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Airborne culprits: A comprehensive review of PM, silica, and TCDD in autoimmune diseases

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ABSTRACT

Autoimmune diseases (ADs) are immunological disorders arising from the breakdown of immune tolerance, influenced by various internal and external factors. Persistent exposure to environmental factors, particularly air pollution, is linked to systemic inflammation, oxidative stress, and apoptosis, which contribute to the development of ADs.

This review examines the impact of air pollutants, including particulate matter, silica, and TCDD, by analyzing epidemiological studies, animal models, and *in vitro* assays. It focuses on how air pollution disrupts the immune system, leading to apoptosis, increased oxidative stress, cytokine production, autoantigen release, autoantibody production, and autoreactivity, which are particularly significant in ADs like rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, and systemic sclerosis. In essence, this approach aims to provide a profound understanding of how exposure to air pollution can initiate or contribute to ADs, offering potential avenues for more targeted preventive and therapeutic strategies.

1. Introduction

Autoimmune diseases (ADs) represent a diverse group of chronic conditions characterized by the breakdown of immunological tolerance, leading to dysfunctions in both the innate and adaptive immune systems. In this process, the inappropriate activation of the immune response leads to inflammation-mediated tissue damage and production of autoantibodies [1]. Consequently, this results in elevated rates of morbidity and mortality, presenting a significant public health challenge [2]. It is estimated that ADs affect approximately 10–12 % of the population [3], exhibiting a distinct gender bias with up to 78 % of cases occurring in women [4]. ADs are categorized into two groups: organ-specific, affecting a single organ (e.g., type 1 diabetes mellitus, Graves' disease), and systemic, affecting multiple organs (e.g., systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjögren's syndrome (SS)) [5]. Despite variations in their epidemiological, pathological, and clinical characteristics, these diseases share common immunogenetic mechanisms, a phenomenon referred to as "autoimmune tautology" [6].

The development of ADs is influenced by multiple factors, including endogenous elements such as gut microbiota, genetic susceptibility, epigenetic changes, and hormonal activity, as well as external factors like infections, exposure to environmental pollution, medications, and vaccines [7]. Large-scale studies have revealed that susceptibility loci contribute to 50 % of the etiology of these disorders [8]. Twin studies have shown that some ADs, like celiac disease, have a strong genetic component, with monozygotic twin concordance rates ranging from 75 % to 83 %. In contrast, diseases like RA, SLE, and SSc have lower concordance rates, suggesting a greater influence of environmental factors [9]. The interactions between individuals and their environment, leading to the breakdown of immune tolerance and, consequently, the development of one or more ADs is known as 'autoimmune ecology' [10].

In recent years, the confluence of climate change, biodiversity loss, and demographic expansion has markedly contributed to the escalation of environmental pollution, particularly the degradation of air quality [11]. Epidemiological studies have demonstrated a correlation between air pollution and non-communicable chronic diseases, including cardiovascular and respiratory diseases, cancer, and ADs [12,13]. Notably, findings from the 2015 Global Burden of Disease Study underscored the severe impact of air pollution, linking it to 6.4 million deaths worldwide. Specifically, deaths attributed to particulate matter (PM) surged from 3.5 million in 1990 to 4.2 million in 2015. This increase can be

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List of abbreviations

ACPA	Anti-citrullinated protein antibodies
ADs	Autoimmune diseases
AhR	Aryl hydrocarbon receptor
ANAs	Anti-nuclear antibodies
ANCA	Anti-neutrophil cytoplasmic antibodies
APC	Antigen-presenting cells
BAFF	B cell activation factor
BALF	Bronchoalveolar lavage fluid
CENP-B	Centromere protein B
CTD	Connective tissue disorders
DCs	Dendritic cells
DNMTs	DNA methyltransferases
ds-DNA	Double stranded DNA
EBV	Epstein-Barr virus
ERK	Extracellular signal-regulated kinase
FGFR2	Fibroblast growth factor receptor 2
GM-CSF	Granulocyte-macrophage colony-stimulating factor
iBALT	Induced bronchial-associated lymphoid tissue
IFN	Interferon
IL	Interleukin
MCP	Monocyte chemoattractant protein
MDA-5	Melanoma differentiation-associated protein 5
MIP	Macrophage Inflammatory proteins
MPO	Myeloperoxidase
NETs	Neutrophil extracellular traps
NFκB	Nuclear factor kappa B
PBMCs	Peripheral blood mononuclear cells
PM	Particulate matter
PR3	Proteinase 3
RA	Rheumatoid arthritis
RNP	Ribonucleoproteins
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SLE	Systemic lupus erythematosus
Sm	Smith antigen
SS	Sjögren's syndrome
SSc	Systemic sclerosis
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TCR	T cell receptor
TGF	Transforming growth factor
TIF-1	Transcriptional intermediary factor 1
TLR	Toll-like receptor
TNF	Tumor necrosis factor
Tregs	Regulatory T cells

attributed to demographic and epidemiological changes, as well as to the growing levels of air pollution in low- and middle-income countries [14]. Annually, around 8.34 million excess deaths are due to fine particulate and ozone air pollution, with approximately 5.13 million linked to fossil fuel use. Consequently, this indicates that up to 82 % of these deaths could be prevented by transitioning away from fossil fuels [15].

Understanding the processes by which air pollutants modulate the immune response and contribute to the pathogenesis of ADs is imperative. Thus, this review aims to delineate the key mechanisms by which PM, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), and silica induce a state of both local and systemic inflammation, triggering and exacerbating ADs. Understanding these processes is essential for developing targeted interventions and mitigating the impact of environmental factors on the increasing prevalence of ADs.

2. Air pollution

Air pollution refers to the presence of harmful substances in the Earth's atmosphere, resulting from human activities or natural processes, with adverse effects on the environment, human health, and other living organisms [16]. These pollutants constitute a complex mixture of biological, chemical, or physical elements, existing in solid, liquid, or gaseous forms and frequently occurring at elevated concentrations, thereby compromising environmental integrity. The primary components of air pollutants include PM, ground-level ozone, carbon monoxide, toxic metals, sulfur oxides, nitrogen oxides, lead, and microorganisms [17]. Additionally, highly toxic substances such as TCDD and silica contribute to air pollution.

2.1. Particulate matter

PM forms in the atmosphere as a heterogeneous mixture of solid and liquid particles suspended in the air, resulting from chemical reactions among various pollutants. It primarily consists of a combination of polycyclic aromatic hydrocarbons, polychlorinated biphenyls, pesticides, volatile compounds, endotoxins, metals, salts, and carbonaceous compounds [18]. According to its origin, PM can be classified as primary particles (i.e., emitted directly into the air) or secondary (i.e., the product of chemical reactions between primary particles). It can also be categorized by size, shape, and composition, using aerodynamic diameter classification, with sizes ranging from 0.005 to 100 μm [18]. Experimental studies classify PM by aerodynamic diameter into three groups: I) Ultrafine PM ($PM_{0.1}$): These are particles with a size equal to or less than 0.1 μm. They are of secondary origin or consist of ultrafine carbon particles; II) Fine PM ($PM_{2.5}$): Particles with a size greater than 0.1 μm and less than 2.5 μm. They can be of secondary origin or fine particles composed of organic carbon, heavy metals, nitrates, sulfates, and clays; III) Coarse PM (PM_{10}): Particles with a size between 2.5 μm and 10 μm. They are usually of primary origin or consist of coarse particles such as fugitive dust and pollen [19].

2.1.1. Molecular and cellular mechanisms of autoimmunity induced by particulate matter

Numerous epidemiological studies have established a robust association between exposure to PM and the onset of ADs, as detailed in Table 1. Specifically, the evidence indicates that PM exposure significantly contributes to the incidence and exacerbation of conditions such as SLE, systemic sclerosis (SSc) and SS. Research consistently demonstrates that exposure to these particles correlates with increased hospitalizations, heightened relapse risks, worsened disease severity, and elevated mortality in SSc patients.

The mechanisms underlying this association involve intricate processes, including systemic inflammation, oxidative stress, epigenetic modifications, dysregulation of the immune response, and mitochondrial damage [20,21]. In humans, lungs are the most exposed organ to the environment, with highly vascularized tissues and essential functions [22]. PM primarily affects the airway epithelium and alveolar spaces, rich in oxidation-sensitive components. PM generates reactive oxygen species (ROS) that induce antioxidant and inflammatory responses in epithelial cells [20]. This leads to lung inflammation, including the formation of inducible bronchial-associated lymphoid tissue (iBALT) [13]. *In vivo* studies have shown that PM exposure leads to the migration and infiltration of neutrophils into the lungs. Huang et al. [23], exposed BALB/c mice to PM_{10}, eliciting a confluence of mixed Th1 and Th2 inflammatory responses. This exposure resulted in the recruitment of neutrophils and the release of Th1 cytokines, such as tumor necrosis factor (TNF)-α and interferon (IFN)-γ. In addition, neutrophils endocytose $PM_{2.5}$, inducing inflammatory responses through

oxidative stress and the release of TNF-α and IL-6 via TLR4 and MyD88 [24]. Moreover, PM_{10} induced eosinophil recruitment along with the release of Th2 cytokines, including interleukin (IL)-5 and IL-13. Additionally, Valderrama et al. [25], revealed that exposure to PM_{10} in murine models induced *in vivo* inflammation. Elevated PM_{10} concentrations induced adverse effects on neutrophils, characterized by cellular apoptosis and release of lactate dehydrogenase. This exposure also increased the production of ROS, IL-8, myeloperoxidase (MPO), neutrophil elastase, and the release of neutrophil extracellular traps (NETs). Consequently, neutrophils infiltrated bronchoalveolar lavage fluid (BALF), leading to histopathological signs of inflammation, coupled with a notable upregulation of CXCL1 expression. These findings strongly support the hypothesis that PM-induced lung inflammation is orchestrated by neutrophils activation (Fig. 1).

Alveolar macrophages play a vital role in the pulmonary immune response by capturing PM and releasing various inflammatory mediators. Importantly, when murine peritoneal macrophages are exposed to low levels of PM, this exposure may predispose cells to an exaggerated inflammatory response upon encountering additional stimuli, such as bacterial toll-like receptor (TLR) ligands like lipopolysaccharide [26]. This phenomenon, commonly referred to as "trained immunity," is characterized by the initial priming of macrophages with one substance, leading to an enhanced production of cytokines upon subsequent re-stimulation with another [27]. In the context of autoimmune processes, the prolonged and elevated reactivity of macrophages could potentially contribute to the deregulation of the immune system, fostering an environment conducive to autoimmune reactions. The development of innate immune memory through the extended activity of these macrophages emphasizes the potential implications of exposure to PM in the development of autoimmunity.

The quantity and duration of exposure to PM can result in various forms of cell death, including apoptosis, autophagy, and necrosis [28,29]. Low levels of PM exposure are linked to apoptosis, characterized by caspase-3 activation. Moderate exposure is associated with autophagy induced by stress signals that inhibit the mechanistic target of rapamycin. On the other hand, intense exposure leads to necrosis, driven by increased production of ROS, DNA damage, and the activation of poly-ADP-ribose-polymerase-1 [29]. Inflammatory mediators generated by neutrophils and macrophages, with a focus on ROS and reactive nitrogen species (RNS), trigger protein alterations, particularly those associated with DNA, resulting in cell necrosis and apoptosis [30]. Furthermore, ROS and RNS play a role in the initiation and liberation of NETs. This phenomenon is linked to elevated levels of IL-17 and IL-23, contributing to the development of iBALT [31,32]. iBALT can activate B cells and differentiate them into plasma cells with autoantibody production potential. Furthermore, several components of NETs, including double-stranded (ds) DNA, granule proteins, and histones, have the potential to trigger autoantibody production and the onset of ADs [33].

In individuals with SLE, the combination of insufficient DNA repair mechanisms and the generation of endogenous DNA damage due to oxidative stress may contribute to heightened apoptosis rates, subsequently triggering the synthesis of autoantibodies [34]. In a study involving NZBW mice, predisposed to lupus and exposed to $PM_{2.5}$, exacerbation of certain SLE manifestations was observed. This included an augmentation in circulating neutrophils, an early onset of proteinuria, and an increase in kidney weight accompanied by the enlargement of the renal cortex [35]. Furthermore, elevated levels of $PM_{2.5}$ have been correlated with anti-dsDNA and the presence of cellular casts in a cohort of SLE patients [36]. On the other hand, PM has been implicated in increasing the incidence and severity of collagen-induced arthritis. This is concomitant with heightened serum levels of anti-collagen type II IgG, anti-citrullinated protein antibodies (ACPA), and proinflammatory cytokines such as IL-6 and TNF-α [37].

PM increases the production of ROS by activating TLR-2 and TLR4. This activation occurs through damage-associated molecular patterns and pathogen-associated molecular patterns. These patterns serve to incite an inflammatory and immune response within alveolar macrophages and airway epithelial cells [38]. Inhibition of TLR2 and TLR4

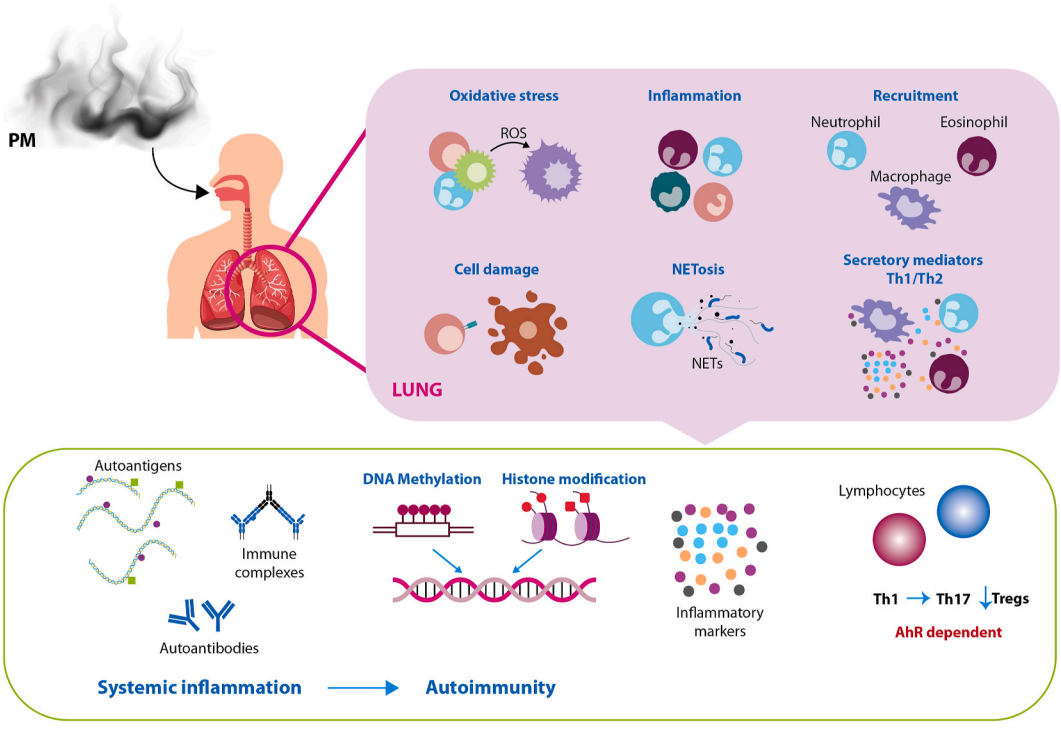

Fig. 1. Cellular Dynamics in PM-Induced Autoimmunity. The progression of autoimmunity induced by exposure to PM encompasses several pivotal stages. These include the consequential effects on lung tissues, intricate cellular responses, mechanisms leading to cell death, inflammatory processes, alterations in the lymphocyte profile, engagement of the AhR pathway, modulation of DNA methylation, and the ensuing transcriptional effects. **Abbreviations:** AhR: Aryl hydrocarbon receptor, NETs: Neutrophil extracellular traps, PM: Particulate matter, ROS: Reactive oxygen species, Th: T helper cells, Tregs: Regulatory T cells.

expression has the potential to prevent $PM_{2.5}$-induced cardiovascular diseases [39]. $PM_{2.5}$-treated skin keratinocytes produced IL-6. This process is initiated when $PM_{2.5}$ binds to TLR5, triggering intracellular signaling through MyD88 and leading to the translocation of nuclear factor-kappa B (NFκB) into the nucleus, where it binds to the IL-6 promoter. Furthermore, the enhanced transcription of IL-6 induced by $PM_{2.5}$ is regulated through epigenetic modifications involving DNA methylation and histone methylation [40]. Additionally, upon exposure to PM, human bronchial epithelial cells secrete a range of inflammatory markers, including leukemia inhibitory factor, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-1α, IL-1β, IL-6, and IL-8. These markers play a significant role in both local and systemic inflammatory responses [41–43].

Exposure to PM also causes changes in the lymphocyte profile towards an effect and inflammatory phenotype. In mice, chronic exposure to $PM_{2.5}$ caused a transition in lung $CD4^+$ T cells from a Th1 to a Th17 profile. Notably, the proportion of regulatory T cells (Tregs) in the lungs remained low, whereas it increased in the bloodstream and spleen [44]. Exposure of peripheral blood mononuclear cells (PBMCs) from patients with ADs and healthy individuals to PM in the air of Krakow led to the upregulation of Th1 and Th17 cells [45]. This indicates changes in the polarization of $CD4^+$ T cell subsets towards a proinflammatory state. This Th17 polarization is dependent on the aryl hydrocarbon receptor (AhR) [46]. AhR is a transcription factor responsible for regulating the expression of enzymes that metabolize xenobiotics. Additionally, it is activated by persistent organic pollutants, including PM and dioxins. Under stable conditions, AhR resides in the cytosol and translocates to the nucleus when bound to a ligand. It interacts with xenobiotic responsive elements in target gene promoters, controlling their transcription. AhR's interactions with other transcription factors, some involved in the immune system, influence gene expression [47]. The AhR pathway plays a role in inflammatory processes and adaptive immune responses, influencing the equilibrium between effector and Tregs, thus contributing to the development of ADs [20]. Collagen-induced arthritis and the Th1/Th17 balance depend on the presence of AhR [48].

Another mechanism at play involves the antigen-presenting cell (APC) maturation through oxidative stress [49,50], providing them with the co-stimulatory molecules necessary for T lymphocyte activation. Supporting this, Castañeda et al. [51], demonstrated that PM enhances dendritic cell (DCs) activation, steering the differentiation of naïve T cells toward a Th17-like phenotype in both *in vitro* and *in vivo*. PM can act as adjuvants, stimulating the development of active immune responses against antigens. Mouse models exposed to PM exhibit an elevated production of antigen-specific cytokines and immunoglobulins [52–54]. Consequently, exposure to air pollution induces oxidative stress in the respiratory pathways, an increase in proinflammatory cytokines, and the maturation of resident DCs that migrate to local lymph nodes [55]. These activated DCs present autoantigens, triggering an autoimmune response.

Numerous studies have emphasized the transcriptional effects after exposure to PM. Vrijens et al. [56], demonstrated alterations in gene expression and activated pathways following $PM_{2.5}$ and PM_{10} exposure in healthy individuals. Investigations on human bronchial epithelial cells exposed to PM during distinct seasons revealed variations in the transcriptome profile [57]. Huang et al. [58], reported genome-wide alterations in gene expression and DNA methylation patterns in bronchial epithelial cells after exposure to $PM_{2.5}$. Tsai et al. [59], observed that PM induces inflammatory responses in RA fibroblast-like synoviocytes, identifying microRNA-137 as a mediator in PM-induced inflammatory pathways. *In vivo* findings in PM-exposed rats demonstrated that activation of MAPK pathways, increased expressions of IL-6 and COX-II through the negative regulation of hsa-miRNA-137, exacerbating RA. A study involving PBMCs from healthy donors and patients with atherosclerosis, RA, and multiple sclerosis exposed to air particles from Krakow revealed increased gene expression associated with chemokine and cytokine signaling, cell adhesion, apoptosis regulation, TLR signaling, cellular metabolism, and Th1 and Th2 cell differentiation [60]. The regulated genes suggest potentially implicated biological mechanisms in the development and progression of ADs.

The intricate interplay between PM and DNA methylation encompasses diverse pathways. PM-generated ROS initiate the oxidation of 5-hydroxy-mC, culminating in consequential DNA methylation. Simultaneously, the presence of ROS triggers interactions between histone deacetylase and DNA methyltransferases (DNMTs)-1, instigating modifications in DNA methylation levels [61]. Furthermore, PM disrupts the normal function of DNMTs binding with DNA and inducing hypomethylation of CpG cytosine residues, thereby perturbing the delicate machinery of DNA methylation [62]. Hypomethylated regions of IFN-regulated genes in naïve $CD4^+$ T cells, B cells and monocytes from SLE patients may be epigenetically poised for rapid induction upon stimulation by air pollution [63]. In a study by Lanata et al. [64], significant hypomethylation associated with a single gene, *UBE2U*, was observed at three sites in SLE patients residing near a major highway. However, another study, which specifically assessed the association between $PM_{2.5}$ levels and DNA methylation in a cohort of SLE patients, revealed hypomethylation in various genes, including *TTC17*, *SGCB*, *CCDC26*, *AFF3*, *KCP*, *VGLL4*, *CNTN2*, *NPHP4*, and *GAPVD1*. It is noteworthy that no CpG site in *UBE2U* reached statistical significance [65].

Prolonged exposure to PM has the potential to induce systemic inflammation and contribute to the development of ADs [66]. Fine and ultrafine particles can easily penetrate the blood-air barrier and accumulate in tissues, thereby enhancing their potential to exert toxic effects as their size decreases [67]. In NOD mice, an experimental model for SS, exposure to PM resulted in peribronchial lymphocytic infiltrates accompanied by a reduction in alveolar space [68]. This suggests that air pollution has the potential to worsen pre-existing lung injuries in individuals with SS. These findings suggest that air pollution may exacerbate pre-existing lung injuries in individuals with ADs, emphasizing the broader impact of prolonged PM exposure on respiratory health and autoimmune conditions.

2.2. Silica

Silica, or silicon oxide, is a naturally occurring compound commonly found in nature as quartz, presenting itself in various forms, including both crystalline and amorphous structures. While silica is ubiquitous and has numerous industrial applications, its impact on human health has garnered significant attention. Continuous exposure to respirable crystalline silica, especially particles smaller than 10 μm, has been linked to various pulmonary pathologies. These include well-known conditions such as silicosis, bronchitis, and an increased risk of developing cancer [69]. Silicosis, in particular, is a progressive and irreversible lung disease caused by the inhalation of crystalline silica dust over an extended period [70].

Moreover, recent research has unveiled another dimension to the health effects of silica exposure. There is accumulating evidence supporting a connection between prolonged exposure to crystalline silica dust in occupational settings and the development of systemic ADs [71]. Occupational settings notorious for silica exposure are often termed "dusty trades," with mining and construction being primary examples. In these environments, materials containing crystalline silica are frequently reduced to dust or small particles, creating an inhalation risk for workers [72]. The implications of silica exposure extend beyond pulmonary issues, raising broader concerns about its potential role in contributing to ADs.

2.2.1. Silica-driven autoimmunity: exploring molecular and cellular mechanisms

When respirable crystalline silica enters the lungs, it initially interacts with macrophages, triggering the activation of diverse cellular and molecular pathways. Through scavenger receptors, macrophages

ingest silica crystals, leading to the release of cytokines such as IL-1β, IFN-γ, TNF-α, transforming growth factor (TGF)-β, macrophage inflammatory proteins (MIP), and monocyte chemoattractant protein (MCP)-1 [73,74]. This process initiates a potent inflammatory response, resulting in lung damage. Moreover, the ingestion of these crystals by macrophages leads to lysosomal dysfunction, with the subsequent release of cathepsin B, prompting macrophage death and the release of ingested silica particles. These silica particles are then phagocytosed again by other macrophages, creating an inflammatory loop and promoting fibrogenesis. Similarly, macrophages derived from human monocytes display impaired efferocytosis, leading to the prolonged presence of apoptotic cells and the subsequent release of intranuclear components. The reduced efferocytosis and the emergence of an M1 phenotype, suggests a potential mechanism contributing to the exacerbation of systemic ADs associated with silica exposure [75,76]. This environment may provide an excess of antigens that are then ingested by activated macrophages or DCs, subsequently migrating to local lymph nodes. Within these lymph nodes, these APC, loaded with apoptotic material, activate T and B cells, thereby inducing an autoimmune response [77]. The body's challenge in eliminating silica from the lungs prolongs this cycle, progressing from an autoimmune response to a systemic AD (Fig. 2).

The exposure to silica in various experimental models has illuminated potential mechanisms underlying autoimmune responses. In a study conducted by Foster et al. [78], wildtype mice, comprising both healthy and lupus-prone strains, along with mice carrying an autoantibody transgene, were subjected to silica exposure. This exposure led to lung damage and elicited autoimmune responses across all strains. Surprisingly, this exposure did not significantly disrupt central B cell tolerance, even in genetically susceptible environments, suggesting that silica may impact alternative checkpoints or require additional interactions for tolerance loss. The unique autoantibody transgene system revealed the presence of transgenic B cells and antibodies in various tissues. Furthermore, silica-induced lung injury subtly altered the regulation of autoreactive B cells, potentially modulating B cell anergy, unmasked by exposure to TLR ligands. In New Zealand mixed mice prone to SLE, silica exposure led to a significant increase in serum antinuclear antibodies (ANAs) and anti-histone antibodies. Elevated titers of these autoantibodies may result from silica-induced apoptosis, leading to an excess of apoptotic material presented to the immune system. Additionally, increased mortality rates were observed, along with indicators such as proteinuria, circulating immune complexes, pulmonary fibrosis, and complement C3 deposition within the kidney [79]. The immune activation observed in this experimental model coincided with an elevation in B1a B and $CD4^+$ T cells in the superficial cervical lymph nodes, an increase in TNF-α levels in BALF, and a decrease in Tregs, favoring a profile of auto-reactivity [80]. Following exposure to crystalline silica in the BALF of NZBWF1 mice, Rajasinghe et al. [81], observed a strong IgG and IgM autoantibody response against lupus-associated autoantigens, including DNA, histones, ribonucleoprotein (RNP), Smith antigen, Ro/SSA, La/SSB, and complement. Moreover, crystalline silica induced the production of autoantibodies targeting autoantigens associated with various autoimmune conditions. These conditions include RA (collagen II, fibrinogen IV, fibrinogen S, fibronectin, and vimentin), SS (α-fodrin), SSc (topoisomerase I), vasculitis (MPO and PR3) and myositis (Mi-2, TIF1-γ, and MDA-5). Consequently, exposure to sodium silicate resulted in heightened levels of serum ANAs and anti-RNP antibodies in Brown Norway rats [82]. Another way in which autoantigens can be released, thereby promoting an autoantibody response, is through the recognition of charged molecular silica particles by neutrophils, triggering the process of NETosis [83].

Exposure to crystalline silica in lupus-prone NZBWF1 mice induced robust inflammatory responses in the lungs, leading to the formation of ectopic lymphoid tissue. Elevated levels of autoantibodies and proinflammatory cytokines, including MCP-1, TNF-α, and IL-6, were observed

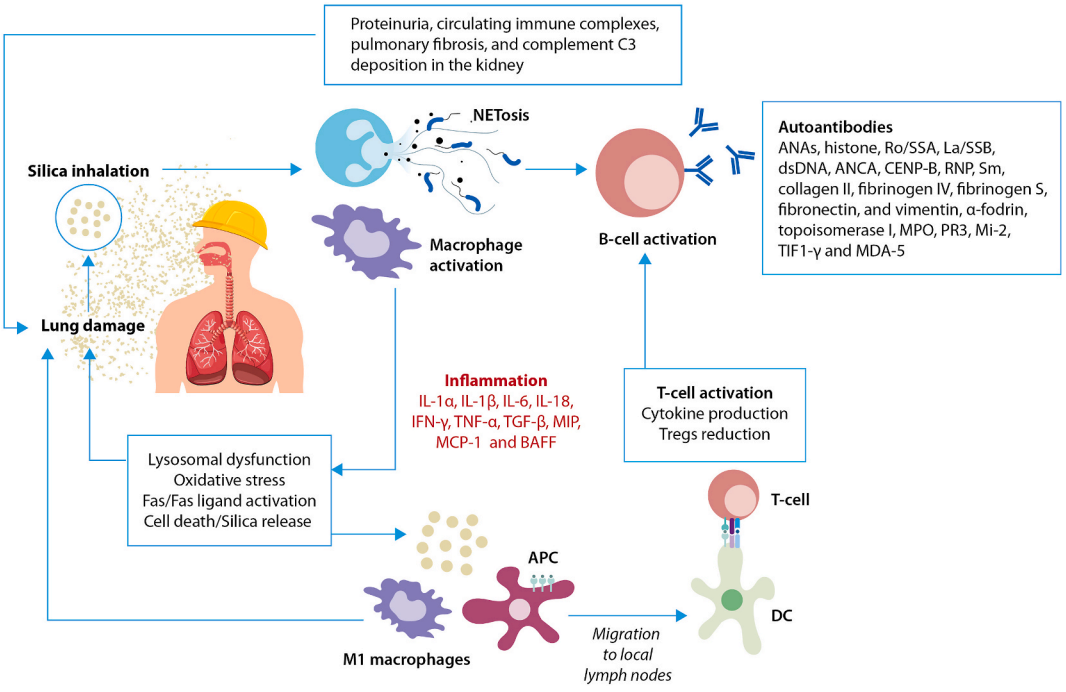

Fig. 2. Impact of Silica Exposure on the Immune Response. Silica induces inflammatory response and lung damage upon phagocytosis by macrophages. Lysosomal dysfunction, oxidative stress, and inflammation contribute to macrophage death, initiating an inflammatory and fibrogenic cycle. This environment promotes antigen presentation in lymph nodes, triggering an autoimmune response. Difficulty in silica elimination prolongs the cycle, progressing towards a systemic AD. **Abbreviations:** ANAs: Anti-nuclear antibodies, ANCA: Anti-neutrophil cytoplasmic antibodies, APC: Antigen-presenting cells, BAFF: B cell activation factor, CENP-B: Centromere protein B, DC: Dendritic cell, ds-DNA: Double stranded DNA, IFN: Interferon, IL: Interleukin, MCP: Monocyte chemoattractant protein, MDA-5: Melanoma differentiation-associated protein 5, MIP: Macrophage Inflammatory proteins, MPO: Myeloperoxidase, PR3: Proteinase 3, RNP: Ribonucleoproteins, Sm: Smith antigen, TGF: Transforming growth factor, TIF-1: Transcriptional intermediary factor 1, TNF: Tumor necrosis factor, Tregs: Regulatory T cells.

in both plasma and BALF [84]. This suggests a close correlation between pulmonary inflammation, ectopic lymphoid neogenesis, and systemic autoimmune responses. Similarly, in a study by Chauhan et al. [85], elevated secretion of IL-1α, IL-1β, IL-6, IL-18, TNF-α, MCP-1, and B cell activation factor (BAFF) was observed in NZBWF1 mice after crystalline silica exposure.

Epidemiological studies have established associations between ADs such as RA, SSc, SLE, and vasculitis/nephritis with anti-neutrophil cytoplasmic antibodies (ANCA) and silica exposure (Table 1). Specifically, silica exposure is associated with an increased risk of these conditions, affecting disease onset, severity, and patient outcomes. In the case of SSc, silica exposure is linked to earlier disease onset, greater severity, and higher mortality rates. For RA, silica exposure is correlated with a higher risk of disease development and elevated autoantibody levels, particularly in ACPA-positive RA. Regarding SLE, silica exposure is associated with an increased risk, especially among those with prolonged industrial exposure.

Prolonged exposure to crystalline silica leads to silicosis, marked by persistent lung inflammation and fibrosis. Individuals diagnosed with silicosis are prone to developing autoimmune conditions characterized by a prominent humoral immune component [72]. Silica exposure combined with smoking in men is associated with a higher risk of developing ACPA-positive RA [86]. Silicosis patients test positive for autoantibodies like ANA, SS-A, CENP-B, and even autoantibodies against molecules associated with apoptosis such as Fas and caspase-8 [87]. Brilland et al. [88], demonstrated that exposure to crystalline silica is associated with notable alterations in the T cell compartment. Specifically, the researchers observed a reduction in the frequency of Tregs, an elevation in the activation status of T cells, and a breakdown in tolerance against autoantigens. Furthermore, individuals exposed to crystalline silica displayed an increased detection of serum autoantibodies, offering additional support for early changes in the T cell compartment before the onset of silicosis or ADs.

2.3. TCDD

2,3,7,8-Tetrachlorodibenzodioxin is a highly toxic organic chemical compound, a member of the dioxin family. Identified as TCDD, it is generated as a byproduct in diverse chemical activities and industrial processes involving chlorophenols and other chlorinated compounds, such as herbicide and bactericide production (e.g., hexachlorophene), as well as the combustion of chlorinated organic compounds.

The persistence of TCDD in the environment raises significant concerns for human health. It is detected in various sources, ranging from meat and fat-rich foods to water and air, commonly associated with environmental contamination and occupational exposure through inhalation, ingestion, or dermal contact. The toxic effects of TCDD are initiated through the formation of the receptor-dioxin complex at the AhR receptor, a pivotal component for the body's detoxification processes. This complex, facilitated by a translocating protein, translocates to cellular DNA, activating genes related to biotransformation enzymes and cell growth/division. If dioxin remains bound, continuous enzyme production ensues. Although a small amount of dioxin undergoes metabolism and elimination, the majority accumulates in body fat [89]. Adverse health effects linked to TCDD exposure encompass dermal toxicity, immunotoxicity, and reproductive consequences (teratogenicity, endocrine disruption, and potential carcinogenic effects). Recognizable signs of severe acute poisoning include chloracne, porphyria, transient hepatotoxicity, as well as peripheral and central neurotoxicity. The estimated half-life of TCDD in humans ranges from 6 to 10 years [90].

2.3.1. TCDD: influence on autoimmune mechanisms

In recent studies investigating the impact of TCDD exposure on various immune-related conditions, significant findings have emerged, shedding light on the intricate relationship between TCDD, inflammatory pathways, and ADs such as RA and SLE.

In a study conducted by Kobayashi et al. [91], the stimulation of RA synoviocytes with TCDD resulted in an increase in the expression of inflammatory cytokines, including IL-1β, IL-6, and IL-8, mediated through the activation of the AhR. This regulatory effect involved two crucial signaling cascades, namely the NFκB and ERK pathways. Furthermore, investigations in Vietnamese individuals with dioxin exposure revealed a positive correlation between elevated dioxin levels and the expression of AhR, IL-1β, TNF-α, and IL-6. The higher incidence of RA in this exposed group compared to the general Vietnamese population, suggests a potential link between dioxin exposure and the development or exacerbation of RA [92]. The correlation identified between AhR expression and inflammatory cytokine levels provides insights into a plausible molecular mechanism through which TCDD exposure may contribute to RA pathophysiology.

Additionally, perinatal exposure to TCDD can lead to more severe and persistent immunosuppression than exposure in adults, as demonstrated in rodent studies. TCDD, crossing the placenta, disrupts the normal maturation of prenatal thymocytes and influences the expression of T-cell receptors and MHC class II molecules in the thymus. During the juvenile stage, mice prenatally exposed to TCDD show an increased presence of peripheral T cells with autoreactive variable beta receptors. These findings suggest that gestational exposure to TCDD may interfere with the typical development of central tolerance in the thymus [93]. Prenatal exposure to TCDD significantly exacerbated the progression of SLE in SNF1 mice, marked by renal immune complex deposition, glomerulonephritis, and mesangial proliferation. Moreover, this exposure had persistent effects on the immune systems, disrupting B cell development and altering immune cell populations. Females displayed reduced IL-10 production, while males exhibited decreased IL-4 production. Notably, both genders showed increased autoreactive T cells, with a distinctive observation that only male mice had elevated levels of anti-dsDNA and cardiolipin autoantibodies [94]. Likewise, the administration of TCDD to time-pregnant high-affinity AhR C57BL/6 mice during gestation revealed significant gender-specific immune dysregulation. Changes were observed in thymic weight, thymocyte percentages, spleen T cell populations, bone marrow B cell progenitors, and an increase in autoantibody titers (dsDNA, ssDNA, and cardiolipin) [95]. Neonatal exposure to TCDD in NFS/sld mice, a model for SS, resulted in autoimmune lesions in the salivary glands and later-phase inflammatory cell infiltrations in various organs. Furthermore, alterations in thymic selection, increased production of Th1 cytokines, and elevated levels of autoantibodies were evident [96]. These findings suggest that prenatal exposure to TCDD induces persistent humoral immune dysregulation and alters cell-mediated responses, potentially elevating the risk of ADs in adulthood.

On the other hand, chronic exposure to TCDD exhibited immunosuppressive effects in a murine model of SLE. Mice exposed to TCDD demonstrated a decreased incidence of albuminuria, diminished levels of anti-DNA antibody and total IgG, as well as alterations in immune parameters, including reduced thymic and splenic weights, shifts in the percentages of specific immune cell populations (such as $CD4^+$ $CD8^+$ thymocytes and splenic $CD4^+$ T cells), an increased percentage of splenic B220+ IgM + B cells, and elevated serum IFN-γ concentration when compared to the control group [97]. Similarly, in Dutch workers occupationally exposed to herbicides and chlorophenoxy contaminants, including TCDD, significant decreases in fractalkine, TGF-α, and fibroblast growth factor 2 were observed, suggesting that exposure to TCDD can suppress the immune system, and alterations in chemokine- and growth factor-dependent pathways could contribute to TCDD toxicity and associated health effects [98]. To further affirm this immunosuppressive effect, it has been demonstrated that TCDD induces the generation of Tregs via the AhR, thereby preventing autoimmune responses in various models, including graft-versus-host response [99], experimental autoimmune encephalitis [100], and Type 1 diabetes in NOD mice [101].

Table 1
Epidemiological evidence demonstrating the association between air pollution and autoimmune diseases.

Disease	Air pollution	Population studied	Result/immune alteration	References
Autoimmune rheumatic diseases	$PM_{2.5}$	Population of Canada (n = 6 million).	Significant association between the incidence of ADs and $PM_{2.5.}$	[103]
Autoimmune rheumatic diseases	$PM_{2.5}$	Population of Canada.	Exposure to $PM_{2.5}$ may be associated with an increased risk of systemic ADs, including SLE, SSc, SS, dermatopolymyositis, and undifferentiated connective tissue disease.	[104]
CTD include RA, SLE, SSc and dermatomyositis	Silica	Patients from France (n = 764).	SSc was significantly more prevalent in the Silica-associated CTD group. Silica-associated CTD was characterized by the frequency of radiological pulmonary fibrosis, altered lung function tests, secondary SS, and ANAs.	[105]
CTD include RA, SLE, SSc, and vasculitis	Silica	Cases of silicosis from the United States (N = 790).	Individuals diagnosed with silicosis have a heightened risk, ranging from two to eight times more likely, of developing RA and SLE. Notably, there is a substantially increased risk of 24 times for the occurrence of SSc and ANCA-associated vasculitis in these individuals.	[106]
SLE	$PM_{2.5}$	Patients from Chile (n = 4062).	The acute increase in air pollution raises the risk of hospitalization with a primary diagnosis of SLE.	[107]
SLE	$PM_{2.5}$	Patients from Brazil (n = 32).	There was no statistical association between PM levels and the activity of SLE.	[108]
SLE	$PM_{2.5}$	Patients from China (n = 546).	Elevated levels of $PM_{2.5}$ are associated with hospital admissions for SLE as well as the risk of relapse.	[109]
SLE	$PM_{2.5}$	Patients from China (n = 8552).	$PM_{2.5}$ is a risk factor for lupus nephritis within one month after exposure.	[110]
SLE	$PM_{2.5}$	Patients from Taiwan (n = 1292).	$PM_{2.5}$ is associated with an increased risk of SLE.	[111]
SLE	$PM_{2.5}$	Patients from the United States (n = 271).	Differential methylation signature in SLE patients with higher exposure to $PM_{2.5}$.	[65]
SLE	PM_{10}	Patients from Brazil (n = 22).	PM_{10} is a risk factor for the activity of juvenile-onset SLE (SLEDAI-2K score >8) approximately 2 weeks after exposure.	[112]
SLE	Silica	SLE patients (n = 265) and healthy individuals (n = 355) from the United States.	Patients with SLE have a history of medium to high silica exposure in agriculture or commerce compared to controls.	[113]
SLE	Silica	SLE patients (n = 95) and healthy individuals (n = 191) from the United States.	Exposure to silica in various industrial occupations in urban settings is linked to an elevated risk of SLE. Prolonged exposure to silica dust is associated with higher risks.	[114]
SLE	Silica	SLE patients (n = 258) and healthy individuals (n = 263) from Canada.	Exposure to silica was associated with an increased risk of SLE, especially in those who never smoked.	[115]
RA	$PM_{2.5}$	Individuals from Taiwan's National Health Insurance system (N = 244,413).	Higher risk of RA in participants exposed to $PM_{2.5}$.	[116]
RA	$PM_{2.5}$	Individuals from South Korea (n = 230,034).	The incidence of RA was positively associated with the increase in $PM_{2.5}$, but not with coarse particles.	[117]
RA	$PM_{2.5}$	Patients from the United States (n = 557).	Exposure to $PM_{2.5}$ is linked to elevated concentrations of ACPA.	[118]
RA	PM	First-degree relatives of a patient with RA from the United States (n = 1767).	The autoantibodies related to RA, as well as sensitive or inflamed joints, are not linked to environmental PM concentrations.	[119]
RA	Silica	Patients from Sweden (n = 31,139).	The study reveals a statistically significant elevation in odds ratios for both seropositive and seronegative RA in men with silica dust exposure.	[120]
RA	Silica	Workers exposed to silica from Sweden (n = 2551).	Workers in foundries exposed to silica encountered a 57 % increase in the likelihood of developing RA. This heightened risk was more pronounced among individuals with prolonged exposure, advanced age, and higher levels of dust exposure during their occupational activities.	[121]
RA	Silica	RA patients (n = 11,285) and healthy individuals (n = 115,249) from Sweden.	Male workers exposed to silica face an increased risk of RA, with seropositive RA rising in correlation with the number of years exposed to silica.	[122]
RA	Silica	Incident cases of RA (n = 577) and controls (n = 659) from Sweden.	Subjects exposed to silica have a moderately higher risk of ACPA-positive RA. Moreover, a significantly increased risk of ACPA-positive RA was observed among current smokers exposed to silica, suggesting an interaction between these exposures.	[86]
RA	Silica derived from hard rock	Miners from Colorado, New Mexico, and Utah (n = 1988).	Workers in hard rock and other underground and surface mining occupations exhibited a three to fourfold elevated risk of developing RA.	[123]
RA	Silica	Workers exposed to silica from Korea (n = 149,948).	More workers exposed to silica without a diagnosis of pneumoconiosis were hospitalized for RA than the general population.	[124]
RA	Silica	Patients with RA and the general population of France.	Women with RA exhibit elevated levels of silica exposure, primarily stemming from cleaning and dusty laundry tasks.	[125]
RA	Dioxins	Individuals exposed (n = 60) and non-exposed (n = 20) from Vietnam.	A significantly higher incidence RA was observed in the exposed group, in contrast to the general Vietnamese population.	[92]
RA and SSc	Silica	General Population (n = 2911) and patients with RA (n = 97) and SSc (n = 100) from France.	In both RA and SSc patients, as well as the control group, the significant lifetime exposure gap to silica was primarily attributed to occupational exposure. Moreover, within both diseases, men consistently exhibited higher exposure scores than women.	[126]
SS	PM	Patients from Argentina (n = 30).	Patients with SS showed a significant association between high levels of air pollution and ocular surface diseases, tear breakup time, vital staining, and impression cytology.	[127]
SS	$PM_{2.5}$ and PM_{10}	Patients from China (n = 1119).	Exposure to $PM_{2.5}$ and PM_{10} was significantly associated with an increased risk of hospitalizations for SS.	[128]
SSc	$PM_{2.5}$	Patients from Thailand (n = 2094).	The exposure to $PM_{2.5}$ increased the risk of overall mortality, as well as death due to pneumonia, pulmonary fibrosis, cardiac involvement, renal impairment, and cancer among patients with SSc.	[129]

(*continued on next page*)

Table 1 (*continued*)

Disease	Air pollution	Population studied	Result/immune alteration	References
SSc	$PM_{2.5}$ and PM_{10}	Patients from Italy (n = 87).	PM_{10} and $PM_{2.5}$ significantly worsened the severity of the Raynaud phenomenon in patients with SSc.	[130]
SSc	$PM_{2.5}$ and PM_{10}	Patients from France (n = 181).	No association was found between exposure to PM and the severity of the disease at the time of diagnosis.	[131]
SSc	Silica	Patients from Canada (n = 1439).	Exposure to silica was associated with an earlier age at diagnosis and increased severity and mortality of the disease.	[132]
SSc	Silica	Patients from Australia (n = 1670).	The highest percentage of silica exposure was identified in males. These patients were more inclined to manifest specific clinical symptoms, as well as the Scl-70 antibody, which is associated with a poorer prognosis.	[133]
SSc	Silica	Patients from Australia (n = 100).	In patients with SSc, the existence of mediastinal and hilar thoracic lymphadenopathy in high-resolution computed tomography was linked to silica exposure and significantly correlated with a more severe progression of interstitial lung disease.	[134]
SSc	Silica	SSc patients (n = 160) and healthy individuals (n = 83) from Australia.	Silica exposure is a determinant factor in male SSc, exhibiting a prolonged latency and clinical features indistinguishable from idiopathic disease.	[135]
SSc	Silica	SSc patients (n = 80) and healthy individuals (n = 50) from Italy.	Occupational exposure to silica dust was documented in a significant proportion of SSc patients. Micro and nanoparticles of silica were detected in the serum of all exposed patients, with significantly higher silicon levels in SSc patients compared to controls. Furthermore, higher silicon levels were observed in patients with occupational exposure, diffuse cutaneous SSc, myositis, and/or pulmonary fibrosis.	[136]

Abbreviations: ACPA: anti-citrullinated protein antibody, ADs: Autoimmune diseases, ANAs: antinuclear antibodies, CTD: connective tissue disorders, PM: particulate matter, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000, SS: Sjögren's syndrome, SSc: Systemic Sclerosis, TCDD: 2,3,7,8-tetrachlorodibenzo-p-dioxin.

In the midst of an expanding body of research that unveils the complex interconnections between exposure to TCDD, inflammatory pathways, and ADs such as RA and SLE, the investigation by Inoue et al. [102], explores a distinctive dimension. Their exploration centers on the capacity of the AhR, activated by TCDD, to trigger the reactivation of the Epstein-Barr virus (EBV) in individuals affected by primary SS. Through meticulous analyses of saliva samples, the study reveals how TCDD amplifies the transcription of the *BZLF1* gene, orchestrating the transition from latent to lytic EBV infection. These findings not only provide fresh perspectives on the physiological effects of dioxins but also contribute to advancing our comprehension of the AhR-dependent pathogenesis underlying ADs.

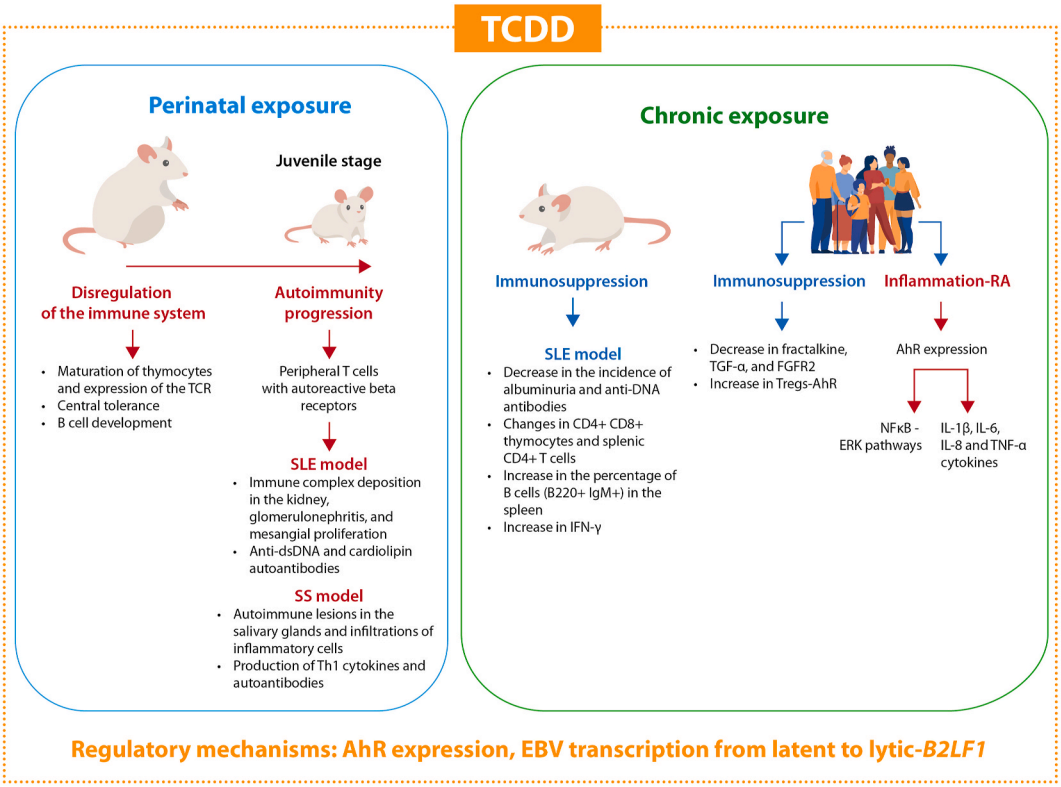

Fig. 3. Timeline and Impact of TCDD on Autoimmune Diseases. The timeline includes the stimulation of inflammatory pathways, perinatal influences, contrasting roles in the immune system, and the unique dimension of EBV reactivation. The intricate balance between pro-inflammatory and immunosuppressive effects highlights the complexity of TCDD's impact on autoimmunity.
Abbreviations: AhR: Aryl hydrocarbon receptor, EBV: Epstein-Barr virus, ERK: Extracellular signal-regulated kinase, FGFR2: Fibroblast growth factor receptor 2, IFN: Interferon, IL: Interleukin, NFκB: Nuclear factor kappa B, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, SS: Sjögren's syndrome, TCDD: 2,3,7,8-tetrachlorodibenzo-p-dioxin, TCR: T cell receptor, TGF: Transforming growth factor, Th: T helper cells, TNF: Tumor necrosis factor, Tregs: Regulatory T cells.

TCDD exhibits a dual role in the immune system, with proinflammatory effects implicated in AD development, particularly in RA and SLE (Fig. 3). Conversely, chronic exposure to TCDD demonstrates immunosuppressive effects, affecting immune cell populations and promoting Tregs generation. The intricate balance between these contrasting effects suggests that TCDD's impact on autoimmunity is complex and context-dependent. Further research is needed to fully comprehend the mechanisms involved, enabling the development of targeted therapeutic strategies for immune-mediated diseases.

3. Conclusions

The expanding body of research elucidating the intricate relationship between exposure to air pollutants and ADs underscores the multifaceted nature of immune responses within the context of environmental factors. The association between PM exposure and the development of ADs is characterized by a cascade of events, including inflammatory responses, oxidative stress, and epigenetic modifications. Inhalation of respirable crystalline silica initiates autoimmune responses by activating macrophages and releasing cytokines, creating a recurrent inflammatory loop that contributes to fibrogenesis and promotes autoimmunity. Conversely, despite its highly toxic nature, TCDD plays a dual role in the immune system. While it activates inflammatory responses associated with ADs such as RA and SLE, chronic exposure reveals immunosuppressive effects, impacting cellular populations and promoting the generation of regulatory T cells.

Both experimental and epidemiological studies consistently support the link between air pollutant exposure and ADs, emphasizing the imperative need to comprehend these mechanisms to address health risks. These findings not only have critical implications for public health, but also underscore the necessity of environmental regulations to prevent and mitigate the burden of ADs in the population. As our understanding of these complex immunological mechanisms increases, it becomes more and more evident that a holistic approach is essential to address the challenges posed by environmental factors in the realm of ADs.

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CRediT authorship contribution statement

Daniel Galeano-Sánchez: Writing – original draft. **Victoria Morales-González:** Writing – original draft. **Diana M. Monsalve:** Writing – original draft. **Carolina Ramırez-Santana:** Writing – review & editing. **Yeny Acosta-Ampudia:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

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Data availability

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

References

[1] I.R. Mackay, Tolerance and autoimmunity, West. J. Med. 174 (2001) 118–123.
[2] M. Mitratza, B. Klijs, A.E. Hak, J.W.P.F. Kardaun, A.E. Kunst, Systemic autoimmune disease as a cause of death: mortality burden and comorbidities, Rheumatology 60 (2021) 1321–1330, https://doi.org/10.1093/rheumatology/keaa537.
[3] G.S. Cooper, M.L.K. Bynum, E.C. Somers, Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases, J. Autoimmun. 33 (2009) 197–207, https://doi.org/10.1016/j.jaut.2009.09.008.
[4] E. Ortona, M. Pierdominici, A. Maselli, C. Veroni, F. Aloisi, Y. Shoenfeld, Sex-based differences in autoimmune diseases, Ann. Ist. Super Sanita 52 (2016) 205–212, https://doi.org/10.4415/ANN_16_02_12.
[5] M. Fridkis-Hareli, Immunogenetic mechanisms for the coexistence of organ-specific and systemic autoimmune diseases, J. Autoimmune Dis. 5 (2008) 1, https://doi.org/10.1186/1740-2557-5-1.
[6] J.-M. Anaya, The autoimmune tautology, Arthritis Res. Ther. 12 (2010) 147, https://doi.org/10.1186/ar3175.
[7] J.-M. Anaya, C. Ramirez-Santana, M.A. Alzate, N. Molano-Gonzalez, A. Rojas-Villarraga, The autoimmune ecology, Front. Immunol. 7 (2016) 139, https://doi.org/10.3389/fimmu.2016.00139.
[8] J.-M. Anaya, L. Gomez, J. Castiblanco, Is there a common genetic basis for autoimmune diseases? Clin. Dev. Immunol. 13 (2006) 185–195, https://doi.org/10.1080/17402520600876762.
[9] D.P. Bogdanos, D.S. Smyk, E.I. Rigopoulou, M.G. Mytilinaiou, M.A. Heneghan, C. Selmi, M. Eric Gershwin, Twin studies in autoimmune disease: genetics, gender and environment, J. Autoimmun. 38 (2012) J156–J169, https://doi.org/10.1016/j.jaut.2011.11.003.
[10] J.-M. Anaya, P. Restrepo-Jimenez, C. Ramirez-Santana, The autoimmune ecology: an update, Curr. Opin. Rheumatol. (2018), https://doi.org/10.1097/BOR.0000000000000498.
[11] S.S. Babatola, Global burden of diseases attributable to air pollution, J. Public Health Africa 9 (2018) 813, https://doi.org/10.4081/jphia.2018.813.
[12] M. Franchini, P.M. Mannucci, Air pollution and cardiovascular disease, Thromb. Res. 129 (2012) 230–234, https://doi.org/10.1016/j.thromres.2011.10.030.
[13] A. Gawda, G. Majka, B. Nowak, J. Marcinkiewicz, Air pollution, oxidative stress, and exacerbation of autoimmune diseases, Cent. J. Immunol. 42 (2017) 305–312, https://doi.org/10.5114/ceji.2017.70975.
[14] A.J. Cohen, M. Brauer, R. Burnett, H.R. Anderson, J. Frostad, K. Estep, K. Balakrishnan, B. Brunekreef, L. Dandona, R. Dandona, V. Feigin, G. Freedman, B. Hubbell, A. Jobling, H. Kan, L. Knibbs, Y. Liu, R. Martin, L. Morawska, C. A. Pope, H. Shin, K. Straif, G. Shaddick, M. Thomas, R. van Dingenen, A. van Donkelaar, T. Vos, C.J.L. Murray, M.H. Forouzanfar, Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015, Lancet (London, England) 389 (2017) 1907–1918, https://doi.org/10.1016/S0140-6736(17)30505-6.
[15] J. Lelieveld, A. Haines, R. Burnett, C. Tonne, K. Klingmüller, T. Münzel, A. Pozzer, Air pollution deaths attributable to fossil fuels: observational and modelling study, BMJ 383 (2023) e077784, https://doi.org/10.1136/bmj-2023-077784.
[16] P.L. Kinney, Climate change, air quality, and human health, Am. J. Prev. Med. 35 (2008) 459–467, https://doi.org/10.1016/j.amepre.2008.08.025.
[17] I. Manisalidis, E. Stavropoulou, A. Stavropoulos, E. Bezirtzoglou, Environmental and health impacts of air pollution: a review, Front. Public Heal. 8 (2020) 14, https://doi.org/10.3389/fpubh.2020.00014.
[18] K.-H. Kim, E. Kabir, S. Kabir, A review on the human health impact of airborne particulate matter, Environ. Int. 74 (2015) 136–143, https://doi.org/10.1016/j.envint.2014.10.005.
[19] X. Niu, Y. Wang, S.S.H. Ho, H.-C. Chuang, J. Sun, L. Qu, G. Wang, K.F. Ho, Characterization of organic aerosols in PM(1) and their cytotoxicity in an urban roadside area in Hong Kong, Chemosphere 263 (2021) 128239, https://doi.org/10.1016/j.chemosphere.2020.128239.
[20] C.-N. Zhao, Z. Xu, G.-C. Wu, Y.-M. Mao, L.-N. Liu, Qian-Wu, Y.-L. Dan, S.-S. Tao, Q. Zhang, N.B. Sam, Y.-G. Fan, Y.-F. Zou, D.-Q. Ye, H.-F. Pan, Emerging role of air pollution in autoimmune diseases, Autoimmun. Rev. 18 (2019) 607–614, https://doi.org/10.1016/j.autrev.2018.12.010.
[21] R.-D. Zhang, C. Chen, P. Wang, Y. Fang, L.-Q. Jiang, X. Fang, Y. Zhao, J. Ni, D.-G. Wang, H.-F. Pan, Air pollution exposure and auto-inflammatory and autoimmune diseases of the musculoskeletal system: a review of epidemiologic and mechanistic evidence, Environ. Geochem. Health 45 (2023) 4087–4105, https://doi.org/10.1007/s10653-023-01495-x.
[22] M.P. Combs, R.P. Dickson, Turning the lungs inside out: the intersecting microbiomes of the lungs and the built environment, Am. J. Respir. Crit. Care Med. 202 (2020) 1618–1620, https://doi.org/10.1164/rccm.202007-2973ED.

[23] K.-L. Huang, S.-Y. Liu, C.C.K. Chou, Y.-H. Lee, T.-J. Cheng, The effect of size-segregated ambient particulate matter on Th1/Th2-like immune responses in mice, PLoS One 12 (2017) e0173158, https://doi.org/10.1371/journal.pone.0173158.
[24] T. Miyake, D. Wang, H. Matsuoka, K. Morita, H. Yasuda, K. Yatera, T. Kanazawa, Y. Yoshida, Endocytosis of particulate matter induces cytokine production by neutrophil via Toll-like receptor 4, Int. Immunopharmacol. 57 (2018) 190–199, https://doi.org/10.1016/j.intimp.2018.02.020.
[25] A. Valderrama, P. Ortiz-Hernández, J.M. Agraz-Cibrián, J.H. Tabares-Guevara, D. M. Gómez, J.F. Zambrano-Zaragoza, N.A. Taborda, J.C. Hernandez, Particulate matter (PM(10)) induces in vitro activation of human neutrophils, and lung histopathological alterations in a mouse model, Sci. Rep. 12 (2022) 7581, https://doi.org/10.1038/s41598-022-11553-6.
[26] A. Gawda, G. Majka, B. Nowak, M. Śróttek, M. Walczewska, J. Marcinkiewicz, Air particulate matter SRM 1648a primes macrophages to hyperinflammatory response after LPS stimulation, Inflamm. Res. Off. J. Eur. Histamine Res. Soc. ... [et Al.] 67 (2018) 765–776, https://doi.org/10.1007/s00011-018-1165-4.
[27] M.G. Netea, J. Quintin, J.W.M. van der Meer, Trained immunity: a memory for innate host defense, Cell Host Microbe 9 (2011) 355–361, https://doi.org/10.1016/j.chom.2011.04.006.
[28] C.A. Pope, A. Bhatnagar, J.P. McCracken, W. Abplanalp, D.J. Conklin, T. O'Toole, Exposure to fine particulate air pollution is associated with endothelial injury and systemic inflammation, Circ. Res. 119 (2016) 1204–1214, https://doi.org/10.1161/CIRCRESAHA.116.309279.
[29] M.S. Peixoto, M.F. de Oliveira Galvão, S.R. Batistuzzo de Medeiros, Cell death pathways of particulate matter toxicity, Chemosphere 188 (2017) 32–48, https://doi.org/10.1016/j.chemosphere.2017.08.076.
[30] M.F. Denny, P. Chandaroy, P.D. Killen, R. Caricchio, E.E. Lewis, B.C. Richardson, K.-D. Lee, J. Gavalchin, M.J. Kaplan, Accelerated macrophage apoptosis induces autoantibody formation and organ damage in systemic lupus erythematosus, J. Immunol. 176 (2006) 2095–2104, https://doi.org/10.4049/jimmunol.176.4.2095.
[31] M.A. Stark, Y. Huo, T.L. Burcin, M.A. Morris, T.S. Olson, K. Ley, Phagocytosis of apoptotic neutrophils regulates granulopoiesis via IL-23 and IL-17, Immunity 22 (2005) 285–294, https://doi.org/10.1016/j.immuni.2005.01.011.
[32] A. Manda-Handzlik, W. Bystrzycka, A. Cieloch, E. Glodkowska-Mrowka, E. Jankowska-Steifer, E. Heropolitanska-Pliszka, A. Skrobot, A. Muchowicz, O. Ciepiela, M. Wachowska, U. Demkow, Nitric oxide and peroxynitrite trigger and enhance release of neutrophil extracellular traps, Cell. Mol. Life Sci. 77 (2020) 3059–3075, https://doi.org/10.1007/s00018-019-03331-x.
[33] K.H. Lee, A. Kronbichler, D.D.-Y. Park, Y. Park, H. Moon, H. Kim, J.H. Choi, Y. Choi, S. Shim, I.S. Lyu, B.H. Yun, Y. Han, D. Lee, S.Y. Lee, B.H. Yoo, K.H. Lee, T. L. Kim, H. Kim, J.S. Shim, W. Nam, H. So, S. Choi, S. Lee, J. Il Shin, Neutrophil extracellular traps (NETs) in autoimmune diseases: a comprehensive review, Autoimmun. Rev. 16 (2017) 1160–1173, https://doi.org/10.1016/j.autrev.2017.09.012.
[34] V.L. Souliotis, P.P. Sfikakis, Increased DNA double-strand breaks and enhanced apoptosis in patients with lupus nephritis, Lupus 24 (2015) 804–815, https://doi.org/10.1177/0961203314565413.
[35] V.Y. Yariwake, J.I. Torres, A.R.P. dos Santos, S.C.F. Freitas, K. De Angelis, S.C. L. Farhat, N.O.S. Câmara, M.M. Veras, Chronic exposure to PM2.5 aggravates SLE manifestations in lupus-prone mice, Part. Fibre Toxicol. 18 (2021) 15, https://doi.org/10.1186/s12989-021-00407-0.
[36] S. Bernatsky, M. Fournier, C.A. Pineau, A.E. Clarke, E. Vinet, A. Smargiassi, Associations between ambient fine particulate levels and disease activity in patients with systemic lupus erythematosus (SLE), Environ. Health Perspect. 119 (2011) 45–49, https://doi.org/10.1289/ehp.1002123.
[37] B. Nowak, G. Majka, M. Śróttek, A. Skałkowska, J. Marcinkiewicz, The effect of inhaled air particulate matter SRM 1648a on the development of mild collagen-induced arthritis in DBA/J mice, Arch. Immunol. Ther. Exp. 70 (2022) 17, https://doi.org/10.1007/s00005-022-00654-9.
[38] J. Shoenfelt, R.J. Mitkus, R. Zeisler, R.O. Spatz, J. Powell, M.J. Fenton, K. A. Squibb, A.E. Medvedev, Involvement of TLR2 and TLR4 in inflammatory immune responses induced by fine and coarse ambient air particulate matter, J. Leukoc. Biol. 86 (2009) 303–312, https://doi.org/10.1189/jlb.1008587.
[39] Y. Le, X. Hu, J. Zhu, C. Wang, Z. Yang, D. Lu, Ambient fine particulate matter induces inflammatory responses of vascular endothelial cells through activating TLR-mediated pathway, Toxicol. Ind. Health 35 (2019) 670–678, https://doi.org/10.1177/0748233719871778.
[40] Y.S. Ryu, K.A. Kang, M.J. Piao, M.J. Ahn, J.M. Yi, Y.-M. Hyun, S.H. Kim, M.K. Ko, C.O. Park, J.W. Hyun, Particulate matter induces inflammatory cytokine production via activation of NFκB by TLR5-NOX4-ROS signaling in human skin keratinocyte and mouse skin, Redox Biol. 21 (2019) 101080, https://doi.org/10.1016/j.redox.2018.101080.
[41] S. Mitschik, R. Schierl, D. Nowak, R.A. Jörres, Effects of particulate matter on cytokine production in vitro: a comparative analysis of published studies, Inhal. Toxicol. 20 (2008) 399–414, https://doi.org/10.1080/08958370801903784.
[42] F. He, B. Liao, J. Pu, C. Li, M. Zheng, L. Huang, Y. Zhou, D. Zhao, B. Li, P. Ran, Exposure to ambient particulate matter induced COPD in a rat model and a description of the underlying mechanism, Sci. Rep. 7 (2017) 45666, https://doi.org/10.1038/srep45666.
[43] T. Fujii, S. Hayashi, J.C. Hogg, R. Vincent, S.F. Van Eeden, Particulate matter induces cytokine expression in human bronchial epithelial cells, Am. J. Respir. Cell Mol. Biol. 25 (2001) 265–271, https://doi.org/10.1165/ajrcmb.25.3.4445.
[44] J.A. Deiuliis, T. Kampfrath, J. Zhong, S. Oghumu, A. Maiseyeu, L.C. Chen, Q. Sun, A.R. Satoskar, S. Rajagopalan, Pulmonary T cell activation in response to chronic particulate air pollution, Am. J. Physiol. Lung Cell Mol. Physiol. 302 (2012) L399–L409, https://doi.org/10.1152/ajplung.00261.2011.
[45] A. Gałuszka-Bulaga, K. Węglarczyk, P. Latacz, K. Jodłowska-Cicio, M. Korkosz, J. Pera, A. Słowik, M. Siedlar, J. Baran, Seasonal variations in the concentration of particulate matter in the air of cracow affect the magnitude of CD4+ T cell subsets cytokine production in patients with inflammatory and autoimmune disorders, Atmosphere 13 (2022), https://doi.org/10.3390/atmos13040529.
[46] M. van Voorhis, S. Knopp, W. Julliard, J.H. Fechner, X. Zhang, J.J. Schauer, J. D. Mezrich, Exposure to atmospheric particulate matter enhances Th17 polarization through the aryl hydrocarbon receptor, PLoS One 8 (2013) e82545, https://doi.org/10.1371/journal.pone.0082545.
[47] C. Esser, A. Rannug, B. Stockinger, The aryl hydrocarbon receptor in immunity, Trends Immunol. 30 (2009) 447–454, https://doi.org/10.1016/j.it.2009.06.005.
[48] T. Nakahama, A. Kimura, N.T. Nguyen, I. Chinen, H. Hanieh, K. Nohara, Y. Fujii-Kuriyama, T. Kishimoto, Aryl hydrocarbon receptor deficiency in T cells suppresses the development of collagen-induced arthritis, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 14222–14227, https://doi.org/10.1073/pnas.1111786108.
[49] B. Bleck, D.B. Tse, I. Jaspers, M.A. Curotto de Lafaille, J. Reibman, Diesel exhaust particle-exposed human bronchial epithelial cells induce dendritic cell maturation, J. Immunol. 176 (2006) 7431–7437, https://doi.org/10.4049/jimmunol.176.12.7431.
[50] S. Becker, J. Soukup, Coarse(PM(2.5-10)), fine(PM(2.5)), and ultrafine air pollution particles induce/increase immune costimulatory receptors on human blood-derived monocytes but not on alveolar macrophages, J. Toxicol. Environ. Health A. 66 (2003) 847–859, https://doi.org/10.1080/15287390306381.
[51] A.R. Castañeda, K.E. Pinkerton, K.J. Bein, A. Magaña-Méndez, H.T. Yang, P. Ashwood, C.F.A. Vogel, Ambient particulate matter activates the aryl hydrocarbon receptor in dendritic cells and enhances Th17 polarization, Toxicol. Lett. 292 (2018) 85–96, https://doi.org/10.1016/j.toxlet.2018.04.020.
[52] B. Granum, P.I. Gaarder, E. Groeng, R. Leikvold, E. Namork, M. Lovik, Fine particles of widely different composition have an adjuvant effect on the production of allergen-specific antibodies, Toxicol. Lett. 118 (2001) 171–181, https://doi.org/10.1016/s0378-4274(00)00292-7.
[53] H. Takano, T. Yoshikawa, T. Ichinose, Y. Miyabara, K. Imaoka, M. Sagai, Diesel exhaust particles enhance antigen-induced airway inflammation and local cytokine expression in mice, Am. J. Respir. Crit. Care Med. 156 (1997) 36–42, https://doi.org/10.1164/ajrccm.156.1.9610054.
[54] M. van Zijverden, A. van der Pijl, M. Bol, F.A. van Pinxteren, C. de Haar, A. H. Penninks, H. van Loveren, R. Pieters, Diesel exhaust, carbon black, and silica particles display distinct Th1/Th2 modulating activity, Toxicol. Appl. Pharmacol. 168 (2000) 131–139, https://doi.org/10.1006/taap.2000.9013.
[55] S.A. Ritz, Air pollution as a potential contributor to the "epidemic" of autoimmune disease, Med. Hypotheses 74 (2010) 110–117, https://doi.org/10.1016/j.mehy.2009.07.033.
[56] K. Vrijens, E. Winckelmans, M. Tsamou, W. Baeyens, P. De Boever, D. Jennen, T. M. de Kok, E. Den Hond, W. Lefebvre, M. Plusquin, H. Reynders, G. Schoeters, N. Van Larebeke, C. Vanpoucke, J. Kleinjans, T.S. Nawrot, Sex-specific associations between particulate matter exposure and gene expression in independent discovery and validation cohorts of middle-aged men and women, Environ. Health Perspect. 125 (2017) 660–669, https://doi.org/10.1289/EHP370.
[57] E. Longhin, L. Capasso, C. Battaglia, M.C. Proverbio, C. Cosentino, I. Cifola, E. Mangano, M. Camatini, M. Gualtieri, Integrative transcriptomic and protein analysis of human bronchial BEAS-2B exposed to seasonal urban particulate matter, Environ. Pollut. 209 (2016) 87–98, https://doi.org/10.1016/j.envpol.2015.11.013.
[58] S.K. Huang, P. Tripathi, L.A. Koneva, R.G. Cavalcante, N. Craig, A.M. Scruggs, M. A. Sartor, F. Deng, Y. Chen, Effect of concentration and duration of particulate matter exposure on the transcriptome and DNA methylome of bronchial epithelial cells, Environ. Epigenetics 7 (2021) dvaa022, https://doi.org/10.1093/eep/dvaa022.
[59] M.-H. Tsai, M.-C. Chi, J.-F. Hsu, I.-T. Lee, K.-M. Lin, M.-L. Fang, M.-H. Lee, C.-W. Lee, J.-F. Liu, Urban particulate matter enhances ROS/IL-6/COX-II production by inhibiting MicroRNA-137 in synovial fibroblast of rheumatoid arthritis, Cells 9 (2020), https://doi.org/10.3390/cells9061378.
[60] A. Gałuszka-Bulaga, J. Hajto, M. Borczyk, S. Gołda, M. Piechota, M. Korostyński, M. Rutkowska-Zapała, P. Latacz, Z. Guła, M. Korkosz, J. Pera, A. Słowik, M. Siedlar, J. Baran, Transcriptional response of blood mononuclear cells from patients with inflammatory and autoimmune disorders exposed to "Krakow smog", Cells 11 (2022) https://doi.org/10.3390/cells11162586.
[61] F.J. Rang, J. Boonstra, Causes and consequences of age-related changes in DNA methylation: a role for ROS? Biology 3 (2014) 403–425, https://doi.org/10.3390/biology3020403.
[62] A. Baccarelli, R.O. Wright, V. Bollati, L. Tarantini, A.A. Litonjua, H.H. Suh, A. Zanobetti, D. Sparrow, P.S. Vokonas, J. Schwartz, Rapid DNA methylation changes after exposure to traffic particles, Am. J. Respir. Crit. Care Med. 179 (2009) 572–578, https://doi.org/10.1164/rccm.200807-1097OC.
[63] L. Rasking, C. Roelens, B. Sprangers, B. Thienpont, T.S. Nawrot, K. De Vusser, Lupus, DNA methylation, and air pollution: a malicious triad, Int. J. Environ. Res. Public Health. 19 (2022), https://doi.org/10.3390/ijerph192215050.
[64] C.M. Lanata, J. Nititham, K. Taylor, R. Nayak, L. Barcellos, S.A. Chung, J. Galanter, L.A. Criswell, CE-48 Residential Proximity to Highways, DNA Methylation and Systemic Lupus Erythematosus, 2016.
[65] O. Solomon, C. Lanata, M. Dall'Era, J. Yazdany, P. Katz, L. Trupin, K. Taylor, J. Nititham, B. Rhead, L. Criswell, DNA methylation changes are associated with

particulate matter 2.5 exposure in SLE patients, in: ARTHRITIS Rheumatol, 111 RIVER ST, WILEY, NJ USA, 2019. HOBOKEN 07030-5774.
[66] D.M. Cooper, M. Loxham, Particulate matter and the airway epithelium: the special case of the underground? Eur. Respir. Rev. an Off. J. Eur. Respir. Soc. 28 (2019) https://doi.org/10.1183/16000617.0066-2019.
[67] P. Thangavel, D. Park, Y.-C. Lee, Recent insights into particulate matter (PM (2.5))-mediated toxicity in humans: an overview, Int. J. Environ. Res. Public Health. 19 (2022), https://doi.org/10.3390/ijerph19127511.
[68] S. Ferraro, N. Orona, L. Villalon, P.H.N. Saldiva, D.R. Tasat, A. Berra, Air particulate matter exacerbates lung response on Sjogren's Syndrome animals, Exp. Toxicol. Pathol. 67 (2015) 125–131, https://doi.org/10.1016/j.etp.2014.10.007.
[69] B.T. Mossman, R.E. Glenn, Bioreactivity of the crystalline silica polymorphs, quartz and cristobalite, and implications for occupational exposure limits (OELs), Crit. Rev. Toxicol. 43 (2013) 632–660, https://doi.org/10.3109/10408444.2013.818617.
[70] C.C. Leung, I.T.S. Yu, W. Chen, Silicosis, Lancet (London, England) 379 (2012) 2008–2018, https://doi.org/10.1016/S0140-6736(12)60235-9.
[71] C.G. Parks, K. Conrad, G.S. Cooper, Occupational exposure to crystalline silica and autoimmune disease, Environ. Health Perspect. 107 (Suppl) (1999) 793–802, https://doi.org/10.1289/ehp.99107s5793.
[72] K.M. Pollard, Silica, silicosis, and autoimmunity, Front. Immunol. 7 (2016) 97, https://doi.org/10.3389/fimmu.2016.00097.
[73] Y. Zhao, C. Hao, L. Bao, D. Wang, Y. Li, Y. Qu, M. Ding, A. Zhao, W. Yao, Silica particles disorganize the polarization of pulmonary macrophages in mice, Ecotoxicol. Environ. Saf. 193 (2020) 110364, https://doi.org/10.1016/j.ecoenv.2020.110364.
[74] X. Liu, S. Fang, H. Liu, X. Wang, X. Dai, Q. Yin, T. Yun, W. Wang, Y. Zhang, H. Liao, W. Zhang, H. Yao, J. Chao, Role of human pulmonary fibroblast-derived MCP-1 in cell activation and migration in experimental silicosis, Toxicol. Appl. Pharmacol. 288 (2015) 152–160, https://doi.org/10.1016/j.taap.2015.07.002.
[75] A. Lescoat, A. Ballerie, M. Lelong, Y. Augagneur, C. Morzadec, S. Jouneau, P. Jégo, O. Fardel, L. Vernhet, V. Lecureur, Crystalline silica impairs efferocytosis abilities of human and mouse macrophages: implication for silica-associated systemic sclerosis, Front. Immunol. 11 (2020) 219, https://doi.org/10.3389/fimmu.2020.00219.
[76] M.S. Thibodeau, C. Giardina, D.A. Knecht, J. Helble, A.K. Hubbard, Silica-induced apoptosis in mouse alveolar macrophages is initiated by lysosomal enzyme activity, Toxicol. Sci. 80 (2004) 34–48, https://doi.org/10.1093/toxsci/kfh121.
[77] J.M. Brown, J.C. Pfau, M.A. Pershouse, A. Holian, Silica, apoptosis, and autoimmunity, J. Immunotoxicol. 1 (2005) 177–187, https://doi.org/10.1080/15476910490911922.
[78] M.H. Foster, J.R. Ord, E.J. Zhao, A. Birukova, L. Fee, F.M. Korte, Y.G. Asfaw, V. L. Roggli, A.J. Ghio, R.M. Tighe, A.G. Clark, Silica exposure differentially modulates autoimmunity in lupus strains and autoantibody transgenic mice, Front. Immunol. 10 (2019) 2336, https://doi.org/10.3389/fimmu.2019.02336.
[79] J.M. Brown, A.J. Archer, J.C. Pfau, A. Holian, Silica accelerated systemic autoimmune disease in lupus-prone New Zealand mixed mice, Clin. Exp. Immunol. 131 (2003) 415–421.
[80] J.M. Brown, J.C. Pfau, A. Holian, Immunoglobulin and lymphocyte responses following silica exposure in New Zealand mixed mice, Inhal. Toxicol. 16 (2004) 133–139, https://doi.org/10.1080/08958370490270936.
[81] L.D. Rajasinghe, Q.-Z. Li, C. Zhu, M. Yan, P.S. Chauhan, K.A. Wierenga, M. A. Bates, J.R. Harkema, A.D. Benninghoff, J.J. Pestka, Omega-3 fatty acid intake suppresses induction of diverse autoantibody repertoire by crystalline silica in lupus-prone mice, Autoimmunity 53 (2020) 415–433, https://doi.org/10.1080/08916934.2020.1801651.
[82] S.M. Al-Mogairen, Role of sodium silicate in induction of scleroderma-related autoantibodies in brown Norway rats through oral and subcutaneous administration, Rheumatol. Int. 31 (2011) 611–615, https://doi.org/10.1007/s00296-009-1327-3.
[83] M. Rizzi, F. Carniato, S. Tonello, M. Migliario, M. Invernizzi, V. Rocchetti, L. Marchese, F. Renò, Charged molecular silica trigger in vitro NETosis in human granulocytes via both oxidative and autophagic pathways, Eur. Rev. Med. Pharmacol. Sci. 22 (2018) 7058–7068, https://doi.org/10.26355/eurrev_201810_16178.
[84] M.A. Bates, C. Brandenberger, I. Langohr, K. Kumagai, J.R. Harkema, A. Holian, J. J. Pestka, Silica triggers inflammation and ectopic lymphoid neogenesis in the lungs in parallel with accelerated onset of systemic autoimmunity and glomerulonephritis in the lupus-prone NZBWF1 mouse, PLoS One 10 (2015) e0125481, https://doi.org/10.1371/journal.pone.0125481.
[85] P.S. Chauhan, J.G. Wagner, A.D. Benninghoff, R.P. Lewandowski, O.K. Favor, K. A. Wierenga, K.N. Gilley, E.A. Ross, J.R. Harkema, J.J. Pestka, Rapid induction of pulmonary inflammation, autoimmune gene expression, and ectopic lymphoid neogenesis following acute silica exposure in lupus-prone mice, Front. Immunol. 12 (2021) 635138, https://doi.org/10.3389/fimmu.2021.635138.
[86] P. Stolt, A. Yahya, C. Bengtsson, H. Källberg, J. Rönnelid, I. Lundberg, L. Klareskog, L. Alfredsson, Silica exposure among male current smokers is associated with a high risk of developing ACPA-positive rheumatoid arthritis, Ann. Rheum. Dis. 69 (2010) 1072–1076, https://doi.org/10.1136/ard.2009.114694.
[87] A. Takata-Tomokuni, A. Ueki, M. Shiwa, Y. Isozaki, T. Hatayama, H. Katsuyama, F. Hyodoh, W. Fujimoto, H. Ueki, M. Kusaka, H. Arikuni, T. Otsuki, Detection, epitope-mapping and function of anti-Fas autoantibody in patients with silicosis, Immunology 116 (2005) 21–29, https://doi.org/10.1111/j.1365-2567.2005.02192.x.
[88] B. Brilland, C. Beauvillain, G. Mazurkiewicz, P. Rucay, Y. Roquelaure, J. Tabiasco, E. Vinatier, J. Riou, P. Jeannin, G. Renier, J.-F. Subra, J.-F. Augusto, T cell dysregulation in non-silicotic silica exposed workers: a step toward immune tolerance breakdown, Front. Immunol. 10 (2019) 2743, https://doi.org/10.3389/fimmu.2019.02743.
[89] R. Kapp, in: Second E. Wexler (Ed.), TCDD (2,3,7,8-Tetrachlorodibenzo-P-Dioxin), Elsevier, New York, 2005, pp. 136–139, https://doi.org/10.1016/B0-12-369400-0/00921-2. P.B.T.-E. of T.
[90] D. Pelclová, P. Urban, J. Preiss, E. Lukás, Z. Fenclová, T. Navrátil, Z. Dubská, Z. Senholdová, Adverse health effects in humans exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), Rev. Environ. Health 21 (2006) 119–138, https://doi.org/10.1515/reveh.2006.21.2.119.
[91] S. Kobayashi, H. Okamoto, T. Iwamoto, Y. Toyama, T. Tomatsu, H. Yamanaka, S. Momohara, A role for the aryl hydrocarbon receptor and the dioxin TCDD in rheumatoid arthritis, Rheumatology 47 (2008) 1317–1322, https://doi.org/10.1093/rheumatology/ken259.
[92] C.H. Nguyen, T. Nakahama, T.T. Dang, H.H. Chu, L. Van Hoang, T. Kishimoto, N. T. Nguyen, Expression of aryl hydrocarbon receptor, inflammatory cytokines, and incidence of rheumatoid arthritis in Vietnamese dioxin-exposed people, J. Immunotoxicol. 14 (2017) 196–203, https://doi.org/10.1080/1547691X.2017.1377323.
[93] R.M.J. Gogal, S.D. Holladay, Perinatal TCDD exposure and the adult onset of autoimmune disease, J. Immunotoxicol. 5 (2008) 413–418, https://doi.org/10.1080/10408360802483201.
[94] A. Mustafa, S. Holladay, S. Witonsky, K. Zimmerman, A. Manari, S. Countermarsh, E. Karpuzoglu, R. Gogal, Prenatal TCDD causes persistent modulation of the postnatal immune response, and exacerbates inflammatory disease, in 36-week-old lupus-like autoimmune SNF1 mice, Birth Defects Res. B. Dev. Reprod. Toxicol. 92 (2011) 82–94, https://doi.org/10.1002/bdrb.20285.
[95] A. Mustafa, S.D. Holladay, M. Goff, S.G. Witonsky, R. Kerr, C.M. Reilly, D. P. Sponenberg, R.M.J. Gogal, An enhanced postnatal autoimmune profile in 24 week-old C57BL/6 mice developmentally exposed to TCDD, Toxicol. Appl. Pharmacol. 232 (2008) 51–59, https://doi.org/10.1016/j.taap.2008.04.015.
[96] N. Ishimaru, A. Takagi, M. Kohashi, A. Yamada, R. Arakaki, J. Kanno, Y. Hayashi, Neonatal exposure to low-dose 2,3,7,8-tetrachlorodibenzo-p-dioxin causes autoimmunity due to the disruption of T cell tolerance, J. Immunol. 182 (2009) 6576–6586, https://doi.org/10.4049/jimmunol.0802289.
[97] J. Li, R.W. McMurray, Effects of chronic exposure to DDT and TCDD on disease activity in murine systemic lupus erythematosus, Lupus 18 (2009) 941–949, https://doi.org/10.1177/0961203309104431.
[98] F. Saberi Hosnijeh, D. Boers, L. Portengen, H.B. Bueno-de-Mesquita, D. Heederik, R. Vermeulen, Plasma cytokine concentrations in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), Front. Oncol. 2 (2012) 37, https://doi.org/10.3389/fonc.2012.00037.
[99] D. Rohlman, S. Punj, J. Pennington, S. Bradford, N.I. Kerkvliet, Suppression of acute graft-versus-host response by TCDD is independent of the CTLA-4-IFN-γ-Ido pathway, Toxicol. Sci. 135 (2013) 81–90, https://doi.org/10.1093/toxsci/kft140.
[100] A. McDonald, A. Nicaise, E.R. Sears, A. Bell, E. Kummari, B.L.F. Kaplan, Potential for TCDD to induce regulatory functions in B cells as part of the mechanism for T cell suppression in EAE, Toxicol. Appl. Pharmacol. 454 (2022) 116259, https://doi.org/10.1016/j.taap.2022.116259.
[101] N.I. Kerkvliet, L.B. Steppan, W. Vorachek, S. Oda, D. Farrer, C.P. Wong, D. Pham, D. V Mourich, Activation of aryl hydrocarbon receptor by TCDD prevents diabetes in NOD mice and increases Foxp3+ T cells in pancreatic lymph nodes, Immunotherapy 1 (2009) 539–547, https://doi.org/10.2217/imt.09.24.
[102] H. Inoue, K. Mishima, S. Yamamoto-Yoshida, R. Ushikoshi-Nakayama, Y. Nakagawa, K. Yamamoto, K. Ryo, F. Ide, I. Saito, Aryl hydrocarbon receptor-mediated induction of EBV reactivation as a risk factor for Sjögren's syndrome, J. Immunol. 188 (2012) 4654–4662, https://doi.org/10.4049/jimmunol.1101575.
[103] N. Zhao, A. Smargiassi, S. Jean, P. Gamache, E.-A. Laouan-Sidi, H. Chen, M. S. Goldberg, S. Bernatsky, Long-term exposure to fine particulate matter and ozone and the onset of systemic autoimmune rheumatic diseases: an open cohort study in Quebec, Canada, Arthritis Res. Ther. 24 (2022) 151, https://doi.org/10.1186/s13075-022-02843-5.
[104] S. Bernatsky, A. Smargiassi, C. Barnabe, L.W. Svenson, A. Brand, R. V Martin, M. Hudson, A.E. Clarke, P.R. Fortin, A. van Donkelaar, S. Edworthy, P. Bélisle, L. Joseph, Fine particulate air pollution and systemic autoimmune rheumatic disease in two Canadian provinces, Environ. Res. 146 (2016) 85–91, https://doi.org/10.1016/j.envres.2015.12.021.
[105] A.C. Koeger, T. Lang, D. Alcaix, B. Milleron, S. Rozenberg, P. Chaibi, J. Arnaud, C. Mayaud, J.P. Camus, P. Bourgeois, Silica-associated connective tissue disease. A study of 24 cases, Medicine (Baltim.) 74 (1995) 221–237, https://doi.org/10.1097/00005792-199509000-00001.
[106] A. Makol, M.J. Reilly, K.D. Rosenman, Prevalence of connective tissue disease in silicosis (1985-2006)-a report from the state of Michigan surveillance system for silicosis, Am. J. Ind. Med. 54 (2011) 255–262, https://doi.org/10.1002/ajim.20917.
[107] S. Cakmak, C. Blanco-Vidal, A.O. Lukina, R. Dales, The association between air pollution and hospitalization for patients with systemic lupus erythematosus in Chile: a daily time series analysis, Environ. Res. 192 (2021) 110469, https://doi.org/10.1016/j.envres.2020.110469.
[108] P.H. Blaskievicz, A.M.C. Silva, V. Fernandes, O.B.P. Junior, W. Shimoya-Bittencourt, S.M.B. Ferreira, C.A.L. da Silva, Atmospheric pollution exposure increases disease activity of systemic lupus erythematosus, Int. J. Environ. Res. Public Health. 17 (2020), https://doi.org/10.3390/ijerph17061984.

[109] C.-N. Zhao, Y.-J. Mei, G.-C. Wu, Y.-M. Mao, Q. Wu, Y.-L. Dan, H.-F. Pan, Effect of air pollution on hospital admissions for systemic lupus erythematosus in Bengbu, China: a time series study, Lupus 28 (2019) 1541–1548, https://doi.org/10.1177/0961203319882503.

[110] H. Bai, L. Jiang, T. Li, C. Liu, X. Zuo, Y. Liu, S. Hu, L. Sun, M. Zhang, J. Lin, W. Xiao, Q. Wang, D. Zhao, H. Wu, X. Kong, W. Gao, W. Hou, M. Seong, Y. Zhang, F. Chen, S. Chen, X. Wu, C. Bao, L. Wang, H. Xu, Acute effects of air pollution on lupus nephritis in patients with systemic lupus erythematosus: a multicenter panel study in China, Environ. Res. 195 (2021) 110875, https://doi.org/10.1016/j.envres.2021.110875.

[111] C.-R. Jung, W.-T. Chung, W.-T. Chen, R.-Y. Lee, B.-F. Hwang, Long-term exposure to traffic-related air pollution and systemic lupus erythematosus in Taiwan: a cohort study, Sci. Total Environ. 668 (2019) 342–349, https://doi.org/10.1016/j.scitotenv.2019.03.018.

[112] E.C. Fernandes, C.A. Silva, A.L.F. Braga, A.M.E. Sallum, L.M.A. Campos, S.C. L. Farhat, Exposure to air pollutants and disease activity in juvenile-onset systemic lupus erythematosus patients, Arthritis Care Res. 67 (2015) 1609–1614, https://doi.org/10.1002/acr.22603.

[113] C.G. Parks, G.S. Cooper, L.A. Nylander-French, W.T. Sanderson, J.M. Dement, P. L. Cohen, M.A. Dooley, E.L. Treadwell, E.W. St Clair, G.S. Gilkeson, J.A. Hoppin, D.A. Savitz, Occupational exposure to crystalline silica and risk of systemic lupus erythematosus: a population-based, case-control study in the southeastern United States, Arthritis Rheum. 46 (2002) 1840–1850, https://doi.org/10.1002/art.10368.

[114] A. Finckh, G.S. Cooper, L.B. Chibnik, K.H. Costenbader, J. Watts, H. Pankey, P. A. Fraser, E.W. Karlson, Occupational silica and solvent exposures and risk of systemic lupus erythematosus in urban women, Arthritis Rheum. 54 (2006) 3648–3654, https://doi.org/10.1002/art.22210.

[115] G.S. Cooper, J. Wither, S. Bernatsky, J.O. Claudio, A. Clarke, J.D. Rioux, P. R. Fortin, Occupational and environmental exposures and risk of systemic lupus erythematosus: silica, sunlight, solvents, Rheumatology 49 (2010) 2172–2180, https://doi.org/10.1093/rheumatology/keq214.

[116] K.-H. Chang, C.-C. Hsu, C.-H. Muo, C.Y. Hsu, H.-C. Liu, C.-H. Kao, C.-Y. Chen, M.-Y. Chang, Y.-C. Hsu, Air pollution exposure increases the risk of rheumatoid arthritis: a longitudinal and nationwide study, Environ. Int. 94 (2016) 495–499, https://doi.org/10.1016/j.envint.2016.06.008.

[117] J.S. Park, S. Choi, K. Kim, J. Chang, S.M. Kim, S.R. Kim, G. Lee, J.S. Son, K.H. Kim, E.Y. Lee, S.M. Park, Association of particulate matter with autoimmune rheumatic diseases among adults in South Korea, Rheumatology 60 (2021) 5117–5126, https://doi.org/10.1093/rheumatology/keab127.

[118] A.M. Alex, G. Kunkel, H. Sayles, J.D. Flautero Arcos, T.R. Mikuls, G.S. Kerr, Exposure to ambient air pollution and autoantibody status in rheumatoid arthritis, Clin. Rheumatol. 39 (2020) 761–768, https://doi.org/10.1007/s10067-019-04813-w.

[119] R.W. Gan, K.D. Deane, G.O. Zerbe, M.K. Demoruelle, M.H. Weisman, J. H. Buckner, P.K. Gregersen, T.R. Mikuls, J.R. O'Dell, R.M. Keating, V.M. Holers, J. M. Norris, Relationship between air pollution and positivity of RA-related autoantibodies in individuals without established RA: a report on SERA, Ann. Rheum. Dis. 72 (2013) 2002–2005, https://doi.org/10.1136/annrheumdis-2012-202949.

[120] O. Wrangel, P. Graff, I.-L. Bryngelsson, L. Fornander, P. Wiebert, P. Vihlborg, Silica dust exposure increases risk for rheumatoid arthritis: a Swedish national registry case-control study, J. Occup. Environ. Med. 63 (2021) 951–955, https://doi.org/10.1097/JOM.0000000000002281.

[121] P. Blanc, L. Andersson, L. Bryngelsson, Risk of rheumatoid arthritis in a cohort of silica-exposed Swedish foundry workers, Eur Respir. Soc. (2016).

[122] A. Ilar, L. Klareskog, S. Saevarsdottir, P. Wiebert, J. Askling, P. Gustavsson, L. Alfredsson, Occupational exposure to asbestos and silica and risk of developing rheumatoid arthritis: findings from a Swedish population-based case-control study, RMD Open 5 (2019) e000978, https://doi.org/10.1136/rmdopen-2019-000978.

[123] P.D. Blanc, L. Trupin, E.H. Yelin, G. Schmajuk, Assessment of risk of rheumatoid arthritis among underground hard rock and other mining industry workers in Colorado, New Mexico, and Utah, JAMA Netw. Open 5 (2022) e2236738, https://doi.org/10.1001/jamanetworkopen.2022.36738.

[124] Y.-S. Min, M.-G. Kim, Y.-S. Ahn, Rheumatoid arthritis in silica-exposed workers, Int. J. Environ. Res. Public Health. 18 (2021), https://doi.org/10.3390/ijerph182312776.

[125] J. Sigaux, C. Cavalin, A. Lescoat, S. El Rharras, O. Macchi, P.-Y. Brillet, L. Sesé, H. Nunes, M.-C. Boissier, P.-A. Rosental, L. Semerano, Are cleaning activities a source of exposure to crystalline silica in women with rheumatoid arthritis? A case-control study, RMD Open 9 (2023), https://doi.org/10.1136/rmdopen-2023-003205.

[126] C. Cavalin, A. Lescoat, J. Sigaux, O. Macchi, A. Ballerie, M. Catinon, M. Vincent, L. Semerano, M.-C. Boissier, P.-A. Rosental, Crystalline silica exposure in patients with rheumatoid arthritis and systemic sclerosis: a nationwide cross-sectional survey, Rheumatology 62 (2023) 2707–2715, https://doi.org/10.1093/rheumatology/keac675.

[127] G. Galperín, M. Berra, M.I. Marquez, M. Mandaradoni, J. Tau, A. Berra, Impact of environmental pollution on the ocular surface of Sjögren's syndrome patients, Arq. Bras. Oftalmol. 81 (2018) 481–489, https://doi.org/10.5935/0004-2749.20180091.

[128] T.-P. Zhang, J. Dou, L. Wang, S. Wang, P. Wang, X.-H. Zhou, C.-M. Yang, X.-M. Li, Exposure to particulate pollutant increases the risk of hospitalizations for Sjögren's syndrome, Front. Immunol. 13 (2022) 1059981, https://doi.org/10.3389/fimmu.2022.1059981.

[129] C. Foocharoen, U. Peansukwech, P. Pongkulkiat, A. Mahakkanukrauh, S. Suwannaroj, Aerosol components associated with hospital mortality in systemic sclerosis: an analysis from a nationwide Thailand healthcare database, Sci. Rep. 11 (2021) 7983, https://doi.org/10.1038/s41598-021-87114-0.

[130] T. Schioppo, O. De Lucia, A. Murgo, R. Caporali, A. Orenti, P. Boracchi, S. Iodice, T. Ubiali, V. Bollati, F. Ingegnoli, The burden of air pollution and temperature on Raynaud's phenomenon secondary to systemic sclerosis, Epidemiol. Prev. 44 (2020) 218–227, https://doi.org/10.19191/EP20.4.P228.052.

[131] A. Roeser, L. Sese, G. Chassagnon, B. Chaigne, B. Dunogue, S. Tran Ba, S. Jebri, P.-Y. Brillet, M.P. Revel, F. Aubourg, R. Dhote, F. Caux, I. Annesi-Maesano, L. Mouthon, H. Nunes, Y. Uzunhan, The association between air pollution and the severity at diagnosis and progression of systemic sclerosis-associated interstitial lung disease: results from the retrospective ScleroPol study, Respir. Res. 24 (2023) 151, https://doi.org/10.1186/s12931-023-02463-w.

[132] A. Muntyanu, R. Milan, E. Rahme, A. LaChance, L. Ouchene, M. Cormier, I. V Litvinov, M. Hudson, M. Baron, E. Netchiporouk, Exposure to silica and systemic sclerosis: a retrospective cohort study based on the Canadian Scleroderma Research Group, Front. Med. 9 (2022) 984907, https://doi.org/10.3389/fmed.2022.984907.

[133] S. Patel, K. Morrisroe, S. Proudman, D. Hansen, J. Sahhar, M.R. Sim, G.-S. Ngian, J. Walker, G. Strickland, M. Wilson, N. Ferdowsi, G. Major, J. Roddy, W. Stevens, M. Nikpour, Occupational silica exposure in an Australian systemic sclerosis cohort, Rheumatology 59 (2020) 3900–3905, https://doi.org/10.1093/rheumatology/keaa446.

[134] A. Ballerie, C. Cavalin, M. Lederlin, A. Nicolas, R. Garlantézec, S. Jouneau, V. Lecureur, C. Cazalets, N. Belhomme, C. Paris, P.-A. Rosental, P. Jégo, A. Lescoat, Association of silica exposure with chest HRCT and clinical characteristics in systemic sclerosis, Semin. Arthritis Rheum. 50 (2020) 949–956, https://doi.org/10.1016/j.semarthrit.2020.08.014.

[135] H. Englert, J. Small-McMahon, K. Davis, H. O'Connor, P. Chambers, P. Brooks, Male systemic sclerosis and occupational silica exposure-a population-based study, Aust. N. Z. J. Med. 30 (2000) 215–220, https://doi.org/10.1111/j.1445-5994.2000.tb00810.x.

[136] C. Ferri, E. Artoni, G.L. Sighinolfi, F. Luppi, G. Zelent, M. Colaci, D. Giuggioli, High serum levels of silica nanoparticles in systemic sclerosis patients with occupational exposure: possible pathogenetic role in disease phenotypes, Semin. Arthritis Rheum. 48 (2018) 475–481, https://doi.org/10.1016/j.semarthrit.2018.06.009.