



Emerging role of air pollution in autoimmune diseases

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ABSTRACT

Autoimmune diseases (ADs) are a broad spectrum of disorders featured by the body's immune responses being directed against its own tissues, resulting in prolonged inflammation and subsequent tissue damage. Recently, the exposure to ambient air pollution has been implicated in the occurrence and development of ADs. Mechanisms linking air pollution exposures and ADs mainly include systemic inflammation, increased oxidative stress, epigenetic modifications induced by exposures and immune response caused by airway damage. The lung may be an autoimmunity initiation site in autoimmune diseases (ADs). Air pollutants can bind to the Aryl hydrocarbon receptor (AHR) to regulate Th17 and Treg cells. Oxidative stress and inducible bronchus associated lymphoid tissue caused by the pollutants can influence T, B cells, resulting in the production of proinflammatory cytokines. These cytokines stimulate B cell and dendritic cells, resulting in a lot of antibodies and self-reactive T lymphocytes. Moreover, air pollutants may induce epigenetic changes to contribute to ADs. In this review, we will concern the associations between air pollution and immune-inflammatory responses, as well as mechanisms linking air pollution exposure and autoimmunity. In addition, we focus on the potential roles of air pollution in major autoimmune diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), and type 1 diabetes mellitus (T1DM).

1. Introduction

Autoimmune diseases (ADs), a category of complex diseases afflicting nearly 5% of the world population [1–3], can target a wide variety of tissues and organs. These diseases are characterized by the loss of self-tolerance and inappropriate activation of immune system, leading to the production of autoantibody and immune-mediated tissue destruction. Studies have revealed that the prevalence and incidence of ADs is increasing worldwide [4,5]. ADs contain a broad spectrum of

disorders, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), type 1 diabetes mellitus (T1DM), etc. Currently, the exact etiopathogenesis of ADs is still not clearly elucidated. Defective regulation, genetic susceptibility and environmental stimuli are responsible for initiating autoimmunity. ADs have a strong genetic background involved [6–8], however, the impact of environmental factors must not be underestimated [9,10].

In recent years, growing attention has been paid to the role of environmental factors to help explain the development of these diseases.

Abbreviations: ACPAs, anti-citrullinated peptide antibodies; ADs, Autoimmune diseases; BALT, Bronchus associated lymphoid tissue; CO, carbon monoxide; CNS, central nervous system; CRP, C-reactive protein; cSLE, childhood-onset systemic lupus erythematosus; DEPs, diesel exhaust particles; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; ESCAPE, European Study of Cohorts for Air Pollution Effects; PM2.5, fine particles; GM-CSF, granulocyte-macrophage colony-stimulating factor; IgG, immunoglobulin G; iBALT, inducible bronchus associated lymphoid tissue; IFN, interferon; IL-1, interleukin-1; IL-6, interleukin-6; IL-8, interleukin-8; IL-17, interleukin-17; IL-18, interleukin-18; IL-23, interleukin-23; MS, multiple sclerosis; NETs, neutrophil extracellular traps; NO2, nitrogen dioxide; NOx, nitrogen oxides; NHBE, Normal Human Bronchial Epithelial; NF-κB, nuclear factor kappaB; NHS, Nurses' Health Study; OR, odds ratio; O3, ozone; PM, particulate matter; PM1.0, very fine particles; Tregs, regulatory T cells; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE disease activity; SO2, sulfur dioxide; T1DM, type 1 diabetes mellitus; TNF, tumor necrosis factor

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Studies have shown that environmental factors accounts for 40–70% of all ADs [11,12]. As the leading environmental risk factor, air pollution causes and exacerbates a number of diseases. Air pollution includes solid, liquid and gases components affects biological systems. Main sources include: industry, vehicle exhaust, forest fires, stationary fuel burners and solid fuel combustion. They include particulate matter (PM) and a mixture of gases (carbon monoxide [CO], nitrogen dioxide [NO₂], ozone [O₃] and sulfur dioxide [SO₂]). PM can be classified according to the nature of particles, that is, biological, chemical, mineral and metal. However, based on particle size, diameter of PM $\leq 10 \mu\text{m}$, $\leq 2.5 \mu\text{m}$, $\leq 1 \mu\text{m}$, $\leq 100 \text{nm}$ are classified as coarse particles (PM₁₀), fine particles (PM_{2.5}), very fine particles (PM_{1.0}) and ultrafine particles (PM_{0.1} or UFPs), respectively. While the mechanism of air pollution affecting the lungs is obvious, the fact how air pollution affects other body systems is still incompletely elucidated. Experimental or population-based investigations have explored the potential effect of air pollution on ADs. It has been shown that exposure to air pollution can elevate both the incidence and severity of autoimmune disease [13,14]. PM in the atmosphere aggravates T1DM, RA, and MS [15–25]. Exposure to silicon, which is found in ambient air, can cause various immunological alterations, including activation of the cellular recruitment, cytokine production, Th1-Treg misbalance or reactive oxygen species release, ultimately involved in the pathogenesis of these diseases [26]. However, the mechanisms linking air pollution to ADs process have proven particularly difficult.

Given the contributions of air pollution in ADs, in this review, we first review prospective mechanisms linking air pollution exposure and autoimmunity. Then we discuss the relationship between air pollution and immune-inflammatory responses. Finally, we envisage the potential roles of air pollution in several major ADs, respectively.

2. Prospective mechanisms linking air pollution exposure and autoimmunity

Air pollution exposure could influence autoimmunity by augmenting autoimmune responses and enhancing systemic inflammation. The hypothesis that exposure to polluted air can cause T cell imbalance, production of proinflammatory cytokines, local pulmonary inflammation, oxidative stress and methylation changes may explain the effect of air pollution on the pathogenesis of ADs. ADs has been suggested to be part of the spectrum of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA), which is defined as several autoimmune conditions/phenomena that are induced following the exposure to substances with adjuvant activity [27–31]. Adjuvants may serve as triggers of various pathological entities of autoimmune etiology. Aluminum can induce production of inflammatory signals and disrupt metal balance within cells, inducing mitochondrial failure and generation of reactive oxygen species [32]. Moreover, the neurotoxicity of aluminum can induce brain inflammation gliosis leading to neurological deficits and contribute to the development of MS [32]. Smoke can provoke oxidative stress, alter the lung microenvironment, and facilitate infections and epigenetic changes to trigger the development of an autoimmune condition [33]. Gold miners exposed to mercury have higher serum autoantibody concentrations suggesting that mercury is an environmental stimulus in the development of autoimmunity [34]. Similarly, air pollutants can also act as adjuvants, thereby induce autoimmune/inflammatory syndrome. Studies have clearly demonstrated that air pollution exposure can stimulate the activation of antigen-presenting cells and T lymphocytes [14]. Reactive metals and volatile chemicals can directly generate free radicals, resulting in the induction of the NF- κ B and MAP kinase pathways [35,36]. PM can inhibit Th1 cells and Tregs [37]. The mRNA of interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor were positively associated with higher PM_{2.5} exposure [38]. In addition, O₃ and SO₂ exposure induced an increased level of serum IL-6 [39]. A study in the mice showed that particles increase the production of antigen-specific immunoglobulins

and cytokines [40]. PM inhalation induced the increased release of proinflammatory cytokines, including TNF- α , IL-1, IL-6 and interleukin-8 (IL-8) [41,42].

Predominant involvement of the airways was found in early asymptomatic RA, suggesting that the lung may be the early initiation site in ADs [43,44]. Local pulmonary inflammation may participate in the pathogenesis of ADs through the following two mechanisms. First, harmful particulate in lung tissue induces protein citrullination and ultimately stimulates anti-citrullinated peptide antibodies (ACPAs) production [45]. ACPA is involved in the development of RA pathogenesis and is a valuable diagnostic marker. 60% of RA patients have diffused idiopathic interstitial lung disease [46]. Bronchiectasis develops, vital capacity diminishes, and an infiltrate of lymphocytes and plasma cells indicates chronic inflammation, relating to the expression of ACPAs. Second, the more extensive inducible bronchus-associated lymphoid tissue (iBALT) induced by air pollution may involved in the pathogenesis of ADs. A mice study showed that chronic inhalation of diesel exhaust stimulates cytokine expression and induces phagocytosis and BALT development [47]. ADs have more well-developed iBALT, showing that iBALT is implicated in local ADs pathogenesis [48]. Additionally, iBALT may activate B cells and differentiate them into plasma cells with autoantibody production potential. Thus, iBALT may be a site of antigen presentation and plays an important role in the transformation of innate immune responses into adaptive immune responses in ADs (Fig. 1).

Air pollution was followed by a significant rise in oxidative stress in the airways, activating nuclear factor kappaB (NF- κ B), and stimulating the production of T helper lymphocytes type 1 (Th1). Moreover, oxidative stress can stimulate alveolar macrophages and airway epithelial cells to express pro-inflammatory cytokines, stimulate dendritic cells to migrate to the local lymph nodes, cause cell necrosis and apoptosis, contribute to the release and activation of neutrophil extracellular traps (NETs) which is accompanied with increased IL-17 and interleukin-23 (IL-23) levels [49]. Through these ways, oxidative stress aggravated systemic inflammation and immune imbalance.

The Aryl hydrocarbon receptor (AHR) pathway is involved in inflammatory processes and adaptive immune responses, and directs the balance between effector and regulatory T cells, ultimately participates in the pathogenesis of ADs [50–54]. The AHR is a ligand-activated transcription factor that responds to toxicants present in PM. PM contains high-affinity AHR ligands which can enhance Treg generation, augment Th17 differentiation and regulate autoimmunity [51,53]. A study in mice model showed that PM enhanced Th17 differentiation by acting on the AHR in T cells [51,53,55]. Another mouse model of RA showed that a lack of AHR in T cells suppressed the development of arthritis, and that Th1/Th17 balance may be involved in this process [56] (Fig. 1).

In addition, short-term exposure to PM_{2.5} may induce decreased methylation at CpG loci of the corresponding inflammation-related genes, consequently involve in the inflammation response and contribute to ADs [57].

3. Population-based studies of air pollution and immune-inflammatory responses

Population-based studies have clearly indicated that air pollution exposure affects the immune system. An Italy study in nonsmokers suggested that exposure to NO₂ and nitrogen oxides (NO_x) influenced IL-17 levels [58]. And exposure to air pollution may lead to oxidative stress, which activates inflammatory responses that primarily involve the “cytokine signaling” pathway [58]. A cross-sectional study in the European Study of Cohorts for Air Pollution Effects (ESCAPE) project showed elevated C-reactive protein (CRP) values are associated with increased annual NO_x concentration [59]. And CRP levels are higher in participants living on a busy (> 10,000 vehicles/day) road than those living on a quiet residential street (< 1000 vehicles/day) [59]. A

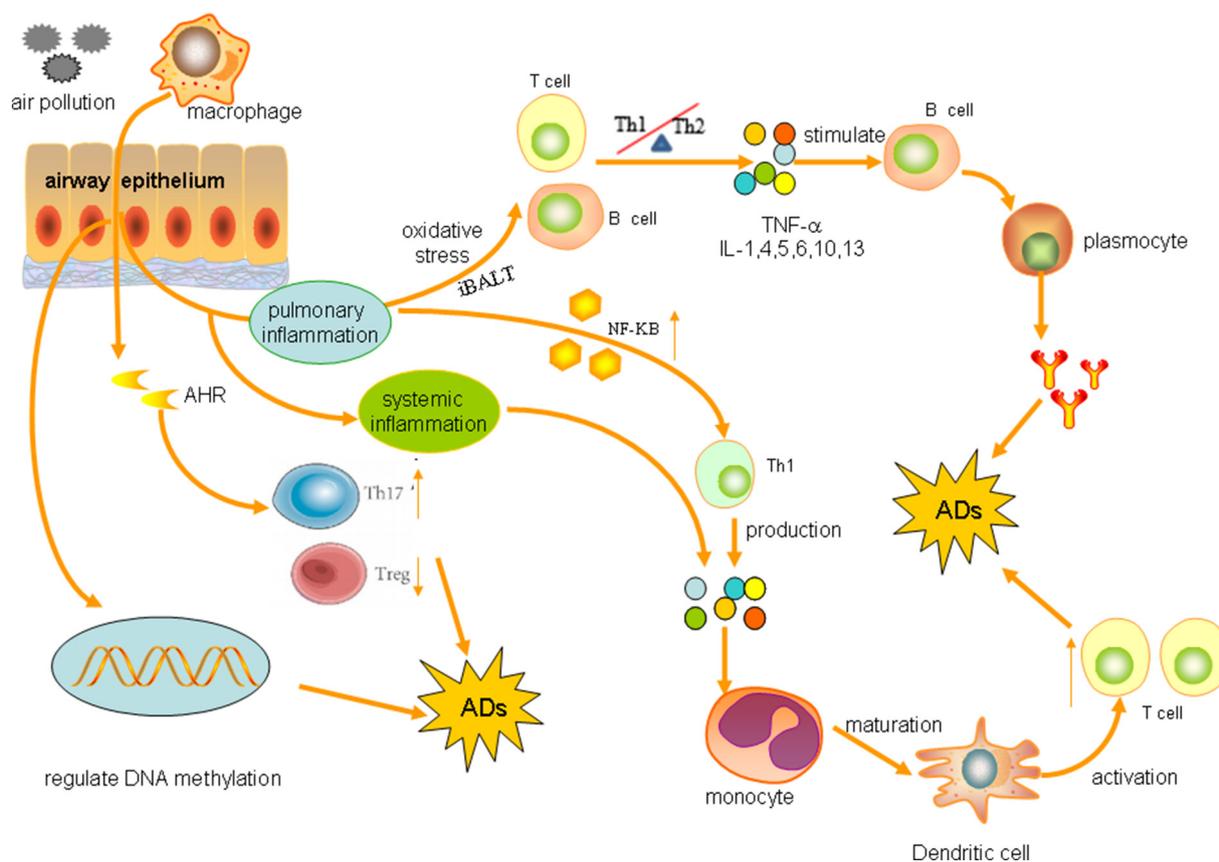


Fig. 1. Potential mechanisms influencing autoimmune diseases through air pollution exposure.

Exposure to air pollutants can result in local pulmonary inflammation and systemic inflammation. Oxidative stress and iBALT caused by the pollutants can influence T, B cells, resulting in the production of proinflammatory cytokines. In addition, air pollution activates NF-κB to regulate Th1, causing the production of proinflammatory cytokines. These cytokines stimulate B cell and dendritic cells, resulting in a lot of antibodies and self-reactive T lymphocytes. Moreover, air pollutants can also bind to the AHR to regulate Th17 and Treg cells. Finally, air pollutants may induce decreased methylation to contribute to ADs. ADs, Autoimmune diseases; iBALT, inducible bronchus associated lymphoid tissue; IL-1, interleukin-1; IL-4, interleukin-4; IL-5, interleukin-5; IL-6, interleukin-6; IL-10, interleukin-10; IL-13, interleukin-13; NF-κB, nuclear factor kappa B; Th1, T helper lymphocytes type 1; Th2, T helper lymphocytes type 2; Th17, T helper lymphocytes type 17; Treg, regulatory T cells; TNF-α, tumor necrosis factor-α;

survey of 17 cities in Central Europe showed that elevated PM levels, particularly PM_{2.5} levels, were associated with the total number of immunoglobulin G (IgG), CD8⁺, CD4⁺ and NK lymphocytes [60]. Similarly, in another study, PM_{2.5} exposure was related to an inflammatory response characterized by elevated levels of circulating CD4⁺, CD8⁺, CD14⁺, CD16⁺, but not CD19⁺ T cells, suggesting that PM_{2.5} exposure lead to increased T lymphocytes [61]. In a children study in Mexico City, exposure to serious air pollutants had increased CD8⁺ T cells and mCD14⁺ monocytes, but reduced numbers of natural killer cells, interferon gamma and granulocyte-macrophage colony-stimulating factor (GM-CSF), indicating its roles in immune dysregulation and systemic inflammation [62]. A hospital-based cohort study in South Korea showed that fibrinogen, acts as a pro-inflammatory regulator by interacting with inflammatory cells [63], was associated with exposure to PM_{2.5}, PM₁₀, SO₂, NO₂ and O₃; white blood counts, a comprehensive indicator of inflammatory stimuli, were positively associated with long-term exposure to PM₁₀, CO and O₃; ferritin involved in the inflammatory process were related to O₃, NO₂, PM_{2.5} and CO; CRP had a relevance with short-term exposure to PM_{2.5}, PM₁₀, CO, and SO₂ [64]. Vidotto et al. showed a delayed association between paediatric rheumatic diseases outburst and SO₂, suggesting a critical role of oxidative stress reaction in autoimmune rheumatic diseases [65]. A study used land-use regression models and bayesian logistic regression models to assess relationship between PM_{2.5}, NO₂ and systemic autoimmune rheumatic diseases (for undifferentiated connective tissue disease, polymyositis, dermatomyositis, SLE, scleroderma, sjogren's

syndrome, polymyositis), showing that PM_{2.5} levels but not NO₂ are related to these diseases [66].

4. Air pollution in autoimmune diseases

4.1. Systemic lupus erythematosus

SLE is an autoimmune disease characterized by chronic inflammation, immune-complex deposition [67]. Genome-wide association studies fail to explain sufficiently the development of this disease, indicate an involvement of environment factors. It is well known that several major components of PM_{2.5}, including trace elements and polycyclic aromatic hydrocarbons, are associated with the prevalence of SLE [67–69].

A study in childhood-onset systemic lupus erythematosus (cSLE) showed that increased PM_{2.5} 4-day moving average was associated with an increase of IL-17 and TNF-α exhaled breath condensate levels [67]. In addition, an increased risk of SLE disease activity (SLEDAI-2K) ≥ 8 was associated with PM_{2.5} 7-day moving average, indicating that systemic inflammation may be triggered by exposure to PM_{2.5} [67]. A study using a clinic cohort of 237 SLE patients showed that elevated PM_{2.5} levels were accompanied with high anti-dsDNA levels, adding weight to effects of air pollution on inflammation and autoimmunity [68]. However, they did not observe associations between PM_{2.5} concentrations and SLEDAI-2K due to the short-term cohort. Similarly, Conde et al. did not observe associations between air

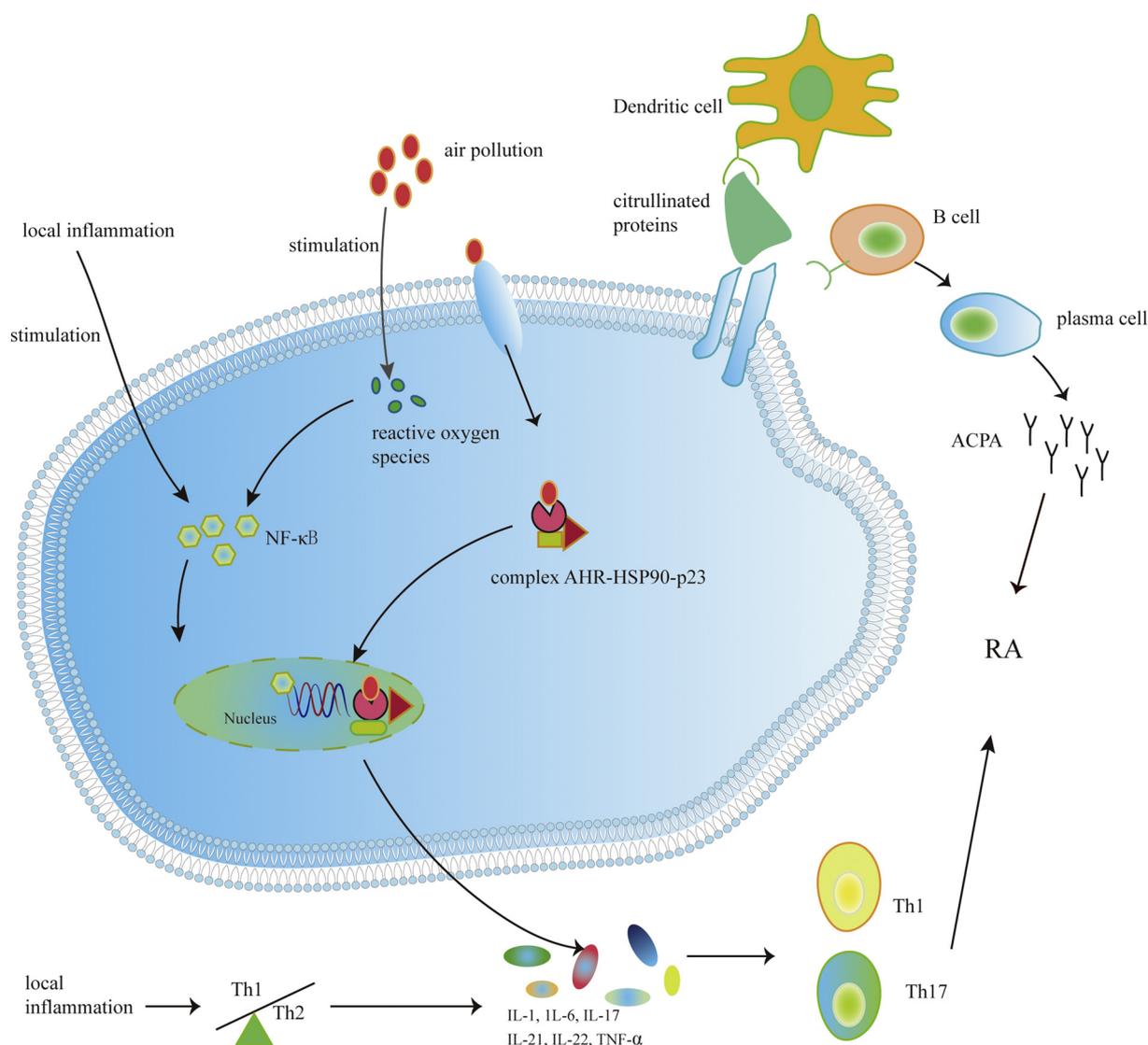


Fig. 2. Schematic representation of mechanisms putatively influencing rheumatoid arthritis through air pollution exposure.

Local pulmonary inflammation and free reactive oxygen species induced by air pollutants can activate NF- κ B. NF- κ B translocates to the nucleus and stimulates the production of IL-1 and IL-6. Air pollutants bind to AHR-HSP90-P23 complex to translocate to the nucleus to regulate the production of IL-17, IL-21 and IL-22. These cytokines can influence Th1 and Th17. Lung and systemic inflammation induce citrullinated proteins, leading to the production of ACPAs. ACPAs, anti-citrullinated peptide antibodies; RA, rheumatoid arthritis; NF- κ B, nuclear factor kappa B; IL-1, interleukin-1; IL-6, interleukin-6; IL-17, interleukin-17; IL-21, interleukin-21; IL-22, interleukin-22; Th1, T helper lymphocytes type 1; Th2, T helper lymphocytes type 2; Th17, T helper lymphocytes type 17; TNF- α , tumor necrosis factor- α .

pollutants (NO₂, SO₂ and PM₁₀) and cSLE [69].

In normal Balb/c mice injected with n-hexadecane (a chemical contained in diesel exhaust), Kuroda et al. showed that non-specific inflammation caused by n-hexadecane led to the production of specific autoantibodies similar to SLE, suggesting that air pollution can be implicated in the development of autoimmune diseases under experimental conditions [70]. In the lupus-prone female NZBWF1 mouse, exposure to crystalline silica led to an elevated level of the cytokines TNF- α , MCP-1 and IL-6 and immunoglobulin levels in bronchoalveolar lavage fluid. And this exposure can contribute to pulmonary inflammation, ectopic lymphoid neogenesis and renal pathology, suggesting that the lung can trigger glomerulonephritis and systemic autoimmunity [71]. Thus, further longitudinal multicenter studies in large urban areas are required to better understand these associations.

4.2. Rheumatoid arthritis

RA is a systemic autoimmune disease characterized by chronic

inflammation and destruction of synovial joints [72]. People with lower socioeconomic status have increased risk of RA and mortality after RA [73]. Inflammatory cytokines, including IL-1b, TNF- α and IL-6, have been demonstrated to influence the pathogenesis of RA [74–76]. ACPA, the most specific biological markers with predictive and prognostic value in RA patients, is increased in sera of patients five to ten years prior to diagnosis with RA. Every one kilometer of distance from emitters of PM_{2.5} and SO₂ was associated with an odds ratio (OR) of 0.81(95%CI, 0.69, 0.96) and 0.92 (95%CI, 0.84–1.00) for ACPA positivity, respectively [77]. Bronchus associated lymphoid tissue (BALT) is associated with ACPA and RA-related lung diseases and therefore may play important roles in autoimmunity processes. Recently, several large epidemiological studies have reported the associations between the incidence of RA and air pollution. It has been shown that the incidence of RA in urban areas was higher than rural areas [78]. In the Nurses' Health Study (NHS) in the United States, after adjustment for multiple confounders, an elevated risk of RA was observed in women living within 50 m of a road than those women living 200 m or farther away

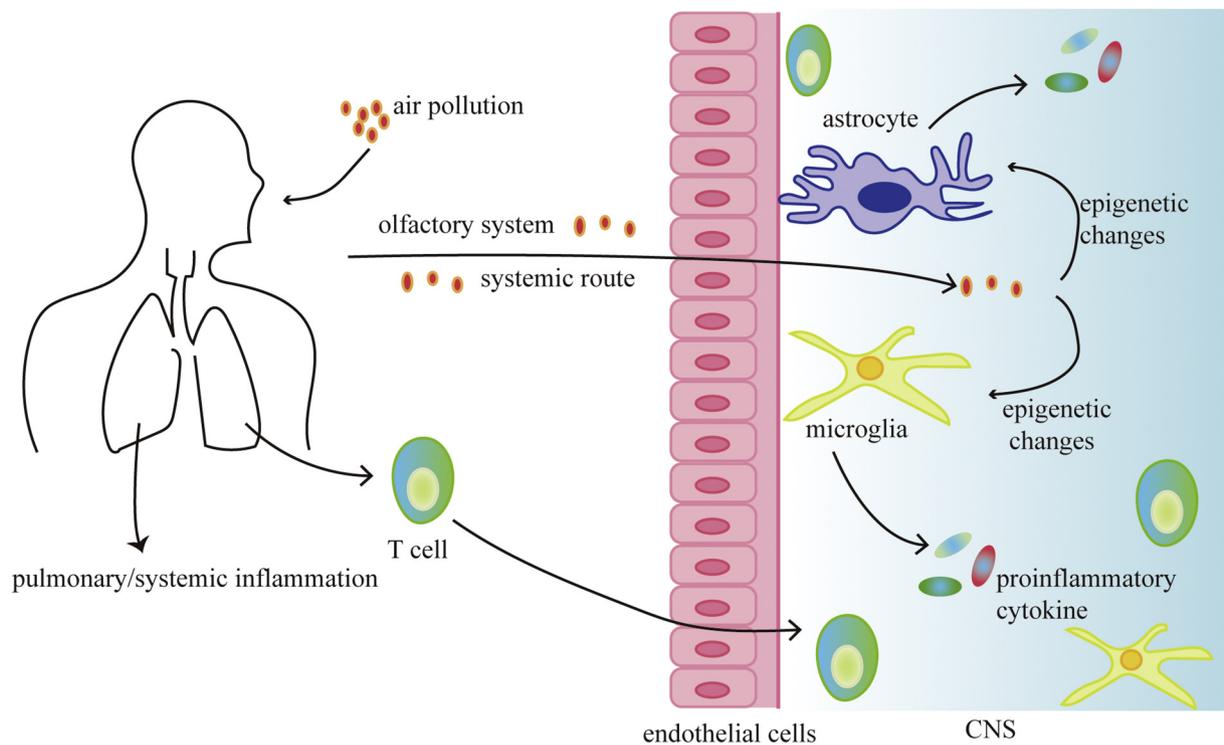


Fig. 3. Potential mechanisms influencing multiple sclerosis through air pollution exposure.

Three main theories hypothesises may contribute to MS. First, inhalation of air pollution increases the oxidative stress and facilitates the entry of pollutants into CNS through systemic route. And lung can activate autoreactive T cells and allow them to enter CNS. Second, air pollutant that deposit in the nose can reach the brain via retrograde axonal transport along the olfactory nerve. Third, air pollutant may cause epigenetic changes of neuroglia, resulting in the production of proinflammatory cytokine.

CNS, central nervous system; MS, multiple sclerosis.

[79]. In the Swedish Epidemiological Investigation of Rheumatoid Arthritis (EIRA) case-control study with 1497 incident RA cases and 2536 controls, no associations between RA and PM10 was observed. However, risks of ACPA-negative phenotype RA incidence were increased in subjects exposed to higher SO₂ concentration and higher NO₂ concentration [80]. A longitudinal and nationwide study in Taiwan observed NO₂ levels but not PM_{2.5} are related to increased risk of RA [18]. However, Roos et al. did not find associations between RA and air pollution (PM_{2.5} and NO_x). In addition, they reported increased RA risk in participants with residence ≤ 50 m from a highway [81]. Therefore, RA may be associated with PM, SO₂, NO₂ and O₃ concentration.

In mice models of collagen-induced arthritis, diesel exhaust particles (DEPs) exposure has been considered to be an important factor in exacerbating the incidence and severity of arthritis [82,83]. Colasanti et al. evaluated the roles of DEPs in Normal Human Bronchial Epithelial (NHBE) cell. And found that DEPs can stimulate the release of interleukin-18 (IL-18); affect cell necrosis, autophagy and apoptosis; induce protein citrullination in NHBE cells, suggesting that chronic exposure to DEPs could be responsible for the generation of RA features in genetically susceptible individuals [84]. Exposure to DEPs may affect the local bronchial epithelial cells to induce autophagy and with it citrullination, creating a substrate for autoreactivity. Autophagy may be involved in the adaptive responses to citrullinated self-peptides [85].

Free reactive oxygen species produced by PM activates nuclear factor kappaB (NF- κ B), which stimulates the production of proinflammatory cytokine including TNF- α and IL6, ultimately leading to joint inflammation. In addition, free reactive oxygen species stimulate chronic lung and systemic inflammation, which promotes citrullinated products and ACPA production, and ultimately cause joint inflammation and erosion [86]. Furthermore, air pollution may further aggravate RA through hypovitaminosis D [87]. Air pollutants such as O₃ can

absorb UVB in the atmosphere, thereby reducing the effectiveness of sun exposure on the synthesis of vitamin D in the skin, and could thus increase RA incidence. Therefore, air pollution can induce protein citrullination, produce ACPAs and more extensive iBALT and stimulate AHR pathway to participate in the development of RA (Fig. 2).

4.3. Multiple sclerosis

MS is an autoimmune disease characterized by inflammatory central nervous system (CNS) demyelination mediated by T cells specific for a myelin antigen. Recently, emerging evidence suggests that air pollution-induced oxidative stress, neuroinflammation, cerebrovascular dysfunction, microglial activation and alterations in the blood-brain barrier are implicated in CNS pathology [88]. Heydarpour et al. observed a significant difference in exposure to SO₂, PM₁₀, NO₂, and NO_x between MS patients and controls suggesting that long-term exposure to air pollutants can act as an environmental risk factor in MS [89]. Several adult MS studies have reported that increased PM₁₀ was associated with increased risk for MS in adults [20,89] and MS relapse [15,23,24,90]. Their findings are not consistent with several studies which reported that PM_{2.5} and PM₁₀ were not associated with MS risk [91,92]. Moreover, SO₂ levels were significantly associated with higher odds for MS [89,92]. Furthermore, O₃ is significantly associated with occurrence of MS relapses in the multi-pollutant model [90].

Although there are numerous studies with controversial results about the effect of air pollution in MS, three main theories hypothesises may contribute to the neurological and immunological outcomes of MS. First, inhalation of air pollution increases the oxidative stress and permeability of the epithelial wall, leads to the release of proinflammatory cytokines and stimulates immune response with activating potentially auto-aggressive T cells to enter the central nervous system [93]. Second, the inhaled particles could be translocated through the

olfactory system and cross the blood–brain barrier [94]. The third plausible mechanism may be related to genes control, and especially epigenetic changes, particularly DNA methylation alterations (Fig. 3).

4.4. Type 1 diabetes mellitus

T1DM is an autoimmune condition that results from the destruction of the insulin-producing beta cells of the pancreas [95]. Genetic susceptibility is a well recognized risk factor for the development of this disease; however, modification frequency of genetic risk factors is not paralleled by rapid epidemiological trend changes, suggesting that other important risk exposures may also contribute to T1DM [96,97]. A systematic review and analysis in 2018 observed a strongly increasing trend of the T1DM incidence among children aged 0–4 years [98]. A study reported that offspring had a higher risk ratio for T1DM in those whose mother exposed to high concentrations of O₃ in the second trimester and high concentrations of NO_x in the third trimester [22]. Hathout et al. showed that children with T1DM have increased O₃ exposure than healthy controls, suggesting that O₃ may be a predisposing factor for the development of T1DM. Children diagnosed before 5 yr of age have higher PM₁₀ exposure than healthy controls [21]. In addition, the authors declared that dioxins and other air pollutants may contribute to the unexpected finding which SO₂ decreased the risk for T1DM [21]. Another study in very young children indicated that high exposure to PM_{2.5}, PM₁₀ and NO₂, but not urbanization-related lifestyle habits, accelerated the manifestation of T1DM [16]. Their finding is partly demonstrated by Ciaula who reported that T1DM incidence rate was positively related to mean yearly PM₁₀, but not to CO, NO_x and O₃ concentrations, suggesting a crucial role for specific pollutants [19]. And their associations were stronger in children with > 5 years at onset. In addition, Ciaula et al. speculate this negative result may be related to their low air concentrations throughout the study area and period.

In a mouse model of T1DM, diabetes can aggravate oxidative stress, lung apoptotic and TNF concentrations, suggesting an increased respiratory vulnerability to DEPs due to diabetes [99]. Nemmar et al. showed that systemic and coagulation events are aggravated in DEPs-exposed diabetic mice [100]. And oxidative stress is responsible for detrimental effects of the pancreas [101]. Study has found that O₃ can adversely affects CD4⁺ cells and alters T-cell-dependent immune responses [102]. O₃ contributed to T1DM by enhancing the presentation of diabetogenic antigens or causing free-radical damage to β-cells [21].

Additionally, recent studies have focused on air pollution associated epigenetic modifications including DNA methylation, microRNA regulation and changes in histone post-translational modifications [103]. Therefore, besides the abnormal immune responses caused by air pollution can contribute to the pathogenesis of T1DM, we also can explore whether air pollution may trigger T1DM through epigenetic mechanisms. Further studies are warranted to elucidate air pollution induced epigenetic inheritance and the effect of air pollution in the diabetogenic mechanism.

Discrepant results between studies indicate the necessity to better elucidate their role in the pathogenesis of these diseases. The difference among these studies may be due to several reasons as follows. First, did not consider the exposures at the workplace or recreational areas. Second, cadmium levels may act as a confounding factor in studies of vehicle-related air pollution [18]. Third, high correlations between various air pollutions should be considered. NO₂ can act as a proxy for PM, and O₃ can aggravate the role of PM by increasing the permeability of respiratory epithelium to PM. Air pollution is characterized by a complex combination of various toxic substances, and it is difficult to study the epidemiological effects of single pollutants in population studies.

5. Conclusions

Emerging evidences have suggested that air pollution is implicated in the development of ADs. The role of air pollution in initiating ADs highlights the interaction of air pollution with the immune system in the lungs and the consequences of long-term inflammation. Based on the population-based studies and mechanism studies in mice, polluted air can cause T cell imbalance, production of proinflammatory cytokines, airway damage, oxidative stress and methylation changes to initiate and aggravate autoimmune diseases. Further studies performed *in vitro* and *in vivo* with advanced molecular biologic techniques, will be used to evaluate potentially serious effects of air pollutants and the mechanisms involved in the onset and the exacerbation of these diseases. If the causal relationship between air pollution exposure and ADs is determined, even if air pollution contributes only a small part of these diseases, the impact of air pollution on the world population will be great. Therefore, it is important to develop public health policies to reduce exposure to air pollution, and to further study its molecular and cellular pathways involved in ADs.

Competing interest

The authors report no conflicts of interest.

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