Leikauf et al. *Experimental & Molecular Medicine* (2020) 52:329–337
https://doi.org/10.1038/s12276-020-0394-0

Experimental & Molecular Medicine

REVIEW ARTICLE Open Access

Mechanisms of ultrafine particle-induced respiratory health effects

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Abstract

Particulate matter (PM) is the principal component of air pollution. PM includes a range of particle sizes, such as coarse, fine, and ultrafine particles. Particles that are <100 nm in diameter are defined as ultrafine particles (UFPs). UFPs are found to a large extent in urban air as both singlet and aggregated particles. UFPs are classified into two major categories based on their source. Typically, UFPs are incidentally generated in the environment, often as byproducts of fossil fuel combustion, condensation of semivolatile substances or industrial emissions, whereas nanoparticles are manufactured through controlled engineering processes. The primary exposure mechanism of PM is inhalation. Inhalation of PM exacerbates respiratory symptoms in patients with chronic airway diseases, but the mechanisms underlying this response remain unclear. This review offers insights into the mechanisms by which particles, including UFPs, influence airway inflammation and discusses several mechanisms that may explain the relationship between particulate air pollutants and human health, particularly respiratory health. Understanding the mechanisms of PM-mediated lung injury will enhance efforts to protect at-risk individuals from the harmful health effects of air pollutants.

Introduction

Particulate matter (PM) is the principal component of indoor and outdoor air pollution. PM includes a range of particle sizes, such as coarse, fine, and ultrafine particles. PM is a complex mixture of materials with a carbonaceous core and associated materials such as organic compounds, acids, and fine metal particles[1–3]. Particles that are <100 nm in diameter are defined as ultrafine particles (UFPs). UFPs are found to a large extent in urban air as both singlet and aggregated particles[4].

UFPs are classified into two major categories based on their source. UFP typically refers to particles that are incidentally generated in the environment, often as byproducts of fossil fuel combustion, condensation of semivolatile substances or industrial emissions, whereas nanoparticles are manufactured through controlled engineering processes[4].

The physical properties of PM, including the mass, surface area, and number/size/distribution of particles, as well as their physical state, influence respiratory health in different ways[2]. The primary exposure mechanism of PM is inhalation[2]. Inhalation of PM exacerbates respiratory symptoms in patients with chronic airway disease, but the mechanisms underlying this response remain unclear.

This review focuses on the adverse effects of exposure to ambient PM air pollution on the exacerbation, progression, and development of respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). Of note, although air quality is improving in the US, UK, and other countries, the association of PM and COPD with asthma persists. For example, Hopke et al.[5] compared the rate of COPD hospitalizations and emergency department visits in New York State before, during, and after the 2008 economic recession. The rate of asthma-related emergency department visits and COPD-related hospitalizations that were associated with each interquartile range increase in the concentration of

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ambient $PM_{2.5}$ (PM that is <2.5 μm in diameter) was higher after the recession (2014–2016) than during (2008–2013) or before (2005–2007) it. For example, each 6.8 μg/m^3 increase in $PM_{2.5}$ on the same day was associated with 0.4%, 0.3%, and 2.7% increases in the rate of asthma-related emergency department visits before, during, and after the time period, respectively, suggesting that the same mass concentration of $PM_{2.5}$ was more toxic after the recession.

Similarly, Doiron et al.[6] used UK Biobank data on 303, 887 individuals aged 40–69 years, with complete covariate data and valid lung function measures. Cross-sectional analyses examined associations between land use regression-based estimates of particulate matter [$PM_{2.5}$ and PM_{10} (PM that is less than 10 μm in diameter)] concentrations with forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), the FEV_1/FVC ratio and COPD (FEV_1/FVC < lower limit of normal). A 5 μg/m^3 increase in $PM_{2.5}$ concentration was associated with reduced FEV_1 and FVC. COPD prevalence was associated with increased concentrations of $PM_{2.5}$ (OR 1.52) and PM_{10} (OR 1.08) per 5 μg/m^3. Robust associations with lung function were observed for males, individuals from lower-income households, and "at-risk" occupations, and increased COPD associations were observed for obese, lower-income, and non-asthmatic participants. Thus, ambient air pollution remains associated with reduced lung function and increased COPD prevalence.

This review offers insights into the mechanisms by which particles influence airway inflammation and discusses several mechanisms that may explain the relationship between particulate air pollutants and human health, particularly respiratory health. PM induces oxidative stress and inflammation, thereby stimulating innate and acquired immune responses in laboratory animals and humans. Understanding the mechanisms of PM-induced lung injury will enhance efforts to protect at-risk individuals from the harmful health effects of air pollutants.

Mechanisms of UFP-induced health effects

UFPs deposit readily in the airways and centriacinar regions of the lung and induce and incite airway diseases such as asthma and COPD and respiratory diseases. Oxidant-mediated cellular damage[4,7], including the production of reactive oxygen species (ROS) and oxidative stress, innate immunity, and adaptive immunity (Fig. 1), can lead to PM-mediated adverse health effects.

Reactive oxygen species and oxidative stress

Oxidative stress is highly implicated in the pathogenesis of respiratory diseases. Reactive radical species are ubiquitous in nature and are produced by endogenous and exogenous sources[8]. Cellular organelles such as

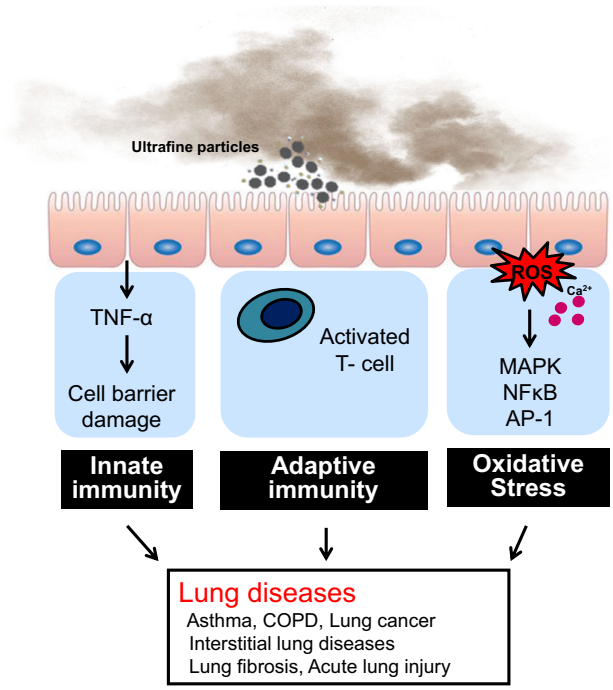

Fig. 1 The proposed mechanism of ultrafine particle (UFP)-induced lung diseases. PM causes the activation of oxidative stress and reactive oxygen species, innate immunity, adaptive immunity, and other mechanisms, leading to the development and exacerbation of respiratory diseases such as bronchial asthma, COPD, lung fibrosis, and lung cancer.

mitochondria and peroxisomes are major sources of ROS and nitrogen species[9]. Production of reactive species by exogenous sources such as environmental toxins and diet promotes the onset of lung diseases[10]. The physical characteristics and the chemical composition of PM play a key role in ROS generation in vitro and in vivo[8–10].

Oxygen is readily reduced by an electron to form oxygen free radicals, such as superoxides[11]. In the presence of iron ions, superoxide acquires a second electron, leading to hydrogen peroxide formation, which generated the extremely reactive hydroxyl radical. Hydroxyl radicals react very quickly with biomolecules, such as proteins, fatty acids, and DNA[12–14]. All molecules in the direct vicinity of the hydroxyl radical will react with this reactive form of oxygen[12–15].

Diesel exhaust particles (DEPs) consist of polyaromatic hydrocarbons, which are hydrophobic molecules that can diffuse easily through cell membranes. As free radicals cause oxidative damage to biological macromolecules, such as DNA, lipids, and proteins, they are believed to be involved in the pathogenesis of many diseases[16]. The particles induce the generation of free radicals, which may lead to an increase in oxidative stress, exacerbating some respiratory symptoms. Metals present on the particle surface, including Fe, Co, Cr, and V, undergo redox

cycling, while Cd, Hg, and Ni, as well as Pb, deplete glutathione and protein-bound sulfhydryl groups, resulting in ROS production[17–20].

PM_{10} exposure at any time during pregnancy is positively associated with levels of mitochondrial 8-hydroxy-2′-deoxyguanosine in maternal blood and umbilical cord blood[21]. PM induces increased mitochondrial oxidative DNA damage during pregnancy in both mothers and their newborns, indicating that particulate air pollution exposure in early life plays a role in increasing systemic oxidative stress at the mitochondrial level, both in the mother and fetus.

The water-insoluble fraction of PM_{10} is similar to the water-soluble fraction of PM_{10} and is also capable of inducing oxidative stress by inducing the generation of hydrogen peroxide and impairing enzymatic antioxidant defense, resulting in oxidative DNA damage and apoptotic cell death through the iron-catalyzed Fenton reaction[22].

Redox reactions regulate signal transduction as important chemical processes. The response of a cell to a reactive oxygen-rich environment often involves the activation of numerous intracellular signaling pathways, which cause transcriptional changes and allow the cells to respond appropriately to the perceived oxidative stress[13,14]. Nuclear factor-κB (NF-κB), activation protein-1 (AP-1), nuclear factor erythroid 2 related factor 2 (Nrf2), and CREB-binding proteins (CBPs) are regulated and influenced by redox status and have been implicated in the transcriptional regulation of a wide range of genes that are involved in oxidative stress and cellular response mechanisms[23].

Nrf2[24] is a major contributor to cellular defense against oxidative damage. There was a significant decrease in the expression of Nrf2 and its upstream regulator genes upon PM_{10} exposure, suggesting that Nrf2 is involved in PM_{10}-induced oxidative damage[24].

Redox status in the nucleus affects histone acetylation and deacetylation status, which regulates inflammatory gene expression by activation of redox-sensitive transcription factors[25]. NF-κB is activated in epithelial cells and inflammatory cells during oxidative stress, leading to the upregulation of many proinflammatory genes[23]. NF-κB is a protein heterodimer that consists of p65 and p50 subunits. NF-κB acts as an inflammatory switch that induces genome-wide epigenetic modification upon ultrafine PM exposure[26]. Many inflammatory genes related to the pathogenesis of asthma are regulated by NF-κB[26].

AP-1 is a protein dimer composed of a heterodimer of Fos and Jun proteins. AP-1 regulates many of the inflammatory and immune genes in oxidant-mediated diseases. Gene expression of gamma-glutamylcysteine synthetase, the rate-limiting enzyme for GSH synthesis, is induced by activation of AP-1. In addition, the family of mitogen-activated protein kinases is directly or indirectly altered by redox changes[27]. Oxidative stress and other stimuli, such as cytokines, activate various signal transduction pathways, leading to the activation of transcription factors, such as NF-kB and AP-1[28].

Binding of transcription factors to DNA elements leads to the recruitment of CBP and/or other coactivators to the transcriptional initiation complex on the promoter regions of various genes[28]. Activation of CBP leads to acetylation of specific core histone lysine residues by intrinsic histone acetyltransferase activity[28–30].

ROS influence airway cells and reproduce many of the pathophysiological features associated with asthma. ROS initiate lipid peroxidation, alter protein structure, enhance the release of arachidonic acid from cell membranes, increase the synthesis and release of chemoattractants, and induce the release of tachykinins and neurokinins[14,15]. This, in turn, augments airway smooth muscle contraction, increases airway reactivity and airway secretions, increases vascular permeability, decreases cholinesterase and neutral endopeptidase activities, and impairs the responsiveness of β-adrenergic receptors[31].

Asthma attacks are associated with the immediate formation of superoxide that persists throughout the late asthmatic response[32]. Allergen challenge in the airways of atopic individuals causes a twofold increase in superoxide generation[32]. Spontaneous and experimental allergen-induced asthma attacks lead to eosinophil and neutrophil activation, during which NADPH oxidase is activated and ROS, such as superoxide and its dismutation product H_2O_2, are rapidly formed[33]. ROS production in people with asthma correlates with the severity of airway reactivity[34]. Asthma is characterized by oxidative modifications[35]. Increased levels of eosinophil peroxidase (EPO) and myeloperoxidase (MPO) parallel the numbers of eosinophils and neutrophils, respectively, and are found at higher than normal levels in peripheral blood, induced sputum and BAL fluid[36] of patients with asthma. Malondialdehyde and thiobarbituric acid-reactive substances have also been detected in urine, plasma, sputum, and BAL fluid in relation to the severity of asthma[37,38]. In addition, 8-isoprostane, a biomarker of lipid peroxidation, is also elevated in exhaled breath condensate from adults and children with asthma[37,38].

Reduced exposure to PM_{10} attenuates age-related declines in lung function, particularly in the small airways[39]. Polymorphisms in glutathione S-transferase (GST) and heme oxygenase-1 (HMOX1) genes, which are important for oxidative stress defense, modify these beneficial effects[39]. A population-based sample of 4365 adults was followed up after 11 years, including questionnaires, spirometry and DNA blood sampling. The benefits of reduced PM_{10} exposure were not equally distributed across the population but were modified by the

individual genetic make-up determining oxidative stress defense[39].

The generation of ROS and nitrogen species is markedly increased during acute asthma attacks[40,41]. Nitric oxide (NO) is a short-lived molecule that causes vasodilation and bronchodilation[42]. In that study, the nitrite concentration in BAL fluid, which is indicative of in vivo generation of NO in the airways, was significantly higher in DEP-exposed animals than in the control group. In another study, alveolar macrophages produced nitrite during in vitro exposure to DEPs (50 μg/ml), with maximal induction 4 h after exposure[43].

The loss of superoxide dismutase (SOD) contributes to oxidative stress during acute episodes of asthma exacerbation[40,41]. Oxidative modification of manganese SOD (MnSOD) is present in asthmatic airway epithelial cells[44]. The loss of SOD activity reflects increased oxidative and nitrative stress in asthmatic patients, suggesting that SOD serves as a surrogate marker of oxidative stress and asthma severity[45].

Catalase catalyzes the decomposition of hydrogen peroxide to water and oxygen, and its activity was found to be 50% lower in BAL fluid obtained from individuals with asthma compared to that of healthy controls[46]. Tyrosine oxidant modifications of catalase occur in asthma, such as chlorination of tyrosine by peroxidase-catalyzed halogenation and oxidative crosslinking of tyrosine to form dityrosine, a product of tyrosyl radicals[46]. The most extensive modification found in asthmatic lungs is tyrosine chlorination, which is 20-fold more extensive than that of tyrosine nitration[47]. In contrast to SOD and catalase, extracellular glutathione peroxidase (GPX) is present at higher than normal levels in the lungs of individuals with asthma[47]. This increase is due to induction of GPX mRNA and protein expression by bronchial epithelial cells in response to increased intracellular or extracellular ROS[47].

During asthma exacerbation in humans, the levels of serum thioredoxin (TRX1) increase and are inversely correlated with airflow[48]. Cigarette smoke induces increased oxidant burden and causes irreversible changes to the protective antioxidant effects in the airways[48]. The smoke-derived oxidants damage airway epithelial cells, inducing direct injury to membrane lipids, proteins, carbohydrates, and DNA, leading to chronic inflammation[48]. Cigarette smoking delivers and generates oxidative stress within the lungs[49]. These imbalances in oxidant burden and antioxidant capacity have been implicated as important contributing factors in the pathogenesis of COPD[49]. However, smoking also causes the depletion of antioxidants, which further contributes to oxidative tissue damage[49].

Glutathione S-transferases (GSTs) are a family of enzymes that play an important role in detoxification by catalyzing the conjugation of many hydrophobic and electrophilic compounds to reduced glutathione (l-g-glutamyl-l-cysteinyl-glycine) and participating in antioxidant defense through a number of mechanisms, including the repair of ROS-induced damage and the detoxification of xenobiotics present in air pollutants[50]. Glutathione present in human epithelial lining fluid is a key enzyme that protects the lungs from oxidative stress[51]. Titanium dioxide (TiO_2) particles activate and deactivate the phosphorylation of several inflammatory proteins in lung epithelial cells, especially the serine and tyrosine phosphorylation of GSTP1, which regulates cell damage and apoptosis following exposure to TiO_2 particles. Collectively, our data suggest that GSTP1 is an important modulator of TiO_2 particle-induced inflammation[52].

The downregulation of antioxidant pathways has also been associated with acute exacerbations of COPD[49]. Disruption of the oxidant/antioxidant balance is important in the pathogenesis of acute lung injury and acute respiratory distress syndrome. Different cytokines and growth factors play a role in the pathogenesis of lung fibrosis[53]. ROS mediate TGF-β formation in lung epithelial cells[53].

Innate immunity

Particles larger than 10 μm generally get caught in the nose and throat and never enter the lungs[54,55]. Particles less than 10 μm but greater than 2 μm land in the tracheobronchial tree and are cleared by mucociliary clearance. Smaller particles can transverse through the airways and deposit in the alveolar region. In this region, phagocytic cells, including neutrophils and macrophages, are recruited to foreign particles by cytokines and chemokines and engulf the particles by phagocytosis[54,55]. The mucociliary escalator then transports particle-laden neutrophils and macrophages[56]. PM induces the release of inflammatory cytokines, such as IL-6, IL-8, GM-CSF, and TNF-α[57], from immune cells (e.g., macrophages) as well as structural airway cells[58,59].

Chitin is commonly found in organisms including parasites, fungi, and bacteria but does not occur in mammalian tissues[60], allowing for selective antimicrobial activity of chitinase. Macrophage-synthesized Ym1 and Ym2 are homologous to chitinase and have chitinase activity[61,62]. Through the IL-4/STAT 6 signal transduction pathway, Ym1 is implicated in allergic peritonitis[63]. Acid mammalian chitinase may also be an important mediator of IL-13-induced responses in Th2 disorders, such as asthma[64]. Indeed, polymorphisms in acid mammalian chitinase are associated with asthma, further supporting the involvement of acid mammalian chitinase in asthma development[65]. DEPs induce airway hyperresponsiveness (AHR), as well as Ym mRNA expression,

which is a Th2 cell-biased response by activated macrophages[66]. The chitinase Ym1 is expressed in the spleen and lungs, with lower expression in the thymus, intestine, and kidney, whereas Ym2 is expressed at high levels in the stomach, with lower levels in the thymus and kidney[66]. Conserved STAT6 sites probably account for the similar, striking induction of Ym1 and Ym2 expression in Th2-type environments. In a murine model of DEP exposure, BALB/c mice intranasally exposed to DEPs followed by a DEP challenge had upregulation of lung-specific expression of Ym1 and Ym2 transcripts relative to that of mice that were not exposed nor similarly challenged[43]. The regulation and function of chitinase have not been well explored in air pollution asthma models. However, in one study, Ym1 was one of the most highly induced IL-4 target genes, exhibiting at least a 70-fold increase in macrophage populations[43]. Alveolar macrophages play an important role in particle-induced airway and lung inflammation via direct production of IL-13.

Proteomics offers a unique means of analyzing expressed proteins and has been successfully used to examine the effects of oxidative stress at the cellular level[67]. In addition to revealing protein modifications, this approach is also used to assess changes in protein expression levels[68]. In a previous study, 20 proteins were identified whose expression levels in the human bronchial epithelial cell line BEAS-2B changed in response to TiO_2 particle exposure[69]. These proteins included defense-related, cell-activating, and cytoskeletal proteins that are implicated in the response to oxidative stress and can be classified into four groups according to the pattern of the TiO_2-induced change in expression over time. One protein, macrophage migration inhibitory factor (MIF, Fig. 2), was also induced

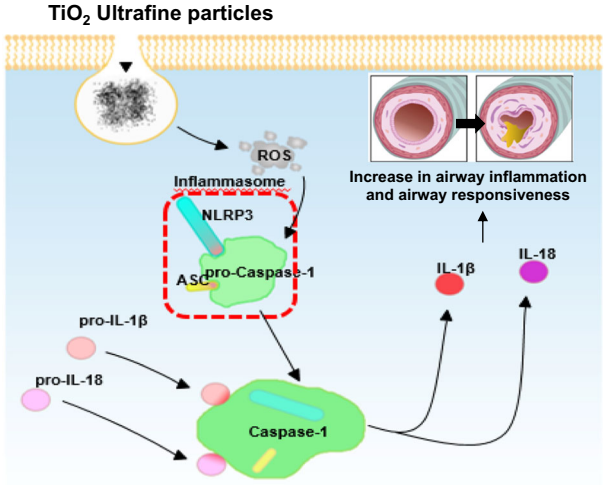

Fig. 2 Schematic of the inflammasome cascade in the lungs of the TiO_2 particle-exposed model.

at the transcriptional level. Similarly, black carbon and diesel exhaust particles induced the protein expression of MIF in BEAS-2B cells. The expression of MIF also increased in the lungs of TiO_2-instilled rats. These results indicate that a portion of these proteins may serve as mediators of or markers for airway disease caused by exposure to PM.

The inflammatory effects of PM_{10} have been demonstrated in experimental animal studies by using direct instillation into the lung prior to human studies that showed pulmonary effects after experimental exposure to PM[17]. Clinically, PM_{10} particles likely provoke airway inflammation via the release of mediators that exacerbate lung disease in susceptible individuals[70]; even a single exposure compromises a host's ability to respond to ongoing pulmonary infections[71]. Fine and UFPs directly stimulate macrophages and epithelial cells to produce inflammatory cytokines such as TNF-α, TGF-β1, GM-CSF, PDGF, IL-6, and IL-8[72], and reactive oxygen species are responsible for acute and chronic lung inflammation[73].

The inflammasome is a multiprotein complex that regulates inflammation by activating specific proinflammatory cytokines, resulting in an effective host immune response[74]. The innate immune system is the first line of host defense, and the inflammasome is essential for maintaining a delicate balance between pro- and anti-inflammatory signals to generate an appropriate immune response without harming the host[74]. The inflammasome is a major regulator of inflammation through its activation of pro-caspase-1, which cleaves pro-interleukin-1β (pro-IL-1β) into its mature form. IL-1β is a critical proinflammatory cytokine that controls the severity of inflammation associated with a wide spectrum of inflammatory diseases. NAIP, CIITA, HET-E, TP-2 (NACHT), and leucine-rich repeat and pyrin domain-containing protein 3 (NLRP3) are key components of the inflammasome complex, and multiple signals and stimuli trigger formation of the NLRP3 inflammasome complex[75]. In our studies[76], AHR and inflammation increased in OVA-sensitized/challenged mice, and these responses were exacerbated by exposure to TiO_2 particles (Fig. 3). TiO_2 particle exposure increased IL-1β and IL-18 expression in OVA-sensitized/challenged mice. UFPs augmented the expression of NLRP3 and caspase-1, leading to the production of active caspase-1 in the lung. Caspase-1 expression was increased and exacerbated by exposure to TiO_2 particles in OVA-sensitized/challenged mice. ROS levels tended to increase in OVA-sensitized/challenged and OVA-sensitized/challenged-plus-TiO_2 particle-exposed mice. Our data demonstrate that inflammasome activation occurred in asthmatic lungs following exposure to particles, suggesting that targeting the inflammasome may assist in controlling particle-induced airway inflammation and AHR.

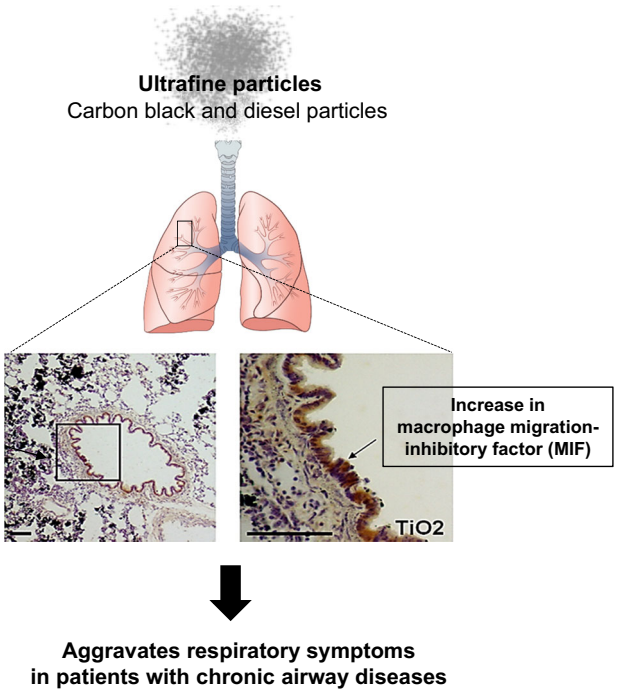

Fig. 3 PM exposure initiates innate immunity through macrophage migration inhibitory factors, leading to exacerbation of respiratory symptoms.

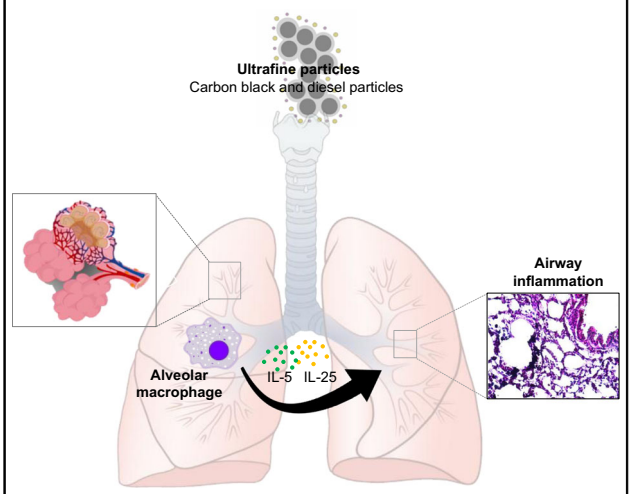

Fig. 4 Th2 cytokine changes in macrophages exposed to TiO_2 particles.

The effect of air pollution-related PM on epithelial barrier function and tight junction (TJ) expression in human nasal mucosa has not been studied to date. Exposure to $PM_{2.5}$ leads to a loss of barrier function in the human nasal epithelium through decreased expression of TJ proteins and increased release of proinflammatory cytokines[77].

Adaptive immunity

PM causes an increase in changes in T cell responses. PM induces a Th2-like microenvironment in the lung, with overproduction of IL-4 and IL-13[68]. Lung IL-13 transcripts increased 24 h after treatment with fine TiO_2 particles (mean diameter = 0.29 μm) compared to that of sham-treated rats[68]. IL-13 levels also increased in the BAL fluids of TiO_2-treated rats 72 h after treatment relative to those of sham-treated rats. To investigate the time- and dose-dependence of macrophage IL-13 production, isolated alveolar macrophages were stimulated with 1, 10, and 40 μg/ml TiO_2 for 24, 48, and 72 h. The control group consisted of untreated alveolar macrophages. IL-13 levels in the supernatants of the macrophage cultures were measured by ELISA. Macrophages cultured for 48 h with TiO_2 produced IL-13 in a dose-dependent manner. In addition, 10 μg/ml TiO_2 significantly enhanced IL-13 production relative to that of the controls. IL-13 protein production increased in a time-dependent manner and peaked 48 h after TiO_2 exposure. Using immunohistochemical staining, we also found that macrophages that were engulfing TiO_2 were the main source of IL-13 in TiO_2 particle-induced lung inflammation. Taken together, our results suggest that alveolar macrophages are major effectors of innate immunity by modulating inflammatory responses towards a Th2 phenotype by producing IL-13, as seen in the adaptive immune response (Fig. 4).

Currently, evidence is not sufficient to demonstrate a direct relationship between particulates and the induction of Th2-like cytokines, including IL-4 and IL-13. TiO_2 particles are a component of PM_{10} found in dusty workplaces in industries that are involved in the crushing and grinding of the mineral ore rutile[78], and 50% of TiO_2-exposed workers have respiratory symptoms accompanied by reduced pulmonary function. Because acute and chronic exposure to TiO_2 particles also induce inflammatory responses in the airways and alveolar spaces of rats[68,79–81], TiO_2-treated rats are a useful model for studying epithelial responses to PM_{10} particles.

PM_{10} or DEPs increase lung inflammation by inhaled allergens or respiratory viral infection by acting as adjuvants. The response may enhance existing allergies or IgE responses to neo-allergens and susceptibility to respiratory infection. This adjuvant effect is exerted by the enhanced production of inflammatory Th2 and/or Th1 cytokines[59]. In animal experiments and human studies, several cytokines and CC chemokines, including IL-4, IL-5, IL-13, GM-CSF, RANTES, MCP-3, and MIP-1, were increased when lymphocytes and macrophages/monocytes were costimulated with particulates in the presence of specific allergens[82]. The immune system responds in different ways depending on the type of particulate. DEPs favor a Th2 response, while asbestos fiber and carbon

particles upregulate both Th1 and Th2 cytokines produced by autologous lymphocytes stimulated by antigen[82].

In addition to adjuvant effects, inhaled inert particles cause a spectrum of pulmonary responses, ranging from minimal changes to marked acute and chronic inflammation. In our study, BALB/c mice were exposed to 100 μg/m³ (low dose) or 3 mg/m³ (high dose) DEPs for up to 12 weeks (1 h/d × 5 d/wk)[83]. AHR increased more in the DEP group than in the control group, and increased more in the high-dose DEP group than in the low-dose DEP group at 4, 8, and 12 weeks. IL-5, IL-13, and interferon-γ increased more in the low-dose DEP group than in the control group at 12 weeks. IL-10 was higher in the high-dose DEP group than in the control group at 12 weeks. Vascular endothelial growth factor was increased in the low-dose and high-dose DEP groups compared to that of the control group at 12 weeks. Transforming growth factor-β increased more in the high-dose DEP group than in the control group at 4, 8, and 12 weeks. The lung collagen content and lung fibrosis were increased in the high-dose DEP group at 8 and 12 weeks. These results suggest that long-term DEP exposure increases AHR, inflammation, lung fibrosis, and goblet cell hyperplasia in a mouse model.

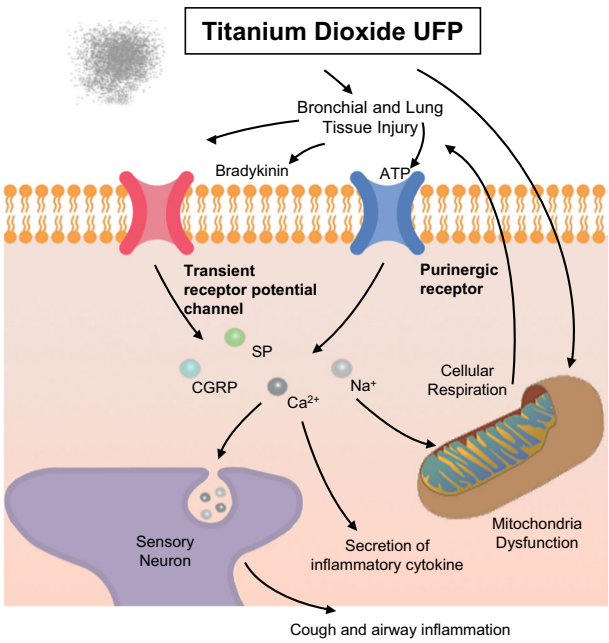

Fig. 5 PM exposure triggers neuroinflammation causing cough and airway inflammation.

Other mechanisms

Neurogenic inflammation in the lung involves airway obstruction, an increase in vascular permeability, extravasation of plasma and leukocytes, mucus hypersecretion and the release of additional inflammatory mediators[84]. The neurogenic inflammatory pathway is associated with the release and activity of neuropeptides such as tachykinins and calcitonin gene-related peptide as a response of sensory neurons to inflammatory mediators and noxious stimuli[84,85]. Transient receptor potential vanilloid 1 (TRPV1) plays a particularly important role in increasing C-fiber excitability and neuronal inflammatory pathways during airway inflammation[86]. ATP and histamine responses to tussive stimuli are activated via P2X receptor-mediated mechanisms[87,88]. P2X7 receptors, which play a role in neuroinflammation, are frequently coexpressed with another P2X receptor, P2X4[89]. Silica nanoparticles inhibit TRPV4 activation and impair the positive modulatory action of TRPV4 channel stimulation on the frequency of ciliary beating in airway epithelial cells[90]. The P2X7 receptor is involved in inflammation triggered by SiO_2 and TiO_2 UFPs by increasing IL-1β secretion, likely through the inflammasome pathway[91]. In our study[92], bradykinin, ATP, substance P and CGRP levels in BALF were increased in OVA mice, and these increases were augmented in OVA plus UFP-exposed mice and in NHBE cells with increasing UFP doses, suggesting that UFPs activate TRPVs and P2X7 and secrete neuromediators that lead to airway inflammation, exacerbating asthma. Our data[92] revealed that TRPV1, TRPV4, P2X4, and P2X7 were involved in the pathogenesis of bronchial asthma and that UFPs exacerbate asthma via a neurogenic mechanism (Fig. 5).

Conclusions

Human and animal studies suggest that PM is involved in the pathogenesis of airway inflammation and exacerbates respiratory diseases. The mechanism of UFP-induced human health effects can be explained by oxidative cellular damage, including innate immunity, adaptive immunity, and reactive oxygen species. Further studies are needed to clarify the mechanism by which UFPs induce health effects to prevent respiratory and human diseases by UFPs.

Acknowledgements
This research was supported by Soonchunhyang University.

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Conflict of interest
The authors declare that they have no conflict of interest.

Received: 10 November 2019 Revised: 20 December 2019 Accepted: 27 December 2019.
Published online: 17 March 2020

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