Journal Pre-proof

Inhaled Microplastics and Lung Health: Immunopathological Effects and Disease Implications

Rajan Thapa, Michael A. Schlesinger, Nisha Panth, Newton Suwal, Saroj Bashyal, Sudarshan Poudel, Sapana Subedi, Urmila Kafle, Sobia Idrees, Rajib Majumder, Bassma H. Elwakil, Mostafa El-Khatib, Suvash C. Saha, Kamal Dua, Rajendra Karki, Keshav Raj Paudel

PII: S2212-4292(25)02213-8

DOI: https://doi.org/10.1016/j.fbio.2025.108036

Reference: FBIO 108036

To appear in: *Food Bioscience*

Received Date: 9 August 2025

Revised Date: 13 October 2025

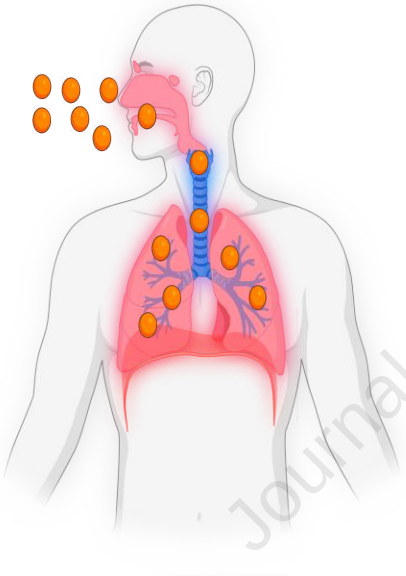
Accepted Date: 30 November 2025

Please cite this article as: Thapa R., Schlesinger M.A., Panth N., Suwal N., Bashyal S., Poudel S., Subedi S., Kafle U., Idrees S., Majumder R., Elwakil B.H., El-Khatib M., Saha S.C., Dua K., Karki R. & Paudel K.R., Inhaled Microplastics and Lung Health: Immunopathological Effects and Disease Implications, *Food Bioscience*, https://doi.org/10.1016/j.fbio.2025.108036.

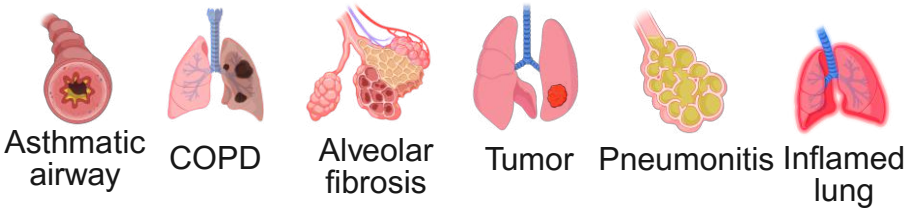
Microplastics (MPs) dominated modern society

- Personal care products
- Textile
- Indoor particulate emissions
- City dust
- Agriculture
- Industrial treatments
- Transportation and road mobility
- Marine coatings

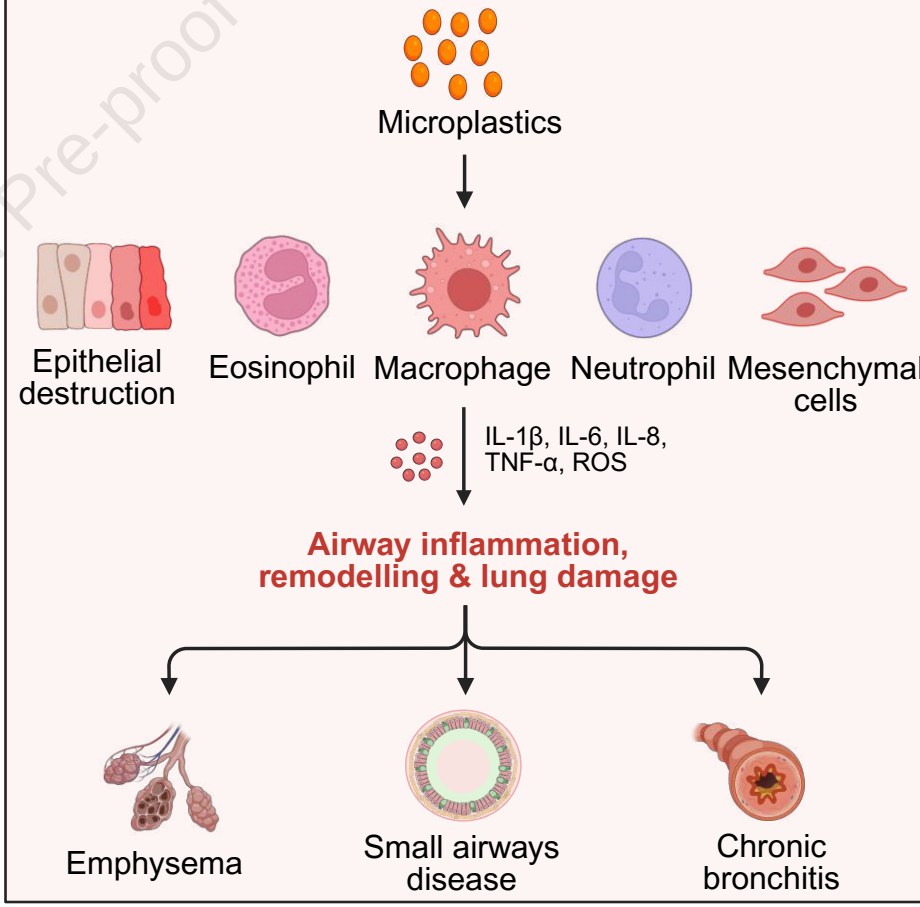
MPs susceptible human respiratory system



MPs trigger chronic inflammatory lung diseases



Molecular basis of lung pathology induced by MPs



Inhaled Microplastics and Lung Health: Immunopathological Effects and Disease Implications

Rajan Thapa[1], Michael A. Schlesinger[2], Nisha Panth[3,4], Newton Suwal[5], Saroj Bashyal[5], Sudarshan Poudel[6], Sapana Subedi[4], Urmila Kafle[7], Sobia Idrees[3], Rajib Majumder[8], Bassma H. Elwakil[9], Mostafa El-Khatib[10], Suvash C. Saha[2], Kamal Dua[4,11,12], Rajendra Karki[13*], Keshav Raj Paudel[3,12,14,15*]

[1]School of Pharmacy, Sungkyungkwan University, Suwon, 16419, Republic of Korea
[2]School of Mechanical and Mechatronic Engineering, University of Technology Sydney, Australia
[3]Centre for Inflammation, Faculty of Science, School of Life Sciences, Centenary Institute and University of Technology Sydney, Sydney, New South Wales, Australia
[4]Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Ultimo, New South Wales, Australia
[5]Department of Pharmacy, Manmohan Institute of Health Sciences, Tribhuvan University, Kathmandu 44600, Nepal.
[6]Faculty of Science and Technology, University of Canberra, ACT 2601, Australia
[7]Department of Biomedical and Nutritional Sciences, University of Massachusetts Lowell, Lowell, Massachusetts, 01854, United States
[8]Applied BioSciences, Macquarie University, NSW 2109, Australia
[9]Medical Laboratory Technology Department, Faculty of Applied Health Sciences Technology, Pharos University in Alexandria, Alexandria, 21526, Egypt
[10]Basic Sciences Department, Faculty of Computer Science and Artificial Intelligence, Pharos University in Alexandria, Canal El Mahmoudia Street, Beside Green Plaza Complex 21648, Alexandria, Egypt
[11] Faculty of Health, Australian Research Centre in Complementary and Integrative Medicine, University of Technology Sydney, Ultimo, New South Wales, Australia
[12]Woolcock Institute of Medical Research, Macquarie University, Sydney, New South Wales, Australia
[13]Department of Biological Sciences, College of Natural Science, Seoul National University, Seoul, 08826, Republic of Korea.
[14]Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun, India
[15]NICM Health Research Institute, Western Sydney University, Westmead, NSW, 2145, Australia

*Corresponding author
Dr. Keshav Raj Paudel, PhD, Centre for Inflammation, Faculty of Science, School of Life Sciences, Centenary Institute and University of Technology Sydney, Sydney, New South Wales, Australia, Keshavraj.paudel@uts.edu.au
A/Prof. Rajendra Karki
Department of Biological Sciences, College of Natural Science, Seoul National University, Seoul, 08826, Republic of Korea rkarki@snu.ac.kr

Abstract

Microplastics (MPs) are pervasive environmental pollutants that pose significant risks to respiratory health, contributing to numerous pulmonary diseases. MPs have been reported to interact with lung epithelial cells, triggering oxidative stress, inflammation, and cellular dysfunction. Exposure to MPs causes reactive oxygen species (ROS) production, depletes antioxidants, and disrupts mitochondrial function, resulting in cell damage, impaired tissue repair, and cellular senescence. Similarly, they dampened the signaling pathways to interfere with autophagy, ferroptosis, and exaggerate injury and epithelial-mesenchymal transition (EMT). Additionally, MPs compromise immune responses by activating inflammatory pathways, weakening the lung's defenses, and increasing susceptibility to infections. Interaction with lung surfactants impairs their function and contributes to abnormal lung dynamics. Furthermore, MPs may serve as vectors for other toxic pollutants, amplifying their harmful effects. In this review, we critically examined the molecular mechanisms through which MPs impact lung health, focusing on oxidative stress, inflammation, immune modulation, and epithelial cell dysfunction. We further highlighted progressive MPs aging and their dynamic interaction with respiratory surfactants, which subsequently enhances their reactivity and toxic potential. Collectively, we critically examine the impact of MPs on human lung health and highlight the urgent need for comprehensive therapeutic strategies to mitigate the potential risks associated with MP inhalation.

Keywords: Microplastic, oxidative stress, asthma, COPD, lung fibrosis, lung surfactants

1. Introduction

1.1 Microplastics Surround Humans in this Plastic Era

The industrial acceleration and overreliance on plastic-based items have been driving modern human life into what people consider the "plastic era". Beginning in the mid-19th century, production and use of plastic products have been rising continuously as they are prominently versatile, physically flexible, economic, and are able to resist various thermal, electrical, and chemical degradation [1]. Humans couldn't deny the use of plastic for even a single day as modern society is completely dependent on plastic products. Drastic increase in plastic based daily utensils has replaced wood, metal or glass use. The annual growth rate of plastic use has been averaged at 8.7 percent between 1950 and 2012 and their total production has been doubled within 20 years; which equals 200 million tons produced in 2000 which grew to 400 million tons in 2020 [2, 3]. Due to the lack of natural decomposability and limited recycling, accumulation of plastic is trending globally. The fragmentation and leakage of plastic after various environmental interactions with ultraviolet radiation, microbial abrasion, and photo-oxidation leads to produce tiny MP particles, which is becoming ubiquitous in our environment [4, 5]. MPs are prominently spread throughout all layers of environmental ecosystems including marine ecosystem, landfills, atmospheric air, fresh and river water systems, and the food chain [7]. Numerous studies have demonstrated the presence of MPs in a variety of food items, including seafood, processed fish and marine foods, dairy products, alcoholic beverages, table salt and water. In addition, detection of MPs in the human placenta has been shown as an indicator of harm on a developing fetus [6].

As the influence of MP in natural ecological phenomena has become a global concern, increasing research has begun to investigate the presence of MPs in various human specimens such as feces, blood and tissues. Detectable concentrations of different MP traits have been reported in various biological samples like blood, urine, respiratory fluids, breast milk, cardiac

tissue, pulmonary tissue, liver, kidney, semen, hands, skin, colon, sputum etc. [7]. Ingestion via food, pulmonary inhalation and trans-dermal infiltration are the principal mechanisms by which MPs get into the systemic circulation and accumulate in highly perfused tissues [8]. Mollusks and fish, key seafood sources, contribute notably to human MP exposure, with reported abundances up to 57.2 and 15.4 items g^{-1}, respectively. Annual exposure is estimated at 8.92×10^4 items from mollusks and 4.6×10^2 from fish, though data for fish remain limited compared to mollusks [9]. Similarly, table salt, contaminated with MPs during seawater crystallization and air exposure, can contribute 12.8–1242.8 MP particles annually when consumed at the WHO-recommended 5 g/day [10]. Drinking water is another source of MP exposure for the human body. If an adult drinks 1.4 L water/day, yearly MP ingestion through drinking water is estimated to be 3.2×10^5 items. However, this value is expected to be variable based on the source of drinking water. For example, it has been reported that if a person's water intake comprises of 83% tap water and 17% bottled water, the annual ingestion of MPs could reach very high levels in the worst-case scenario with almost 4.69×10^9 items with water contributing 3.9×10^3 pieces of MPs [9]. Beyond seafood, drinking water and salt, packaging, beverages, vegetables, and other foods also contribute to MP ingestion. Their small size and resistance to corrosion enable MPs to survive chewing and digestion, reaching the stomach intact, where they can release hazardous adsorbed substances such as heavy metals, pollutants, and antibiotics [7]. Chemical stability and insusceptibility to macrophages shaped their safety from metabolic decomposition and immune cells mediated phagocytosis in liver and allowed them to circulate in blood stream [11]. Similarly, MPs and nano-plastics (NPs) can penetrate the skin not only intracellularly or transcellularly but also through sweat glands, hair follicles, and wounds. Their lipophilic surface properties enhance skin penetration and weaken the stratum corneum's barrier function [12]. Once MPs arrived in systemic circulation, blood translocate and accumulates in densely perfused organs like the heart, kidney, lungs, brain etc.

and potentially induces health hazardous issues like gastrointestinal abnormalities, respiratory problems and neurotoxicity (Supplementary data). Far beyond, Surface charge and chemical modifications of MPs/NPs influence cell interactions; positively charged particles readily bind to negatively charged cell surfaces, promoting intracellular accumulation and potential cellular damage [13]. Collectively, these findings highlight the widespread distribution of MPs and related particles across ecosystems, exerting significant ecological impacts and affecting human health and daily life.

1.2 The Lung's Vulnerability Towards MPs

Human lungs have an intricate anatomical positioning and complex physiological functioning which is inherently susceptible to environmental pollutants including MPs. It bears the huge surface area, more than 70 m^2, a necessity for the efficient gaseous exchange which indirectly facilitates persistent exposure to inhaled particles. Histological monitoring of lung tissues has revealed the presence of plastic MPs from the environment that have entered the respiratory tree which has been deposited in lungs [14]. Among the various modes of MP intake in the human body, evidence has shown that inhalation is a major mechanism since MP abundance has been shown to exist in either indoor or outdoor air which consistently scored the highest rank out of other factors such as seafood, drinking water, table salt or dust which also implies a vulnerability of the lung towards MP exposure [15]. A systematic analysis of MP impact on human health has demonstrated the respiratory system as a primary entrance to induce potential toxicities [16]. MP deposition inside the respiratory network is determined by particle size and aerodynamic properties. Larger MPs, typically those greater than 10 μm, are usually adsorbed in the upper airway tracts and cleared by mucociliary action. In contrast, smaller MPs, particularly those less than 2.5 μm, can bypass these defenses and reach deep into the alveolar regions [17]. Unlike the gastrointestinal tract, which expels MPs through peristalsis and enzymatic activity, the lungs depend on the mucociliary escalator, which is ineffective against

nanosized MPs. Cellular dynamics of pulmonary tracts and respiratory physiology regulates the kinetics of MPs throughout the respiratory organs as depicted in **figure 1**. These minute particles evade clearance, infiltrate deep into the alveoli, and persist within lung tissues, posing a risk of systemic translocation and heightened toxicity. Lacking efficient degradation or excretion mechanisms, the lungs serve as a primary reservoir for MP accumulation, making them particularly susceptible to long-term damage as compared to other organs [18, 19]. Fibrous MPs of 10 microns can persistently accumulate in lungs while particles smaller than 1 micron can be concentrated in deeper alveolar tissue, even translocating into the systemic and lymphatic circulation *via* diffusion, passive cellular penetration or active transport [20, 21]. Another factor contributing to pulmonary susceptibility is the potential interference of MPs with pulmonary surfactant—a lipid-protein complex crucial for maintaining alveolar stability and reducing surface tension. Studies have shown that MPs can disrupt the biophysical function of pulmonary surfactants, leading to impaired lung mechanics and altered pulmonary function [22]. Polystyrene microplastics (PS-MPs) exhibit a stronger affinity for pulmonary surfactant phospholipids compared to its protein components. Additionally, polystyrene facilitates the oxidation of ascorbic acid to dehydroascorbic acid, promoting hydrogen peroxide (H_2O_2) formation in simulated lung fluid. This process subsequently elevates hydroxyl radical (-OH) levels, leading to disruptions in surfactant phase behavior, surface tension regulation, and membrane structural integrity [23]. Alterations in surface tension consequently influence nanoparticle mobility and contribute to the collapse of the surfactant film. Additionally, *in vitro* studies have demonstrated that PS-MPs compromise trans-epithelial resistance by diminishing tight junction proteins. Following PS-MP exposure, there is an upregulation of matrix metallopeptidase 9 and surfactant protein A, indicating a potential reduction in lung tissue repair capacity and an increased risk of pulmonary damage. The impairment of the epithelial barrier function facilitates the infiltration of external agents such as allergens and toxins into

166 the interstitium and bloodstream, heightening the risk of respiratory disorders like asthma and
167 chronic obstructive pulmonary disease (COPD) [24, 25].
168
169 **Figure 1 here**
170 **Figure 1. Respiratory deposition and clearance dynamics of airborne micro/nano-plastics**
171 **(AMNPs).** AMNPs interact with the respiratory tract depending on their particle size. Larger
172 particles (5-10 μm) predominantly deposit in the nasal cavity and pharynx due to inertial
173 impaction and gravitational settling. Intermediate-sized particles (2-5 μm) can penetrate deeper,
174 reaching the tracheobronchial airways. Ultrafine particles (<1 μm) have the potential to reach
175 the alveolar gas-exchange zones, and particles smaller than 0.5 μm may translocate into
176 systemic circulation and lymphatic channels. Deposition is influenced by Brownian motion,
177 gravitational settling, and airway flow dynamics. Once deposited, AMNPs can accumulate in
178 lysosomes of epithelial cells or macrophages. The respiratory system initiates host clearance
179 responses, including mucociliary transport, coughing or sneezing reflexes, phagocytic uptake
180 by alveolar macrophages, and drainage *via* lymphatic pathways. These processes determine the
181 residence time of particles in the lung and their potential systemic distribution. Figure has been
182 reproduced from Gou, Zixuan, et al., [26]
183
184 Polystyrene microplastics (PS-MPs) exhibit a stronger affinity for pulmonary surfactant
185 phospholipids compared to its protein components. Additionally, polystyrene facilitates the
186 oxidation of ascorbic acid to dehydroascorbic acid, promoting hydrogen peroxide (H_2O_2)
187 formation in simulated lung fluid. This process subsequently elevates hydroxyl radical (-OH)
188 levels, leading to disruptions in surfactant phase behavior, surface tension regulation, and
189 membrane structural integrity [23]. Alterations in surface tension consequently influence
190 nanoparticle mobility and contribute to the collapse of the surfactant film. Additionally, *in vitro*

191 studies have demonstrated that PS-MPs compromise trans-epithelial resistance by diminishing
192 tight junction proteins. Following PS-MPs exposure, there is an upregulation of matrix
193 metallopeptidase 9 and surfactant protein A, indicating a potential reduction in lung tissue
194 repair capacity and an increased risk of pulmonary damage. The impairment of the epithelial
195 barrier function facilitates the infiltration of external agents such as allergens and toxins into
196 the interstitium and bloodstream, heightening the risk of respiratory disorders like asthma and
197 chronic obstructive pulmonary disease (COPD) [24, 25]. The detrimental effects of different
198 MP isomer on lung health in diverse experimental studies have been shown in table 1.

199 **Table 1. Impact of MP on lung health across different experimental models**

MPs type	Experimental model	Results	Ref.
Polystyrene	MLE12 cells	1. Promoted cellular senescence	[27]
Polystyrene	A549 cells	1. Reduced cell viability and proliferation. 2. Suppressed metabolic functions.	[28]
Polyethylene	A549 cells	1. Inhibited cell viability. 2. Triggered nitrite accumulation and created nitrosative stress.	[29]
Di (2-ethylhexyl) phthalate and polystyrene	BALB/c mice	1. Enhanced ROS and malondialdehyde production and disrupted redox homeostasis. 2. Promoted Th2 polarization of immune cells by increasing IL-4 and reducing IFN-γ production.	[30]
Fibrous polyamide nylon	Female BALB/c mice	1. Stimulated asthma progression by activating NLRP3 signaling pathway and promoting IL-1β and caspase-1 expressions. 2. Changed the microbiota composition of asthmatic mice.	[31]
Polystyrene	BEAS-2B cells	1. Triggered apoptosis. 2. Destruct pulmonary epithelium and promoted inflammatory responses. 3. Reduced TEER value and ZO-1 expressions.	[32]
Polystyrene	A549 cells	1. Caused inflammation by inducing TLR2 mediated inflammasome.	[33]

		2. Modulated NF-κB signaling pathway and provoked oxidative stress and apoptosis.	
Polystyrene	C57BL/6 mice	1. Impeded cellular antioxidant mechanism. 2. Upregulated respiratory and systemic inflammation. 3. Altered mitochondrial dynamics and promoted ER tension to worsen COPD progression.	[34]
Positively charged polystyrene	BEAS-2B cells	1. Created high oxidative stress. 2. Promoted inflammatory responses. 3. Accumulated in and caused lysosomal deformation and induced autophagic cell deaths.	[35]
MPs derived from industrial waste plastic	A549 cells	1. Induced genotoxicities. 2. Break cytoskeleton and actin structure.	[36]
Polyethylene and polyvinyl chloride	A549 cells	1. Stimulated senescence associated secretary phenotype production and directed cells towards senescence. 2. Dampened redox homeostasis.	[37]
Polyethylene and polyvinyl chloride	BALB/c mice	1. Limited physical performance of mice. 2. Generated systemic inflammation. 3. Accumulated senescent cells inside the lungs. 4. Caused pulmonary inflammation.	[37]

Given the persistent nature of MPs and NPs in the respiratory system, their ability to induce oxidative stress, inflammation, and epithelial disruption underscores the lungs' heightened susceptibility to long-term damage.

2. Literature search method

For this review, relevant literatures were identified using keyword-based searches in multiple scientific databases, including PubMed, Google Scholar, Scopus, Web of Science, and ScienceDirect. Keywords encompassed terms related to "microplastics" and "lung health" to capture studies examining their exposure, mechanistic effects, and associated respiratory outcomes. No restrictions were applied regarding publication year, language, or study design,

and all relevant articles available up to the date of the search were considered. Both peer-reviewed research articles and other pertinent scientific reports were included. The selection process prioritized relevance to the review topic, aiming to provide a comprehensive overview of current evidence, rather than following a formal systematic review or meta-analytic protocol.

3. The impacts of MPs on various respiratory diseases

3.1 MPs exaggerate Asthma

Asthma, a growing global health burden, affects over 300 million people worldwide, predominantly emerging in childhood or adulthood is chronic respiratory disease not only compromises individual well-being but also imposes significant challenges on caregivers, reduces work productivity, and carries substantial economic consequences [38]. In 2019, asthma impacted around 262 million individuals and was responsible for 455,000 deaths. Environmental triggers such as air pollution, dust mites, mold, and occupational chemicals increase asthma risk and severity [39]. Emerging evidence also suggests that inhaled MPs may exacerbate asthma by inducing pulmonary inflammation, mucus secretion, and airway hyper-reactivity.

Various MPs and plastic pollution derivatives in environment trigger the pathological hallmarks associated with progression of allergic asthma (**Figure 2**). Hypersecretion of IL-17A from Th17 or mast cells trigger lipid peroxidation and induce ferroptosis of human bronchiole epithelial cells, a common molecular inflammatory mechanism in allergic asthma [40]. After exposure to plastic-derived pollutants to ovalbumin-induced asthmatic mice model, crucial biomarker of ferroptosis, namely malondialdehyde (MDA), IL-1β, TNF-α are significantly upregulated and reactive oxygen species (ROS) accumulation was surprisingly augmented intensifying the symptomatic worseness of asthma. In contrast, ELISA analysis revealed the significant suppression of antioxidant mechanisms GSH and GPX4 while Fe^{2+} and HIF-1α

level were notably increased [41]. Similarly, PS-MPs dysregulate amino acid and lipid metabolism and simultaneously provoked ferroptosis related biomarkers but alleviate ROS neutralizing enzymes at mRNA transcriptional level. Moreover, it causes iron homeostasis imbalance and ferroptosis *via* TLR4, a key receptor involved in epithelial cell differentiation and respiratory inflammation in asthma, mediated signaling [42]. MP exposure increased both inspiratory and expiratory resistance while reducing pulmonary dynamic compliance. At the organelle level, lung mitochondria showed fragmentation, disrupted and blurred cristae, and transformation into dysfunctional vacuoles in model mice [41]. Pulmonary epithelial cells, together with airway liquids, mucus, and apical junctions, form a selective barrier against pathogens, toxins, and pollutants. In asthma, dysregulation of tight and adherent junctions is commonly observed due to airway inflammation [43]. In house dust mites (HDM)-induced asthmatic mice, MPs markedly reduced key epithelial barrier proteins (occludin, claudin-1, E-cadherin, ZO-1) and increased FITC-dextran fluorescence, indicating enhanced respiratory barrier permeability [44]. Airway inflammation and remodeling are key factors in asthma pathogenesis. MPs promote inflammatory cell infiltration, subepithelial collagen deposition, goblet cell hyperplasia, and upregulate Muc5ac transcription [44, 45]. They also activate the NLRP3 signaling axis, increasing IL-1β and Caspase-1 expression in OVA-induced asthmatic mice [46]. Impaired lung microbiome composition has been well explained by many researchers as a pivotal factor for numerous chronic respiratory infections and clinical cohort of asthma endorsed disturbed pulmonary microbial milieu [47, 48]. MPs selectively impede abundance of microbiota, specifically Bacteria, Firmicutes, Clostridia, Lachnospirales which have been resulting in more severe asthmatic symptoms [46]. Current understanding of asthma pathogenesis highlights proteomic and metabolomic regulation. Hsp90α disrupts epithelial barrier integrity in MPs-mediated asthma by inhibiting E-cadherin/β-catenin complexation, loosening junctions, and promoting a Th2-dominated hyperinflammatory environment [49].

Xu et al. demonstrated that MPs-induced Hsp90α overexpression drives airway remodeling and epithelial rigidity in HDM-induced asthma, acting via the PI3K-Akt-mTOR pathway in alveolar smooth muscle cells to modulate proliferation, inflammation, and immune responses [50]. K. Lu et al. reported that MPs exposure affects clusters of genes involved in stress responses, immune crosstalk, and cell death in asthma. Genes encoding B-cell receptors, IgD, and B and T lymphocyte attenuator receptors were overexpressed, blocking transcription of several heat shock proteins. In contrast, this study reported reduced levels of Hsp90 and other isomers, linked to asthma severity after PS-MPs exposure [51]. The emerging role of transient receptor potential ankyrin-1 (TRPA1), initially considered a neuronal ion channel, has gained attention in asthma as it infiltrates inflammatory cells in the respiratory epithelium, causing structural alterations and bronchoconstriction, notably via neutrophil and eosinophil infiltration. Co-exposure to PS-MPs and DEHP increased calcium influx, upregulated TRPA1, CGRP, and Substance P, and induced p38-MAPK phosphorylation, highlighting the TRPA1–p38-MAPK cascade in allergic asthma [30]. MPs-induced respiratory epithelial damage in asthma is linked to metabolic patterns of sterols, cholesterol, and alcohol. Fatty acids stimulate macrophages to release IL-1β, IL-6, and TNF-α and alter M1/M2 polarization. MPs exposure also activates ATP citrate lyase, promoting glycolysis and generating acetyl-CoA from mitochondrial citrate, a key precursor for cholesterol and fatty acid biosynthesis [52]. Beyond their direct effects, the surface characteristics and adsorptive capacity of MPs facilitate the transfer of environmental toxins, allergens, pathogens, pollens, and endotoxins, thereby influencing allergic asthma pathophysiology [53-55]. Collective evidence suggests that MPs, originating from environmental pollutants or entering the human body through various routes, can directly affect lung physiology and significantly exacerbate asthma.

Figure 2 here

Figure 2: Association of microplastic inhalation with asthma exacerbation

Inhaled microplastics exacerbate asthma by disrupting epithelial barrier integrity, promoting inflammation, and impairing redox homeostasis. Key tight junction proteins (occludin, claudin-1, E-cadherin, ZO-1) are downregulated, compromising epithelial structure. Concurrently, increased IL-17A, Th17 cells, mast cells, and proinflammatory cytokines (IL-1β, TNF-α) amplify airway inflammation via TLR4 signaling. Microplastics further induce ferroptosis and oxidative damage through enhanced ROS, lipid peroxidation, Fe^{2+} accumulation, and HIF-1α elevation, alongside suppression of antioxidant systems including GSH and GPX4. ZO-1; Zona occludin-1, IL; Interleukin, TNF-α; Tumor necrosis factor-α, TLR4; Toll like receptor 4, ROS; Reactive oxygen species, HIF-1α; Hypoxia inducible factor-1α, GSH; Glutathione, GPX4; Glutathione peroxidase 4. Figure has been drawn using Biorender.com.

3.2 Influences of MPs on COPD

COPD is a major global health concern and the fourth leading cause of death, responsible for 3.5 million deaths in 2021 (5% of global deaths). It disproportionately affects low- and middle-income countries, where 90% of deaths under 70 occur, and ranks eighth in disability-adjusted life years [56]. COPD causes vary by economic status: tobacco smoking accounts for over 70% of cases in high-income countries, but only 30-40% in low- and middle-income countries, where household air pollution is a major risk factor. This chronic lung disease, including emphysema and chronic bronchitis, leads to airflow restriction, lung damage, mucus buildup, and symptoms such as cough, wheezing, shortness of breath, and fatigue. Smoking is the primary risk factor for COPD, and recent evidence links it to increased MP exposure. Smokers show a higher abundance and diversity of MP polymers, with elevated MP concentrations in sputum and bronchoalveolar lavage, highlighting a potential link between inhaled MPs and respiratory damage [57, 58]. Positive association between Bisphenol A's physiological level

and COPD incidence, and higher susceptibility of individuals having various phthalates towards respiratory morbidity among COPD patients strongly indicate the risk of MP polymer on COPD pathobiology [59, 60]. *In vitro* instillation of PS-MPs resulted in compromised respiratory efficiency as it strongly attenuated EF50 and Penh value. Differential gene enrichment revealed the significant alteration in genetic expression and chronic exposure leads to significant change in COPD related gene and disease progression [61]. COPD epithelial cells respond differently to MPs compared to normal and asthmatic cells. MPs reduced transepithelial electrical resistance in COPD monolayers, an effect reversed by co-culture with macrophages. In contrast, normal epithelium showed the opposite trend, highlighting how macrophage-epithelial interactions and proteolytic protein secretion can disrupt barrier integrity [52]. Intricate cellular environment of COPD involves proactive interactions between chemokines and immune cells. Elevated level of CXCL1, CXCL5 and CXCL8 in disease pathobiology is highly accountable to upregulate movement of neutrophils and monocytes towards airway's epithelium [62]. MPs treatment to COPD epithelial cells triggers chemoattractant initiated reaction cascade and recruit neutrophils, monocyte and macrophages to the respiratory airway and putatively weakened intercellular cohesion. This also favors epithelial cell's kinesis and displacement, mesenchymal transition subsequently enhanced lung carcinogenic and fibrotic susceptibility [52, 61]. Chronic MP exposure induces alveolar airway remodeling, airway wall thickening, and collagen deposition-hallmarks of experimental COPD. Lung tissue damage was further linked to protease–antiprotease imbalance, with PS-MPs promoting intercellular detachment and epithelial motility *via* modulation of α-antitrypsin and MMP-9 expression [61]. Disorganization of subcellular organelles and their performance alteration is another key feature of COPD physiology. In most of the cases, disbalance of mitochondrial physiology, endoplasmic reticulum stress and severe damage of mitochondrial electron transport chain are molecular mechanisms responsible for the key clinical symptoms

of COPD [63]. Gene ontology analysis suggested dysfunction of forementioned organelles and induction of lung injuries upon MP stimulation. Disproportion of mitochondrial fusion versus fission homeostasis and exacerbation of ER stress were found to be plausible mechanism of inducible COPD at subcellular level [61]. Despite all this evidence, MP was found to be a potential regulator of ferroptosis and cellular oxidative stress tangle. Escalation of iron content and MDA following distinctly suppressed antioxidant enzymes GPX4 created a dynamic network of redox tension and ferroptosis to induce COPD related lungs injuries [61]. MPs impact lung health at the epigenetic level, affecting long non-coding and circular RNAs. Exposure stimulates proinflammatory cytokines (IL-6, TNF-α, IL-1β), upregulates ncRNAs XLOC_031479, circRNA_014924/006603, and represses ncRNA XLOC_014188 and circRNA_003982 [64]. Additionally, macrophage activation and inflammatory cell recruitment are key mediators of disease pathogenesis. In MP-treated models, macrophages respond via TLR4, altering IL-10 secretion, while polyamide modulates CCR2 and suppresses monocyte recruitment, dampening inflammation [52, 65]. In conclusion, studies explaining the impact of MP on COPD are limited but above-mentioned evidence signifies the paramount influence on disease pathobiology.

3.3 MPs and pulmonary fibrosis

Pulmonary fibrosis (PF) is a complex multicellular process marked by impaired alveolar epithelial regeneration and persistent activation of fibroblasts and immune cells. It is characterized by irreversible lung function decline, chronic cough, dyspnea, and reduced quality of life. Lung transplantation benefits only a small subset, while most patients depend on antifibrotic therapy with supportive and palliative care. Despite advances, treatments merely slow progression, and prognosis remains poor, with median survival of 2–3 years. This high disease burden places substantial socioeconomic strain [66]. Exposure to environmental factors, including air pollution, pesticides, metal dust, silica, and benzo(a)pyrene, has been associated

with the development of PF, particularly in high-risk occupational groups such as agricultural and metal workers [67].

Emerging evidence links MPs to PF by inducing local inflammation, epithelial injury, and aberrant epithelial-fibroblast crosstalk that drive stromal differentiation and extracellular matrix (ECM) remodeling. In animal models, 3-week intratracheal instillation of PS-MPs markedly increased α-SMA and collagen expression, producing PF [68]. Overexpression of smooth muscle actin-α (α-SMA) is inversely associated with E-cadherin to preserve the epithelium integrity of alveolar cells. The overexpression of α-SMA tends epithelial cells to transform into mesenchymal state, producing myofibroblast which are responsible for collagen-I secretions in fibrotic lungs [69]. MPs remarkably enhanced the protein level of Krebs von den lungen-6 in pulmonary tissue of mice [68] which was previously proved as a potential indicator of idiopathic pulmonary fibrosis (IPF) [70, 71]. Tissue stiffness and reduced elastic recoil, key features of PF, were observed in C57BL/6 mice after tire-wear MP (TWMP) exposure, which impaired pulmonary function by increasing tissue damping and elastance (measured via forced oscillation). TWMPs also elevated total cell numbers, notably increasing lymphocytes while reducing macrophages, thereby influencing tissue damage and inflammatory responses [72]. Additionally, MPs shifted histological arrangements of respiratory tissue towards fibrotic lung dominant architecture by inducing small capillaries congestion, alveolar wall thickening, stenosis, fibrous tissue hyperplasia and perivascular lymphocyte infiltration [72]. Fibroblast hyperproliferation drives ECM remodeling and fibrosis, yet studies show that injured epithelial cells regulate this process. Notably, fibroblasts co-cultured with MP-pretreated epithelial cells became hyperactivated, producing excessive α-SMA, vimentin, and collagen, unlike fibroblasts directly exposed to MPs [68]. Ferroptosis is emerging as a key inflammatory mechanism in fibrosis, particularly IPF, with nasal PS-MP exposure elevating iron levels, upregulating ASCL4, suppressing GPX4, and amplifying lipid

peroxidation in lung tissue in a concentration-dependent manner [73]. At transcription level, MPs are reported to promote expression of pro-fibrotic gene marker namely TGF-β1, pro-collagen I, fibronectin, and connective tissue growth factor [74]. Histopathological analysis revealed severe respiratory abnormalities, including alveolar congestion, RBC leakage, adenomatous fluid accumulation, and hemosiderosis after MP exposure in animal models. MP polymeric dust was transported via the lymphatic system and localized in cytoplasmic and nuclear sites of respiratory cells, while increased histiocyte proliferation and reticulin fiber deposition shaped a fibrotic lung environment [75].

Numerous signaling mechanisms responsible for cell growth, survival, proliferation and modulation are key components of PF's molecular pathogenesis. Activation of TGF-β signaling and sequential complexation with various downstream Smad proteins has a supreme role in different cellular processes like collagen synthesis, hyperplasia, loss of paracellular contact and trans-differentiation into myofibroblasts which are highly essential for fibrosis [76, 77]. Inhalation of PS-NP to immunocompromised mouse revealed that upregulation of TGF-β1 mediated signaling and overexpression of Smad1/2 proteins promotes fibrotic status of respiratory tissue by releasing pro-fibrotic cytokines and collagen [74]. Similarly, cGAS-STING mediated signaling cascades trigger a spectrum of senescence associated secretory proteins phenotype like IL-6, IL-8, p16, p21 and INF-β, which are vital inflammatory modulators in bleomycin-induced PF [78]. Interconnection between MPs and cGAS-STING signaling in PF is established via ferroptosis mediated inflammation of alveolar cells. GPX4 has been identified as an essential upstream protein for the activation of cGAS and STING signaling axis and to induce ferroptosis in MPs exposed to animal and alveolar epithelial cell models [73]. ROS stimulated p-38 activation expedited the nuclear translocation of NF-kB and induced mitochondrial damage, a key molecular aspect in FP progression [79]. Other signaling mechanisms such as TLR2/NF-kB, NLRP3 and NF-kB/NLRP3 are also validated for their

prominent role in PF pathophysiology. These pathways work in regulating inflammatory reactions, shifting macrophage polarization from Th2 state to Th1 dominated configuration, immune modulation and redox state alteration [80, 81]. In conclusion, the significant impact of MPs on pulmonary fibrosis (PF) and associated lung damage warrants considerable attention. Further verification in randomized clinical cohorts is necessary to develop new diagnostic and therapeutic strategies.

3.4 Tumorigenic tendency of MPs in lungs

Lung cancer, the leading cause of cancer mortality worldwide, accounted for 2.48 million new cases and 1.81 million deaths in 2022 (18% of all cancer deaths) [82]. With <20% five-year survival, its management is hindered by late diagnosis, resistance, heterogeneity, and metastasis, underscoring the urgent need for novel therapies, early detection, and personalized treatments [47, 83]. Recent studies highlighted the considerable carcinogenic risk posed by MPs, attributed to their widespread environmental presence and distinct physicochemical properties. These particles act as carriers for carcinogens such as polycyclic aromatic hydrocarbons (PAHs) and polychlorinated biphenyls (PCBs), promoting their bioaccumulation and systemic distribution through the food chain. This process heightens human exposure, potentially contributing to an increased risk of cancer development [84]. According to Zhao et al., tissues from human malignancies contained significantly higher levels of MPs than normal tissues. Three polymers, namely PS, PVC, and PE were most associated with tumor tissues, with lung cancer masses showing the highest MP burden and greatest polymer diversity [85]. Several other studies have also confirmed the presence of MPs in lung tissues. One such study detected polymeric MPs, including polyethylene and polypropylene, in 13 out of 20 tissue samples, with particle sizes measuring less than 5.5 μm [86]. Another study identified 65 microfibers, including 24 MPs larger than 25 μm, from 100 human lung tissue samples. Accumulation of these microfibers increased with patient age. Notably, lung cancer tumors contained a

435 significantly higher proportion of MPs (two-thirds of the detected microfibers) compared to
436 healthy tissues [87]. Continuous exposure of A549 cells to amorphous polypropylene MPs for
437 a week doubled their proliferation in a dose-dependent manner. Remarkably, even very low
438 MP doses similarly accelerated proliferation of NCI-H1650 non-small cell lung cancer cells
439 after 7 days. Notch1 signaling, a key regulator in lung cancer, was activated by polypropylene
440 MPs alongside enhanced proliferation, directly correlating with morphological changes in
441 NCI-H1650 and A549 cells, including elongation. These morphological changes could
442 potentially play a paramount role in accelerating metastasis. Additionally, MPs were found to
443 be potentiate the expression of Ki-67 gene in *in vitro* study, which are consistently associated
444 with drug resistance in cancer treatment [88]. In contrast, Goodman et al., reported opposite
445 and quite different context regarding the impact of MPs on A549 cells. Prominent decrease in
446 metabolic activity and proliferation rate after incubated with MPs have been observed in their
447 experimental design, but trypan blue staining did not demonstrate any excess cell death at any
448 timepoint. Instead, cells lost their paracellular contact, detached from neighbor cells and extend
449 filopodia projection together with small lamellipodia in between [89]. Filopodia and
450 lamellipodia, key cytoskeletal components driving cellular motility and metastasis, suggest that
451 MPs may promote cancer cell metastasis independently of proliferation. Similarly, Zhang et al.
452 reported that Bisphenol A (BPA) rapidly phosphorylates ERK1/2 via GPCR/EGFR signaling,
453 upregulating MMP-2 and MMP-9, zinc-dependent endopeptidases critical for cancer cell
454 migration and invasion [90]. Moreover, BPA was able to attenuate apoptosis of A549 cells by
455 blocking the ROS generation and proline oxidation via peroxisome proliferator-activated
456 receptor-γ (PPARγ). It significantly escalated the cellular differentiation and hindered apoptotic
457 induction by PPARγ agonist [91]. Additionally, urinary concentration of BPA has been found
458 to have positive association with adult lung cancer thus suggested its potential lung tumorigenic
459 tendency [92]. Overall, current evidence suggests that MPs may both promote and suppress

lung carcinogenesis, with outcomes highly dependent on exposure dose, polymer type, cellular context, and underlying molecular signaling pathways.

3.5 Continuous exposure to MPs and risk of occupational hypersensitivity pneumonitis

Occupational hypersensitivity pneumonitis (OHP) is an immune-mediated lung disorder marked by lymphocytic and granulomatous inflammation of airways, alveoli, and interstitium, triggered by non-IgE allergic responses to bacteria, fungi, animal/plant proteins, chemicals, or metals [93]. Recently, recurrent exposure to plastic fiber in various textiles or polystyrene manufacturing areas are gaining attention of developing OHP [94]. In 2020, a clinical case report documented a 66-year-old individual diagnosed with hypersensitivity pneumonitis following prolonged occupational exposure in the polyethylene terephthalate (PET) manufacturing industry, where he had worked from 1992 to 2013. The patient had a prior history of asbestos exposure and was diagnosed with asbestosis in 2012. By 2017, high-resolution computed tomography revealed a mild but progressive decline in pulmonary function, accompanied by inspiratory clicks on auscultation and a reduced diffusion capacity for carbon monoxide. These findings led to a diagnosis of OHP, with terephthalic acid and dimethyl terephthalate precursors in PET production, identified as the probable causative agents [95]. Similarly, another case of a 46-year-old employee at a yacht manufacturing company presented with progressively worsening shortness of breath, chest tightness, and persistent coughing over the span of two months. Notably, these symptoms appeared to correlate directly with exposure to the work environment. OHP was suspected likely to be triggered by exposure to dimethyl terephthalate and styrene. Since treatments with systemic antibiotics, inhaled bronchodilators, and corticosteroids, offered only marginal symptom relief, later, radiological imaging revealed a widespread interstitial lung pattern, and spirometry tests indicated restrictive lung impairment. Significant symptom resolution and improved lung function were ultimately achieved through oral corticosteroid therapy and complete avoidance

485 of the workplace exposure, underscoring the critical role of environmental factors in the
486 progression and management of OHP [96]. Manet al. described the risk of OHP if lung
487 continuously exposed to the raw components of plastic polymer manufacturing. They have
488 hypothesized the possible role of plastic exposure based on the case study where a female
489 engaged in processed hot plastic manufacturing presented significant number of HP antigenic
490 proteins and finally died after clinical confirmation of OHP [97]. This clinical evidence
491 potentially endorses the possible impact of MPs and other plastic polymer to cause OHP.
492

493 **4. Molecular and physiological mechanism of MP in respiratory diseases**

494 **4.1 Epithelial cell destruction/dysregulation**

495 Lung epithelia constitute several traits of epithelial cells essential for efficient anatomical and
496 physiological functioning with least proliferative ability. Smooth gaseous exchanges,
497 coordination with innate immune responses, mediating inflammatory reactions and protect
498 respiratory system by creating a physical barrier to block invasion of environmental toxicants,
499 bacteria, virus or other pathogens are the fundamental functional basis of respiratory epithelial
500 cells whose alteration/destruction directly influence the lung health stimulating the risk of
501 several pathological circumstances like COPD, asthma, pneumonia etc. [98]. Multiple factors
502 responsible for alteration of physiochemical nature and anatomical integrity of respiratory
503 epithelia are reported till date. Environmental pollutants dynamics and individual lifestyle are
504 inherently associated with epithelial cells efficiency and structural resilience [99]. Recently,
505 MPs are the rising concern of researchers, activists, global health agencies and
506 environmentalist which are emerging as a potential risk factor for human health, particularly
507 respiratory system [100]. Structural alteration and physiological dysregulation of lung epithelia
508 is a common hallmark of numerous respiratory diseases which have been indicated as a
509 potential target of MPs after inhalation. Exposure of polystyrene plastic particles to A549 cells,

a model described for respiratory epithelial cells, imparted cellular toxicities and dragged them towards apoptotic process repressing viability. Nucleic acid staining further revealed cell cycles arrest at S phase [101]. Moreover, plastic particles not only diminished the viability of human nasal primary epithelial cells but also reduced mitochondrial membrane potential (MMP) and sensitized the cells to induce epithelial injury. In particular, smaller polymers had a greater MMP reducing potential compared to larger particles [102]. As a protective strategy, cells adopt the autophagic process when such environmental pollutants harm their routine functions. In severely toxic cases, normal autophagic responses get hijacked and cells undergo autophagic death [103]. MPs have been demonstrated to inhibit autophagic flux in *in-vitro* nasal epithelial cells by accelerating intracellular autophagosome accumulation and modulating expression of key autophagic marker LC3-II and *p62* [102]. Positively charged PS-MPs provoked protein expression and cellular secretion of pro-inflammatory cytokines in human bronchial epithelial cells and *in-vivo* animal models. Augmentation of PERK-EIF2α and ATF4-CHOP pathways to exaggerate ER stress and deformation of lysosomal integrity likely induced autophagic death after PS-MPs treatments in bronchial epithelial cells [104]. Textile polystyrene, nylon microfiber and their leachates have been reported for their inherent properties to suppress growth of human epithelial based lung organoids. Additionally, epithelial cell trans-differentiation was also dampened by nylon fiber and their components. Specifically, alveolar differentiation has been speculated to be mostly affected as it drastically lowered the expression of *pro-SPC*, a key marker of alveolar differentiation, while expression of *p63, ACT* and *Scgb1a1*, marker for basal, ciliated and club cells respectively, were not with a prominent reduction in their nuclear localization. This suggested cumulative effects on total lung epithelial organoid differentiations [105]. At the transcriptional level, genes responsible for the differentiation of club, basal, ciliated and goblet cells were stimulated when exposed to nylon fibers. Two transcriptional genes, namely *Tuba1a* and *Scgb1a1*, particularly considered as

ciliated and club cells differentiation marker respectively, have been found to be significantly upregulated after exposure to nylon fiber suggesting the complex genetic regulation of cellular differentiation that might be affected by several factors like experimental design, concentration of plastic polymer and composition of organoid models [106].

External toxic particulate matter can disrupt the integrity of epithelial barriers, mediate chronic inflammation, induce cell injury, remodel the alveolar structure and increase epithelial permeability and make epithelial cells dysfunctional [107]. PS-MPs exposure on BEAS-2B based *in vitro* experimental setting reduced transepithelial electrical resistance (TEER) and blocked ZO-1 expression loosening the epithelial barrier rigidity and diminishing their protective abilities [108]. Similarly, persistent exposure to nylon fiber profoundly repressed the signaling molecules secretions intended for epithelial growth and development via Notch1 and Notch2 signaling pathways. Ligands Jagged 1, Jagged 2, Bmp4 and Bmp7 expression level was calculated at very submaximal level after being treated with nylon fibers and dampening the subsequent Notch signaling cascade [106]. Using mRNA sequence analysis, remarkable suppression of proliferation markers such as proliferation marker protein 67 (Mki67), Forkhead box protein 341 M1 (Foxm1), and polo-like kinase 1 (Plk1) by nylon fibers confirmed the altered epithelial cell proliferation process in dose dependent manner [106]. Epithelial barrier integrity relies on intercellular cohesion, where claudins and occludins form tight junctions with ECM support. While high TEER values and optimal ZO-1 ensure barrier strength, MMP-mediated ECM proteolysis weakens rigidity and promotes cellular mobility [109, 110]. PS-MPs disrupt epithelial barrier integrity by suppressing TEER resistance and ZO-1 expression while upregulating MMP-9 and SP-A, thereby weakening tight junctions, promoting ECM proteolysis, and impairing pulmonary homeostasis [24]. Similarly in an *in vivo* experiment, tire wear MPs downregulated the E-cadherin release and prevented it from epithelium cytoskeletons assembling with actin filaments destabilizing epithelial architectural integrity

[72]. Twinfilin-1 is another cytoskeletal protein essential to regulate actin filament dynamics of epithelium, monitor EMT and trigger ECM navigation to facilitate cell migrations [111]. Immortalized normal human BEAS-2B cells constitute limited twinfilin-1 level, showing spot-like appearance specifically enriched in myofibrils of actin filaments to preserve strong well-stretching and adhering properties when growing in a culture plate. Stimulation of BEAS-2B cells by tire wear MPs showed a fractured cytoskeleton backbone, skeleton network missing and stressed actin fiber disappearance by catalyzing expression of twinfilin-1. These MPs mediated cytoskeleton rearrangement and morphological alterations which encouraged epithelial cells to migrate rapidly and lose cellular connections [72]. EMT of human respiratory epithelium contributes to several pathophysiological progress and emphasized the possibility of carcinogenic potency acquisition by epithelial cells [112]. After exposure to polyethylene MPs, BEAS-2B and A549 cells underwent morphological transformation resembling the characteristic nature of EMT. RT-PCR analysis unveiled the overstimulation of master transcriptional factors such as *Snail1, Snail2* and *ZEB1* which are required to initiate EMT in epithelial cells. Besides, the key markers of EMT, vimentin and N-cadherin were also found to be upsurged after polyethylene MPs treatment suggesting their potency to attribute EMT behavior by reprogramming genetic sequencing in applied cell lines [113]. Coal dust nanoparticles induced inflammasome activation has been co-associated with EMT via the NLRP3 pathway. AECs came up with diminished epithelial marker E-cadherin and upregulation of mesenchymal marker molecules N-cadherin and EMT driving factor TGFβ1 after coal dust exposure which phenomena have been suspended if MCC950 (selective NLRP3 inhibitor) is induced in the cells [114]. Exposure of polystyrene MPs to experimental mice models promotes the sensitivity of lung tissue inflammasome activation by increasing protein translation of NLRP3 associated inflammasome components, namely NLRP3, ASC and caspase-1 via NF-kB signaling activation [65]. Based on several key findings and emerging

hypotheses, the detrimental effects of MPs and related plastic materials on structural and functional integrity of respiratory epithelium is a critical issue which needs further investigations in large clinical cohort studies and different contextual aspects relevant to the global status of plastic populations. Overall impacts of MPs on epithelium destruction and their consequent on lung diseases are depicted in **figure 3**.

Figure 3 here

Figure 3. Microplastic-induced disruption of pulmonary epithelial integrity and lung pathology. This schematic illustrates the mechanistic effects of inhaled microplastics on the bronchial and alveolar epithelium. Once internalized, MPs induce redox imbalance by reducing the activity of key antioxidant enzymes, including GSH-Px, CAT, and SOD, and promote mitochondrial dysfunction, leading to ROS accumulation. MPs also trigger inflammatory responses, mediated by cytokines such as TNF-α, IL-6, IL-1β, and TGF-β, which together with oxidative stress contribute to cytotoxicity and epithelial cell apoptosis. These stressors independently and collectively lead to epithelial barrier dysfunction, including disrupted tight junctions and impaired intercellular adhesion, as well as excessive airway mucus production. Structural and functional disturbances extend to bronchial and alveolar architecture, compromising pulmonary surfactant function and tissue elasticity. Over time, these pathological alterations promote the development or progression of chronic respiratory diseases, including asthma, COPD, pulmonary fibrosis, emphysema, and lung cancer. GSH-Px; Glutathione peroxidase, CAT; Catalase, SOD; Sodium dismutase, TNF-α; Tumor necrosis factor-α, IL; Interleukin, TGF-β; Transforming growth factor-β. This figure was reproduced from Lu, Kuo, et al. [37].

4.2 Redox imbalance

Human lungs, a versatile organ of our body with constant exposure to external environment. Persistent interaction with oxygen, human lungs are extremely prone to various components of biologically derived reactive oxygen species such as oxygen free radicals, hydroxyl radicals, hydrogen peroxide, singlet oxygen species, reactive nitrogen species or other xenobiotics derived reactive oxygen metabolites. Lung extracellular epithelial lining fluid conserves the strong antioxidant system and detoxifies free radicals, xenobiotics and other reducing agents principally via GSH and associated redox components [115]. Inflammation of airway epithelial interspace and altered redox homeostasis led to glutathione imbalance which is constantly implicated in most of the inflammatory lung diseases [116, 117]. Observations conducted by Land and Wilson deeply intensified the importance of redox modulation in evolutional conservation of perinatal lung development and respiratory epithelium role as they promptly responded to hypoxia and hyperoxia condition [118]. The amount of oxygen has also been shown to be relevant in a study done by Rahman et al., where the oxygen provided to fetal and perinatal lung cells distinctly influenced the morphogenesis of redox-sensitive signaling pathways like NF-kB mediated transepithelial Na+ transport and luminal fluid clearance [115]. Epithelial cells and ECM constitutively express various antioxidant enzymes to maintain pulmonary redox homeostasis. Sodium dismutase (SOD), glutathione peroxidase (GPX), peroxiredoxin (PRX), thioredoxin (TRX) and glutathioredoxin (GRX) collectively form a powerful antioxidant cascade which sequentially detoxifies and neutralizes toxic oxidative metabolites. In addition to this fact, enzyme independent antioxidant small molecules like ascorbic acid, glutathione, uric acid and α-tocopherol abundantly appear in respiratory fluids and assist to maintain oxidative homeostasis in lung cells [119].

The pathobiology of MP induced lung diseases exhibits multiple aspects of cellular symptoms like chronic inflammations, autophagy, ferroptosis, apoptosis, EMT, immune modulation,

genetic reprogramming etc. Among which ROS profoundly have been found to be a driving molecular mechanism. In mammalian models, MP dependent ROS accumulation concomitantly reduce GSH, mitochondrial membrane potential and calcium concentration at endoplasmic reticulum [120]. Cellular senescence of A549 lung epithelial cell lines was positively linked with intracellular ROS level after PVC stimulations. Massive generation of ROS followed by PVC treatment triggered gene protein expression of *p16, p21* and *IκBα* along with SA-β-gal positive dominant cell populations measured with flow cytometry analysis [121]. PS-MPs induced oxidative stress, damaged chicken lungs and induced pulmonary toxicity by provoking autophagic responses. Phosphorylation and subsequent inactivation of PI3K/Akt/mTOR signaling cascade together with LC3 overexpression and *p62* degradation highlighted ROS stressed pulmonary environment to dampen the PS-MPs exposed chicken lungs [122]. Introduction of polystyrene terephthalate nano plastic into A549 cells also resulted in intense ROS stress by triggering mitochondrial membrane depolarization, which may advocate free electron leakage from respiratory electron chain [123]. As we previously mentioned, MPs are highly labile to change their surface behavior and can interact with wide range of environmental toxic reagents or air particulate matter, diverse types of surface modification interestingly found to be associated with differential ROS inducing capability. For instance, exposure of pure PS particles constituted less ROS accumulation potency compared to carboxylic and amine labeled PS particles in A549 cell lines after 6 hours of treatment [124]. An unexpected but interesting observation has been seen in case of polyethylene terephthalate NPs intervened intracellular ROS generations. Massive accumulation of ROS has been observed in respiratory epithelial cell lines, such as human nasal epithelial and alveolar epithelial cells, but it could not induce any significant ROS in colorectal adenocarcinoma and hepatic carcinoma cell lines, namely Caco2 and HepG2 cells [123, 125]. This peculiar evidence suggests that lungs redox physiology is more prone towards MPs influence compared to other

organ systems, but it needs more advanced and specifically designed study to get further validation. Phenol-formaldehyde, a widely utilizing resin in glues, paints, wood preservatives and textile industry, is one of the common source of MPs in air which has been proposed to induce oxidative stress in pulmonary tissue which is considered as one of the major toxicological mechanism of pulmonary physiology and systemic immune mechanism [126, 127]. Photoaged phenol-formaldehyde derived MPs had a higher oxidation potential compared to normal MPs, observed on ascorbate and dithiothreitol assay, which ultimately brought severe toxic effects to lung epithelial cells [128].

At the sub-cellular level, mitochondria are considered as an energy supplier and highly stress-sensitive organelles throughout the life cycle. Detrimental effects of environmental toxins on mitochondrial physiology can be manifested in multiple ways like interruption of electron transfer in cellular respiratory chain, loss of morphological integrity and oxidative stress [129]. Stimulation of alveolar epithelial cells with PS-MPs selectively associated with mitochondrial ROS hyperproduction since MitoTEMPO, a specific mitochondrial ROS scavenger, reversed the hyper-oxidative condition towards normal redox state and disrupted mitochondrial potential has been repaired [130]. This mechanistic interplay is further validated by involvement of iron ion to produce ROS through Fenton reactions. It has been reported that excessive iron production after MPs stimulation exaggerated intracellular ROS concentrations and form a vicious sequential cycle to trigger ferroptosis [131, 132]. PS-MPs mediated oxidative stress potentially destruct mitochondria which can further accelerate ROS overproduction. Besides, enhanced iron concentration and lipid peroxidation at mitochondria results in accumulation of dysfunctional mitochondria at airway epithelium, a common hallmarks for various lung diseases [130]. Similarly, a well-established relationship has been proposed between excessive mitochondrial ROS production and induction of autophagy in different stressed conditions. PS-MP generated ROS induced mitochondrial damage has been implicated in autophagy

685 modulation of BEAS-2B cells and *in vivo* animal experimental setup [133, 134]. At a sub-
686 cellular level, a dysregulated autophagic event has been observed as it blocked the *p62*
687 degradation and enhanced autophagosome accumulation, but expression level of LC3-II
688 remains unchanged [135]. Additionally, a valid connection between NOX4 expression and
689 oxidative stress has been hypothesized and tested to modulate EMT process in alveolar A549
690 cells. Silencing of NOX4 gene on PS-MPs treated A549 cells reversed the elevated ROS level,
691 suppressed MMP2 expression, and upregulated E-cadherin level, nullifying plastic induced
692 toxicities on cell viability. MPs induced NOX4 mediated oxidative tension has led alveolar
693 epithelial cells to acquire enhanced migration potency, loose intercellular contact, and reduced
694 cell viability [136]. Annangi, Balasubramanyam *et al*., has stated that polystyrene terephthalate
695 NPs highly sensitize the redox homeostasis of human nasal epithelial cells. After persistent
696 exposure to specified plastic polymer, massive accumulation of plastic induced ROS was
697 directly concurred with concentration of plastic inside the cells and their accumulation at
698 various sub-cellular regions [135]. Recently, altered energy metabolism of fundamental cellular
699 levels including nucleotides, co-enzymes, amino acids and nitrogen has become a subject of
700 new focus as such changes deteriorate cellular performance, intensify inflammation and trigger
701 intolerable oxidative tension. To elucidate the possible mechanism of increased oxidative stress
702 after prenatal exposure of PS-MP, the level of glutathione, oxidized glutathione and MDA on
703 lung tissue of 7-days old off-springs have been measured. PS-MPs not only enhanced
704 mentioned oxidative stress mediators, but it also enhanced 8OH-dG expressions indicating
705 increased DNA peroxidation and lipid peroxidation to induce oxidative stress on lungs [137].
706 Moreover, a lipid peroxidation repair proteins GPX4, antioxidant enzymes SOD and GSH-Px
707 were inhibited after exposure to PS-MP in TC-1 cells which denotes the dysregulation of
708 antioxidant mechanism and altered redox balance [138]. All this evidence suggests a potential
709 impact of MPs on cellular redox regulation mechanism of respiratory system to cause unwanted

health issues.

4.3 Immune modulation

The immune architecture of pulmonary system conserves the extensive network of innate and adoptive immunity to protect lungs from various external pathogens, environmental toxins and other exogenous antigens. Compromised immune mechanisms are the recurrent pathological manifestations of multiple infectious lung diseases, chronic inflammatory diseases and autoimmune lung diseases [139]. The respiratory system is highly prone to pathogens not only because of its anatomical positioning and functional sensitivity, but also because of compromised immune environments. High oxygen tension in alveolar environments has recently emerged as a susceptible factor for such an environment. An oxygen sensing protein, namely prolyl hydroxylase domain, selectively found only in T cells and suppress inflammatory immune responses, harness T cell's ability to identify and attack pathogens [140]. Most of the pathogens and exogenous substances responsible for a myriad of respiratory diseases affect pulmonary immune systems ways paramount to disease pathobiology. MPs and their leachate have been extensively identified as immune modulators [141]. Normally, organisms activate immune defenses to mitigate MP-induced stress. Upon MP exposure, macrophages and dendritic cells initiate immune responses by secreting cytokines. In mice, MP exposure elevates neutrophil levels and immunoglobulin A (IgA) concentrations while activating immune signaling pathways. Similarly, zebrafish and grouper exhibit gut microbiota dysbiosis and upregulation of immune-related genes. These findings underscore the immunomodulatory effects of MPs across different species [142].Polystyrene is a specific type of plastic which has been shown experimentally to weaken cellular immunity and sensitize cells towards influenza-A viral (IAV) infections. Type I interferon binds to their membrane receptor to induce interferon stimulate genes (ISGs), which can block viral replications, trigger infected cells apoptosis and regulate adoptive immunity [143]. Interferon-inducible

735 transmembrane-3 (IFITM-3), a typical ISG particularly involved in prevention of viral particle
736 endocytosis into cytoplasm. Specifically, it abrogates envelop protein mediated membrane
737 hemi-fusion of virus to host cells and disrupts the early process of viral replication [144].
738 Polystyrene when co-exposed with IAV to A549 cells significantly downregulated IFITM-3
739 expression and facilitates IAV endocytosis. Additionally, it also suppresses TNF-β expression
740 which further points to its potential role in immune modulation during IAV infection [145].
741 Retinoic acid inducible gene-1 like receptor (RIG-1R) are the cytoplasmic RNA helicase
742 responsible for eliciting antiviral immunity. Upon stimulation by foreign antigen, RIG-1R type
743 pattern recognition receptor get activated and induce downstream signaling cascade to generate
744 antiviral immune response via transcription of type I interferon and other inflammatory
745 cytokines [146]. Similarly, autophosphorylation mediated oligomerization of TANK-binding
746 kinase (TBK) and serine phosphorylation of INF regulatory factor -3 are key signaling events
747 to elicit RIG-1R dependent antiviral immunity. PS-MP significantly blocked the
748 phosphorylation of TBK and suppressed INF-I secretions at transcriptional level and promoted
749 IAV infections [145].
750 In response to various autoimmune diseases and exogenous pathogens, IgG play key role in
751 both initiation and resolution phase by regulating chronic autoimmune inflammations. They
752 participate in complement system to drive innate immune cells activation such as neutrophils,
753 mast cells, macrophages, eosinophils etc. [147]. In HDM induced asthmatic experimental mice,
754 MP provoked IgG secretion, macrophages accumulation and got co-localized with CD68,
755 ionized calcium binding adopter molecule and CD206, key markers of macrophage activation.
756 Additionally, infiltration of eosinophils and lymphocytes significantly surged in BALF. Besides,
757 gene functional network analysis revealed that MP trigger the activation of immune cell related
758 genes which are responsible for transcriptional regulation of B cell receptor, B and T
759 lymphocyte attenuator and IgD [51]. Number of neutrophils and other inflammatory cytokines

760 such as eotaxin, TNF-α, IL-12 and IL-13 is also increased after treatment with polystyrene and
761 association was dose dependent [148]. In general, phagocytosis of pathogens by innate immune
762 cells is considered as a common phenomenon for live pathogens who have biological ligand to
763 get engulfed. However, Park *et al*., surprisingly discovered that neutrophils have strong affinity
764 towards PS-MP and confirmed their intracellular accumulation using scanning electron
765 microscope [149]. In similar ways, Rahman *et al*., conducted an *In-vivo* investigation to check
766 the impact of polyethylene terephthalate MP on various signaling networks associated with
767 interferon responses in mouse lung epithelial cells. Complete gene expression analysis
768 suggested that most of the altered signaling pathway were directly associated with immune
769 responses like IL-1 mediated cytokine signaling, antiviral response and T cell receptor
770 signaling, MHC-1 dependent antigen presentation and interferon-alpha/beta and cytosolic
771 sensors of pathogen-associated DNA responses [150]. Major pathological mechanism
772 fundamentally linked to MPs-induced multiple respiratory problems are graphically illustrated
773 in figure 4.
774
775 **Figure 4 here**
776 **Figure 4. Schematic illustration of microplastic-induced pathological mechanisms in the**
777 **lungs.** (A) MPs trigger epithelial barrier disruption by upregulating inflammatory cytokines
778 (TNF-α, IL-1β, IL-6, IFN-γ), which promote apoptosis and impair cell cycle progression.
779 Accumulation of autophagosomes and reduced autophagic flux further weakens epithelial
780 integrity by downregulating ZO1 and E-cadherin while increasing MMP9 expression, leading
781 to decreased TEER and compromised barrier rigidity. (B) MPs induce redox imbalance via
782 excessive ROS production and mitochondrial damage, resulting in oxidative stress and
783 autolytic degradation. Antioxidant defenses (SOD, GPX4, GSH-Px) are suppressed, promoting
784 lipid and DNA peroxidation. (C) MPs dysregulate immune responses by altering cytokine

profiles (e.g., IL-12, IL-13, TNF-α) and activating IFITM3 and TBK signaling pathways, which enhance endocytosis and inflammation while suppressing interferon (INF1) expression, contributing to heightened infection susceptibility. TNF-α, tumour necrosis factor-α; IL, interleukin; IFN, interferon; ZO-1, zonula occludens-1; MMP-9, matrix metalloproteinase-9; TEER, transepithelial electrical resistance; ROS, reactive oxygen species; SOD, superoxide dismutase; GPX4, glutathione peroxidase 4; GSH-Px, glutathione peroxidase; IFITM3, interferon-induced transmembrane protein 3; TBK, TANK-binding kinase. Figure has been drawn from Biorender.com.

4.4 Interaction with lung surfactants

Lung surfactant (LS) ubiquitously covers the aqueous epithelial lining of alveolus primarily form by type II alveolar cells. Biochemical composition is made up of 80% of phospholipid components (most abundantly dipalmitoylphosphatidylcholine (DPPC) along with phosphatidylcholine, phosphatidylinositol, phosphatidylethanolamine, phosphatidylglycerol, neutral cholesterol in minor concentration) and about 20% of LS-specific proteins [151]. LS is not only essential to reduce interfacial surface tension between alveolar epithelial cells and inhaled air, which protect lungs from alveolar collapse during exhalation, but also creates a first-line physical barrier to prevent pathogen entry.

Extraneous materials, when interacting with LS components, can have potential effects in changing the physiological composition of lung cells which might impart negative impacts on lung functioning, even causing various respiratory diseases [152]. The friction-less LS film has been also described for its immunological role against inhaled substances and pathogens at alveolar capillary space [153]. Recently, several studies have confirmed that MPs can interact physically as well as chemically with LS molecules and alter their composition, biophysical function and fluid behavior. Dose dependent function of MP has been observed in raising of

surface tension and repressing foaming ability of LS, both are critical factors to attribute proper lung performance [154]. Li *et al.* utilized molecular dynamic simulations to determine the impacts of small nano plastic on simulated surfactant film. Nano plastic particles changed structural arrangement, fluidity and interfered with the biophysical properties of simulated surfactant film promoting film damage [155]. Similar effects have been induced by engineered polystyrene microbeads on LS phase behavior and surface characteristics [23]. On calf lungs derived natural LS preparation, namely infasurf, MP disturbed the uniformity of phospholipid and enhanced film compressibility altering biophysical functions [156]. Among the phospholipid and protein components, MP has greater affinity towards phospholipid adsorption (90%) as opposed to protein adsorption (10% and they form a protective corona around plastic particle subsequently reducing the elasticity of the surfactants.

Formation of complex between phospholipid and MP influenced the hydrodynamic behavior of particles by reducing zeta potential value which accelerates their agglomeration and alters their transport and distribution in systemic circulation. Agglomerated bulk particles may lose their potency to enter systemic circulation and get accumulated in deep alveolar tissue [154]. On investigation of different phospholipid derivatives on zeta potential modulation of MP, DPPC alone has been found to be capable enough to decrease it, which suggested the significance of DPPC on MP interaction, but further studies are needed to explore the exact chemistry behind these chemistry [23]. Additionally, MPs can mediate fatty acid oxidation and induce oxidative stress in cell membrane vicinity. Such oxidative stress alters protein secondary structures, dysregulate protein folding which has been hypothesized for the possible reason of reduced foaming abilities of LS [154]. Such interactions imply the significant influence of MP on fluid dynamics and physiological mechanistic of lungs. Since limited studies are available till now, more advanced and specialized investigations need to explore their impacts in multiple dimensions of lung physiology.

5. Surface character modification and aging of MP

As we previously mentioned, MP exhibits dynamic physicochemical properties such as high specific surface area, low density and small size. Ubiquitously populated MP are common carrier for various environmental pollutants and toxic metal ions to various living organism. For instance, interaction of MP with Pb^{2+} ion significantly changes their environmental behavior, bioavailability, fate and toxicity. Since they hold only physical connection without forming strong covalent bonds, metal ions can easily get detached when exposed in water [157]. Surface charge dynamics of MP were also found to be crucial to determine their toxicity in lungs epithelium. Positively charged PS-MP imparted higher detrimental effect to A549 cells compared to neutral particles [136]. P^H has distinct impact on surface characteristics of different MP derivatives. At pH 3, FTIR spectrum of polystyrene and its terephthalate showed a characteristic peak of carbonyl stretching, indicating surface oxidation [158]. Changes in physical and chemical behavior of MP subjected by various environmental factors like water, photo radiation, microorganisms, reducing agents and oxidants accelerate MP aging. Halle *et al.* reported that as MPs undergo aging, their polymeric chains degrade, generating free radicals. These radicals interact with atmospheric oxygen, forming peroxy-radicals, which subsequently trigger the production of alcohols, acids, aldehydes, and unsaturated compounds [159]. Song et al. similarly observed that the aging process of MPs led to the formation of surface cracks and an increased presence of oxygen-containing functional groups, which significantly influenced their adsorption properties. Furthermore, as MPs degrade into nano plastics, their surface-to-mass ratio rises, enhancing their ability to penetrate lipid membranes and intensifying their intracellular toxicity [122, 160]. Interestingly, when polystyrene and polyethylene formed complex with strong surfactant molecule sodium dodecyl benzene sulfonate (SDBS), a significant reduction in Gibbs free energy of adsorption system has been observed. Such complex exhibited significantly higher saturated adsorption abilities for several

broad-spectrum antibiotics namely norfloxacin and oxytetracycline. SDBS imparted electronegativity on MP's surface, reduced specific surface area and reduced fluid permeability [161]. Carbonyl index, the proportion of C = O and CH_3 stretching, is another measure to determine surface oxidation during polymer aging. Following weathering, high-density polyethylene and pristine polymer were observed with prominently enhanced carbonyl index suggesting augmented surface oxidation. Change in surface polarity during MP aging is another key reason for their altered adsorption behavior. It has been reported that weathering of several plastic polymer imparts more polar surface character, nucleophile rich functional group, for e.g. oxygen, and subsequently promotes hydrophobic organic contaminant like methylene blue, phenanthrene [162]. In conclusion, surface chemistry and physical features of MP can have strong interaction with LS which may potentially attribute essential role in lung pathogenesis, but further detailed studies are still needed to explore the exact mechanism.

6. Challenges and limitations

With societal advancement, human exposure to MPs has become nearly unavoidable, posing a significant threat to health. Extensive research has investigated the adverse effects of airborne MPs on human health, with evidence suggesting their harmful impact on the respiratory system. However, the precise toxic mechanisms remain unclear, and challenges persist in developing effective strategies for prevention and treatment [163]. Research on the prevention and treatment of MPs exposure faces several challenges. One major limitation is the insufficient amount of data on respiratory exposure in vulnerable populations, such as infants, pregnant women, and the elderly [164]. Moreover, indoor MP exposure often exceeds outdoor levels, yet scientific data on indoor MPs remain scarce. Investigating their presence, exposure pathways, and health impacts is crucial to understanding potential risks and reinforcing the need for mitigation strategies [165]. Detecting, characterizing, and quantifying MPs in lung tissue presents significant methodological challenges. The scientific community requires

highly sensitive, high-throughput techniques and standardized protocols for accurate assessment. Additionally, research on the incidence and health effects of MPs, particularly in the respiratory system, remains limited. Most experimental studies rely on commercially available MPs with uniform properties, which may not accurately reflect real-world exposure [166]. Current research is predominantly based on *in vitro* and animal models, with limited population-based studies, highlighting the need for further investigations.

7. Conclusion and future prospectives

MPs have become an inevitable part of daily life due to their widespread use in various industries, including food packaging, healthcare, and consumer products. The continuous release of MPs into the environment through physical abrasion, photooxidation, and microbial degradation has resulted in their accumulation in terrestrial and aquatic ecosystems. Consequently, human exposure to these particles is unavoidable. Lungs and the respiratory system are particularly vulnerable to MP-induced damage. MPs interact with lung cells, leading to epithelial dysfunction, oxidative stress, ER stress, lysosomal damage, and mitochondrial deregulation, all of which are linked to respiratory diseases such as asthma, COPD, and lung cancer. Different types of MP polymers can cause varying degrees of toxicity, further complicating their impact on lung health.

Given the pervasive presence of MPs in our environment, future research should focus on systematically elucidating particle-specific toxicokinetic, dose-response relationships, and long-term cumulative effects in humans. Advanced in vitro models such as air–liquid interface cultures and organoids can help simulate realistic pulmonary exposure. Integrating multi-omics approaches (proteomics, metabolomics, and epigenomics) will provide insights into molecular mechanisms underlying MP-induced respiratory disorders. Furthermore, epidemiological studies are needed to correlate environmental exposure with disease prevalence. Such research will guide the development of preventive strategies, regulatory policies, and targeted therapy

910 to reduce MP-related health risks and protect lung functions.

911

912 **Authors' contributions**

913 Conceptualization: Rajan Thapa, Keshav Raj Paudel, Rajendra Karki
914 Funding acquisition: Keshav Raj Paudel, Rajib Majumder, Kamal Dua, Rajendra Karki
915 Methodology: Rajan Thapa
916 Project administration: Keshav Raj Paudel, Kamal Dua
917 Resources: Keshav Raj Paudel, Kamal Dua
918 Software: Rajan Thapa, Michael A. Schlesinger, Sudarshan Poudel
919 Supervision: Keshav Raj Paudel, Rajendra Karki, Suvash Shah
920 Validation: Rajan Thapa, Sapana Subedi, Urmila Kafle, Sobia Idrees, Bassma H. Elwakil
921 Visualization: Rajan Thapa, Nisha Panth, Newton Suwal, Saroj Bashyal, Mostafa El-Khatib
922 Writing original draft: Rajan Thapa, Nisha Panth, Newton Suwal,
923 Writing review editing: Michael A. Schlesinger, Newton Suwal, Saroj Bashyal, Sapana Subedi,
924 Sudarshan Poudel, Nisha Panth, Urmila Kafle, Sobia Idrees, Rajib Majumder, Bassma H.
925 Elwakil, Mostafa El-Khatib, Suvash C. Shah, Kamal Dua, Rajendra Karki, Keshav Raj Paudel
926

927 **Funding**

928 This project is supported by funding from Maridulu Budyari Gumal - The Sydney Partnership
929 for Health, Education, Research and Enterprise (SPHERE)-2023 for Keshav Raj Paudel, Rajib
930 Majumder, and Kamal Dua. This work was supported by Creative-Pioneering Researchers
931 Program through Seoul National University (3344-20240032 to RK), the National Research
932 Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (RS-2023-
933 00251395 and RS-2025-00554099 to RK), the Bio&Medical Technology Development
934 Program of the National Research Foundation (NRF) funded by the Korea government (MSIT)
935 (RS-2024-00440738 to RK) and the BK21 Research Fellowship from the Ministry of
936 Education, Science and Technology, Republic of Korea (to Rajendra Karki).

937

Acknowledgments

Rajan Thapa is supported by the Global Korea Scholarship-2022, R&D track, fully funded by the government of the Republic of Korea and would like to acknowledge the National Institute for International Education (NIIED) and Keimyung University, Republic of Korea, for their support. Keshav Raj Paudel would like to acknowledge the funding support from the TSANZ-Maurice Blackburn grant-in-aid 2021 and the Australian Respiratory Council grant for the bushfire project. We acknowledge the HEAL (Healthy Environments and Lives) National Research Network, which receives funding from the National Health and Medical Research Council (NHMRC) Special Initiative in Human Health and Environmental Change (Grant No. 2008937).

Data availability

Not applicable.

Code availability

Not applicable.

Declarations

Conflict of 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.

Ethics approval

Not applicable.

Consent to participate

All authors agreed on participation.

Consent for publication

All authors agreed on the publication.

963 **References**

964 1. Thompson, R.C., et al., *Our plastic age.* Philosophical Transactions of the Royal
965 Society B - Journals, 2009. **364**(1526): p. 1973-6.
966 2. Cowger, W., et al., *Global producer responsibility for plastic pollution.* Science
967 Advances, 2024. **10**(17): p. eadj8275.
968 3. Gourmelon, G., *Global plastic production rises, recycling lags.* Vital Signs, 2015. **22**:
969 p. 91-95.
970 4. Wang, C., J. Zhao, and B. Xing, *Environmental source, fate, and toxicity of*
971 *microplastics.* Journal of Hazardous Materials, 2021. **407**: p. 124357.
972 5. de Souza Machado, A.A., et al., *Microplastics as an emerging threat to terrestrial*
973 *ecosystems.* Global Change Biology, 2018. **24**(4): p. 1405-1416.
974 6. Kannan, K. and K. Vimalkumar, *A Review of Human Exposure to Microplastics and*
975 *Insights Into Microplastics as Obesogens.* Frontiers in Endocrinology, 2021. **12**: p.
976 724989.
977 7. Li, Y., et al., *Microplastics in the human body: A comprehensive review of exposure,*
978 *distribution, migration mechanisms, and toxicity.* Science of the Total Environment,
979 2024. **946**: p. 174215.
980 8. Ribeiro, F., et al., *Accumulation and fate of nano-and micro-plastics and associated*
981 *contaminants in organisms.* Trends in Analytical Chemistry, 2019. **111**: p. 139-147.
982 9. Wu, P., et al., *Absorption, distribution, metabolism, excretion and toxicity of*
983 *microplastics in the human body and health implications.* Journal of Hazardous
984 Materials, 2022. **437**: p. 129361.
985 10. Yang, D., et al., *Microplastic Pollution in Table Salts from China.* Environmental
986 Science & Technology, 2015. **49**(22): p. 13622-7.
987 11. Lee, S., et al., *Toxicity Study and Quantitative Evaluation of Polyethylene Microplastics*

in ICR Mice. Polymers, 2022. **14**(3).

12. Celebi Sozener, Z., et al., *Environmental factors in epithelial barrier dysfunction.* The Journal of Allergy and Clinical Immunology, 2020. **145**(6): p. 1517-1528.

13. Wu, Y., et al., *Investigation of pulmonary toxicity evaluation on mice exposed to polystyrene nanoplastics: The potential protective role of the antioxidant N-acetylcysteine.* Science of the Total Environment, 2023. **855**: p. 158851.

14. Pauly, J.L., et al., *Inhaled cellulosic and plastic fibers found in human lung tissue.* Cancer Epidemiology, Biomarkers & Prevention, 1998. **7**(5): p. 419-428.

15. Zhang, Q., et al., *A Review of Microplastics in Table Salt, Drinking Water, and Air: Direct Human Exposure.* Environmental Science & Technology, 2020. **54**(7): p. 3740-3751.

16. Chartres, N., et al., *Effects of Microplastic Exposure on Human Digestive, Reproductive, and Respiratory Health: A Rapid Systematic Review.* Environmental Science & Technology, 2024. **58**(52): p. 22843-22864.

17. Saha, S.C. and G. Saha, *Effect of microplastics deposition on human lung airways: A review with computational benefits and challenges.* Heliyon, 2024. **10**(2): p. e24355.

18. Mohanan, N., et al., *Microbial and Enzymatic Degradation of Synthetic Plastics.* Frontiers in Microbiology, 2020. **11**: p. 580709.

19. Wang, Y.F., et al., *Impact of microplastics on the human digestive system: From basic to clinical.* World Journal of Gastroenterology, 2025. **31**(4): p. 100470.

20. Wright, S.L. and F.J. Kelly, *Plastic and human health: a micro issue?* Environmental Science & Technology, 2017. **51**(12): p. 6634-6647.

21. Vethaak, A.D. and H.A. Leslie, *Plastic debris is a human health issue*. 2016, ACS Publications.

22. Lu, K., et al., *Microplastics, potential threat to patients with lung diseases.* Frontiers in

Toxicology, 2022. **4**: p. 958414.

23. Shi, W., et al., *Potential health risks of the interaction of microplastics and lung surfactant.* Journal of Hazardous Materials, 2022. **429**: p. 128109.

24. Yang, S., et al., *In vitro evaluation of nanoplastics using human lung epithelial cells, microarray analysis and co-culture model.* Ecotoxicology and Environmental Safety, 2021. **226**: p. 112837.

25. Zhao, C., et al., *Respiratory exposure to PM2.5 soluble extract disrupts mucosal barrier function and promotes the development of experimental asthma.* Science of the Total Environment, 2020. **730**: p. 139145.

26. Gou, Z., et al., *Airborne micro- and nanoplastics: emerging causes of respiratory diseases.* Part Fibre Toxicol, 2024. **21**(1): p. 50.

27. Luo, H., et al., *The regulation of circRNA_kif26b on alveolar epithelial cell senescence via miR-346-3p is involved in microplastics-induced lung injuries.* Sci Total Environ, 2023. **882**: p. 163512.

28. Goodman, K.E., et al., *Exposure of human lung cells to polystyrene microplastics significantly retards cell proliferation and triggers morphological changes.* Chemical research in toxicology, 2021. **34**(4): p. 1069-1081.

29. Gautam, R., et al., *Evaluation of potential toxicity of polyethylene microplastics on human derived cell lines.* Sci Total Environ, 2022. **838**(Pt 2): p. 156089.

30. Han, Q., et al., *Co-exposure to polystyrene microplastics and di-(2-ethylhexyl) phthalate aggravates allergic asthma through the TRPA1-p38 MAPK pathway.* Toxicology Letters, 2023. **384**: p. 73-85.

31. Wu, Q., et al., *Lung microbiota participated in fibrous microplastics (MPs) aggravating OVA-induced asthma disease in mice.* Food Chem Toxicol, 2024. **190**: p. 114776.

32. Yang, S., et al., *In vitro evaluation of nanoplastics using human lung epithelial cells,*

microarray analysis and co-culture model. Ecotoxicol Environ Saf, 2021. **226**: p. 112837.

33. Cao, J., et al., *Exposure to polystyrene microplastics triggers lung injury via targeting toll-like receptor 2 and activation of the NF-kappaB signal in mice.* Environ Pollut, 2023. **320**: p. 121068.

34. Yang, S., et al., *Inhalation exposure to polystyrene nanoplastics induces chronic obstructive pulmonary disease-like lung injury in mice through multi-dimensional assessment.* Environ Pollut, 2024. **347**: p. 123633.

35. Jeon, M.S., et al., *Polystyrene microplastic particles induce autophagic cell death in BEAS-2B human bronchial epithelial cells.* Environ Toxicol, 2023. **38**(2): p. 359-367.

36. Bengalli, R., et al., *Characterization of microparticles derived from waste plastics and their bio-interaction with human lung A549 cells.* J Appl Toxicol, 2022. **42**(12): p. 2030-2044.

37. Jin, W., et al., *Microplastics exposure causes the senescence of human lung epithelial cells and mouse lungs by inducing ROS signaling.* Environ Int, 2024. **185**: p. 108489.

38. Yang, C.H., et al., *Global burden of asthma in young adults in 204 countries and territories, 1990-2019: Systematic analysis of the Global burden of disease study 2019.* Preventive Medicine Reports, 2024. **37**: p. 102531.

39. Organization, W.H., *Asthma*. 2024.

40. Song, J., et al., *Molecular mechanism of interleukin-17A regulating airway epithelial cell ferroptosis based on allergic asthma airway inflammation.* Redox Biology, 2023. **68**: p. 102970.

41. Wei, H., et al., *Mechanisms of exacerbation of Th2-mediated eosinophilic allergic asthma induced by plastic pollution derivatives (PPD): A molecular toxicological study involving lung cell ferroptosis and metabolomics.* Science of the Total Environment,

2024. **946**: p. 174482.

42. Kang, H., et al., *Inhaled polystyrene microplastics impaired lung function through pulmonary flora/TLR4-mediated iron homeostasis imbalance.* Science of the Total Environment, 2024. **946**: p. 174300.

43. Georas, S.N. and F. Rezaee, *Epithelial barrier function: at the front line of asthma immunology and allergic airway inflammation.* The Journal of Allergy and Clinical Immunology, 2014. **134**(3): p. 509-20.

44. Hu, J.Q., et al., *Co-exposure to polyethylene microplastics and house dust mites aggravates airway epithelial barrier dysfunction and airway inflammation via CXCL1 signaling pathway in a mouse model.* International Immunopharmacology, 2025. **146**: p. 113921.

45. Hussain, M. and G. Liu, *Eosinophilic Asthma: Pathophysiology and Therapeutic Horizons.* Cells, 2024. **13**(5).

46. Wu, Q., et al., *Lung microbiota participated in fibrous microplastics (MPs) aggravating OVA-induced asthma disease in mice.* Food and Chemical Toxicology, 2024. **190**: p. 114776.

47. Thapa, R., et al., *Influence of gut and lung dysbiosis on lung cancer progression and their modulation as promising therapeutic targets: a comprehensive review.* MedComm, 2024. **5**(12): p. e70018.

48. Kozik, A.J. and Y.J. Huang, *The microbiome in asthma: Role in pathogenesis, phenotype, and response to treatment.* Annals of Allergy, Asthma & Immunology, 2019. **122**(3): p. 270-275.

49. Ye, C., et al., *The role of secreted Hsp90alpha in HDM-induced asthmatic airway epithelial barrier dysfunction.* BMC Pulmonary Medicine, 2019. **19**(1): p. 218.

50. Xu, M., et al., *Microplastic exposure induces HSP90alpha secretion and aggravates*

asthmatic airway remodeling via PI3K-Akt-mTOR pathway. Ecotoxicology and Environmental Safety, 2025. **291**: p. 117828.

51. Lu, K., et al., *Detrimental effects of microplastic exposure on normal and asthmatic pulmonary physiology.* Journal of Hazardous Materials, 2021. **416**: p. 126069.

52. Paplinska-Goryca, M., et al., *The impaired response of nasal epithelial cells to microplastic stimulation in asthma and COPD.* Scientific Reports, 2025. **15**(1): p. 4242.

53. Thio, B.J., J.H. Lee, and J.C. Meredith, *Characterization of ragweed pollen adhesion to polyamides and polystyrene using atomic force microscopy.* Environmental Science & Technology, 2009. **43**(12): p. 4308-13.

54. Thio, B.J. and J.C. Meredith, *Quantification of E. coli adhesion to polyamides and polystyrene with atomic force microscopy.* Colloids and Surfaces B: Biointerfaces, 2008. **65**(2): p. 308-12.

55. Wang, C., et al., *Polystyrene microplastics significantly facilitate influenza A virus infection of host cells.* Journal of Hazardous Materials, 2023. **446**.

56. Organization, W.H., *Chronic obstructive pulmonary disease (COPD)*. 2024, WHO.

57. Lu, W., et al., *New Evidence of Microplastics in the Lower Respiratory Tract: Inhalation through Smoking.* Environmental Science & Technology, 2023. **57**(23): p. 8496-8505.

58. Huang, S., et al., *Detection and Analysis of Microplastics in Human Sputum.* Environmental Science & Technology, 2022. **56**(4): p. 2476-2486.

59. Zhou, R., et al., *Association of urinary bisphenol A with chronic obstructive pulmonary disease-related diseases: evidence from the National Health and Nutrition Examination Survey database (2005-2016).* Environmental Science and Pollution Research, 2023. **30**(12): p. 33170-33180.

60. Quiros-Alcala, L., et al., *A cross sectional pilot study to assess the role of phthalates on*

respiratory morbidity among patients with chronic obstructive pulmonary disease. Environmental Research, 2023. **225**: p. 115622.

61. Yang, S., et al., *Inhalation exposure to polystyrene nanoplastics induces chronic obstructive pulmonary disease-like lung injury in mice through multi-dimensional assessment.* Environmental Pollution, 2024. **347**: p. 123633.

62. Donnelly, L.E. and P.J. Barnes, *Chemokine receptors as therapeutic targets in chronic obstructive pulmonary disease.* Trends in Pharmacological Sciences, 2006. **27**(10): p. 546-53.

63. Bialas, A.J., et al., *The Role of Mitochondria and Oxidative/Antioxidative Imbalance in Pathobiology of Chronic Obstructive Pulmonary Disease.* Oxidative Medicine and Cellular Longevity, 2016. **2016**: p. 7808576.

64. Prado, Y., et al., *Small Plastics, Big Inflammatory Problems.* Advances in Experimental Medicine and Biology, 2023. **1408**: p. 101-127.

65. Kwabena Danso, I., et al., *Pulmonary toxicity assessment of polypropylene, polystyrene, and polyethylene microplastic fragments in mice.* Toxicology Research, 2024. **40**(2): p. 313-323.

66. Maher, T.M., et al., *Global incidence and prevalence of idiopathic pulmonary fibrosis.* Respiratory Research, 2021. **22**(1): p. 197.

67. Siswanto, S. and B. Wardhani, *Association of Environmental Pollutants Exposure with Pulmonary Fibrosis: A Mini Review of Molecular Mechanism Mediated.* Pharmaceutical Sciences and Research, 2022. **9**(2).

68. Li, X., et al., *Intratracheal administration of polystyrene microplastics induces pulmonary fibrosis by activating oxidative stress and Wnt/beta-catenin signaling pathway in mice.* Ecotoxicology and Environmental Safety, 2022. **232**: p. 113238.

69. Ma, W.H., et al., *Protective effects of GHK-Cu in bleomycin-induced pulmonary fibrosis*

via anti-oxidative stress and anti-inflammation pathways. Life Sciences, 2020. **241**: p. 117139.

70. Sakai, M., et al., *A novel lung injury animal model using KL-6-measurable human MUC1-expressing mice.* Biochemical and Biophysical Research Communications, 2013. **432**(3): p. 460-5.

71. Elhai, M., J. Avouac, and Y. Allanore, *Circulating lung biomarkers in idiopathic lung fibrosis and interstitial lung diseases associated with connective tissue diseases: Where do we stand?* Seminars in Arthritis and Rheumatism, 2020. **50**(3): p. 480-491.

72. Li, Y., et al., *Inhaled tire-wear microplastic particles induced pulmonary fibrotic injury via epithelial cytoskeleton rearrangement.* Environment International, 2022. **164**: p. 107257.

73. Zhang, J., et al., *Polystyrene microplastics induce pulmonary fibrosis by promoting alveolar epithelial cell ferroptosis through cGAS/STING signaling.* Ecotoxicology and Environmental Safety, 2024. **277**: p. 116357.

74. Jin, Y.J., et al., *Characterisation of changes in global genes expression in the lung of ICR mice in response to the inflammation and fibrosis induced by polystyrene nanoplastics inhalation.* Toxicology Research, 2023. **39**(4): p. 1-25.

75. Agarwal, D.K., et al., *Some biochemical and histopathological changes induced by polyvinyl chloride dust in rat lung.* Environmental Research, 1978. **16**(1-3): p. 333-41.

76. Eickelberg, O., *Endless healing: TGF-beta, SMADs, and fibrosis.* FEBS Letters, 2001. **506**(1): p. 11-4.

77. Rahimi, R.A. and E.B. Leof, *TGF-beta signaling: a tale of two responses.* Journal of Cellular Biochemistry, 2007. **102**(3): p. 593-608.

78. Zhang, J., et al., *The role of cGAS-STING signaling in pulmonary fibrosis and its therapeutic potential.* Frontiers in Immunology, 2023. **14**: p. 1273248.

79. Woo, J.H., et al., *Polypropylene nanoplastic exposure leads to lung inflammation through p38-mediated NF-kappaB pathway due to mitochondrial damage.* Particle and Fibre Toxicology, 2023. **20**(1): p. 2.

80. Li, S., et al., *Di (2-ethylhexyl) phthalate and polystyrene microplastics co-exposure caused oxidative stress to activate NF-kappaB/NLRP3 pathway aggravated pyroptosis and inflammation in mouse kidney.* Science of the Total Environment, 2024. **926**: p. 171817.

81. Cao, J., et al., *Exposure to polystyrene microplastics triggers lung injury via targeting toll-like receptor 2 and activation of the NF-kappaB signal in mice.* Environmental Pollution, 2023. **320**: p. 121068.

82. Zhou, J., et al., *Global burden of lung cancer in 2022 and projections to 2050: Incidence and mortality estimates from GLOBOCAN.* Cancer Epidemiol, 2024. **93**: p. 102693.

83. Siegel, R.L., et al., *Cancer statistics, 2023.* CA: A Cancer Journal for Clinicians, 2023. **73**(1): p. 17-48.

84. Yazarkan, Y., et al., *The Relationship Between Microplastics and Nanoplastics with Cancer: An Emerging Health Concern.* Uluslararasi Hematoloji-Onkoloji Dergisi, 2024. **34**(2): p. 102-112.

85. Zhao, J., et al., *Detection and quantification of microplastics in various types of human tumor tissues.* Ecotoxicology and Environmental Safety, 2024. **283**: p. 116818.

86. Amato-Lourenco, L.F., et al., *Presence of airborne microplastics in human lung tissue.* Journal of Hazardous Materials, 2021. **416**: p. 126124.

87. Chen, Q.Q., et al., *An emerging role of microplastics in the etiology of lung ground glass nodules.* Environmental Sciences Europe, 2022. **34**(1).

88. Hong, J., et al., *Amplified Lung Cancer Hazards from Surface Defects in Aged Polypropylene Microplastics.* SSRN.

89. Goodman, K.E., et al., *Exposure of Human Lung Cells to Polystyrene Microplastics Significantly Retards Cell Proliferation and Triggers Morphological Changes.* Chemical Research in Toxicology, 2021. **34**(4): p. 1069-1081.

90. Zhang, K.S., et al., *Bisphenol A stimulates human lung cancer cell migration via upregulation of matrix metalloproteinases by GPER/EGFR/ERK1/2 signal pathway.* Biomedicine & Pharmacotherapy, 2014. **68**(8): p. 1037-43.

91. Kim, K.Y., J.H. Ahn, and H.G. Cheon, *Apoptotic action of peroxisome proliferator-activated receptor-gamma activation in human non small-cell lung cancer is mediated via proline oxidase-induced reactive oxygen species formation.* Molecular Pharmacology, 2007. **72**(3): p. 674-85.

92. Qu, J., et al., *Association between urinary bisphenol analogue concentrations and lung cancer in adults: A case-control study.* Environmental Pollution, 2022. **315**: p. 120323.

93. Quirce, S., et al., *Occupational hypersensitivity pneumonitis: an EAACI position paper.* Allergy, 2016. **71**(6): p. 765-79.

94. Winiarska, E., M. Jutel, and M. Zemelka-Wiacek, *The potential impact of nano- and microplastics on human health: Understanding human health risks.* Environmental Research, 2024. **251**(Pt 2): p. 118535.

95. Sartorelli, P., et al., *A case of hypersensitivity pneumonitis in a worker exposed to terephthalic acid in the production of polyethylene terephthalate.* International Journal of Occupational Medicine and Environmental Health, 2020. **33**(1): p. 119-123.

96. Volkman, K.K., J.G. Merrick, and M.C. Zacharisen, *Yacht-maker's lung: A case of hypersensitivity pneumonitis in yacht manufacturing.* Wisconsin Medical Journal, 2006. **105**(7): p. 47-50.

97. Man, M.A., et al., *Fatal hypersensitivity pneumonitis after chemical occupational exposure.* Romanian Journal of Morphology and Embryology, 2017. **58**(2): p. 627-34.

98. Guillot, L., et al., *Alveolar epithelial cells: master regulators of lung homeostasis.* The International Journal of Biochemistry & Cell Biology, 2013. **45**(11): p. 2568-73.

99. Aghapour, M., et al., *Role of air pollutants in airway epithelial barrier dysfunction in asthma and COPD.* European Respiratory Journal, 2022. **31**(163).

100. He, T., et al., *Research progress on the cellular toxicity caused by microplastics and nanoplastics.* Journal of Applied Toxicology, 2023. **43**(11): p. 1576-1593.

101. Xu, M., et al., *Internalization and toxicity: A preliminary study of effects of nanoplastic particles on human lung epithelial cell.* Science of the Total Environment, 2019. **694**: p. 133794.

102. Annangi, B., et al., *Hazard Assessment of Polystyrene Nanoplastics in Primary Human Nasal Epithelial Cells, Focusing on the Autophagic Effects.* Biomolecules, 2023. **13**(2).

103. Martinez-Garcia, G.G. and G. Marino, *Autophagy role in environmental pollutants exposure.* Progress in Molecular Biology and Translational Science, 2020. **172**: p. 257-291.

104. Jeon, M.S., et al., *Polystyrene microplastic particles induce autophagic cell death in BEAS-2B human bronchial epithelial cells.* Environmental Toxicology, 2023. **38**(2): p. 359-367.

105. Song, S., et al., *Inhalable Textile Microplastic Fibers Impair Airway Epithelial Differentiation.* American Journal of Respiratory and Critical Care Medicine, 2024. **209**(4): p. 427-443.

106. Song, S., et al., *Inhalable textile microplastic fibers impair lung repair*. 2022, European Respiratory Society.

107. Hogg, J.C., *Pathophysiology of airflow limitation in chronic obstructive pulmonary disease.* Lancet, 2004. **364**(9435): p. 709-21.

108. Dong, C.D., et al., *Polystyrene microplastic particles: In vitro pulmonary toxicity*

assessment. Journal of Hazardous Materials, 2020. **385**: p. 121575.

109. Vermeer, P.D., et al., *MMP9 modulates tight junction integrity and cell viability in human airway epithelia.* American Journal of Physiology - Lung Cellular Molecular Physiology, 2009. **296**(5): p. L751-62.

110. Godfrey, R., *Human airway epithelial tight junctions.* Microscopy research and technique, 1997. **38**(5): p. 488-499.

111. Bockhorn, J., et al., *MicroRNA-30c targets cytoskeleton genes involved in breast cancer cell invasion.* Breast Cancer Research and Treatment, 2013. **137**(2): p. 373-82.

112. Das, V., et al., *The basics of epithelial-mesenchymal transition (EMT): A study from a structure, dynamics, and functional perspective.* Journal of Cellular Physiology, 2019. **234**(9): p. 14535-14555.

113. Traversa, A., et al., *Polyethylene Micro/Nanoplastics Exposure Induces Epithelial-Mesenchymal Transition in Human Bronchial and Alveolar Epithelial Cells.* International Journal of Molecular Sciences, 2024. **25**(18).

114. Zhang, Y., et al., *Coal dust nanoparticles induced pulmonary fibrosis by promoting inflammation and epithelial-mesenchymal transition via the NF-kappaB/NLRP3 pathway driven by IGF1/ROS-mediated AKT/GSK3beta signals.* Cell Death Discovery, 2022. **8**(1): p. 500.

115. Rahman, I., S.R. Yang, and S.K. Biswas, *Current concepts of redox signaling in the lungs.* Antioxidants & Redox Signaling, 2006. **8**(3-4): p. 681-9.

116. Rahman, I., *Regulation of glutathione in inflammation and chronic lung diseases.* Mutation Research, 2005. **579**(1-2): p. 58-80.

117. Rahman, I. and W. MacNee, *Lung glutathione and oxidative stress: implications in cigarette smoke-induced airway disease.* American Journal of Physiology, 1999. **277**(6): p. L1067-88.

118. Land, S.C. and S.M. Wilson, *Redox regulation of lung development and perinatal lung epithelial function.* Antioxidants & Redox Signaling, 2005. **7**(1-2): p. 92-107.

119. Checa, J. and J.M. Aran, *Airway Redox Homeostasis and Inflammation Gone Awry: From Molecular Pathogenesis to Emerging Therapeutics in Respiratory Pathology.* International Journal of Molecular Sciences, 2020. **21**(23).

120. Liu, Z., et al., *Polystyrene microplastics induced female reproductive toxicity in mice.* Journal of hazardous materials, 2022. **424**: p. 127629.

121. Jin, W., et al., *Microplastics exposure causes the senescence of human lung epithelial cells and mouse lungs by inducing ROS signaling.* Environment International, 2024. **185**: p. 108489.

122. Das, A., *The emerging role of microplastics in systemic toxicity: Involvement of reactive oxygen species (ROS).* Science of the Total Environment, 2023. **895**: p. 165076.

123. Zhang, H., et al., *Pulmonary toxicology assessment of polyethylene terephthalate nanoplastic particles in vitro.* Environment International, 2022. **162**: p. 107177.

124. Shi, X., et al., *Cytotoxicity and Genotoxicity of Polystyrene Micro- and Nanoplastics with Different Size and Surface Modification in A549 Cells.* International Journal of Nanomedicine, 2022. **17**: p. 4509-4523.

125. Roursgaard, M., et al., *Genotoxicity of Particles From Grinded Plastic Items in Caco-2 and HepG2 Cells.* Frontiers in Public Health, 2022. **10**: p. 906430.

126. Feng, S., et al., *Adhesives formulated from bark bio-crude and phenol formaldehyde resole.* Industrial crops and products, 2015. **76**: p. 258-268.

127. Ayres, J.G., et al., *Evaluating the toxicity of airborne particulate matter and nanoparticles by measuring oxidative stress potential—a workshop report and consensus statement.* Inhalation toxicology, 2008. **20**(1): p. 75-99.

128. Zhu, K., et al., *Enhanced cytotoxicity of photoaged phenol-formaldehyde resins*

microplastics: Combined effects of environmentally persistent free radicals, reactive oxygen species, and conjugated carbonyls. Environment International, 2020. **145**: p. 106137.

129. Yao, Y., et al., *The Toxicity Of Metallic Nanoparticles On Liver: The Subcellular Damages, Mechanisms, And Outcomes.* International Journal of Nanomedicine, 2019. **14**: p. 8787-8804.

130. Yang, S., et al., *Ferritinophagy mediated by oxidative stress-driven mitochondrial damage is involved in the polystyrene nanoparticles-induced ferroptosis of lung injury.* ACS Nano, 2023. **17**(24): p. 24988-25004.

131. Wang, Y. and M. Tang, *PM2. 5 induces ferroptosis in human endothelial cells through iron overload and redox imbalance.* Environmental pollution, 2019. **254**: p. 112937.

132. Xie, Y., et al., *Ferroptosis: process and function.* Cell Death & Differentiation, 2016. **23**(3): p. 369-379.

133. Lim, S.L., et al., *Targeted metabolomics reveals differential biological effects of nanoplastics and nanoZnO in human lung cells.* Nanotoxicology, 2019. **13**(8): p. 1117-1132.

134. Liu, T., et al., *Polystyrene microplastics induce mitochondrial damage in mouse GC-2 cells.* Ecotoxicology and Environmental Safety, 2022. **237**: p. 113520.

135. Annangi, B., et al., *Effects of true-to-life PET nanoplastics using primary human nasal epithelial cells.* Environmental Toxicology and Pharmacology, 2023. **100**: p. 104140.

136. Halimu, G., et al., *Toxic effects of nanoplastics with different sizes and surface charges on epithelial-to-mesenchymal transition in A549 cells and the potential toxicological mechanism.* Journal of Hazardous Materials, 2022. **430**: p. 128485.

137. Yu, H.R., et al., *Exploring Oxidative Stress and Metabolic Dysregulation in Lung Tissues of Offspring Rats Exposed to Prenatal Polystyrene Microplastics: Effects of*

Melatonin Treatment. Antioxidants, 2024. **13**(12).

138. Ji, Y., et al., *Realistic Nanoplastics Induced Pulmonary Damage via the Crosstalk of Ferritinophagy and Mitochondrial Dysfunction.* ACS nano, 2024. **18**(26): p. 16790-16807.

139. Gopallawa, I., et al., *A four-part guide to lung immunology: Invasion, inflammation, immunity, and intervention.* Frontiers in Immunology, 2023. **14**: p. 1119564.

140. Clever, D., et al., *Oxygen Sensing by T Cells Establishes an Immunologically Tolerant Metastatic Niche.* Cell, 2016. **166**(5): p. 1117-1131 e14.

141. Segovia-Mendoza, M., et al., *How microplastic components influence the immune system and impact on children health: Focus on cancer.* Birth Defects Research, 2020. **112**(17): p. 1341-1361.

142. Zhi, L., et al., *Immunotoxicity of microplastics: Carrying pathogens and destroying the immune system.* Trends in Analytical Chemistry, 2024. **177**: p. 117817.

143. Schneider, W.M., M.D. Chevillotte, and C.M. Rice, *Interferon-stimulated genes: a complex web of host defenses.* Annual review of immunology, 2014. **32**(1): p. 513-545.

144. Anafu, A.A., et al., *Interferon-inducible transmembrane protein 3 (IFITM3) restricts reovirus cell entry.* Journal of Biological Chemistry, 2013. **288**(24): p. 17261-17271.

145. Wang, C., et al., *Polystyrene microplastics significantly facilitate influenza A virus infection of host cells.* Journal of Hazardous Materials, 2023. **446**: p. 130617.

146. Kawai, T. and S. Akira, *Toll-like receptor and RIG-I-like receptor signaling.* Annals of the New York Academy of Sciences, 2008. **1143**: p. 1-20.

147. Hematianlarki, M. and F. Nimmerjahn, *Immunomodulatory and anti-inflammatory properties of immunoglobulin G antibodies.* Immunological Reviews, 2024. **328**(1): p. 372-386.

148. Xia, Q., et al., *Inhalation of Microplastics Induces Inflammatory Injuries in Multiple*

Murine Organs via the Toll-like Receptor Pathway. Environmental Science & Technology, 2024. **58**(42): p. 18603-18618.

149. Park, K.M., et al., *Polystyrene microplastics induce activation and cell death of neutrophils through strong adherence and engulfment.* Journal of Hazardous Materials, 2024. **480**: p. 136100.

150. Rahman, L., et al., *Polyethylene Terephthalate Microplastics Generated from Disposable Water Bottles Induce Interferon Signaling Pathways in Mouse Lung Epithelial Cells.* Nanomaterials, 2024. **14**(15).

151. Castillo-Sanchez, J.C., A. Cruz, and J. Perez-Gil, *Structural hallmarks of lung surfactant: Lipid-protein interactions, membrane structure and future challenges.* Archives of Biochemistry and Biophysics, 2021. **703**: p. 108850.

152. Zhao, Q., et al., *Interaction of inhalable volatile organic compounds and pulmonary surfactant: Potential hazards of VOCs exposure to lung.* Journal of Hazardous Materials, 2019. **369**: p. 512-520.

153. Garcia-Mouton, C., et al., *The Lord of the Lungs: The essential role of pulmonary surfactant upon inhalation of nanoparticles.* European Journal of Pharmaceutics and Biopharmaceutics, 2019. **144**: p. 230-243.

154. Cao, Y., et al., *Interactions between inhalable aged microplastics and lung surfactant: Potential pulmonary health risks.* Environmental Research, 2024. **245**: p. 117803.

155. Li, L., et al., *Molecular modeling of nanoplastic transformations in alveolar fluid and impacts on the lung surfactant film.* Journal of Hazardous Materials, 2022. **427**: p. 127872.

156. Xu, X., et al., *Microplastics and nanoplastics impair the biophysical function of pulmonary surfactant by forming heteroaggregates at the alveolar–capillary interface.* Environmental Science & Technology, 2023. **57**(50): p. 21050-21060.

157. Purwiyanto, A.I.S., et al., *Concentration and adsorption of Pb and Cu in microplastics: Case study in aquatic environment.* Marine Pollution Bulletin, 2020. **158**: p. 111380.
158. Chen, Y., et al., *Surface characteristic and sinking behavior modifications of microplastics during potassium permanganate pre-oxidation.* Journal of Hazardous Materials, 2022. **422**: p. 126855.
159. Ter Halle, A., et al., *To what extent are microplastics from the open ocean weathered?* Environmental Pollution, 2017. **227**: p. 167-174.
160. Yan, Y., et al., *Aging behavior of microplastics accelerated by mechanical fragmentation: alteration of intrinsic and extrinsic properties.* Environmental Science and Pollution Research, 2023. **30**(39): p. 90993-91006.
161. Xue, X., et al., *Adsorption characteristics of antibiotics on microplastics: The effect of surface contamination with an anionic surfactant.* Chemosphere, 2022. **307**(Pt 4): p. 136195.
162. Bhagat, K., et al., *Aging of microplastics increases their adsorption affinity towards organic contaminants.* Chemosphere, 2022. **298**: p. 134238.
163. Osman, A.I., et al., *Microplastic sources, formation, toxicity and remediation: a review.* Environmental Chemistry Letters, 2023: p. 1-41.
164. Sripada, K., et al., *A Children's Health Perspective on Nano- and Microplastics.* Environmental Health Perspectives, 2022. **130**(1): p. 15001.
165. Sharma, N., et al., *Microplastic residues in clinical samples: A retrospection on sources, entry routes, detection methods and human toxicity.* Trends in Analytical Chemistry, 2024. **173**: p. 117618.
166. Gou, Z., et al., *Airborne micro- and nanoplastics: emerging causes of respiratory diseases.* Particle and Fibre Toxicology, 2024. **21**(1): p. 50.

Figure 1

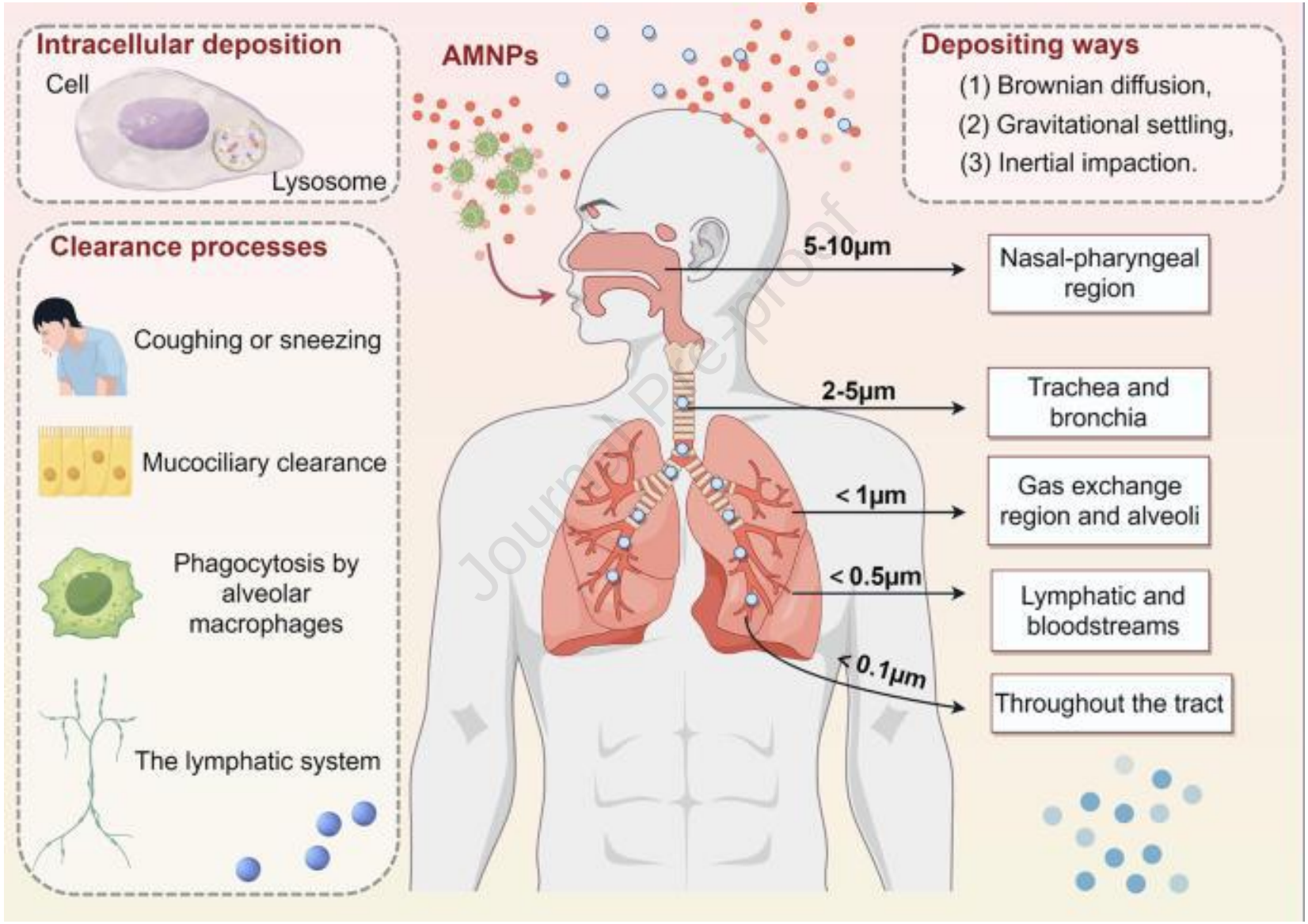

Intracellular deposition
Cell
Lysosome
Clearance processes
Coughing or sneezing
Mucociliary clearance
Phagocytosis by alveolar macrophages
The lymphatic system
AMNPs
Depositing ways
(1) Brownian diffusion,
(2) Gravitational settling,
(3) Inertial impaction.
5-10μm
Nasal-pharyngeal region
2-5μm
Trachea and bronchia
< 1μm
Gas exchange region and alveoli
< 0.5μm
Lymphatic and bloodstreams
< 0.1μm
Throughout the tract

Figure 2

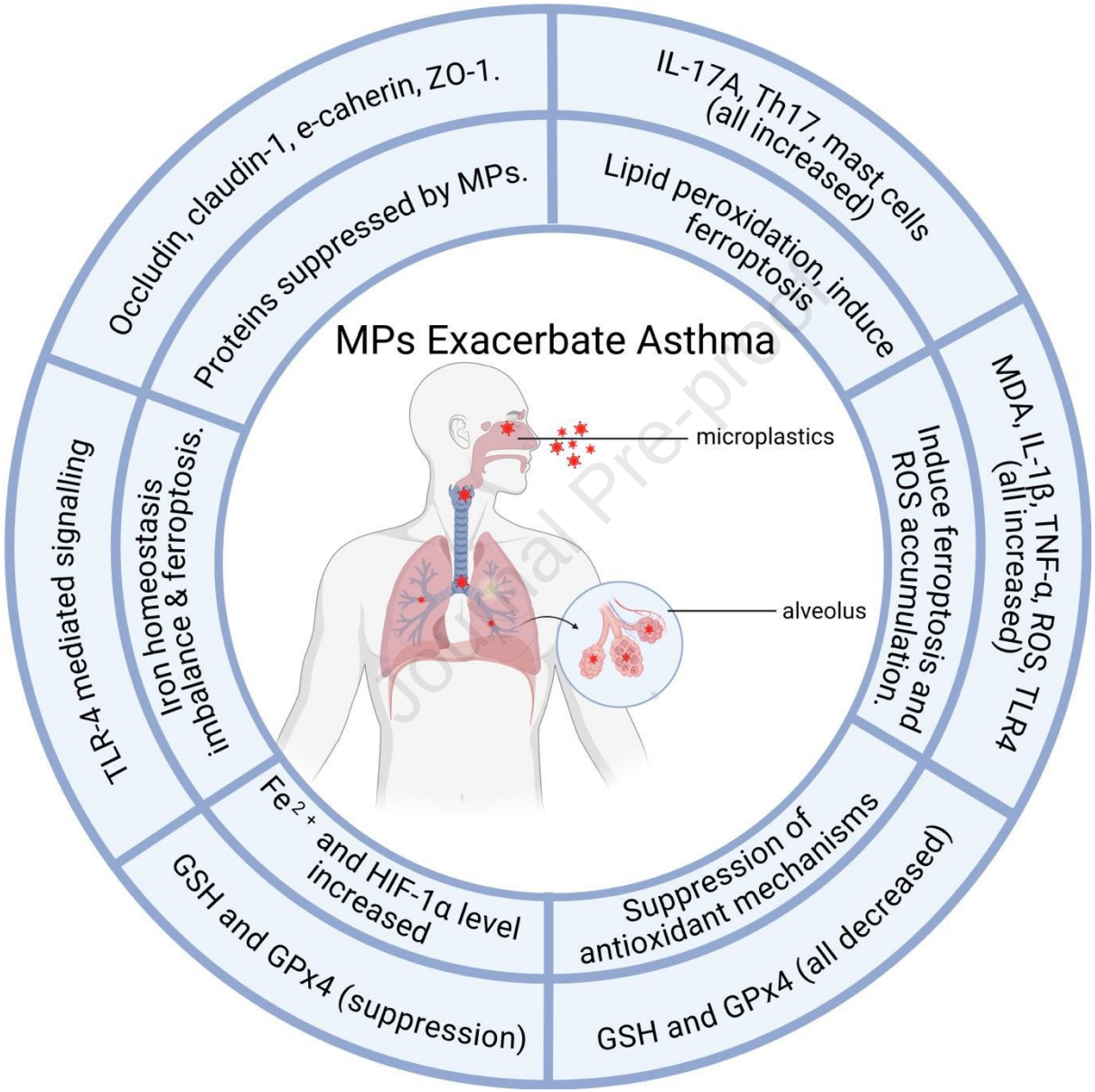

MPs Exacerbate Asthma
microplastics
alveolus
Occludin, claudin-1, e-caherin, ZO-1.
Proteins suppressed by MPs.
IL-17A, Th17, mast cells (all increased)
Lipid peroxidation, induce ferroptosis
MDA, IL-1β, TNF-α, ROS, TLR4 (all increased)
Induce ferroptosis and ROS accumulation.
TLR-4 mediated signalling
Iron homeostasis imbalance & ferroptosis.
Fe2+ and HIF-1α level increased
Suppression of antioxidant mechanisms
GSH and GPx4 (suppression)
GSH and GPx4 (all decreased)

Figure 3

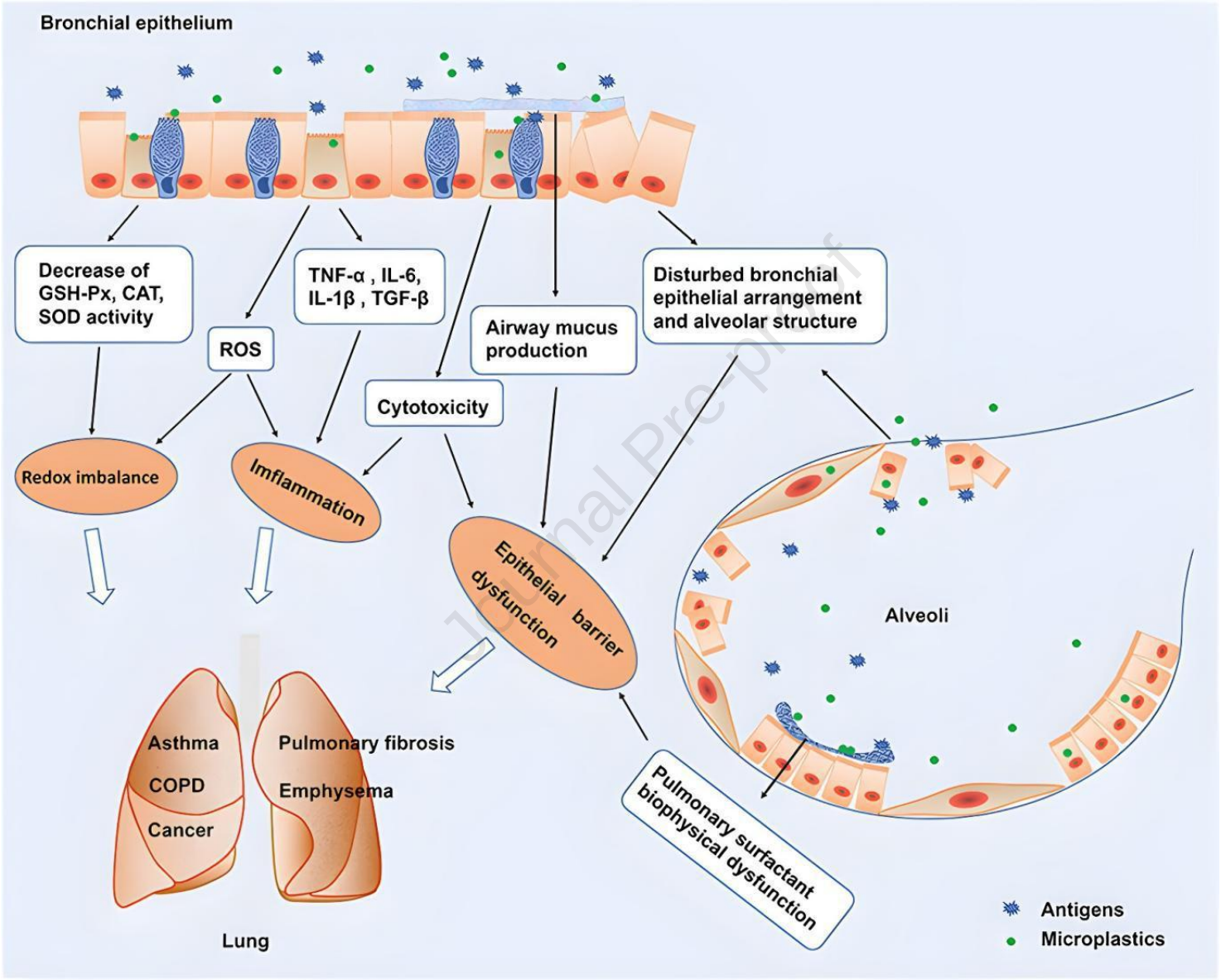
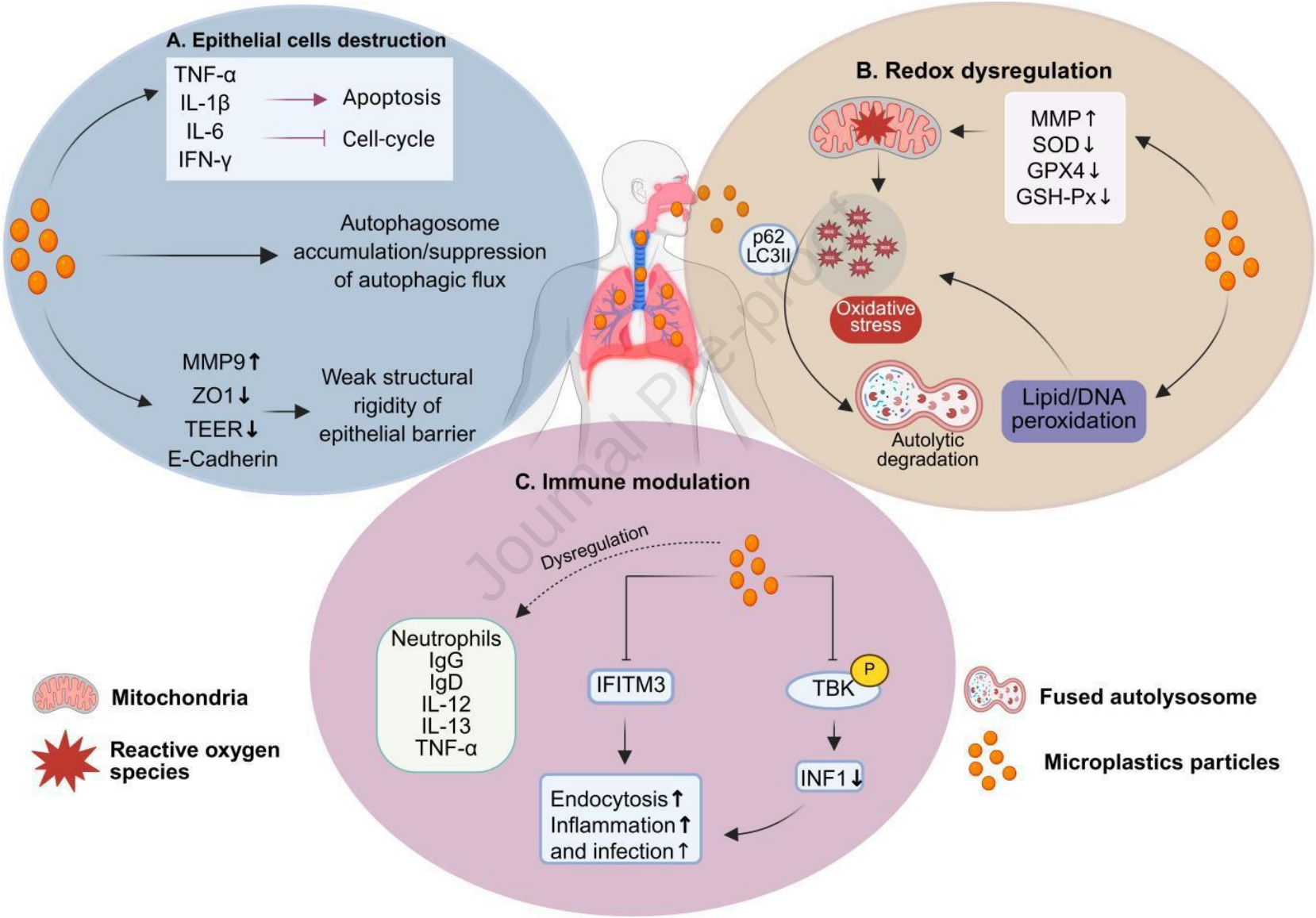

Bronchial epithelium
Decrease of GSH-Px, CAT, SOD activity
ROS
TNF-α , IL-6, IL-1β , TGF-β
Airway mucus production
Disturbed bronchial epithelial arrangement and alveolar structure
Cytotoxicity
Redox imbalance
Imflammation
Epithelial barrier dysfunction
Alveoli
Asthma
COPD
Cancer
Pulmonary fibrosis
Emphysema
Lung
Pulmonary surfactant biophysical dysfunction
Antigens
Microplastics

Figure 4


A. Epithelial cells destruction
TNF-α
IL-1β
IL-6
IFN-γ
Apoptosis
Cell-cycle
Autophagosome accumulation/suppression of autophagic flux
MMP9↑
ZO1↓
TEER↓
E-Cadherin
Weak structural rigidity of epithelial barrier
B. Redox dysregulation
MMP↑
SOD↓
GPX4↓
GSH-Px↓
p62
LC3II
Oxidative stress
Lipid/DNA peroxidation
Autolytic degradation
C. Immune modulation
Dysregulation
Neutrophils
IgG
IgD
IL-12
IL-13
TNF-α
IFITM3
TBK
P
INF1↓
Endocytosis↑
Inflammation↑
and infection↑
Mitochondria
Reactive oxygen species
Fused autolysosome
Microplastics particles

Highlights

- Microplastics are emerging hazardous materials that negatively impact human health.
- Humans are exposed to microplastics *via* inhalation, oral ingestion, and dermal contact.
- Microplastic can trigger the pathological events such as oxidative stress, inflammation, senescence, and gut dysbiosis.
- Microplastics exposure leads to progression of respiratory diseases.

Declaration of interests

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: