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The impact of airborne particulate matter-based pollution on the cellular and molecular mechanisms in chronic obstructive pulmonary disease (COPD)

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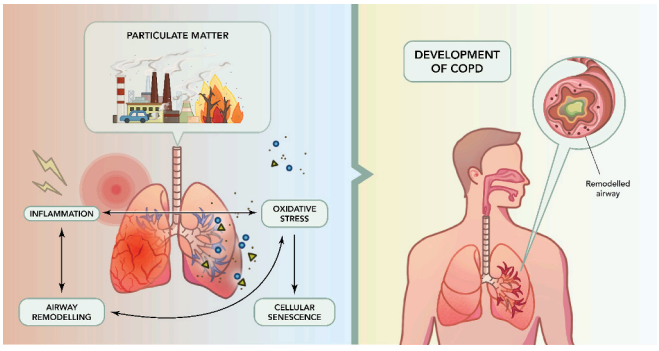
HIGHLIGHTS

- Inhalation of air pollution can lead to chronic respiratory disease.
- Numerous pathophysiological mechanisms can be induced by particulate matter.
- Chronic inflammation and oxidative stress can be induced by air pollution exposure.
- Particulate matter is a genuine global health and environmental issue.
- There is an urgent need for greater action to decrease global airborne pollution.

GRAPHICAL ABSTRACT



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ABSTRACT

Inhalation of particulate matter (PM), one of the many components of air pollution, is associated with the development and exacerbation of chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD). COPD is one of the leading causes of global mortality and morbidity, with a paucity of therapeutic options and a significant contributor to global health expenditure. This review aims to provide a mechanistic understanding of the cellular and molecular pathways that lead to the development of COPD following chronic PM exposure. Our review describes how the inhalation of PM can lead to lung parenchymal destruction and cellular senescence due to chronic pulmonary inflammation and oxidative stress. Following inhalation of PM, significant increases in a range of pro-inflammatory cytokines, mediated by the nuclear factor kappa B pathway

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are reported. This review also highlights how the inhalation of PM can lead to deleterious chronic oxidative stress persisting in the lung post-exposure. Furthermore, our work summarises how PM inhalation can lead to airway remodelling, with increases in pro-fibrotic cytokines and collagen deposition, typical of COPD. This paper also accentuates the interconnection and possible synergism between the pathophysiological mechanisms leading to COPD. Our work emphasises the serious health consequences of PM exposure on respiratory health. Elucidation of the cellular and molecular mechanisms can provide insight into possible therapeutic options. Finally, this review should serve as a stark reminder of the need for genuine action on air pollution to decrease the associated health burden on our growing global population.

1. Introduction

Since the eighteenth century, industrialisation and human activity in growing urban and industrial areas has led to vast reductions in air quality, including increased pollutant gases and particulate matter (PM) (Fowler et al., 2020). Currently, in 2024, according to the World Health Organization (WHO), 99 % of the world's population lives in places where air pollution levels exceed WHO limits, with approximately 6.7 million deaths each year occurring from exposure to ambient and household air pollution (World Health Organisation, 2024).

Air pollution has many components, such as gases (e.g. ozone, oxygen, carbon dioxide, carbon monoxide, sulphur oxides, and nitrogen oxides), volatile organic compounds (VOCs), and PM (Kaur et al., 2022). PM consists of an intricate mixture of microscopic particles and liquid droplets that enter the atmosphere. PM originates from various sources, but two main contributors include motor vehicle and roadway emissions, also known as traffic-related air pollution (TRAP) (Matz et al., 2019), and biomass fuel combustion. Other sources include emissions from power plants, industrial processes (e.g. agricultural and garbage burning), large-scale demolition and reconstruction and natural hazards such as bushfires (Yuk et al., 2022). These PM sources contribute to both ambient and household air pollution (Kaur et al., 2022).

1.1. PM characterisation

PM is commonly characterised by the size (aerodynamic diameter) of the particles (Table 1) (Pizzorno and Crinnion, 2017). Particles that are "coarse" range from 2.5 to 10 μm in diameter and are typically denoted as PM_{10}. However, it is worth noting that PM_{10} includes all particles <10 μm. Coarse particles are commonly located near dusty roads, highways, and industrial areas. Particles that are "fine", range from 0.1 to 2.5 μm in diameter, and are denoted as $PM_{2.5}$. Particles that are "ultrafine" (UFP), also known as nanoparticles, are <0.1 μm in diameter ($PM_{0.1}$). These ultrafine particles exhibit greater solubility compared to larger particles (Schraufnagel, 2020).

The abundance and composition of PM can vary depending on the geographic location. Cities that have relatively low levels of ambient PM include cities such as Sydney, Australia (annual average < 20 $\mu g/m^3$) (Paton-Walsh et al., 2019; Schuliga and Bartlett, 2019). In Australia, factors such as a relatively low population density, a relatively small manufacturing industry, and proactive emission reduction policies all contribute to the low levels of ambient PM (de Jesus et al., 2020). Conversely, densely populated and heavily industrialised cities, such as Beijing, Delhi and Hong Kong, have a much higher concentration of PM (annual average > 100 $\mu g/m^3$) (Elzein et al., 2020; Schuliga and Bartlett, 2019). Moreover, the chemical composition and the abundance of PM can vary depending on the geographical location within a city (e.g. roadside versus underground railway stations (Smith et al., 2020)), the time of the year (e.g. spring versus winter), and the source of PM (natural versus anthropogenic) (Song et al., 2020). This combination of variables contributes to the heterogeneous chemical composition of PM. For example, PM emitted from coal combustion commonly comprises toxic heavy metals such as, As, Cd, Cr, Cu, Pb and Zn (Gao et al., 2018). Conversely, indoor PM, typically emitted from biomass combustion used in heating or cooking, has a high abundance of organic compounds such as levoglucosan, alkanes and polycyclic aromatic hydrocarbons (PAHs) (Lai et al., 2019).

1.2. Health effects of PM exposure

Upon inhalation of polluted air, PM will reach the pharynx whereby the PM can either be respired and enter the lower respiratory system or swallowed, travelling to the gastrointestinal system. Additionally, once PM is respired and reaches the trachea and bronchi, mucociliary action will remove some of this PM, further contributing to the PM that is then ingested. These are the two predominant routes by which PM enters the

Table 1
A comparison of the heterogeneity of particulate matter (PM) and how this can correspond to the size, origin, composition, lung deposition site and the potential health effects.

Characteristics	PM_{10} (2.5–10 μm)	$PM_{2.5}$ (0.1–2.5 μm)	$PM_{0.1}$ (<0.1 μm)	References
Origin	Generated from construction sites, landfills, agricultural activities, as well as emissions from wildfires and burning of brush or waste.	Generated from emissions from motor vehicles, road dust, and combustion of biomass and oil.	Forest fires, viruses, vehicle and power plant emissions, and tobacco smoking.	(California Air Resources Board, 2024; Morawska and Buonanno, 2021)
Composition	Dust, coal, metal oxides, elemental aggregates (Ba, Cr, Cu, Mo, Pd, Sb, Zn, and Zr), and sea salt	Black carbon, elemental aggregates (Ba, Cr, Cu, Mo, Pd, Sb, Zr, S, Cd, V, Ni, Zn, Fe, Li, Mn, and Ti), nitrates, sulphates, and organic compounds.	Organic compounds, black carbon, sulphates, trace elements, and small amounts of Na and Cl.	(Cass et al., 2000; Kaur et al., 2022; Masri et al., 2015; Oroumiyeh et al., 2022; Zhou et al., 2022)
Location of deposition in lung	Reaches lower respiratory tract (i.e. trachea, bronchi, and bronchioles).	Reaches peripheral airways (i.e. distal bronchioles and alveolar ducts).	Escape bronchial-mucociliary clearing and reaches deep into the respiratory tract. These particles are so fine they can enter systemic circulation.	(Kaur et al., 2022; Kwon et al., 2020; Peters et al., 2006)
Potential pathogenic effect of particle	Due to the large size, is retained in the mucus layer and is eliminated from airways by mucociliary clearance. However, endotoxins or trace elements associated with the particles can stay in the mucus lining and trigger adverse events.	Due to their size, they can remain suspended and persist in the airway for longer. Due to this, it can irritate the mucus lining, causing adverse events.	Due to their small size, these particles remain in the respiratory tract and body for long periods of time, resulting in prolonged mucus irritation and potentially chronic adverse events.	(Kaur et al., 2022; Kwon et al., 2020; Ling and van Eeden, 2009)

human body, inhalation and oral ingestion (Thompson, 2018). Oral ingestion of PM can lead to a range of pathologies, including PM-induced cellular toxicity, inflammation, increased permeability and changes to the gut microbiome (Kish et al., 2013; Mutlu et al., 2011). Inhalation of PM exposes the lungs and the respiratory system to significant health ramifications (Chen and Hoek, 2020; Pizzorno and Crinnion, 2017). The size of PM is particularly important as this dictates the location of PM deposition within the lung (Fig. 1, Table 1).

Strong epidemiological and experimental evidence has emerged to show that exposure to PM is correlated with a diverse range of adverse health outcomes (Chen et al., 2022; Chen and Hoek, 2020). In 2020, a systematic review of 107 epidemiological studies found that chronic exposure to $PM_{2.5}$ at levels below the WHO Air Quality Guidelines (AQG) mean annual exposure of 10 $\mu g/m^3$ was associated with increased mortality from respiratory diseases such as chronic obstructive pulmonary disease (COPD), acute lower respiratory tract infection, and cardiovascular disease (Chen and Hoek, 2020). In 2019, many countries and cities had ambient PM_{10} levels below the WHO's recommended AQG of 20 $\mu g/m^3$. However, epidemiological studies showed adverse lung health effects persisted with chronic exposure to PM_{10} at these levels (Schuliga and Bartlett, 2019). Considering this new evidence, in 2021, the WHO revised its AQG to a recommended maximal annual average $PM_{2.5}$ exposure of 5 $\mu g/m^3$ and PM_{10} exposure of 15 $\mu g/m^3$ (World Health Organisation, 2021). This highlights the growing body of evidence that exposure to even very low levels of PM is a genuine public health concern. The aim of this review is to collate the emerging evidence to facilitate a better mechanistic understanding of how the inhalation of PM can lead to the development of COPD. Additionally, we will review the impact of PM on the main pathophysiological features of this disease.

2. Chronic obstructive pulmonary disease

COPD is a lung disease characterised by the obstruction of airflow (Hogg et al., 2004). The disease is caused by prolonged exposure to harmful particles or gases such as cigarette smoke or air pollution, including PM (Agarwal et al., 2023). COPD is a progressive, chronic, incurable disease, but it is preventable and manageable (Kaur et al., 2022).

Common symptoms of COPD include breathlessness after exertion, wheezing, coughing, sputum production (mucus or phlegm), poor skeletal muscle function and wasting. One of the main risk factors for COPD is smoking, where the majority of people diagnosed with COPD currently smoke or have a smoking history. According to the WHO, tobacco smoking accounts for over 70 % of COPD cases in high-income countries (World Health Organisation, 2023b). Additionally, in an ongoing prospective Dutch population-based cohort study (the Rotterdam Study), it was found that 41 % of COPD patients were current smokers, 42.6 % were former smokers, and the incidence rate of COPD was 8.9/1000 person-years (Terzikhan et al., 2016). Other risk factors include ambient and household air pollution and a low body mass index (<20 kg/m^2), which was associated with worse pulmonary function and a higher risk of future severe exacerbation and mortality (Putcha et al., 2022; Song et al., 2023). Childhood asthma, dust exposure, and diet are also risk factors (Holtjer et al., 2023).

Impaired lung growth, leading to dysanapsis, and poor baseline respiratory function has also been identified as a risk factor for the development of COPD (Ralalage and Hurst, 2023; Yang et al., 2022). Postnatal air pollution exposure has been linked to the early life development of airway obstruction and dysanapsis, potentially predisposing these individuals to developing COPD (Bourbeau et al., 2022; McGinn et al., 2023). Experimental data has supported this concept, reporting that prenatal and postnatal PM exposure in mice reduces alveoli and compromises lung development (de Barros Mendes Lopes

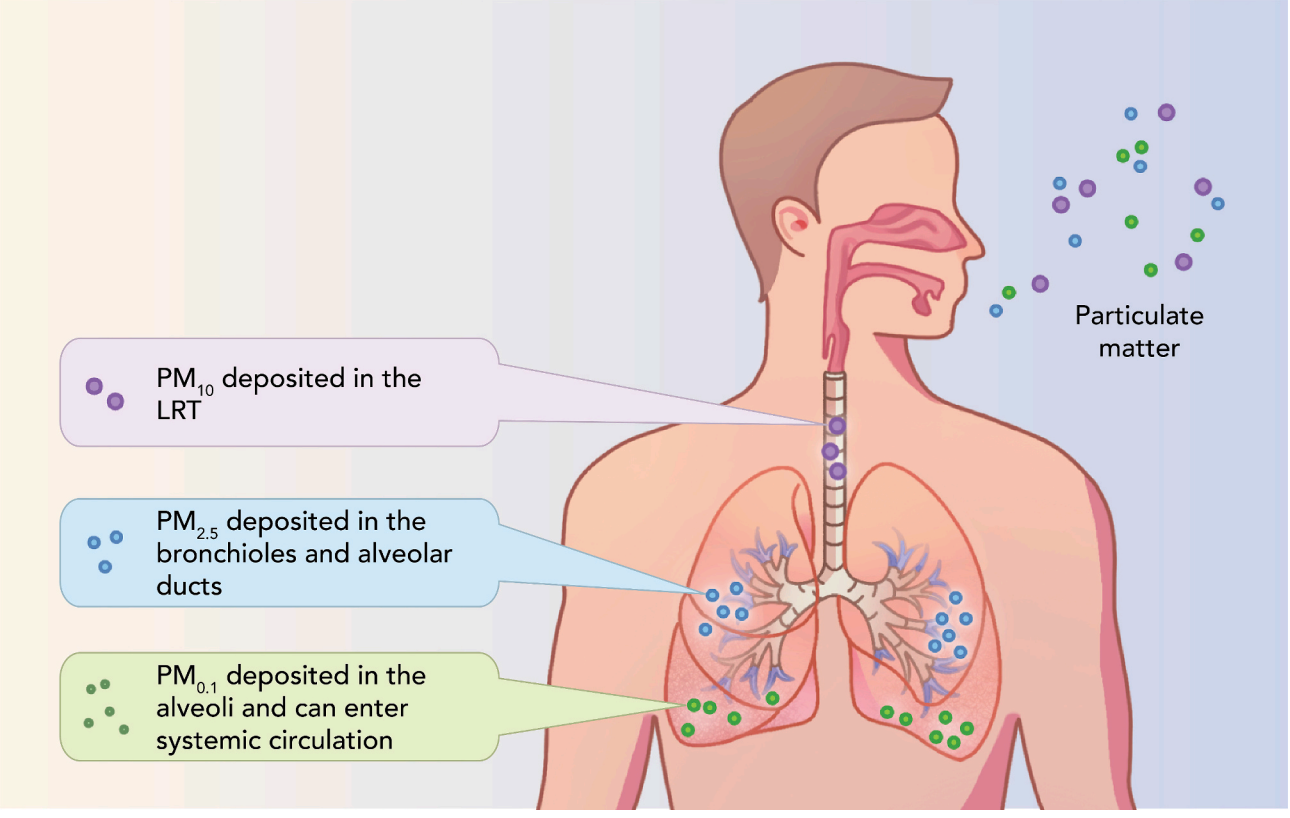

Fig. 1. The aerodynamic diameter of particulate matter (PM) influences the site of PM deposition within the respiratory system. LRT = lower respiratory tract.

et al., 2018). This highlights how early-life environmental exposures can predispose individuals to developing COPD later in life.

2.1. Epidemiology of COPD

COPD typically manifests in individuals over 40 years of age (Agarwal et al., 2023). Based on records from the WHO, COPD accounted for 3.23 million deaths in 2019 and continues to grow worldwide (World Health Organisation, 2023a). In 2020, the prevalence of COPD was estimated to be 10.6 % of the world's population (479 million cases) (Boers et al., 2023). The number of cases is projected to increase, and by 2050, it is estimated that COPD will have a prevalence of 9.5 % (591 million cases) (Boers et al., 2023). The latest data indicates that in 2021, COPD was the fourth leading cause of mortality (Naghavi et al., 2024) and the sixth leading cause of disability-adjusted life years (Vollset et al., 2024).

More specifically, focusing on Australia in 2017–2018, it was estimated that 464,000 (4.8 %) of people in Australia over the age of 45 had COPD (Australian Institute of Health and Welfare, 2024). Although COPD is often associated with smoking, an estimated 25 % to 45 % of COPD patients have never smoked (Ruvuna and Sood, 2020). Therefore, it is vital to address global risk factors, such as air pollution, as they increasingly contribute to the incidence of COPD.

2.2. Pathophysiology of COPD

COPD presents as a heterogeneous disease with irreversible airflow limitation, destruction of alveoli, and chronic inflammation (Han et al., 2010; Kaur et al., 2022). The pathogenesis of COPD is complex and not fully understood. However, it is thought to involve multiple mechanisms, including protease-antiprotease imbalances, changes to lung epithelium, epigenetic modifications, disturbances in autophagy, and dysfunction of mitochondria (Agarwal et al., 2023; Kaur et al., 2022). These mechanisms are regulated through various signalling pathways, with inflammation and oxidative stress playing central roles (Barnes, 2016; Kirkham and Barnes, 2013).

The COPD disease state first begins when lung tissue is exposed to irritants, such as tobacco smoke and PM, damaging the lung tissue. Damage can be done to either bronchi (causing chronic bronchitis), alveoli (causing emphysema), or both (Candela et al., 2019). Shortness of breath is the main symptom of emphysema, with coughing and hypersecretion of mucus being modest. In contrast, mucus hypersecretion is the main symptom of chronic bronchitis, with shortness of breath being modest (Candela et al., 2019; Hogg et al., 2004).

Regardless of the COPD phenotype, damage to the lung tissue triggers an inflammatory response. This inflammatory response recruits neutrophils and macrophages to the damaged area, releasing multiple inflammatory mediators. These mediators are predominantly proteases (e.g. neutrophil elastase, matrix metalloproteins), which in normal tissue repair are balanced by antiproteases (e.g. alpha-1 antitrypsin) to regulate the breakdown of damaged connective tissue and elastin (Kaur et al., 2022; Wise, 2022). However, in patients with COPD, protease activity exceeds antiprotease activity, causing further lung tissue breakdown, lung parenchymal destruction and mucus hypersecretion (Agarwal et al., 2023; Wise, 2022). With extended exposure to irritants, inflammation becomes chronic in the lung parenchyma. There is also an excess of growth factors and cytokines, activated fibroblasts and other mechanisms which are involved in airway remodelling (James and Wenzel, 2007; Kayalar et al., 2024; Oudijk et al., 2003).

Upon damage to the lung tissue, a repair and remodelling process is initiated whereby restoration of epithelium and connective tissue occurs – this is known as airway remodelling and directly results in the thickening of small airway walls (Hogg et al., 2004). Thickening of, alveolar epithelium, airway smooth muscle, reticular basement membrane, and submucosal mucous glands also occurs as part of this repair and remodelling process (James and Wenzel, 2007). In 2004, Hogg et al. showed that the buildup of inflammatory mucous exudates within the airway lumen and infiltration of the airway walls by immune cells occurs as a result of small airway remodelling (Hogg et al., 2004). Moreover, due to the protease-mediated destruction of elastin in the lung, there is a loss of elastic recoil in the airways (Agarwal et al., 2023).

The pathophysiology of COPD also includes the loss of small airways and alveoli (Black et al., 2008). In 1968, Hogg et al. experimentally demonstrated that the small airways are the site of airflow limitation in COPD (Hogg et al., 1968). The reduced number of small airways and the fibrosis of the small airways results in a smaller lumen cross-section, ultimately leading to an inability for gas to leave the lungs during expiration. This is known as gas trapping and can cause dynamic hyperinflation of the lungs (James and Wenzel, 2007). Furthermore, there is a component of dynamic airway collapse which can further restrict airflow (James and Wenzel, 2007). This collapse of the small airways restricting airflow is most likely due to a combination of factors, including a loss of elastic recoil in the lung parenchyma, a reduction in attachments to the airway walls, and a decrease in the stiffness of the airway walls (James and Wenzel, 2007). Ultimately, as a result of all these factors, there is a decrease in oxygen and carbon dioxide exchange in the lungs (James and Wenzel, 2007).

Remodelling of lung parenchyma and mucous hypersecretion lead to the typical symptoms of COPD, such as impairment of lung function seen through wheezing, coughing of phlegm and breathlessness, as measured through a decrease in the forced expiratory volume in 1 s (FEV_1) (Hogg et al., 2004). This can also be observed by using lung imaging, where lung hyperinflation occurs due to trapped air from airway collapse during exhalation. As the disease progresses, impairment of gas exchange is common and can identified by an increase in blood carbon dioxide (CO_2) due to the inability to exhale CO_2 (Agarwal et al., 2023).

2.3. Impact of PM exposure on the development and progression of COPD

As discussed, COPD was traditionally associated with smoking tobacco; however, a notable proportion of individuals who develop COPD have never smoked (Lamprecht et al., 2011; Ruvuna and Sood, 2020). Hence, it is paramount to understand why individuals who have never smoked develop COPD and elucidate the possible risk factors. One plausible explanation is that COPD was induced by PM exposure in this sub-population of never-smokers. Whilst there is strong epidemiological evidence highlighting the association between PM exposure and COPD, a detailed mechanistic understanding of the cellular and molecular pathways of PM-induced COPD is still in its infancy. Researchers have developed both in vitro and in vivo models of PM-induced lung disease to understand the mechanistic pathophysiology (Abbas et al., 2019; Chan et al., 2019; Refsnes et al., 2023; Wang et al., 2021). The hallmark features of chronic inflammation, oxidative stress and airway remodelling found in COPD have all been shown in experimental models following exposure to PM (Fig. 2).

3. Cellular and molecular mechanisms of PM-induced COPD

3.1. Chronic respiratory inflammation and PM exposure

PM inhalation has been shown to induce respiratory inflammation in experimental murine models through cellular and molecular signalling pathways. In one study, Li et al. modelled a high level of $PM_{2.5}$ exposure (591 μg/mouse/week) akin to the exposure found in many cities in China (Li et al., 2020). Following a three-month exposure period, the mice developed $PM_{2.5}$-induced COPD. One contributing mechanism to the development of COPD was the chronic inflammation-associated tissue destruction and the alterations in cytokine expression leading to airway remodelling and decreased lung function (Fig. 2, Table 2). Analysis of the bronchoalveolar lavage fluid (BALF) demonstrated a pro-inflammatory environment through an increase in neutrophil and macrophage recruitment and an increase in pro-inflammatory cytokines,

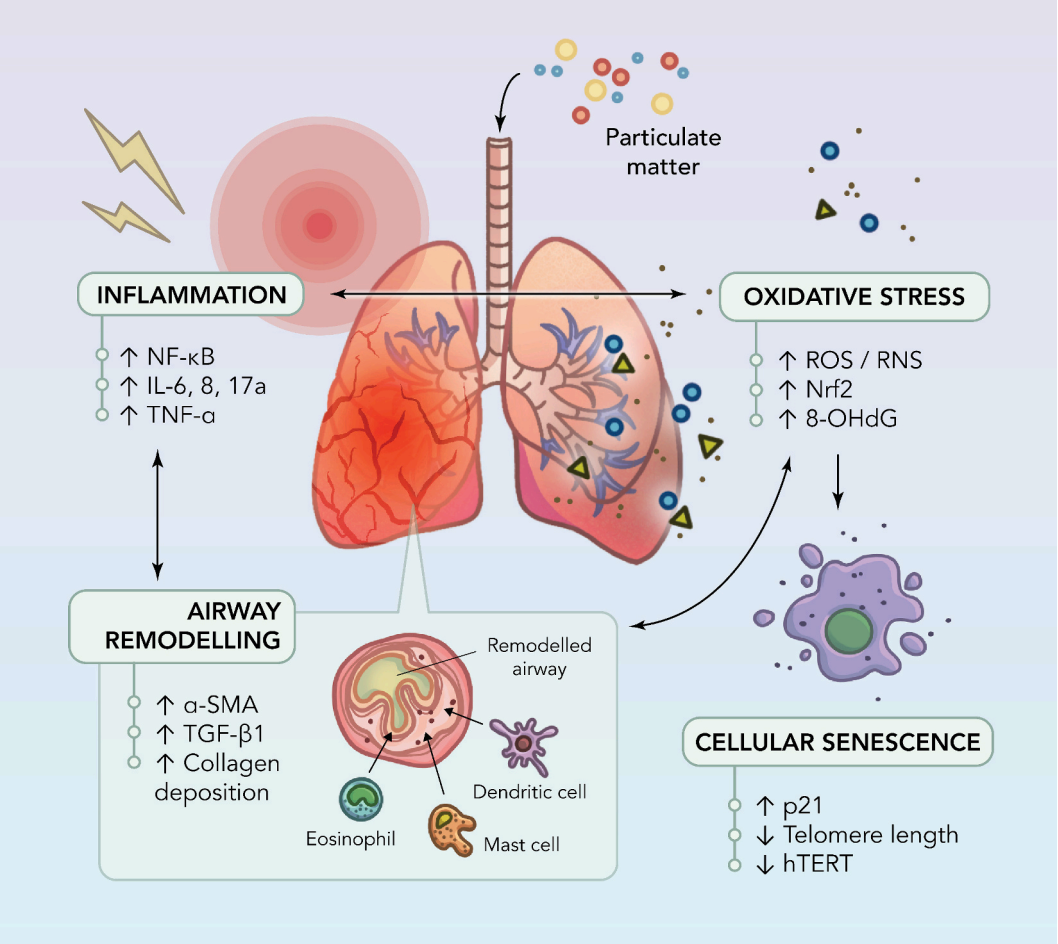

Fig. 2. A graphical depiction of four pathophysiological mechanisms contributing to PM-induced lung damage and COPD. NF-κB = nuclear factor kappa B. IL = interleukin. TNF = tissue necrosis factor. ROS = reactive oxygen species. RNS = reactive nitrogen species. Nrf2 = nuclear factor erythroid 2-related factor 2. 8-OHdG = 8-hydroxy-2′-deoxyguanosine biomarker. *α*-SMA = alpha smooth muscle-actin. TGF-β1 = transforming growth factor beta 1. hTERT = human telomerase reverse transcriptase gene.

interleukin (IL)-6, IL-8, tumour necrosis factor (TNF)-α, IL-17a and interferon (IFN)-γ (Li et al., 2020). A similar pro-inflammatory environment was reported in rats with pre-existing COPD and then exposed to PM with a marked increase in neutrophils and eosinophils, secretion of IL-1β, IL-4, and granulocyte-macrophage colony-stimulating factor (GM-CSF) detected in the BALF (Wang et al., 2020). These results are consistent with previously reported persistent respiratory inflammation seen in COPD (Gan et al., 2004; Hogg et al., 2004).

An Australian group of researchers used a drastically lower $PM_{2.5}$ exposure protocol (5 μg/mouse/day) to model conditions similar to those found in Australia (Wang et al., 2021). The research demonstrated that even at this markedly lower level of $PM_{2.5}$ exposure, a COPD-like pathology was seen through significant pulmonary inflammation, lung damage and airway remodelling in the mice. Despite the considerable difference in the $PM_{2.5}$ exposure levels between the two studies, each found a significant increase in macrophage and neutrophil infiltration into the lung (Li et al., 2020; Wang et al., 2021). Furthermore, Wang and colleagues uncovered the dangers associated with $PM_{2.5}$ exposure during pregnancy, whereby the adult offspring with no direct exposure to PM exhibited marked pulmonary inflammation (Wang et al., 2021). This highlights a possible epigenetic predisposition to developing COPD; however, this requires further investigation.

The nuclear factor kappa B (NF-κB) pathway regulates the production of many inflammatory cytokines (Liu et al., 2017). Emerging experimental evidence has indicated that exposure to $PM_{2.5}$ induces an inflammatory phenotype in exposed mice, whereby immune cell infiltration and pro-inflammatory cytokine release is activated through the NF-κB pathway (Barbier et al., 2023). This same pro-inflammatory pathway is also activated by both PM_{10} exposure (Dai et al., 2020) and a particular subset of PM – diesel exhaust particles (Daniel et al., 2021). Interestingly, in one study, the authors found that 12 weeks post cessation of intranasal $PM_{2.5}$, cytokine expression and inflammation remained significantly elevated in the lungs of mice exposed to $PM_{2.5}$ compared to controls (Barbier et al., 2023). This research suggests that the activation of the NF-κB molecular pathway, and the subsequent persistent inflammation, contributes to the development of COPD induced by PM exposure.

Studies using human volunteers or primary cells have also demonstrated the respiratory dangers and inflammation associated with PM exposure. One particular study found that primary human nasal epithelial cells treated with $PM_{2.5}$ exhibited increased cellular permeability, increased pro-inflammatory cytokine production, and decreased epithelial barrier function through the decreased expression of tight junction-associated proteins (Zhang et al., 2020). Additionally, Zhang and colleagues concluded that this epithelial dysfunction caused by $PM_{2.5}$ exposure could predispose the individual to a higher risk of developing other inflammatory respiratory conditions such as rhinitis and rhinosinusitis. Respiratory inflammation induced by PM exposure was also reported in a Dutch study that exposed 31 volunteers to 5 h of ambient PM (Janssen et al., 2015). This acute exposure period was sufficient to increase nasal and respiratory inflammation. These human studies support the results obtained from in vivo models that have

Table 2
In vivo and in vitro studies exploring the deleterious impact of PM on the cellular and molecular mechanisms involved in the pathophysiology of COPD.

Animals/cells used	Exposure type	Treatment protocol	Exposure duration	Key findings	Reference
Male C57BL/6J mice	Intratracheal instillation	$PM_{2.5}$ 591 μg/week	2 or 3 months	Chronic inflammation associated tissue destruction. Airway remodelling and decreased lung function.	(Li et al., 2020)
Virgin female BALB/c mice and offspring	Intranasal instillation to dams	$PM_{2.5}$ 5 μg/day	6 weeks prior to mating, during gestation and lactation	Significant pulmonary inflammation, airway remodelling and immune cell infiltration into lung. Mitochondrial oxidative stress. Adult offspring with no direct exposure exhibited marked pulmonary inflammation.	(Wang et al., 2021)
Male A/JOlaHsd mice	Intranasal instillation	$PM_{2.5}$ 10 μg, 3 days/week[a]	4 weeks + 12-week recovery period for a sub-group of mice	Activation of NF-κB pathway. Immune cell infiltration and pro-inflammatory cytokine release. Oxidative damage to DNA and proteins. Chronic inflammation persisted in lungs following 12-week recovery period.	(Barbier et al., 2023)
Male ICR mice	Mouth-nose inhalation	$PM_{2.5}$ 398 μg/m^3, 4 h/day, 5 days/week	25 days	Pulmonary oxidative stress and inflammation induced by $PM_{2.5}$ exposure. Strongly association of negative health outcomes with the relative concentration of PAH and heavy metals within the PM.	(Zhou et al., 2022)
Male C57BL/6J and IL-6 KO mice	Intratracheal instillation	PM[b] 200–350 μg/ day	7 or 14 days	Oxidative stress-induced increase in pulmonary and plasma ICAM-1 and IL-6 following PM exposure in WT mice. Minimal effect of PM exposure on ICAM-1 expression in IL-6 KO mice. Increased ICAM-1 expression mediated through IL-6/AKT/STAT/NFκB signalling pathway.	(Liu et al., 2018)
Male Sprague Dawley rats	Whole body exposure chamber	DEP, a model PM, generated from 2 L diesel engine at an average level of 1030 μg/m^3, 4 h/day, 6 days/week	2–8 weeks	Remodelled small airways. Goblet cell hyperplasia and mucus hypersecretion. Increased levels of oxidative stress markers found in serum and increased inflammation.	(Fang et al., 2024)
Male Sprague Dawley rats	Whole body exposure chamber	Average $PM_{2.5}$ exposure of 740 μg/m^3, 4 h/day, 6 days/week	8 weeks	Airway remodelling and peribronchiolar immune cell infiltration. Significant increase in peribronchial TGF-β, collagen I, collagen III, MUC5ac and MUC5b.[d]	(Wang et al., 2020)
C57BL/6 mice	Intratracheal instillation	$PM_{2.5}$ 100 μg, 2 days/week	4 weeks	Airway remodelling, emphysema, smooth muscle hyperplasia and decreased lung function. Increased expression of Wnt5a, β-Catenin, PDGFRβ, and Tenascin C proteins in mouse lung tissue.	(Zou et al., 2021)
C57BL/6 mice	Intratracheal instillation	$PM_{2.5}$ 100 μg, 2 days/week	4 weeks	Wnt5a/JNK/NF-κB pathway activation. Increased production of α-SMA, collagen I, collagen III, IL-6, IL-8, and TNF-α.	(Zou et al., 2023)
Male Wistar rats	Nose-only inhalation	Average $PM_{2.5}$ exposure of 1328 μg/m^3, 5 h/day, 5 days/week	4 weeks	Significant decrease in lung function. Mucous hypersecretion. Significant increase in pro-inflammatory cytokine expression and oxidative damage.	(Feng et al., 2019)
Male C57BL/6J mice	Nose-only inhalation	Average $PM_{2.5}$ exposure of 820 μg/m^3, 4 h/day, 5 days/week	12 weeks	Significant increase in pro-inflammatory cytokines and leukocyte infiltration into pulmonary tissue. Damage to alveoli and airway hyperresponsiveness.	(Lu et al., 2021)
Male Sprague Dawley rats	Nose-only inhalation	Average a$PM_{2.5}$[c] exposure of 1.13 g/m^3, 1 h/day, 7 days/week	4 or 8 weeks	Significant reduction in pulmonary function. Significant increases in oxidative stress, pulmonary immune cell infiltration and pro-inflammatory cytokine expression.	(Yan et al., 2017)
HBEC3-KT	$PM_{2.5}$ suspension added to cell culture medium	Road tunnel $PM_{2.5}$, PM_{10} and $PM_{0.18}$ 100 μg/mL	3–20 h	PM collected from different road tunnel sites induced variable toxic and inflammatory effects. On average, $PM_{2.5}$ induced a more potent pro-inflammatory cytokine response than the PM_{10} or $PM_{0.18}$.	(Refsnes et al., 2023)
BEAS-2B	$PM_{2.5}$ resuspended in DMSO to create O-PM	PM-equivalent/cm^2 1–30 μg	6–72 h	Organic fraction of PM2.5 induced cellular toxicity but no significant increase in pro-inflammatory cytokines. Significant increases in Nrf2 and 8-OHdG expression.	(Abbas et al., 2019)
BEAS-2B	$PM_{2.5}$ resuspended in cell culture medium	$PM_{2.5}$ 0–200 μg/mL	24 h	Comparison of $PM_{2.5}$ collected from 2 major Chinese cities showed differential oxidative and toxic potency between the two sites, partially explained by the difference in PAH content. A better understanding of how the remaining unidentified components of the $PM_{2.5}$ induce oxidative stress, and the subsequent development of COPD require further investigation.	(Jin et al., 2019)
A549 Kmb17 BEAS-2B	$PM_{2.5}$ suspension added to cell culture medium	$PM_{2.5}$ 12.5–400 μg/mL	24 h	Comparison of PM from 2 Chinese cities during 2 seasons found that the ROS production in three respiratory cells lines was correlated with the amount of PAH within the PM.	(Song et al., 2020)
A549 U937	PM[b] resuspended in either water or DMSO to create W-PM and O-PM solutions	W-PM or O-PM 0–100 μg/mL	24 h	O-PM induced significantly more ROS, ICAM-1 and IL-6 expression than W-PM, ultimately leading to increased inflammation and oxidative stress.	(Liu et al., 2018)

(*continued on next page*)

Table 2 (*continued*)

Animals/cells used	Exposure type	Treatment protocol	Exposure duration	Key findings	Reference
Primary human nasal AEC	W-PM and O-PM from $PM_{2.5}$ applied apically to ALI cultures	W-PM 3–30 μg/cm^2 culture area. O-PM 0.045–4.5 μg/cm^2 culture area.	2 × 24-hour stimulations	Significant transcriptomic response from mucociliary epithelium treated with O-PM but not W-PM. MUC5AC mucus hypersecretion. Increased MUC5AC$^+$ secretory cells and downregulated ciliated cell transcription factors *FOXJ1* and *MCIDAS*.	(Montgomery et al., 2020)
Primary human nasal AEC	$PM_{2.5}$ applied apically to ALI cultures	$PM_{2.5}$ 0–12 μg/mm^2	12 or 24 h	Abnormal ciliary beat frequency and pattern following $PM_{2.5}$ exposure, possibly mediated by mitochondrial dysfunction.	(Jia et al., 2019)
HFL-1 IMR-90 WI-38 A549	$PM_{2.5}$ and PM_{10} suspended in PBS.	$PM_{2.5}$ and PM_{10} 0–25 μg/cm^2	7 days	Human lung fibroblasts but not alveolar epithelial cells (A549) treated with $PM_{2.5}$ and PM_{10} resulted in ROS activation of DNA damage response signalling axis, p53 phosphorylation and cellular senesce.	(Jin et al., 2023)
A549	PM dissolved in DMSO	PM[e] 5–200 μg/mL	24 h	Downregulation of hTERT, cell cycle arrest and cellular senesce induced following exposure to 200 μg/mL of PM.	(Chang-Chien et al., 2021)

Note: $PM_{0.18}$ = particulate matter <0.18 μm. DMSO = dimethyl sulfoxide. Nrf2 = nuclear factor erythroid 2-related factor 2. 8-OHdG = 8-hydroxy-2′-deoxyguanosine biomarker. PAH = polycyclic aromatic hydrocarbons. IL = interleukin. KO = knockout. WT = wild type. TNF = tumour necrosis factor. AEC = airway epithelial cells. O-PM = organic-extractable PM. W-PM = water-soluble PM. ALI = air liquid interface. PBS = phosphate buffered saline. hTERT = human telomerase reverse transcriptase gene.

[a] 24 hour treatment protocol reported in study but omitted from this table.

[b] Standard Reference Material 1649b, purchased from National Institute of Standards and Technology, USA.

[c] Artificial $PM_{2.5}$ created to model the typical chemical and physical properties of $PM_{2.5}$ found in Beijing China during 2014.

[d] This study also investigated the additive effect of PM following induction of COPD via cigarette smoke and chronic infection.

[e] Standard Reference Material SRM-1648a, purchased from National Institute of Standards and Technology, USA.

presented the deleterious effects of PM on the respiratory system.

Whilst there is now compelling evidence that PM induces inflammation within the respiratory system, by its very nature PM is heterogeneous in composition. For example, PM sampled from road tunnels in Norway induced inflammation and toxicity in vitro with $PM_{2.5}$ inducing a more potent response than PM_{10} (Refsnes et al., 2023). On the other hand, when analysing the organic component of $PM_{2.5}$ (O-PM) collected from Lebanon on cultured human respiratory epithelial cells, the authors found that O-PM did not induce any inflammation, but did induce cellular toxicity (Abbas et al., 2019). This highlights the complex nature of PM and emphasises the need for further investigation to explore how the different components of PM induce cellular responses, such as inflammation. Furthermore, owing to the many components within PM, synergistic effects (e.g. inflammation, toxicity, etc.) between these different components can be present (Xu et al., 2020).

3.2. Oxidative stress and PM exposure

Oxidative stress, a biological perturbation whereby an increase in oxidants overwhelms the innate antioxidant defence mechanisms, is involved in the pathogenesis of many chronic respiratory diseases (Dua et al., 2019). Its role in the development and progression of COPD has been very well established (Barnes et al., 2003). There is also evidence that this oxidative stress can then amplify inflammatory pathways, such as NF-κB (Barnes, 2000). Developing evidence has shown that exposure to PM induces oxidative stress within the mitochondria contributing to the associated lung damage (Wang et al., 2021). In a recent study that exposed mice intranasally to $PM_{2.5}$, the cellular redox signalling pathway, nuclear factor erythroid 2-related factor 2 (Nrf2) was activated dose-dependently (Barbier et al., 2023). Despite the activation of this protective redox pathway, oxidative damage to DNA (investigated via the 8-hydroxy-2′-deoxyguanosine (8-OHdG) biomarker) and oxidative damaged proteins (carbonylation) was noted. This oxidative stress and chronic inflammation persisted following the cessation of $PM_{2.5}$, indicating the antioxidant mechanisms were insufficient in preventing the sustained oxidative damage induced by $PM_{2.5}$. These results support a similar study where the researchers, using an in vitro model, found significant increases in Nrf2 and 8-OHdG expression in human bronchial epithelial (BEAS-2B) cells after 24 h of O-PM exposure (Abbas et al., 2019). However, contrary to other aforementioned research, no increase in inflammatory cytokines was recorded. This highlights that whilst interplay and synergism between inflammation and oxidative stress pathways often exist, the two mechanisms can also occur independently.

The heterogeneous composition of PM means that a variety of oxidants can be found within the PM with variable and possibly synergistic or antagonistic effects on the oxidant-antioxidant balance within the body (Hou et al., 2024; Jin et al., 2019). A recent study explored the oxidative effects of $PM_{2.5}$ sampled from two different geographical regions of China (Song et al., 2020). Whilst $PM_{2.5}$ collected from one area induced a significant increase in reactive oxygen species (ROS) in all three respiratory cell lines investigated, $PM_{2.5}$ collected from another region did not induce the same effect. The authors found an important relationship, the ROS production correlated with the relative amount of polycyclic aromatic hydrocarbons (PAHs) found within the PM. This same relationship was also substantiated in a recent in vivo study (Zhou et al., 2022). On the other hand, transition metals such as Cu and Fe, commonly found within PM, can produce oxidative stress-inducing superoxide radicals and nitric-oxide radicals (Hou et al., 2024; Yang et al., 2016). It is worth noting that, whilst the mass of PAH and transition metals contained within the PM is often <10 %, the oxidative effects of these components can account for a significantly larger proportion of the ROS generated (Jin et al., 2019).

Intracellular adhesion molecule-1 (ICAM-1) is a cell surface receptor involved in the chemotaxis of immune cells to the site of inflammation and an important mediator of inflammatory responses (Bui et al., 2020). Liu et al. explored the effects of $PM_{2.5}$-induced oxidative stress on the expression of ICAM-1 (Liu et al., 2018). The results detailed how the ROS produced from the organic fraction of $PM_{2.5}$ activated the IL-6/AKT/STAT3/NF-κB signalling pathway, which increased the amount of ICAM-1 in A549 cell lysates cultured in vitro. This increase in ICAM-1 was also seen in the lung tissue of mice and patients previously diagnosed with COPD (Liu et al., 2018). This highlights how PM-derived ROS can act as intracellular messengers activating inflammatory cascades within the lung. Furthermore, this also demonstrates the positive feedback cycle between oxidative stress and inflammation, which occurs in both exacerbations and the development of chronic inflammatory respiratory diseases, such as COPD (Bui et al., 2020).

3.3. Airway remodelling and PM exposure

A common hallmark feature of COPD is the remodelling of the small airways due to inflammation and oxidative stress. This was recently demonstrated using rats exposed to a model PM, diesel exhaust particles (Fang et al., 2024). Following an exposure period of up to 8 weeks, typical features of COPD, such as small airway remodelling, mucus hypersecretion, and inflammation, were reported. PM has also been shown to aggravate COPD through airway remodelling (Wang et al., 2020). This has been demonstrated through marked increases in peribronchial fibronectin deposition (Zhao et al., 2019). As such, it is important to investigate how PM initiates and aggravates COPD in order to identify the mechanisms and pathways that can be targeted in the treatment of COPD.

The exact mechanism through which PM induces airway remodelling is unknown; however, some factors such as chronic airway inflammation and injury, oxidative stress, abnormal repair, and the Wingless-related integration site 5a (Wnt5a)/β-Catenin pathways have been suggested (Kayalar et al., 2024). Inflammatory cells such as neutrophils, macrophages, mast cells, lymphocytes, and innate lymphoid cells not only play a role in COPD-related inflammation but also in airway remodelling. Wang et al. reported that macrophages are directly involved in airway remodelling by secreting elastin-degrading enzymes and inflammatory factors (IL-1β, tumour necrosis factor-α (TNF-α), IL-8, and ROS) that act directly and indirectly on airway structural cells, causing remodelling (Wang et al., 2018).

Experimental evidence has proposed that PM can induce airway remodelling through oxidative stress. In a 2020 study, researchers exposed rats to repeated cigarette smoke inhalation and bacterial infection for 8 weeks to induce COPD (Wang et al., 2020). Increases in Mucin (MUC) 5ac, MUC5b, collagen I, collagen III, profibrotic cytokine α-smooth muscle-actin (SMA) and transforming growth factor- (TGF-) β1 in the lung tissue, all indicated airway remodelling. As part of the same study, the authors exposed a different group of rats to real-time concentrated PM without the prior 8 weeks of smoke and bacterial infection to induce COPD. The results of this study indicated that the PM exposure alone was sufficient in developing a COPD-like phenotype in the mice similar to the cigarette smoke and bacterial infection induction of COPD. Significant airway remodelling, peribronchiolar immune cell infiltration, and increases in TGF-β, collagen I, collagen III, MUC5ac and MUC5b were all recorded in mice exposed to PM. The airway remodelling was attributed to oxidative stress as antioxidant levels were decreased, as opposed to oxidants which were increased (Wang et al., 2020). It is worth noting that the rats with COPD induced by cigarette smoke exposure and bacterial infection then subsequently exposed to PM displayed the most severe pathophysiological perturbations.

The Wnt5a/β-Catenin pathway has been suggested as one of many mechanisms of airway remodelling due to PM exposure. For example, researchers in 2021 demonstrated that $PM_{2.5}$ exposure led to airway remodelling, emphysema, smooth muscle hyperplasia, and decreased lung function in mouse lung tissue (Zou et al., 2021). The authors found increased expression of Wnt5a, β-Catenin, PDGFRβ, and Tenascin C proteins in mouse lung tissue. Furthermore, the results indicated that in human bronchial smooth muscle cells (HBSMCs), there was an increased expression of Wnt5a, β-Catenin, TGF-β1, CyclinD1, and c-myc mRNAs. These findings suggested that $PM_{2.5}$ exposure induced HBSMC proliferation, leading to airway remodelling through the Wnt5a/β-Catenin signalling pathway (Zou et al., 2021).

It has also been postulated that $PM_{2.5}$ exposure induces lung inflammation and fibrosis by activating the Wnt5a/JNK pathway in airway smooth muscle cells (Qu et al., 2019; Zou et al., 2023). A histological investigation of mouse small airways and lung tissue showed that the Wnt5a/JNK/NF-κB pathway was activated following exposure to $PM_{2.5}$. This activated pathway then promoted the production of α-SMA, collagen I and collagen III and increased the production of IL-6, IL-8, and TNF-α. These results suggest that $PM_{2.5}$ exposure stimulates pro-inflammatory cytokine expression and collagen deposition in airway smooth muscle cells, causing inflammation and fibrosis mediated through the Wnt5a/JNK pathway and the subsequent development of COPD (Zou et al., 2023).

The reviewed research has illustrated how PM can cause an increase in airway remodelling through various mechanisms, including, but not limited to, inflammation, oxidative stress, Wnt5a/β-Catenin and Wnt5a/JNK pathways. Irrespective of the pathway, there is an increase in airway remodelling, leading to COPD or worsening of the disease. Identifying these pathways in which PM causes airway remodelling is imperative to finding therapeutic targets. For example, BOX5 (a Wnt5a antagonist) has been shown to alleviate $PM_{2.5}$-induced-COPD outcomes in mice and inhibit $PM_{2.5}$-induced increases in PCNA, α-SMA, Wnt5a, β-Catenin, PDGFRβ and Tenascin C protein expression in HBSMCs (Zou et al., 2021). Additionally, BOX5 has also been shown to block activation of the Wnt5a/JNK pathway and inhibit the effects of $PM_{2.5}$ on fibrosis and inflammation in airway smooth muscle cells (Zou et al., 2023).

3.4. Epithelial plasticity and PM exposure

PM can also affect respiratory epithelial plasticity, causing decreased function and integrity (Kayalar et al., 2024). Studies have suggested that air pollutant exposure may trigger the transformation of columnar cells into metaplastic squamous cells, and vice versa, indicating abnormal repair and regeneration (Tata et al., 2021). Moreover, other researchers have proposed that IL-6, a pro-inflammatory cytokine induced by PM, can impact epithelial plasticity (Mutlu et al., 2007; Nazariah et al., 2013). Yet there is an opportunity for further research to develop a robust understanding of the impact of PM on epithelial plasticity.

3.5. Mucociliary function and PM exposure

The main function of mucociliary action is to trap dust (such as PM) and act as the primary innate defence against viral and bacterial pathogens (Bustamante-Marin and Ostrowski, 2017). However, exposure to PM causes mucociliary dysfunction, deteriorates epithelial barrier integrity, and ultimately leads to cellular inflammation (Kayalar et al., 2024). The exact underlying mechanisms of PM-induced mucociliary dysfunction are still being elucidated, although it is thought to involve cellular and molecular changes to airway epithelium (Montgomery et al., 2020).

To explore the cellular and molecular perturbations of mucociliary dysfunction as a result of $PM_{2.5}$ exposure, Montgomery et al. investigated the transcriptomic response of primary human nasal epithelia exposed to $PM_{2.5}$. This study utilised air liquid interface (ALI) cultures and exposed the cells to either water-soluble $PM_{2.5}$ (W-PM) or O-PM. A significant transcriptomic response was seen in mucociliary epithelium treated with O-PM but not W-PM. The expression of 424 genes, including activation of aryl hydrocarbon receptor signalling and IL-1 was noted following exposure to O-PM. At a higher dose of O-PM, 1240 genes were impacted. This suggests that $PM_{2.5}$ exposure can modify airway epithelial gene expression in a dose-dependent manner (Montgomery et al., 2020). From here, the authors generated a gene network and found that genes *CYP1A1, IL1A,* and *IL1B* exhibited high connectivity, indicating the potentially critical nature of these genes in the transcriptional response to PM exposure (Montgomery et al., 2020). >100 mucus secretory expression genes, including transcriptional mediators of mucus metaplasia (*SPDEF* and *FOXA3*) were activated following exposure to PM. O-PM also induced MUC5AC mucus hypersecretion through increases in $MUC5AC^{+}$ secretory cells and down-regulated ciliated cell transcription factors *FOXJ1 and MCIDAS*. As a result, this epithelial remodelling highlights how $PM_{2.5}$ exposure can lead to poor respiratory outcomes (Montgomery et al., 2020).

Recent experimental work has shown that $PM_{2.5}$ also impacts the ciliary motion of primary human nasal epithelial cells (Jia et al., 2019). The ciliary beat frequency and pattern – two important indicators of

ciliary beat function were scrutinized. Following exposure of the ALI cultures to $PM_{2.5}$ for 12 h, ciliary coverage decreased, with no effect on the proliferation of basal cells. Ciliary beat frequency results were variable, considering the time of exposure and the dose of $PM_{2.5}$. Ciliary beat frequency increased after 12 h, whilst 24 h of $PM_{2.5}$ exposure increased ciliary beat frequency in lower doses yet decreased beat frequency at higher doses. The results also demonstrated that $PM_{2.5}$ affects the ciliary beat pattern, and total levels of cellular ATP and mitochondrial membrane potential were decreased. These results suggest that $PM_{2.5}$ exposure impacts the overall cilia function of human nasal epithelial cells, and mitochondrial dysfunction may play a role (Jia et al., 2019). A detailed understanding of all the underlying mechanisms of PM-induced mucociliary dysfunction are yet to be explained, thus further research is required.

3.6. Cellular senescence and PM exposure

Cellular senescence has been defined as a dysfunctional cell state where senescent cells are under cell cycle arrest, meaning they are unable to proliferate (Jha et al., 2024). It is typically associated with age, but it can be linked with DNA damage as a result of environmental stress factors, such as PM (Thomas et al., 2024). As shown in Fig. 3, prolonged PM exposure has been shown to induce cellular senescence of normal lung fibroblasts ((Chang-Chien et al., 2021; Jin et al., 2023) and macrophages (Thomas et al., 2024).

An in vitro study on lung cell cultures assessed the activation of cellular senescence mechanisms following exposure to PM (Jin et al., 2023). Lung fibroblast and epithelial cell lines were subjected to PM_{10} and $PM_{2.5}$. The research found that exposure to PM resulted in ROS activating the DNA damage response signalling axis in lung fibroblasts but not respiratory epithelial cells. Increased p53 phosphorylation was recorded following PM exposure, which ultimately led to cellular senescence through an increase in p21 expression with no effect on the p16-pRB pathway (Jin et al., 2023). The authors also investigated the effects of water-soluble antioxidants, such as vitamin C and N-Acetyl Cysteine and found these antioxidants had reduced PM-induced senescence by suppressing the ROS production. This suggests that antioxidants could pose as a promising therapeutic intervention for PM-induced senescence in lung tissue (Jin et al., 2023).

Conversely, another study in 2021 exposed human lung epithelial cells to PM for 24 h (Chang-Chien et al., 2021). The researchers demonstrated that exposure to PM decreased cell viability and elevated lactate dehydrogenase (LDH) levels in the culture medium. Specifically, the research highlighted that PM exposure led to telomere shortening, induction of G0/G1 phase arrest, and heightened expression of senescence markers (Chang-Chien et al., 2021). On a cellular level, PM exposure upregulated p21 and downregulated proliferating cell nuclear antigen (PCNA) and human telomerase reverse transcriptase gene (hTERT) expression, with no significant impact on p53 expression. These results indicate that PM exposure leads to cellular senescence in lung epithelial cells through the downregulation of hTERT and PCNA through a p53-independent induction of p21 expression, telomere shortening, and G0/G1 arrest (Chang-Chien et al., 2021). This contrasts with the aforementioned study, where p53 phosphorylation increased p21 expression (Jin et al., 2023), highlighting the inconsistency between PM exposure and cellular senescence in human lung tissue. This inconsistency may be attributed to the source, or the dose of PM used. As such, more studies are needed to fully conclude the exact pathophysiological mechanism induced by PM exposure, along with the effects of differing compositions of PM and its impact on cellular senescence.

PM has also been linked to senescence-related impaired immune function, yet the exact mechanisms through which this happens are not entirely understood. One study sought to determine whether PM could drive macrophage senescence (Thomas et al., 2024). Bone marrow-derived macrophages were exposed to PM from several locations in the United States, leading these macrophages to adopt a senescent phenotype. Increased IL-1α secretion, senescence-associated β-galactosidase activity, and reduced proliferation distinguished this phenotype (Thomas et al., 2024). Furthermore, this phenotype was distinctly different to that elicited by a different environmental exposure, house dust mite. This study demonstrated that inhibition of the phagolysosome-15-lipoxygenase pathway in macrophages reduced senescence markers. These results suggest that phagocytosis of PM by macrophages (e.g. alveolar macrophages) promotes cellular senescence (Thomas et al., 2024).

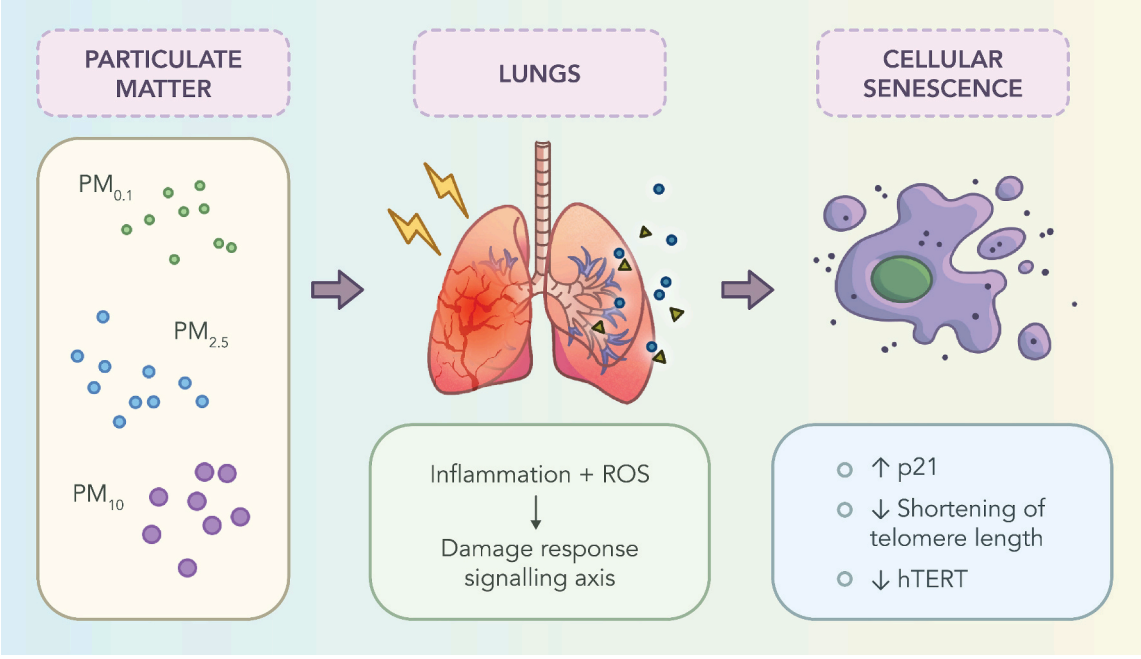

Fig. 3. A graphical summary of how cellular senescence can contribute to PM-induced lung damage and COPD. ROS = reactive oxygen species. hTERT = human telomerase reverse transcriptase gene.

4. Limitations

Our research only focused on PM-induced COPD, meaning there are many other potential PM-induced lung diseases, such as asthma, that were not within the scope of this review. There is also evidence to suggest that PM not only impacts the respiratory system but can also affect different body systems by entering systemic circulation through our lungs. Some examples include cancer (Schraufnagel, 2020), cardiovascular (myocardial infarction, hypertension, thrombosis, and coronary heart disease) (Nelin et al., 2012), neurological (Alzheimer's disease, Parkinson's disease, depression, and anxiety) (Li et al., 2022), and metabolic (kidney and liver diseases) (Chen et al., 2022). The development and exacerbation of allergic diseases like atopic dermatitis can also be associated with PM exposure (Kim et al., 2021). However, the exact connections between PM-induced lung diseases and other PM-induced diseases are yet to be determined. More research is warranted to elucidate these possible connections.

A further limitation to our review of PM-induced COPD was the large volume of literature based on $PM_{2.5}$, compared to $PM_{0.1}$ and PM_{10}. The smaller number of studies on PM_{10} may be attributed to the fact that PM_{10} only reaches the lower airways and is usually removed by natural airway defences (Misiukiewicz-Stepien and Paplinska-Goryca, 2021) and therefore may not impact COPD to the same extent as $PM_{2.5.}$ The lack of studies on $PM_{0.1}$ could be attributed to the fact that $PM_{0.1}$ is harder to replicate in a laboratory setting and is more challenging to detect. However, there is a growing suggestion that $PM_{0.1}$ may be more dangerous than $PM_{2.5}$ due to the physical characteristics and the ability to evade natural lung defence mechanisms (Table 1). These sized particles can cause increased pulmonary inflammation and are retained in the lungs for a longer period of time (Schraufnagel, 2020). Additional research can further illuminate the role of PM_{10} and $PM_{0.1}$ in lung-related PM-induced diseases such as COPD.

5. Future directions

Whilst there is strong retrospective epidemiological evidence that chronic PM exposure is associated with an increased risk in the development of chronic respiratory diseases, most of the mechanistic studies described in this review used in vitro and in vivo models. Additional work translating this mechanistic research into human clinical studies would strengthen the body of research and may provide novel insight into pathophysiological mechanisms not previously described. Furthermore, with the expanding mechanistic evidence, there is an ever-growing need for additional research to investigate possible pharmacological inhibitors of these pathways. This may also uncover possible preventative treatments that could decrease disease severity. Further investigation of the interaction between multiple toxic environmental stimuli, such as real-time chronic air pollution exposure, would better represent the true environmental exposure. Many of the epidemiological studies discussed focused on outdoor ambient PM exposure. However, indoor or household PM exposure during biomass combustion for heating or cooking can drastically exceed outdoor exposure levels (Holmes et al., 2011; Li et al., 2012). This very high acute exposure may be an important factor in the development of COPD and warrants additional investigation. Additional research to explore the additive toxic effects of PM and e-cigarette vapour or cigarette smoke would also provide interesting novel insights into the development of COPD.

A large proportion of in vivo studies reviewed in this paper used only male animals for the research. This is a limitation to the evidence presented, as sexual dimorphism occurs in respiratory diseases (Reddy and Oliver, 2023). An example of the pathophysiological difference between males and females was demonstrated using a cigarette smoke-induced mouse model of COPD (Tam et al., 2016). Female mice exhibited increased small airway remodelling, TGF-β activation and oxidative stress compared to the male mice. Future in vivo studies should consider using both sexes to explore the sexual dimorphism in PM-induced COPD.

Considering that the chemical composition of the PM is an important factor influencing health outcomes (Zhou et al., 2022), additional research to understand how these individual chemicals activate the respective cellular and molecular pathways in COPD may provide genuine health benefits. This may provide insight into the development of targeted therapies. Developing a greater understanding of the toxic components within PM would also help implement international environmental and health policy to decrease these specific emissions.

There were considerable differences between research projects in the exposure systems used and the dose of PM administered (Table 2). Some research projects used airborne PM that was captured and then solubilised in solution (Chan et al., 2019; Song et al., 2020; Wang et al., 2021) before conducting in vitro or in vivo experiments. In comparison, other research used airborne PM exposure models, which provide a more genuine representation of lung exposure (Wang et al., 2020; Zhou et al., 2022). This difference in exposure may explain some of the reported differences. This also highlights an area requiring further investigation to understand if these different exposure methods affect the cellular and molecular pathways activated.

6. Conclusion

In this review, we summarised the current literature exploring the cellular and molecular mechanisms between PM exposure and the development of COPD. This review showcased how many of the same mechanisms typical in COPD induced by other exposures, such as tobacco smoke, are prevalent in PM-induced COPD. The highly variable composition of PM makes determining a finite list of pathophysiological mechanisms difficult. However, this review found four major overarching mechanistic categories: chronic inflammation, oxidative stress, airway remodelling, and cellular senescence. These can all be induced by respiration of airborne PM, emphasising that chronic PM inhalation can lead to the development of COPD. This work detailed the considerable interactions between the pathophysiological mechanisms, highlighting the vicious cycles that can pursue.

This expanding area of research accentuates the serious respiratory health implications of airborne PM exposure. With a rapidly expanding global population, an increase in urban density, and the continuing rise of PM, it is critical that more research is done on PM-induced COPD to elucidate all pathophysiological mechanisms. This will allow for corrective actions to prevent disease and treat PM-induced COPD using pharmacological therapies targeting the affected pathways. Furthermore, this research can guide environmental policymakers to develop legislation to reduce global air pollution and ultimately the health burden from this 'invisible killer' affecting millions of lives around the world.

CRediT authorship contribution statement

Hudson C. Taylor-Blair: Writing – review & editing, Writing – original draft, Conceptualization. **Alexander Chi Wang Siu:** Writing – review & editing, Writing – original draft, Conceptualization. **Adam Haysom-McDowell:** Writing – review & editing. **Sofia Kokkinis:** Writing – review & editing. **Ayeh Bani Saeid:** Writing – review & editing. **Dinesh Kumar Chellappan:** Visualization. **Brian G.G. Oliver:** Writing – review & editing, Supervision. **Keshav Raj Paudel:** Writing – review & editing, Supervision. **Gabriele De Rubis:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Kamal Dua:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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