heavy metals and PAHs and cytokine concentration is clearly more than animal studies.

In addition to chemical features, the activated pathway of inflammation is also essential. There is not robust evidence confirming the PM_{2.5} transfer to the parenchymal cells using endocytosis. Therefore, the induced inflammation in in vitro

studies is probably related to the activation of some signaling pathways from the surface of the cell membrane. It can be true in animal studies, although the source of secreted inflammatory cytokines is not clear and can be from parenchymal cells, connective tissue cells, or immune cells.

Table 3 shows that the most prevalent secreted cytokines in in vitro studies are proinflammatory, including INF- γ , IL-1 β , IL-6, IL-8, and TNF- α . Generally, the target cells of these mediators are innate immune cells such as macrophages and neutrophils. Some of them are common between in vitro and animal studies. Moreover, as indicated in Table 4, animal studies show a more complete inflammatory responses to PM_{2.5} exposure. Some measured mediators in animal studies such as IL-12 and IL-13 induce differentiation of naive T cells into T helper 1 cells and anti-inflammatory effects.

The other parallel mechanism, which can initiate the inflammation, is autophagy. Following the entrance to the cell, PM_{2.5} can induce autophagy (Deng et al. 2013). In many in vitro studies, autophagy was an uncompleted and unsuccessful mechanism against PM_{2.5}, and it decreased the cell viability and caused cell destruction and release of the particulates into the intercellular space again. In this situation, several damage-associated molecular patterns (DAMPs) are released in the intercellular space (Zhao et al. 2019). These DAMPs are recognized using the pattern recognition receptors (PRRs) in the innate immune cells such as macrophages, dendritic cells (DCs), and monocytes and stimulate the recruitment of additional innate immune cells (Abbas et al. 2019a). After the inflammation induction, the wound healing process

or the anti-inflammatory step, including repairing mechanism, would be initiated (Wolters et al. 2014), which is a critical step since the suggested pathophysiology for IPF is an abnormal wound healing process due to the uncontrolled repair. Both types of inflammation (types I and II) can happen in wound healing at normal conditions (Wilson and Wynn 2009). Type I includes secretion of IL-1 β , IL-6, IL-8, INF- γ , TNF- α , and IgG2 antibodies and recruitment of innate immune cells, including macrophages and neutrophils. Afterwards, T lymphocytes, especially T helper 1 cells (Th1) and regulatory T cells (Treg), are recruited to balance inflammatory and anti-inflammatory reactions by signaling to fibroblast for collagen secretion and repairing (Abbas et al. 2019a). Type II inflammation includes secretion of IL-4, IL-5, and IL-13 to recruit the eosinophils and basophils and then to signal to Th2 cells to regulate inflammation and then to induce repair mechanisms (Gandhi et al. 2016). In IPF, continuous deposition of collagen and other ECM proteins occurs as an abnormal process, which means that anti-fibrotic mediators are not being secreted sufficiently, or the collagen deposition and fibroblast differentiation activation pathway are activated continuously. In other words, IPF is a completed but unfinished wound healing process. The initiation of this step directly depends on antigen-presenting by innate immune cells (Strieter 2008). Neutrophils do not have the antigen-presenting capability but other cells, including macrophages, natural killer (NK) cells, and DCs, which can make epitope to present antigen to lymphocytes (Abbas et al. 2019a). The PM_{2.5} can have various components, but, as reported in many studies, there is not any polypeptide structure in their composition (Li et al. 2016). Therefore, the innate immune cells cannot perform the antigen-presenting and lymphocytes, especially Th1, cannot be recruited. Th1 recruitment is necessary for the activation of Treg (Wing and Sakaguchi 2010). Thus, anti-inflammatory responses cannot be activated. Besides, since the lack of antigen-presenting capabilities, the recruitment of Th2 cells is unlikely too. Therefore, the inflammation will continue until full clearance of PM_{2.5} from the lung. Thus, recruitment and differentiation of myofibroblasts to fibroblast for the repair of the destructed tissue is rare.

Increased bronchiolar level of IL-4, IL-13, and TGF- β is reported in many studies as diagnostic indicators of IPF. However, according to the extracted data, none of the included animal studies reported a significant increase of TGF- β , IL-4, or IL-13 following exposure to PM_{2.5}. Lack of antigen-presenting capability and absence of an increase in the levels of IL-4 and IL-13 show that IPF following the exposure to PM_{2.5} is rare and maybe non-existent.

The other possible disease following inflammation is emphysema. The first step of phagocytosis by innate immune cells is the secretion of several proteolytic enzymes to destruct antigens and facilitate phagocytosis (Abbas et al. 2019a). The action of proteolytic enzymes can be regulated using anti-

elastase enzymes, such as α 1 anti-trypsin (α 1-AT). Emphysema is possible among individuals with a genetic defect in the production of α 1-AT (Taraseviciene-Stewart and Voelkel 2008). In normal individuals, the most approved scenario for the development of emphysema is over-secretion of protease and elastase enzymes such as serine protease, matrix metalloproteinase-12 (MMP-12), and elastase by neutrophils and macrophages following exposure to an antigen and induction of predominant inflammation (Sharafkhaneh et al. 2008). The secretion of these proteolytic enzymes is a robust diagnostic indicator for emphysema (Taraseviciene-Stewart and Voelkel 2008). Besides these enzymes, several studies indicated that MMP-9 would be secreted following the inflammation to destruct the collagen of the basement membrane and facilitate monocyte migration from blood to the alveolar region (McMillan et al. 2004). Several studies reported that the clearance of PM_{2.5} from the lung takes too long. Moreover, PM_{2.5} have no polypeptide components. Thus, the secretion of protease enzymes can continue for a long time endlessly. Additionally, several studies reported that PM_{2.5} phagocytosis could damage the macrophages and destruct them and cause PM_{2.5} to be released again (Geng et al. 2006). Therefore, the secretion of protease enzymes will continue until the full clearance of PM_{2.5} from the lung. Because of continuous exposure to PM_{2.5}, these reactions seem to be permanent. There was no data in our included animal studies regarding the measurement of these protease enzymes. However, available results confirm that inflammation in lung follows exposure to PM_{2.5}. Therefore, the destruction of connective tissue proteins seems possible after exposure to PM_{2.5}, while the severity of destruction is very mild and needs a very long time to make a significant tissue damage.

The secretion of INF- γ is another issue concerning the initial response of cells, which are exposed to PM_{2.5}. It has been measured in both types of studies, and almost all of them reported significant increases in INF- γ level following exposure to PM_{2.5}. Generally, after pathogen recognition, especially in viral infections, INF- γ is secreted by infected cells to induce cellular immune response using the stimulation of protein kinase R (PKR) production (Wingate et al. 2009). In the case of PM_{2.5}, the produced PKR has no target antigen due to the absence of any double-stranded RNA in PM_{2.5} compositions. If PKR deposition continues for a long time, it can induce cell apoptosis or lead the cell to the autophagy pathway (Kim et al. 2007). Both apoptosis and autophagy can signal macrophage recruitment. In normal circumstances such as following the exposure to viruses, the apoptosis has practical function to prevent the virus from spreading, but PM_{2.5} induce unnecessary apoptosis in pneumocytes (Dagher et al. 2006). This event can reduce the population of parenchymal cells and cause a decrease in lung function, a condition like obstructive diseases.

Finally, the findings of this study showed that, because of the chemical structure of PM_{2.5}, they could induce a

permanent inflammation without any antigen-presenting to activate repair mechanisms. Therefore, the tissue destruction and incidence of obstructive diseases are more likely compared to fibrosis. This directly depends on the exposure period to PM_{2.5} and the dosage. The existence of any mechanism to induce adaptive immunity against PM_{2.5} is unclear and must be investigated. Also, there is no information about the other components of PM_{2.5} that may have receptors in pneumocytes. Moreover, it is not clear whether or not there is any pathway for the activation of anti-inflammatory response against the induced inflammation by PM_{2.5}.

Additionally, it is not clear why some of the PM_{2.5} can enter the cells, and the others cannot. The response to this question could help in distinguishing between initial inflammatory responses of damaged cells and the prediction of the next steps of inflammation. Moreover, because of the absence of any human studies in this field, the pathological effects of long-term exposures to PM_{2.5} in human lungs are not apparent and must be further investigated to validate these findings (Deng et al. 2013; Moon et al. 2018; Roh and Sohn 2018).

Limitations

Several limitations restricted the conclusions from the included articles. The exposure procedure in several included studies was single-dose exposure, and their results were only compared with their control group. There was no capability to merge their results with other studies to find a correlation between inflammatory response and dose/duration of exposure. Pathological pieces of evidence are significant to illustrate the inflammation in tissues, but just a few articles had pathological investigations. We found several short period animal studies about the inflammatory effects of PM_{2.5} on lung cells, which included pathological evaluation. However, those articles lacked the chemical analysis of particulate, which is a critical data and had been excluded from this review. Another limitation of this study was related to the selected exposure doses in animal studies. The exposure doses were not selected according to the respiration rates of animals. Therefore, we could not extrapolate the animal results to the human. There was no co-culture study in *in vitro* studies. Thus, there were no results about innate immune cells that responded to inflammatory cytokines secreted from the lung cells.

Conclusion

According to the *in vitro* and animal studies, urban PM_{2.5} activates the inflammatory pathway that involves innate immune responses initiated from exposed/damaged lung parenchymal cells. PM_{2.5} cannot activate adaptive immune

responses because of their chemical nature. However, this condition strengthens the development of obstructive diseases such as emphysema and weakens the probability of restrictive diseases such as IPF because the exposure to PM_{2.5} and following inflammation is permanent in urban areas. More detailed and robust evidence about the inflammatory effects of long-term exposure to PM_{2.5} would have to come from human studies such as cohort or cross-sectional studies on highly exposed persons. The adaptation mechanisms to balance inflammatory and anti-inflammatory pathways in humans are unclear and need further investigations. Moreover, the effect of seasonal changes in PM_{2.5} exposure dose on inflammation is unclear. Also, variations in the composition of particulates need to be investigated further.

Acknowledgements The authors are grateful to Dr. Kaveh Sadeghi at the Virology Department, School of Public Health, Tehran University of Medical Sciences, for scientific support.

Author contribution HRS and SR extracted data and wrote manuscript. MY designed the study and search strategy. BJ discussed the results.

Data availability All of the used datasets during the current study are available online.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

References

- Abbas AK, Lichtman AH, Pillai S (2019a) Basic immunology e-book: functions and disorders of the immune system. Elsevier Health Sciences
- Abbas I, Badran G, Verdin A, Ledoux F, Roumie M, Lo Guidice JM, Courcot D, Garçon G (2019b) *In vitro* evaluation of organic extractable matter from ambient PM_{2.5} using human bronchial epithelial BEAS-2B cells: cytotoxicity, oxidative stress, pro-inflammatory response, genotoxicity, and cell cycle deregulation. *Environ Res* 171: 510–522
- Akhtar US, McWhinney RD, Rastogi N, Abbatt JP, Evans GJ, Scott JA (2010) Cytotoxic and proinflammatory effects of ambient and source-related particulate matter (PM) in relation to the production of reactive oxygen species (ROS) and cytokine adsorption by particles. *Inhal Toxicol* 22:37–47
- Chilosi M, Poletti V, Rossi A (2012) The pathogenesis of COPD and IPF: distinct horns of the same devil? *Respir Res* 13:3
- Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, Balakrishnan K, Brunekreef B, Dandona L, Dandona R, Feigin V, Freedman G, Hubbell B, Jobling A, Kan H, Knibbs L, Liu Y, Martin R, Morawska L, Pope CA III, Shin H, Straif K, Shaddick G, Thomas M, van Dingenen R, van Donkelaar A, Vos T, Murray CJL, Forouzanfar MH (2017) Estimates and 25-year trends of the global

- burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet* 389: 1907–1918
- Cosio MG, Majo J, Cosio MG (2002) Inflammation of the airways and lung parenchyma in COPD: role of T cells. *Chest* 121:160S–165S
- Cottin V, Hansell DM, Sverzellati N, Weycker D, Antoniou KM, Atwood M, Oster G, Kirchgaessler KU, Collard HR, Wells AU (2017) Effect of emphysema extent on serial lung function in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 196:1162–1171
- Dagher Z, Garçon G, Billet S, Gosset P, Ledoux F, Courcot D, Aboukais A, Shirali P (2006) Activation of different pathways of apoptosis by air pollution particulate matter (PM_{2.5}) in human epithelial lung cells (L132) in culture. *Toxicology* 225:12–24
- Dagher Z, Garçon G, Gosset P, Ledoux F, Surpateanu G, Courcot D, Aboukais A, Puskaric E, Shirali P (2005) Pro-inflammatory effects of Dunkerque city air pollution particulate matter 2.5 in human epithelial lung cells (L132) in culture. *J Appl Toxicol* 25:166–175
- Deiuliis JA et al (2012) Pulmonary T cell activation in response to chronic particulate air pollution. *Am J Phys Lung Cell Mol Phys* 302:L399–L409
- Deng X, Zhang F, Rui W, Long F, Wang L, Feng Z, Chen D, Ding W (2013) PM_{2.5}-induced oxidative stress triggers autophagy in human lung epithelial A549 cells. *Toxicol in Vitro* 27:1762–1770
- Dergham M, Lepers C, Verdin A, Cazier F, Billet S, Courcot D, Shirali P, Garçon G (2015) Temporal–spatial variations of the physicochemical characteristics of air pollution particulate matter (PM_{2.5–0.3}) and toxicological effects in human bronchial epithelial cells (BEAS-2B). *Environ Res* 137:256–267
- Dominici F, Peng RD, Bell ML, Pham L, McDermott A, Zeger SL, Samet JM (2006) Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *Jama* 295:1127–1134
- El-Bayoumi E, Silvestri GA (2008) Bronchoscopy for the diagnosis and staging of lung cancer. In: *Seminars in respiratory and critical care medicine*. vol 03. © Thieme Medical Publishers, pp 261–270
- Feng S, Gao D, Liao F, Zhou F, Wang X (2016) The health effects of ambient PM_{2.5} and potential mechanisms. *Ecotoxicol Environ Saf* 128:67–74
- Gandhi NA, Bennett BL, Graham NM, Pirozzi G, Stahl N, Yancopoulos GD (2016) Targeting key proximal drivers of type 2 inflammation in disease. *Nat Rev Drug Discov* 15:35–50
- Gao J, Peng X, Chen G, Xu J, Shi G-L, Zhang Y-C, Feng Y-C (2016) Insights into the chemical characterization and sources of PM_{2.5} in Beijing at a 1-h time resolution. *Sci Total Environ* 542:162–171
- Gavett SH, Haykal-Coates N, Copeland LB, Heinrich J, Gilmour MI (2003) Metal composition of ambient PM_{2.5} influences severity of allergic airways disease in mice. *Environ Health Perspect* 111: 1471–1477
- Geng H, Meng Z, Zhang Q (2006) In vitro responses of rat alveolar macrophages to particle suspensions and water-soluble components of dust storm PM_{2.5}. *Toxicol in Vitro* 20:575–584
- Gualtieri M, Øvrevik J, Holme JA, Perrone MG, Bolzacchini E, Schwarze PE, Camatini M (2010) Differences in cytotoxicity versus pro-inflammatory potency of different PM fractions in human epithelial lung cells. *Toxicol in Vitro* 24:29–39
- Happo M et al (2010) Seasonal variation in chemical composition of size-segregated urban air particles and the inflammatory activity in the mouse lung. *Inhal Toxicol* 22:17–32
- He M, Ichinose T, Kobayashi M, Arashidani K, Yoshida S, Nishikawa M, Takano H, Sun G, Shibamoto T (2016) Differences in allergic inflammatory responses between urban PM_{2.5} and fine particle derived from desert-dust in murine lungs. *Toxicol Appl Pharmacol* 297:41–55
- He M, Ichinose T, Yoshida S, Ito T, He C, Yoshida Y, Arashidani K, Takano H, Sun G, Shibamoto T (2017) PM_{2.5}-induced lung inflammation in mice: differences of inflammatory response in macrophages and type II alveolar cells. *J Appl Toxicol* 37:1203–1218
- He R-W, Shirmohammadi F, Gerlofs-Nijland ME, Sioutas C, Cassee FR (2018) Pro-inflammatory responses to PM_{2.5} from airport and urban traffic emissions. *Sci Total Environ* 640:997–1003
- Hong Z, Guo Z, Zhang R, Xu J, Dong W, Zhuang G, Deng C (2016) Airborne fine particulate matter induces oxidative stress and inflammation in human nasal epithelial cells. *Tohoku J Exp Med* 239:117–125
- Hou T, Liao J, Zhang C, Sun C, Li X, Wang G (2018) Elevated expression of miR-146, miR-139 and miR-340 involved in regulating Th1/Th2 balance with acute exposure of fine particulate matter in mice. *Int Immunopharmacol* 54:68–77
- Hsu C-Y et al (2017) Ambient PM_{2.5} in the residential area near industrial complexes: spatiotemporal variation, source apportionment, and health impact. *Sci Total Environ* 590:204–214
- Huang K-L, Liu S-Y, Chou CC, Lee Y-H, Cheng T-J (2017a) The effect of size-segregated ambient particulate matter on Th1/Th2-like immune responses in mice. *PLoS One* 12
- Huang Q, Chi Y, Deng J, Liu Y, Lu Y, Chen J, Dong S (2017b) Fine particulate matter 2.5 exerted its toxicological effect by regulating a new layer, long non-coding RNA. *Sci Rep* 7:1–9
- Jin W, Wang L (2019) Role of rapid on site evaluation in preliminary diagnosis of pulmonary infection during bronchoscopy. *Eur Respiratory Soc*
- Kim I, Lee K, Lee S, Kim SD (2019) Characteristics and health effects of PM_{2.5} emissions from various sources in Gwangju, South Korea. *Sci Total Environ* 696:133890
- Kim KM, Pae H-O, Zheng M, Park R, Kim Y-M, Chung H-T (2007) Carbon monoxide induces heme oxygenase-1 via activation of protein kinase R-like endoplasmic reticulum kinase and inhibits endothelial cell apoptosis triggered by endoplasmic reticulum stress. *Circ Res* 101:919–927
- King TE Jr, Pardo A, Selman M (2011) Idiopathic pulmonary fibrosis. *Lancet* 378:1949–1961
- Kulkarni N, Pierse N, Rushton L, Grigg J (2006) Carbon in airway macrophages and lung function in children. *N Engl J Med* 355:21–30
- Kumar V, Abbas AK, Fausto N, Aster JC (2014) Robbins and Cotran pathologic basis of disease, professional edition e-book. Elsevier health sciences
- Lauer FT, Mitchell LA, Bedrick E, McDonald JD, Lee WY, Li WW, Olvera H, Amaya MA, Berwick M, Gonzales M, Currey R, Pingitore NE Jr, Burchiel SW (2009) Temporal–spatial analysis of US–Mexico border environmental fine and coarse PM air sample extract activity in human bronchial epithelial cells. *Toxicol Appl Pharmacol* 238:1–10
- Leclercq B, Alleman LY, Perdrix E, Riffault V, Hapillon M, Strecker A, Lo-Guidice JM, Garçon G, Coddeville P (2017) Particulate metal bioaccessibility in physiological fluids and cell culture media: toxicological perspectives. *Environ Res* 156:148–157
- Lewis JB, Bodine JS, Gassman JR, Muñoz SA, Milner DC, Dunaway TM, Egbert KM, Monson TD, Broberg DS, Arroyo JA, Reynolds PR (2018) Transgenic up-regulation of Claudin-6 decreases fine diesel particulate matter (DPM)-induced pulmonary inflammation. *Environ Sci Pollut Res* 25:18179–18188
- Li D, Zhang R, Cui L, Chu C, Zhang H, Sun H, Luo J, Zhou L, Chen L, Cui J, Chen S, Mai B, Chen S, Yu J, Cai Z, Zhang J, Jiang Y, Aschner M, Chen R, Zheng Y, Chen W (2019) Multiple organ injury in male C57BL/6J mice exposed to ambient particulate matter in a real-ambient PM exposure system in Shijiazhuang, China. *Environ Pollut* 248:874–887
- Li H, Wang Q, Yang M, Li F, Wang J, Sun Y, Wang C, Wu H, Qian X (2016) Chemical characterization and source apportionment of PM_{2.5} aerosols in a megacity of Southeast China. *Atmos Res* 181:288–299

- Lin G, Fu J, Jiang D, Hu W, Dong D, Huang Y, Zhao M (2014) Spatio-temporal variation of PM_{2.5} concentrations and their relationship with geographic and socioeconomic factors in China. *Int J Environ Res Public Health* 11:173–186
- Liu Q, Baumgartner J, Zhang Y, Schauer JJ (2016) Source apportionment of Beijing air pollution during a severe winter haze event and associated pro-inflammatory responses in lung epithelial cells. *Atmos Environ* 126:28–35
- Liu S, Zhang W, Zhang F, Roepstorff P, Yang F, Lu Z, Ding W (2019) TMT-based quantitative proteomics analysis reveals airborne PM_{2.5}-induced pulmonary fibrosis. *International journal of environmental research and public health* 16:98
- McMillan SJ et al (2004) Matrix metalloproteinase-9 deficiency results in enhanced allergen-induced airway inflammation. *J Immunol* 172:2586–2594
- Medzhitov R (2008) Origin and physiological roles of inflammation. *Nature* 454:428–435
- Miller MR, Borthwick SJ, Shaw CA, McLean SG, McClure D, Mills NL, Duffin R, Donaldson K, Megson IL, Hadoke PWF, Newby DE (2009) Direct impairment of vascular function by diesel exhaust particulate through reduced bioavailability of endothelium-derived nitric oxide induced by superoxide free radicals. *Environ Health Perspect* 117:611–616
- Moon D et al (2018) Altered proinflammatory cytokines and M1 polarization induced by PM_{2.5} in alveolar macrophages. *Appl Ecol Environ Res* 16:7699–7712. https://doi.org/10.15666/aecer/1606_76997712
- Pieterse B, Felzel E, Winter R, Van Der Burg B, Brouwer A (2013) PAH-CALUX, an optimized bioassay for AhR-mediated hazard identification of polycyclic aromatic hydrocarbons (PAHs) as individual compounds and in complex mixtures. *Environ Sci Technol* 47:11651–11659
- Prieto-Parra L, Yohannessen K, Brea C, Vidal D, Ubilla CA, Ruiz-Rudolph P (2017) Air pollution, PM_{2.5} composition, source factors, and respiratory symptoms in asthmatic and nonasthmatic children in Santiago, Chile. *Environ Int* 101:190–200
- Raaschou-Nielsen O, Beelen R, Wang M, Hoek G, Andersen ZJ, Hoffmann B, Stafoggia M, Samoli E, Weinmayr G, Dimakopoulou K, Nieuwenhuijsen M, Xun WW, Fischer P, Eriksen KT, Sørensen M, Tjønneland A, Ricceri F, de Hoogh K, Key T, Eeftens M, Peeters PH, Bueno-de-Mesquita HB, Meliefste K, Oftedal B, Schwarze PE, Nafstad P, Galassi C, Migliore E, Ranzi A, Cesaroni G, Badaloni C, Forastiere F, Penell J, de Faire U, Korek M, Pedersen N, Östenson CG, Pershagen G, Fratiglioni L, Concin H, Nagel G, Jaensch A, Ineichen A, Naccarati A, Katsoulis M, Trichopoulos A, Keuken M, Jedynska A, Kooter IM, Kukkonen J, Brunekreef B, Sokhi RS, Katsouyanni K, Vineis P (2016) Particulate matter air pollution components and risk for lung cancer. *Environ Int* 87:66–73
- Radan M, Dianat M, Badavi M, Mard SA, Bayati V, Goudarzi G (2019) In vivo and in vitro evidence for the involvement of Nrf2-antioxidant response element signaling pathway in the inflammation and oxidative stress induced by particulate matter (PM₁₀): the effective role of gallic acid. *Free Radic Res* 53:210–225
- Roh JS, Sohn DH (2018) Damage-associated molecular patterns in inflammatory diseases. *Immune netw* 18
- Ruwanpura S, McLeod L, Anderson G, Jenkins B (2017) Novel role of inflammasomes in the molecular pathogenesis of emphysema. In: D97. Impact of inflammation on acute lung injury. American Thoracic Society, pp A7328–A7328
- Sato A et al (2017) Diagnosis and clinical course of patients referred with chest X-ray abnormalities and suspected of nontuberculous mycobacterial lung disease. In: B62. Non-tuberculous mycobacteria: clinical aspects and cases. American Thoracic Society, pp A3966–A3966
- Sharafkhaneh A, Hanania NA, Kim V (2008) Pathogenesis of emphysema: from the bench to the bedside. *Proc Am Thorac Soc* 5:475–477
- Strieter RM (2008) What differentiates normal lung repair and fibrosis? Inflammation, resolution of repair, and fibrosis. *Proc Am Thorac Soc* 5:305–310
- Taraseviciene-Stewart L, Voelkel NF (2008) Molecular pathogenesis of emphysema. *J Clin Invest* 118:394–402
- Wang S et al (2017) Exposure to high level PM_{2.5} causes increased central blood pressure. *Circulation* 136:A19823–A19823
- Wilson M, Wynn T (2009) Pulmonary fibrosis: pathogenesis, etiology and regulation. *Mucosal Immunol* 2:103–121
- Wing K, Sakaguchi S (2010) Regulatory T cells exert checks and balances on self tolerance and autoimmunity. *Nat Immunol* 11:7–13
- Wingate P, McAulay K, Anthony I, Crawford D (2009) Regulatory T cell activity in primary and persistent Epstein–Barr virus infection. *J Med Virol* 81:870–877
- Wolters PJ, Collard HR, Jones KD (2014) Pathogenesis of idiopathic pulmonary fibrosis. *Ann Rev Pathol Mech Dis* 9:157–179
- Zhang Y, Lang J, Cheng S, Li S, Zhou Y, Chen D, Zhang H, Wang H (2018) Chemical composition and sources of PM₁ and PM_{2.5} in Beijing in autumn. *Sci Total Environ* 630:72–82
- Zhao Y, Zhang H, Yang X, Zhang Y, Feng S, Yan X (2019) Fine particulate matter (PM_{2.5}) enhances airway hyperresponsiveness (AHR) by inducing necroptosis in BALB/c mice. *Environ Toxicol Pharmacol* 68:155–163

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.