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Review

Molecular and Immunological Mechanisms Associated with Diesel Exhaust Exposure

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Abstract: Air pollution, particularly from vehicular emissions, has emerged as a critical environmental health concern, contributing to a global estimated 7 million premature deaths annually. Diesel exhaust, a major component of urban air pollution, contains fine particulate matter and gases that evade respiratory filtration, penetrating deep into the lungs and triggering oxidative stress, inflammation, and immune dysregulation. Epidemiological and in vitro studies have linked diesel exhaust exposure to respiratory diseases such as asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and lung cancer, with immunological mechanisms playing a central role. Diesel exhaust particles induce oxidative stress, impair macrophage phagocytosis, and skew T-cell polarization toward pro-inflammatory Th2 and Th17 responses, exacerbating chronic inflammation and tissue damage. Despite these insights, significant gaps remain in understanding the precise immunomodulatory pathways and long-term systemic effects of diesel exhaust exposure. While animal models and in vitro studies provide valuable data, they often fail to capture the complexity of human exposure and immune responses. Further research is needed to elucidate the mechanisms underlying diesel exhaust-induced immune dysregulation, particularly in vulnerable populations with pre-existing respiratory conditions. This review focuses on summarizing the current knowledge and identifying gaps that are essential for developing targeted interventions and policies to mitigate the adverse health impacts of diesel exhaust and improve respiratory health outcomes globally.

Keywords: diesel exhaust; particulate matter; pulmonary diseases; inflammation; immune response

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Academic Editor: Huangxian Ju

Received: 9 February 2025
Revised: 30 March 2025
Accepted: 17 April 2025
Published: 21 April 2025

Citation: Singh, N.; Sharma, S. Molecular and Immunological Mechanisms Associated with Diesel Exhaust Exposure. *Targets* **2025**, *3*, 14. https://doi.org/10.3390/targets3020014

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1. Introduction

Air pollution has recently become a significant environmental factor adversely impacting human health. According to the World Health Organization (WHO), in 2023, an estimated 7 million premature deaths occur worldwide annually due to air pollution. WHO reports indicate that over 99% of the urban population resides in areas where air pollution surpasses the recommended WHO limits [1]. Urban areas, particularly in low- and middle-income countries, are disproportionately affected due to rapid industrialization, urbanization, and increased reliance on fossil fuels for transportation and energy. Major sources of urban air pollution include vehicular emissions, industrial activities, construction, and the burning of biomass and coal for cooking and heating. In many cities, the concentration of pollutants such as particulate matter $PM_{2.5}$ and NO_2 far exceeds the WHO-recommended limits. For example, the WHO's annual mean limit for $PM_{2.5}$ is 5 $\mu g/m^3$, but many cities, especially in South Asia, the Middle East, and Africa, regularly experience levels exceeding 50 $\mu g/m^3$ [2]. Over the past few decades, the transportation

sector has emerged as a major contributor to environmental pollution, particularly in both developed and developing countries, with consequential effects on the climate [3]. Apart from vehicular emissions playing a crucial role in exposing populations to these pollutants, emissions from motor vehicles significantly contribute to the overall burden of greenhouse gases [4]. Transport, specifically the road sector, accounts for approximately 16% of the 24% of global CO_2 emissions produced by the transportation sector [5]. The escalating number of on-road vehicles has further positioned vehicular pollution as a major contributor to the growing issue of air pollution.

Together, these studies present diesel exhaust as a prominent anthropogenic pollutant on a global scale [6]. Diesel exhaust is a complex mixture of solid and liquid particles suspended in gaseous matter [7]. It consists of two components: soot and gases. The gaseous component in diesel exhaust consists mainly of various gases like CO, NO_x, SO_x, etc., and the diesel soot mainly consists of diesel exhaust particles (DEPs) and traces of heavy metals. DEPs include particles with sizes ranging from <0.1 μm to 10 μm in diameter. Ultra-fine particles (<0.1 μm) consist of carbon core and are associated with mutagens and polycyclic aromatic hydrocarbons (PAHs) [8]. Organic compounds that are found adsorbed to these particle surfaces are individually known to have harmful effects on human health, and many of them have been defined as mutagenic and carcinogenic [9]. A positive correlation between particulate pollution and adverse health effects, including increased respiratory disorders, has been seen in epidemiological studies [10]. Based on its toxicity, DEPs have been characterized as a major carcinogen by the WHO [11]. A recent pre-clinical investigation of human exposure to diesel exhaust, depicted increased nasal IL-6 concentration and fractional exhaled nitric oxide [12].

DEPs, a significant constituent of diesel exhaust, have been implicated in various adverse effects, including reduced lung function and lung inflammation [13]. In 2012, the International Agency for Research on Cancer designated diesel exhaust as a Group 1 human carcinogen based on a comprehensive case–control study [14]. This extensive investigation quantifies the risk of lung cancer associated with occupational exposure to diesel exhaust. The study revealed a proportional increase in lung cancer risk with higher respirable elemental carbon intensity. The risk was notably elevated for workers in the lowest quartile of exposure [14].

In summary, this review emphasizes the adverse effects of DEPs on lung function, inflammation, and the heightened risk of lung cancer, drawing attention to the necessity of targeted interventions. The paper also addresses the novel link between diesel exhaust, a major particulate matter source, and its potential association with the severity and mortality of pulmonary disease and its immune-modulatory effects. While providing valuable insights, the review underscores the need for further mechanistic studies to unravel the intricate pathways connecting particulate matter, diesel exhaust, and the complex dynamics of respiratory health and viral pandemics.

2. Pathogenic Mechanism Associated with Diesel Exhaust Particulates

Diesel exhaust particulate matter is a complex mixture of particles spanning nanometers to micrometers. Coarse particles with a diameter of 10 μm have the ability to reach the bronchiolar region of the lungs, where some are cleared by lung fluid, while others have been actively engulfed by macrophages, thereby restricting their entry to the lung epithelial barrier [15]. $PM_{2.5}$ and PM_1, known as fine and ultrafine particles, can evade phagocytosis and cross the lung epithelial membrane, reaching various body organs and leading to kidney failure, brain stroke, heart failure, etc. Research, including studies on susceptible populations, has demonstrated acute health effects of PM_{10}, particularly at high concentrations, while limited impacts are observed in normal healthy individuals [16].

Diesel exhaust exposure initiates a cascade of molecular and cellular events that ultimately lead to the manifestation of pulmonary diseases. The process begins with the inhalation of DEPs, which deposit in the airways and alveoli. Ultrafine particles in diesel exhaust, characterized by their small size, could penetrate the lung alveolar region, compromising macrophage phagocytosis (Figure 1). These particles, composed of adsorbed PAHs, induce the generation of reactive oxygen species (ROS) in epithelial cells, macrophages, and dendritic cells [17]. The resulting oxidative stress causes lipid peroxidation and DNA damage, leading to cellular injury and the release of alarmins such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) from damaged epithelial cells [18]. These alarmins eventually activate the innate immune cells, including macrophages and dendritic cells, which phagocytose DEPs and release pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α) and chemokines (e.g., CCL2, CXCL8) [19]. However, studies have indicated that the adverse effects of ultrafine particles may be linked, in part, to their inhibitory effects on phagocytosis, resulting in the failure of macrophage clearance [20].

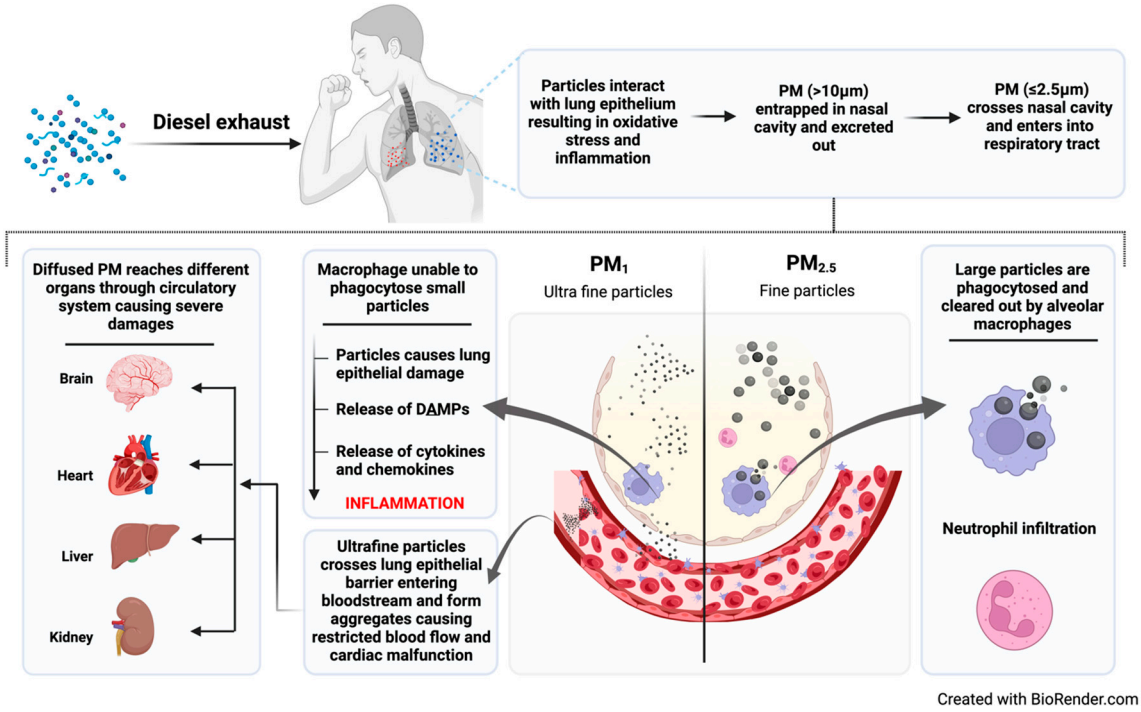


Figure 1. Mechanistic action of particulate matter in alveolar sac.

The activation of innate immune cells triggers downstream signaling pathways, including NF-κB and MAPK (p38, JNK, ERK), which amplify the production of pro-inflammatory mediators [21]. Concurrently, cytokines such as IL-6 and IL-23 activate the STAT3 pathway, promoting the differentiation of T-helper 17 (Th17) cells, while IL-4 activates STAT6, driving Th2 polarization [22]. This skewed T-cell response is further exacerbated by the suppression of regulatory T-cells (Tregs), which normally maintain immune tolerance. The dominance of Th2 and Th17 responses leads to the recruitment of eosinophils and neutrophils, respectively, causing chronic airway inflammation in the airways [23]. Th2 cytokines (IL-4, IL-5, IL-13) promote eosinophil infiltration, IgE production, and mucus hypersecretion, while Th17 cytokines (IL-17) drive neutrophilic inflammation and tissue damage. Over time, the persistent inflammation and oxidative stress result in structural changes in the lungs, including airway remodeling, fibrosis, and alveolar destruction caused due to continuous particulate matter exposure [24]. This in turn triggers a complex interplay of oxidative stress, innate and adaptive immune activation, and chronic inflammation, culminating

in the development and exacerbation of pulmonary diseases. This mechanistic understanding underscores the importance of mitigating diesel exhaust exposure to protect respiratory health.

Additionally, the dose–response relationship between diesel exhaust exposure and immune responses is influenced by both the concentration of DEPs and the duration of exposure, with these factors determining the magnitude and nature of the immune response. At low concentrations, short-term exposure typically triggers mild, transient inflammation characterized by the activation of epithelial cells and macrophages, accompanied by limited cytokine release (e.g., IL-6, TNF-α) [25]. In such cases, the immune response primarily involves innate immunity, with minimal T-cell polarization, and the immune system is often able to resolve the inflammation without long-term consequences [26]. However, even low-concentration exposure can exacerbate symptoms in individuals with pre-existing conditions like asthma, as their airways are already primed for hyperresponsiveness [27]. In contrast, high concentrations of diesel exhaust induce robust oxidative stress, leading to significant epithelial damage and the activation of dendritic cells and macrophages [17]. High-concentration exposure also drives strong Th2 and Th17 polarization, with suppressed regulatory T-cell (Treg) activity, leading to prominent eosinophilic and neutrophilic inflammation. This type of exposure increases the risk of acute exacerbations in asthma and COPD and may even initiate chronic inflammation in otherwise healthy individuals.

3. Inflammation and Diesel Exhaust

Inflammatory pathways:

Diesel exhaust exposure is well-established as a potent inducer of inflammation, particularly in the respiratory system [28,29]. The inhalation of DEPs and gases initiates a cascade of events leading to the activation of various inflammatory pathways [30–32]. This activation of inflammatory pathways is caused by poor clearance of DEPs by macrophages, leading to accumulation in the respiratory system [33]. Eventually, a brief exposure to high levels of diesel exhaust leads to a clear systemic and pulmonary inflammatory response [34]. Key components of this diesel exhaust-induced inflammatory response include the release of inflammatory mediators, chemokines, and cytokines, creating a pro-inflammatory microenvironment in the lungs.

Chemokines and cytokines, pivotal in directing immune cell migration to sites of inflammation, play a crucial role in the immune response triggered by diesel exhaust [30,35]. Diesel exhaust exposure induces the release of pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α), contributing to the establishment of a pro-inflammatory microenvironment within the respiratory system [31,32]. Simultaneously, diesel exhaust stimulates the production of chemokines, promoting the infiltration of immune cells into the respiratory tract [33,36]. Furthermore, diesel exhaust-induced activation of resident immune cells, including macrophages and epithelial cells, through mediators like ChemR23 and CCR2, underscores the complexity of diesel exhaust on inflammatory response modification [28,37,38].

Oxidative Stress:

One of the intricate ways by which diesel exhaust exerts its inflammatory effects is through the generation of oxidative stress. The particles present in diesel exhaust comprise redox-active components that disturb the delicate balance between the production of ROS and the body's antioxidant defense mechanisms [39]. This disruption in equilibrium results in oxidative stress, a phenomenon known to cause cellular damage and intensify the inflammatory response. The oxidative stress induced by diesel exhaust has notable repercussions on the functionality of mitochondria within lung cells, leading to impairment and increased

apoptosis [40,41]. Mitochondrial dysfunction, in turn, exacerbates the generation of ROS, establishing a self-perpetuating cycle of oxidative stress and inflammation [42]. A recent study established a therapeutic role of resveratrol (potent antioxidant) in mice exposed to diesel exhaust [43]. This study showed treatment with resveratrol mitigates the progression of diesel exhaust-induced pulmonary fibrosis by regulating the SIRT1/FoxO3 signaling axis [43]. Oxidative stress induced by diesel exhaust exposure can lead to a concerning physiological consequence known as hypoxia, where oxygen availability in tissues becomes compromised. In the context of hypoxia, oxidative stress exacerbates inflammation and constriction of airways, compromising the exchange of oxygen and carbon dioxide in the lungs. Current studies have defined confounding evidence of the potential role of hypoxia on genetic alterations. The hypoxia-induced genetic variation plays a significant role in predisposing individuals to other health-related issues like hypertension, like people residing at high and low altitudes [44,45]. This genetic alteration in response to environmental stress may significantly increase pre-disposition to particulate matter exposure. Diesel exhaust contains a plethora of ROS and fine particulate matter that, upon inhalation, generate an oxidative burden within the respiratory system. Additionally, DEPs have the capacity to directly interact with cellular DNA, initiating genetic mutations and causing DNA damage [46]. This damage prompts cellular responses that not only contribute to inflammation but also carry potential long-term implications for respiratory health.

In summary, the various mechanisms through which diesel exhaust triggers inflammation involve the induction of oxidative stress, mitochondrial dysfunction, and direct interactions with cellular DNA, culminating in genetic mutations and damage. These intricate processes collectively underscore the multifaceted impact of diesel exhaust on modifying inflammatory responses within the respiratory system. The identified pathways highlight the need for ongoing research to delve deeper into the underlying mechanisms, providing a more comprehensive understanding of the health risks associated with environmental pollutant exposure. Such knowledge will be instrumental in shaping strategies to mitigate the adverse effects on respiratory health and overall well-being.

4. Immunomodulatory Impacts of Diesel Exhaust

Exposure to diesel exhaust profoundly affects various components of the immune system, influencing both innate and adaptive responses in various respiratory diseases (Figure 2). These immunomodulatory effects extend to the function of immune cells, reshaping their behavior in ways that can impact respiratory health. Noteworthy effects include impaired phagocytosis, dysregulated cytokine production, and compromised antigen presentation. As mentioned before, DEPs can impair the phagocytic capacity of macrophages, hindering their ability to engulf and eliminate pathogens efficiently [30]. Additionally, diesel exhaust-induced alterations in macrophage behavior extend to dysregulated cytokine production, with studies pointing towards upregulation of pro-inflammatory cytokines, such as IL-6 and TNF-α [33]. Moreover, exposure to diesel exhaust has been associated with compromised antigen presentation by macrophages, a critical process in initiating adaptive immune responses [47]. These modifications foster an environment conducive to sustained inflammation and heightened susceptibility to infections.

Similarly, diesel exhaust profoundly affects neutrophils, critical components of the innate immune system. DEPs disrupt neutrophil chemotaxis, impairing their migration to infection sites and compromising pathogen clearance. Recent studies demonstrated exposure to diesel leads to an increase in neutrophil infiltration, releasing a serine protease called neutrophil elastase [48]. This neutrophil elastase causes irreversible cellular damage to the underlying basement membrane and lung architecture. The study also highlights a reduced level of Elafin, a known inhibitor of neutrophil elastase, in response to diesel

exhaust. Additionally, diesel exhaust exposure heightens the production of ROS by neutrophils, potentially inducing oxidative stress and inflammation. Diesel exhaust inhibits neutrophil apoptosis and phagocytosis by macrophages, prolonging their survival and contributing to persistent inflammation within the respiratory system.

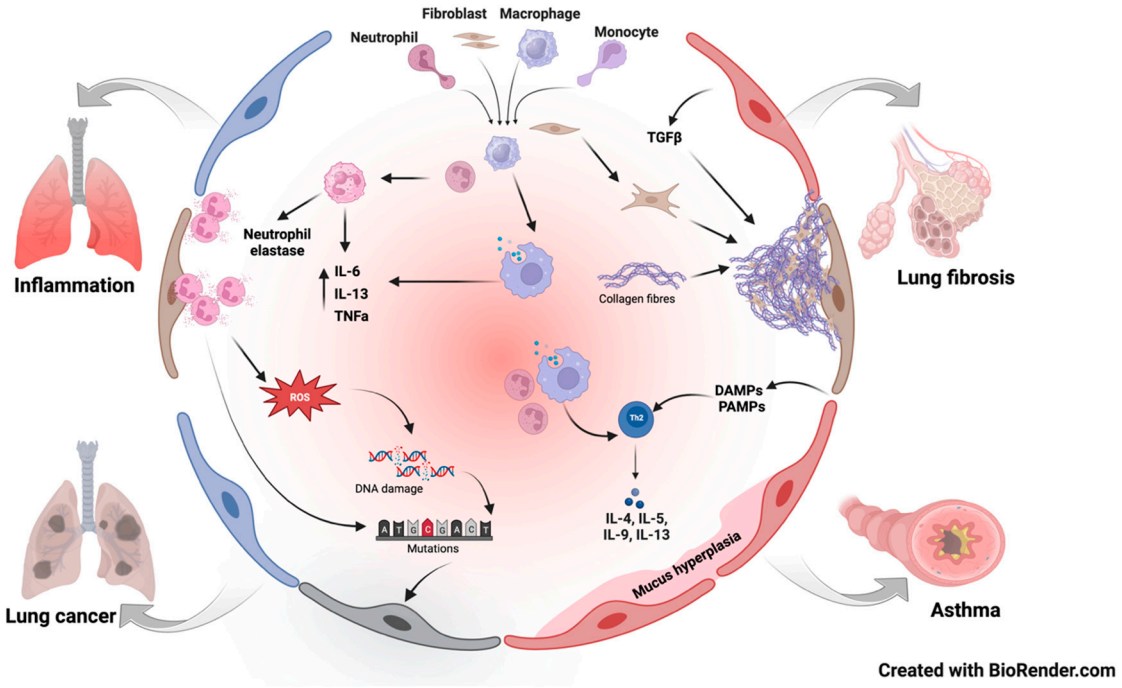


Figure 2. Pathways involved in diesel exhaust-induced respiratory diseases.

Furthermore, DEPs also act as adjuvants, amplifying immune responses to environmental allergens, and studies show that when DEPs are co-exposed with allergens, they promote Th2-biased responses in the lungs [49]. This occurs partly because of maturation of dendritic cells enhances antigen presentation to naïve T cells and triggers secretion of Th2-polarizing cytokines [50], while organic compounds in DE, like polycyclic aromatic hydrocarbons (PAHs), further amplify this effect by activating the aryl hydrocarbon receptor (AhR), a transcription factor that modulates T-cell fate, intensifying the allergic immune response. In addition to these Th2 effects, DE exposure can drive Th17 differentiation, characterized by IL-17 production, through inflammatory signals like IL-6 and TGF-β, which rise in response to DE-induced epithelial damage and macrophage activation, making Th17 cells, known for their pro-inflammatory nature, key contributors to tissue damage, especially in chronic exposure scenarios [51].

The shift toward Th17 polarization can perpetuate chronic inflammation and tissue damage, as IL-17 recruit's neutrophils that release proteases, harming lung tissue and promoting fibrosis, a hallmark of these diseases [52]. This is worsened by the potential loss of immune tolerance, as reduced Treg function allows autoreactive T cells to escape regulation, possibly contributing to autoimmunity in conditions like systemic lupus erythematosus or rheumatoid arthritis with lung involvement [53,54], where environmental triggers like DE could exacerbate the diseases phenotype. The exact outcome of DE on T-cell polarization depends on factors like exposure duration, concentration, and individual variables such as genetics or pre-existing conditions, with acute exposure likely boosting Th2 responses and chronic exposure potentially shifting toward Th17 or mixed profiles, affecting urban populations near heavy traffic most severely, as research data tie DE to higher asthma rates and possibly autoimmune disease flares [55,56]. In conclusion, diesel exhaust alters T-cell polarization by promoting Th2 and Th17 responses while potentially suppressing

Tregs, primarily through oxidative stress, adjuvant effects, and cytokine shifts, leading to worsened allergic inflammation and airway dysfunction in asthma. Diesel exhaust particles (DEPs) have been found to skew T-cell polarization toward a Th2 and Th17 phenotype; this is mediated by the ability of DEPs to induce oxidative stress and activate signaling pathways such as NF-κB and MAPK in an immune cell population, which in turn produce cytokines like IL-4, IL-5, IL-13, and IL-17 [57]. Major cytokines or chemokines involved in diesel exhaust-induced inflammation are listed in Table 1

Table 1. Major cytokines, chemokines, and signaling pathways involved in diesel exhaust-induced inflammation.

Category	Key Molecules	Role in Diesel Exhaust-Induced Inflammation	Associated Diseases
Cytokines	IL-4, IL-5, IL-13 [58–60]	Promote Th2 polarization, eosinophil recruitment, IgE production, and mucus hypersecretion.	Asthma
	IL-17 [61]	Drives Th17-mediated neutrophilic inflammation and tissue damage.	Asthma, COPD, Autoimmune lung conditions
	IL-1β, IL-6, TNF-α [62–64]	Enhance pro-inflammatory signaling, recruit immune cells, and amplify tissue inflammation.	COPD, Autoimmune lung conditions
	TGF-β [43,65]	Promotes fibrosis and tissue remodeling; suppresses Treg activity in chronic inflammation.	Autoimmune lung conditions
Chemokines	IL-8 (CXCL8) [66]	Attracts neutrophils to sites of inflammation, contributing to neutrophilic inflammation.	COPD, Severe asthma
	CCL2 (MCP-1) [38]	Recruits monocytes and macrophages to inflamed tissues.	COPD, Asthma
	CCL5 (RANTES) [67]	Attracts eosinophils, T-cells, and monocytes, amplifying allergic and inflammatory responses.	Asthma
Signaling Pathways	NF-κB [68,69]	Activated by DEP-induced oxidative stress; promotes transcription of pro-inflammatory cytokines and chemokines.	Asthma, COPD, Autoimmune lung conditions
	MAPK (p38, JNK, ERK) [70,71]	Mediates cellular responses to oxidative stress and inflammation; regulates cytokine production.	Asthma, COPD, Autoimmune lung conditions
	STAT6 [72]	Critical for Th2 differentiation and IL-4/IL-13 signaling.	Asthma
	STAT3 [73,74]	Essential for Th17 differentiation and IL-6/IL-23 signaling.	Asthma, COPD, Autoimmune lung conditions
	PI3K/AKT [75]	Regulates cell survival, inflammation, and immune cell activation in response to DEPs.	Asthma, COPD

Diesel exhaust-induced inflammation and modulation of immune cell activity pose a significant risk to the delicate balance of immune tolerance, leading to autoimmune diseases. The immunomodulatory effects triggered by diesel exhaust exposure may play a pivotal role in disrupting immune tolerance, potentially leading to the initiation or worsening of autoimmune conditions [55]. In the context of autoimmune interstitial lung diseases (AILDs), where the immune system erroneously targets lung tissue, resulting in persistent inflammation and scarring, diesel exhaust emerges as a potential contributor. Numerous studies suggest that diesel exhaust may foster the progression of AILDs by further disrupting immune homeostasis and sustaining prolonged inflammation within the respiratory system [33]. Understanding the nuanced relationship between diesel exhaust and immune dysregulation is essential for developing targeted approaches to mitigate the adverse effects on respiratory health.

In summary, the impact of diesel exhaust on immune cell function, particularly in macrophages and neutrophils, extends to far-reaching consequences for respiratory health. The alterations in immune cell function contribute to an increased susceptibility to respiratory infections and the exacerbation of pre-existing conditions. An in-depth exploration is warranted to unveil potential long-term consequences associated with chronic exposure, as

well as to devise preventive strategies and therapeutic interventions. Recognizing these immunomodulatory effects is pivotal for advancing our comprehension of the intricate dynamics between diesel exhaust exposure and respiratory health, ultimately guiding efforts to safeguard individuals from the potential long-term implications of chronic exposure.

5. Intricate Interplay Between Diesel Exhaust and Respiratory Diseases

Diesel exhaust exposure has distinct and often more pronounced effects on individuals with pre-existing respiratory conditions such as asthma or chronic obstructive pulmonary disease (COPD) compared to healthy individuals. These differences arise due to the pre-existing inflammatory state, compromised lung function, and altered immune responses in these populations. For example, in individuals with asthma, DEPs exacerbate Th2-driven inflammation, which is already a hallmark of the disease [76]. DEPs amplify the production of Th2 cytokines such as IL-4, IL-5, and IL-13, leading to increased eosinophil infiltration, IgE production, and airway hyperresponsiveness [77]. In contrast, healthy individuals exposed to diesel exhaust may experience a milder Th2 response, as their immune systems are not primed for such reactivity. Additionally, DEPs can induce Th17 responses, which are particularly relevant in severe asthma phenotypes characterized by neutrophilic inflammation. This Th17 skewing is more pronounced in asthmatic individuals, potentially leading to corticosteroid resistance and worsening disease severity [78].

Comparative studies also highlight differences in systemic immune responses between healthy individuals and those with pre-existing conditions. For instance, diesel exhaust exposure in asthmatic or COPD patients can lead to systemic inflammation, as evidenced by elevated levels of C-reactive protein (CRP) and other inflammatory markers in the blood [79]. This systemic inflammation can contribute to comorbidities such as cardiovascular disease, which are already more prevalent in these populations. In contrast, healthy individuals may exhibit a more localized immune response confined to the lungs. Overall, the impact of diesel exhaust on immunity is significantly magnified in individuals with pre-existing respiratory conditions, underscoring the need for targeted interventions and stricter air quality regulations to protect these vulnerable populations. Various cytokines exert differential effects on the pathogenesis of pulmonary fibrosis with different molecular mechanisms, as listed in Table 2. The section below discusses in detail the pathological insights of diesel exhaust in various respiratory diseases.

Table 2. Summarizing diesel exhaust contributes to different pulmonary diseases at the molecular level.

Disease	Key Molecular Mechanisms	Cytokines/Chemokines Involved	Immune Cell Responses	Outcome/Pathology
Asthma	-Th2 polarization driven by DEP-induced oxidative stress and NF-κB/MAPK activation [80] -Th17 polarization exacerbates neutrophilic inflammation in severe asthma [77]	IL-4, IL-5, IL-13, IL-17, TSLP	Eosinophil recruitment, IgE production, Th2/Th17 skewing	Airway inflammation, hyperresponsiveness, mucus hypersecretion, severe asthma phenotypes.
COPD	-Th1/Th17 polarization due to DEP-induced pro-inflammatory signaling [81] -Suppression of Tregs and impaired resolution of inflammation [82]	IL-1β, IL-6, IL-8, IL-17, TNF-α	Macrophage activation, neutrophil infiltration	Chronic inflammation, tissue destruction, emphysema, increased exacerbations.
Autoimmune Lung Conditions	-Th17 polarization and reduced Treg activity promote tissue inflammation and fibrosis [33,55]	IL-17, TGF-β, IFN-γ	Th17 dominance, Treg suppression	Alveolar inflammation, tissue injury, fibrosis, progression of interstitial lung disease.

Asthma:

Asthma is characterized by chronic airway inflammation, marked by mucus production, and results in airway hyperresponsiveness [83]. Over the last 50 years, there has been a notable surge in asthma prevalence in developed countries, with potential attributions to improved diagnostic capabilities and increased environmental pollution [84]. The existing literature extensively explores the correlation between air pollution and asthma, shedding light on its implications for pre-existing asthma conditions [27,85–88]. Studies involving patients demonstrate an accelerated manifestation of symptoms and increased incidence associated with elevated levels of particulate matter or DEPs [85]. The age of individuals during exposure emerges as a crucial factor influencing asthma incidence, with studies revealing a link between pollutant exposure during early life and subsequent asthma development [89]. In China, the prevalence of asthma among urban children has quadrupled in the past decade, emphasizing the global impact of environmental factors on childhood asthma. Moreover, early investigations on DEPs and childhood asthma reveal an inverse relationship between lung function and traffic intensity, as well as smoke concentration [90,91]. Studies with children having a family history of asthma further highlight the association of even low concentrations of particulate matter PM2.5 during early stages with asthma onset [92].

Mouse studies provide insights into the exacerbation of airway hyperresponsiveness and the development of pathogenic Th2/Th17 cells in response to DEP exposure to allergens [93]. Diesel exhaust exerts a substantial impact on asthma from an immunological perspective, as demonstrated in various studies, particularly in murine models [93,94]. This immunological response involves the release of pivotal cytokines, including IL-33, IL-25, TSLP, and IL-17a. These cytokines collectively contribute to the immunopathogenesis of asthma, fostering inflammatory reactions and enhancing airway hypersensitivity. IL-33, IL-25, and TSLP are implicated in activating Th2 cells, central players in allergic responses, while IL-17a is involved in recruiting inflammatory cells and initiating pro-inflammatory pathways [83]. The intricate interplay of these immunological responses induced by DEP exposure intensifies asthma symptoms and advances the progression of the condition. Cumulatively, existing studies underscore the significant impact of diesel exhaust on asthma prevalence, calling for comprehensive investigations into the multifaceted relationship for devising targeted interventions and therapeutic strategies, necessitating ongoing research.

Chronic Obstructive Pulmonary Disease

Numerous review articles have comprehensively explored the connection between occupation and chronic obstructive pulmonary disease (COPD), assessing exposure risks in-depth [95–100]. Recent research underscores the association between COPD development and exposure to diverse airborne pollutants, establishing a positive correlation with air pollution. Urban pollution has been identified as a contributor, exacerbating responses in individuals already afflicted with COPD [101]. In individuals with COPD, diesel exhaust exposure further exacerbates the chronic inflammation and oxidative stress that underlie the disease. COPD is characterized by a predominance of Th1 and Th17 responses, which contribute to tissue destruction and emphysema [102]. DEPs enhance these responses by promoting the release of pro-inflammatory cytokines such as IL-1β, IL-6, and IL-17 while also suppressing anti-inflammatory regulatory T-cells (Tregs) [82]. This imbalance exacerbates lung damage and accelerates disease progression. In contrast, healthy individuals may experience a transient inflammatory response to diesel exhaust, but their immune systems are better equipped to resolve this inflammation without long-term consequences. Furthermore, the impaired mucociliary clearance and reduced antioxidant capacity in

COPD patients make them more susceptible to the harmful effects of DEPs, leading to increased exacerbation rates and hospitalizations [103].

Inhalation of diesel exhaust components triggers inflammation in the respiratory tract, activating immune cells such as macrophages and neutrophils [104]. This immune cell activation leads to the release of pro-inflammatory cytokines and other mediators, fostering persistent inflammation in the airways, a hallmark of COPD [105]. Additionally, diesel exhaust induces oxidative stress due to the presence of ROS and oxidants, which can damage cellular components and exacerbate the inflammatory response. The activation of immune cells and the induction of epigenetic changes further contribute to the chronic inflammatory state associated with COPD [105]. DEPs have been shown to induce specific histone modifications that contribute to the dysregulation of genes involved in inflammation and oxidative stress, key processes in COPD. For example, exposure to DEPs has been linked to decreased histone acetylation (e.g., H3K9ac and H4K16ac) at the promoters of anti-inflammatory genes, leading to their transcriptional repression [106]. This suppression can exacerbate the inflammatory response in the airways, a hallmark of COPD [107]. Additionally, diesel exhaust has been associated with increased histone methylation (e.g., H3K4me3 and H3K27me3) at pro-inflammatory gene loci, further promoting the expression of inflammatory mediators and contributing to chronic lung damage [107]. The impact of diesel exhaust-induced histone modifications extends beyond immediate gene regulation, potentially leading to long-term epigenetic memory and sustained changes in gene expression patterns. These modifications can alter the recruitment of transcription factors and other chromatin-associated proteins, perpetuating a pro-inflammatory and oxidative state in the lungs. Moreover, diesel exhaust exposure can impair lung defense mechanisms, compromising ciliary function and mucociliary clearance, thereby increasing susceptibility to respiratory infections that can exacerbate COPD symptoms [107].

The recent literature provides statistical insights into the specific impact of diesel exhaust on COPD risk in the human population [108]. A case–control study involving 388 COPD patients unveils higher odds ratios, computed through logistic regression, associating COPD with diesel exhaust and other exposures [109]. Additionally, studies reveal a positive correlation between particulate matter (both coarse and fine particles) levels and increased COPD manifestation [110]. However, further research is essential to fully ascertain the culpability of diesel exhaust in the onset of COPD.

Further, in vitro studies focusing on diesel exhaust (DE) exposure reveal comparable activation of oxidative stress-related gene HMOX1, as well as markers of integrated stress response, CHOP, and GADD34, in cells sourced from COPD donors and controls [69]. Extensive investigations into the role of macrophages in COPD highlight their pivotal involvement in orchestrating pulmonary inflammation [111]. The adverse effects of DEPs on alveolar macrophage activation have been thoroughly examined [112,113]. Furthermore, studies utilizing motor vehicular exhaust demonstrate the release of various cytokines in airway cells capable of inducing COPD [114]. This multifaceted immunological impact underscores the importance of mitigating diesel exhaust exposure as a crucial public health strategy in the prevention and management of COPD.

Pulmonary fibrosis

Pulmonary fibrosis is a progressive and irreversible lung disease characterized by a significant reduction in lung capacity, primarily attributed to the abnormal deposition of collagen and the activation of key cellular players such as fibroblasts, myofibroblasts, and macrophages [115]. These activated cells contribute to the excessive production of extracellular matrix components, further impairing lung function [116]. Extensive research has explored the correlation between particulate matter and lung fibrosis, revealing noteworthy findings. Particulate matter with a diameter of 10 μm or less (PM10) has been

implicated in inducing an upregulation of platelet-derived growth factor (PDGF) [117]. Concurrently, PM10 activates NF-kB, a transcription factor known for inhibiting apoptosis and promoting cellular proliferation [118]. In murine models, exposure to PM10 leads to the differentiation of myofibroblasts and an enhanced production of collagen within the lungs. Moreover, PM10 exposure is associated with an increase in the expression of matrix metalloproteinases (MMPs) and E-cadherin, contributing to the fibrotic process [119].

Exposure to diesel exhaust is linked to adverse health effects, with a focus on the immunological aspects concerning pulmonary fibrosis. The PAHs and metals in diesel exhaust trigger an inflammatory response and oxidative stress in the lungs driven by the activation of immune cells like macrophages and neutrophils, potentially causing cellular damage and inflammation [120]. Prolonged exposure may activate fibroblasts, key players in tissue repair, leading to the excessive production of collagen and other matrix components associated with fibrosis. Diesel exhaust exposure has also been implicated in promoting epithelial–mesenchymal transition (EMT) in lung cells, a process contributing to tissue remodeling [121]. While these immunological responses provide insights into the potential mechanisms linking diesel exhaust to pulmonary fibrosis, the complex nature of this relationship warrants further research to comprehensively understand the underlying pathways and individual variations in susceptibility.

In experimental models of lung fibrosis using carbon nanoparticles, an augmentation in neutrophils and macrophages has been observed without a concurrent increase in eosinophils [122]. This discrepancy results in the exacerbation of pulmonary fibrosis characteristics, highlighting the complex and nuanced effects of particulate matter on the immune response and fibrotic pathways. DEPs, along with their fuel-borne catalyst by-product, cerium oxide, have been identified as potent activators of alveolar macrophages and lymphocytes. This activation triggers the release of proinflammatory cytokines, such as interleukin-12 (IL-12) by macrophages and interferon-gamma (IFN-γ) by lymphocytes [123]. Morphometric analysis further confirms the co-localization of collagen in lung tissues in response to the instillation of DEPs with cerium oxide, underscoring their role in promoting fibrotic changes [124]. The intricate interplay between particulate matter, immune activation, and collagen deposition underscores the complex pathophysiology of pulmonary fibrosis, shedding light on potential targets for therapeutic interventions aimed at mitigating the progression of this debilitating lung disease.

Lung Cancer

Exposure to diesel exhaust has been associated with various adverse health effects, and emerging evidence links it to the development and progression of lung cancer [107]. The International Agency for Research on Cancer (IARC) categorized diesel exhaust as a Group 1 carcinogen in 2012. Numerous studies have investigated the link between exposure to diesel exhaust and the risk of developing lung cancer, often utilizing elemental carbon as an indicator [125]. Reviews, cohort studies, and epidemiological meta-analyses consistently support the notion that exposure to diesel exhaust is associated with an increased risk of lung cancer [126–128]. Specifically, individuals occupationally exposed to diesel exhaust exhibit a significantly higher risk compared to their unexposed counterparts. Cohort studies within the trucking industry reveal an elevated cancer risk with prolonged working years due to consistent exposure to diesel and other vehicle emissions [129,130]. The literature reports an 18% rise in lung cancer risk among drivers exposed to diesel exhaust [131].

Diesel exhaust may interfere with immune surveillance mechanisms, impairing the recognition and clearance of cancer cells by cytotoxic T cells and natural killer cells [132]. Current research has provided significant evidence of the T-cell population playing a crucial role in managing different tumors [133]. Prolonged exposure to diesel exhaust is associated with immunosuppressive effects, weakening the body's defense mechanisms against

cancer cells and promoting their evasion of immune surveillance. Furthermore, research highlights a multifactorial connection between diesel exhaust and cancer, with inflammation and toxicity playing crucial roles in tumor initiation [125]. Diesel exhaust-induced inflammation activates immune cells such as macrophages and neutrophils, releasing pro-inflammatory cytokines and ROS that contribute to DNA damage and the transformation of normal cells into cancerous cells [134,135]. The PAHs, nitro-PAHs, and other mutagenic compounds in DEPs, upon inhalation, deposit in the lungs and penetrate epithelial cells [127,136,137]. These compounds are metabolized by cytochrome P450 enzymes into reactive intermediates, which generate ROS. The resulting oxidative stress causes direct DNA damage, including double-strand breaks, base modifications, and the formation of DNA adducts [137]. This damage often leads to mutations in critical genes such as TP53 (a tumor suppressor gene) and KRAS (an oncogene), both of which are frequently implicated in lung cancer [138]. Rat model studies indicate that exposure to diesel exhaust can induce lung tumor formation through mechanisms involving oxidative stress and the creation of DNA adducts [139,140]. In vitro studies on human bronchiolar epithelial cells (HBECs) exposed to diesel exhaust particulates (DEP) reveal DEP-induced regulation of CYP1A1, IL-1β, PGE2, and PGF2α, potentially contributing to acute inflammation and carcinogenesis [141]. In addition to direct DNA damage, DEPs activate key pro-inflammatory signaling pathways, such as NF-κB and MAPK (p38, JNK, ERK) [142]. These pathways are triggered by the interaction of DEPs with pattern recognition receptors (e.g., TLR4) on epithelial cells and macrophages, leading to the release of pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α) and chemokines (e.g., CXCL8) [143]. The chronic inflammatory microenvironment created by these mediators promotes cell proliferation, inhibits apoptosis, and supports angiogenesis, all of which are hallmarks of cancer. Furthermore, DEPs can induce epigenetic modifications, such as DNA methylation and histone acetylation, which silence tumor suppressor genes or activate oncogenes, contributing to malignant transformation [106,107]. Diesel exhaust also prompts significant neutrophil infiltration and elevates Leukotriene B4 (LTB4) levels in the lungs, with LTB4-dependent inflammation implicated in promoting lung tumor growth [135]. These findings collectively underscore the intricate and comprehensive mechanisms through which diesel exhaust may contribute to the development of lung cancer.

Overall, diesel exhaust exposure is linked to epigenetic changes that influence the expression of genes involved in immune regulation and tumor suppression. This may contribute to the dysregulation of immune responses, increasing susceptibility to lung cancer. Diesel exhaust exposure shapes the tumor microenvironment by promoting the recruitment of immunosuppressive cells, such as myeloid-derived suppressor cells and regulatory T cells, fostering conditions conducive to tumor growth. Individual genetic factors may also play a role in determining susceptibility to the effects of diesel exhaust exposure, influencing an individual's risk of developing lung cancer. Understanding these immunological insights is crucial for developing preventive strategies and therapeutic interventions to mitigate the impact of diesel exhaust exposure on lung cancer development, highlighting the importance of reducing environmental exposure to diesel exhaust and other air pollutants to protect public health.

6. Conclusions

Emissions from combustion engines, particularly those used in transportation, represent a major contributor to environmental pollution, significantly affecting densely populated areas. Fine particles, measuring less than 4 μm, evade standard filtration mechanisms, reaching deep into the lungs and either settling in the alveoli or crossing into surrounding tissues. This process initiates a cascade of inflammatory responses, disrupts immune

balance, and compromises the body's ability to maintain tolerance, potentially leading to autoimmune disorders and heightened vulnerability to infections. The involvement of key immune cells, such as neutrophils and macrophages, underscores the complex interplay between these particles and the immune system, which is central to the development of chronic respiratory conditions, including asthma, COPD, and malignancies.

The impact of diesel exhaust on respiratory diseases extends to the realm of immunology, as the intricate interplay between the pollutants and the immunological alterations in different respiratory diseases (Figure 3). Chronic inflammation not only contributes to the manifestation and exacerbation of respiratory diseases but also disrupts the delicate balance of immune regulation. Prolonged exposure to diesel exhaust has been shown to compromise the immune system's ability to mount an effective defense against respiratory infections, rendering individuals more susceptible to pathogens. Furthermore, the oxidative stress induced by diesel pollutants may adversely affect immune cell function, impairing the body's capacity to combat diseases. Understanding the immunological implications of diesel exhaust exposure is essential for devising effective strategies to protect respiratory health and enhance the immune response in populations at risk.

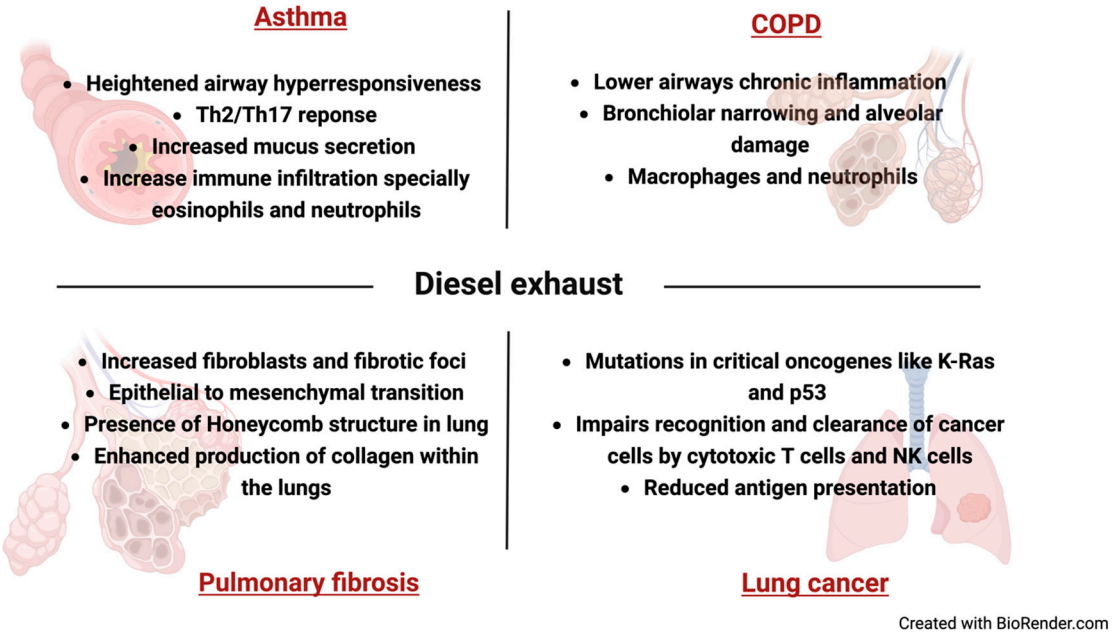


Figure 3. Immuno-pathological changes in lung associated diesel exhaust associated pulmonary diseases.

Efforts to understand the link between these emissions and respiratory ailments have largely depended on population-based and laboratory studies. While these approaches yield important data, they often fall short of capturing the full scope of systemic immune effects or the specific toxicity of such emissions. Animal models, with their complex biological networks, provide a more holistic view, revealing how exposure influences disease susceptibility and progression. However, much remains unknown about the precise mechanisms driving immune dysregulation and disease onset. Advancing research in this area is vital to uncover these pathways and develop effective strategies to counteract the detrimental health impacts of prolonged exposure to these pollutants.

Author Contributions: N.S.: conceptualization, writing—original draft, reviewing, and editing. S.S.: reviewing and editing. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not Applicable.

Informed Consent Statement: Not Applicable.

Data Availability Statement: Not Applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

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