Autoimmunity Reviews 18 (2019) 62–72

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Systemic sclerosis and exposure to heavy metals

Isabelle Marie*

Department of Internal medicine, CHU Rouen, INSERM U 905, University of Rouen IFRMP, Institute for Biochemical Research, Rouen, France

ARTICLE INFO

Keywords:
Systemic sclerosis - environmental factors - occupational factors
crystalline silica
Solvents
Trichloroethylene
Ketones - welding fumes - pesticides

ABSTRACT

As a mirror image of the Roman god Janus Bifrons, the environment has a hidden face. To highlight this hidden face of the environment in the field of systemic sclerosis (SSc) will allow to identify responsible agents emerging in the future. To date, there is, in fact, a growing scientific evidence that environmental factors have a crucial impact on both alterations and modulation of epigenetic determinants, resulting in SSc onset and progression. It has been well established that there is a marked correlation between SSc onset and occupational exposure to crystalline silica and organic solvents. More recently, an association between SSc and exposure to heavy metals has further been found, including: antimony, cadmium, lead, mercury. These latter findings interestingly underscore that occupational exposure to heavy metals should be systematically checked in all SSc patients at diagnosis, as the identification of the occupational toxic agent will allow its interruption, which may result in potential improvement of SSc outcome.

1. Introduction

Systemic sclerosis (SSc) is a complex systemic inflammatory disorder affecting the skin and other organs [1–5]. The condition is characterized by three histopathologic features: (i) both structural and functional vascular lesions, associated with progressive endothelial damage, reduction in the number of capillaries, thickening of arterial walls, and obliterative vasculopathy; (ii) perivascular and tissue infiltration of mononuclear inflammatory cells at early stages of SSc. Histological analyses of skin biopsy specimens have shown prominent CD4 + cellular infiltration with overexpression of cellular adhesion molecules in both vessels and interstitium; and (iii) increased synthesis and excessive deposition of extracellular matrix, resulting in fibrotic destruction of internal organs during the course of SSc [3,6–11].

The pathogenesis of SSc still remains unclear, although multiple genetic, epigenetic and environmental risk factors have been incriminated. Genome-wide association series have, in fact, identified increasing number of genes contributing to SSc pathogenesis, although the low penetrance of genetic risk factors and concordance in twins have been underscored. Thus, the inheritance of genes alone is unsufficient for developing SSc. Non-encoded regulation of gene expression provided by epigenetic mechanisms plays a crucial role in SSc susceptibility that is still being studied; these epigenetic modifications can result from inherited DNA sequences and environmental exposures. Altogether, it is increasingly thought that interactions between environmental factors and epigenetic features lead to the onset and progression of SSc in genetically susceptible patients (Fig. 1) [3,12,13]. Three main epigenetic features are thought to determine the epigenome in SSc, *i.e.*:

- **DNA methylation**, resulting in dysregulation of:
  - CD4+ T cells which appear to be hypomethylated. CD4+ T cell in association with reduced expression of methylation-regulating genes: DNA methyltransferase-1 (DNMT1), methyl-CpG-binding domain (MBD) 3 and 4 [6,14]. CD40L gene promoter has also been found to be hypomethylated and transcriptionally active in CD4+ T cells [6,15]. In female patients with SSc, the presence of demethylated CD40L regulatory elements on the inactive X chromosome results in CD40L overexpression [6,15]. Furthermore, the promoter of CD70 is hypomethylated, leading to the overexpression of CD70 by CD4+ Tcells in SSc patients [6,15];
  - endothelial cells. In SSc patients, CpG hypermethylation of the bone morphogenetic protein receptor factor type 2 (BMPR2) may lead to higher vulnerability of endothelial cells to apoptosis and oxidation damage [16];
  - fibroblasts. Hypermethylated fibroblasts have been found in dermal fibroblasts from SSc patients; histological analyses of skin biopsy specimens have also shown higher levels of methylation regulatory genes DNMT1, MBD1 and methyl-CpG-binding protein (MECP) 2 in SSc patients than in controls [3,6].
- **Histone alterations**, leading to dysfunction in transcription and modulation of gene expression [3,6]. In experimental models of

* Corresponding author at: Département de Médecine Interne, CHU de Rouen, 76031 Rouen, Cedex, France.
E-mail address: isabelle.marie@chu-rouen.fr.

https://doi.org/10.1016/j.autrev.2018.11.001

Available online 04 November 2018

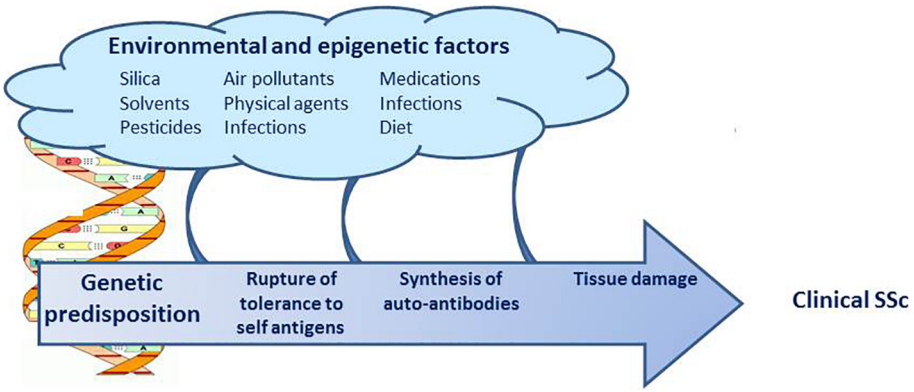

Fig. 1. Interplay between environmental factors, epigenetics and genetics in SSc.

skin/lung fibrosis and in SSc skin biopsy samples and explanted fibroblasts, analyses have demonstrated increased lesional tissue p300 levels, promoting histone H4 hyperacetylation and transforming growth factor β (TGF-β)-induced transcription of fibrotic genes [17,18]. Additionally, the histone deacetylase sirtuin 1 has been found to be reduced in human and mouse fibroblasts in culture as well as in murine model of fibrosis by effects of blocking Smad-dependent transcription [18].

- **MicroRNA profile impairment**, resulting in a pro-fibrotic process [6,12,19]. SSc patients, compared with healthy subjects, have been found to exhibit:
  - *ex vivo* lower levels of miR-29 (which has a master antifibrotic action on collagen I and III and extracellular matrix components *via* inhibition of expression of COL1-A1, COL1-A2, and COL1-A) [9,12,20,21];
  - higher values of: 1) miR-92a in dermal fibroblasts and in sera, leading to decreased levels of metalloprotease 1 [9]; and 2) miR-143-3p, which were predictive of SSc severity [22];
  - reduced levels of miR-129- 5p in dermal fibroblasts, resulting in elevated expression of collagen I and connective tissue growth factor (CTGF) [23]

2. Environmental factors and SSc

Many environmental factors have been incriminated to play a role in SSc pathogenesis, which can be divided into: occupational chemical agents, physical agents, air pollutants, infections, diet, foods and dietary contaminants.

2.1. Occupational chemical agents

A marked correlation has been found between SSc onset and occupational exposure to chemical agents, especially crystalline silica and organic solvents (Fig. 2).

- **Crystalline silica**: Bramwell [24] was the first to describe SSc in Scottish stonemasons. In 1957, Erasmus [25] has reported a higher incidence of SSc in gold miners exposed to crystalline silica, compared with the general population (2/1000 *vs.* 0.35/1000). Previous case–control series have found a correlation between crystalline silica and SSc [26–28]. A 2014 case–control study has also demonstrated a marked association between SSc and crystalline silica exposure (OR 5.32, 95% CI 2.25–13.09); the risk was stronger in SSc patients with high level of crystalline silica exposure (OR 9.68, 95%CI 2.14–59.43) [29]. Interestingly, occupational exposure to crystalline silica has further been found to be a predictive parameter of SSc severity, as SSc exposed patients more often exhibited: 1) diffuse cutaneous SSc ($P = .02$); 2) digital ulcers ($P = .05$) and lower median value of left ventricular ejection fraction ($P = .006$); and 3) interstitial lung disease (ILD) ($P = .0004$), that was also more severe in the group of silica-exposed patients with SSc, as shown by lower median values of forced vital capacity (FVC) ($P = .004$) and diffusing capacity of the lungs for carbon monoxide (DLCO) ($P = .01$) on pulmonary function tests and more common honeycombing ($P = .045$) pattern on high resolution computed tomography (HRCT) scan [30].

The pathogenic mechanisms of crystalline silica remain unclear in the development of SSc. Because silica is a strong T cell adjuvant, dysregulated immune response triggered by crystalline silica in genetically predisposed subjects could lead to tissue damage and systemic inflammatory response [31]. Experimental series have shown that silica, administered intratracheally or intravenously, may interact with alveolar macrophages resulting in immune dysfunction and notably to:

- activation of T and B lymphocytes, responsible for cytokine synthesis (Tumor necrosis factor [TNF], interleukin-1b, Tranforming growth factor [TGF-β]) and autoantibody production. In addition, chronic exposure to silica has been found to activate both responder

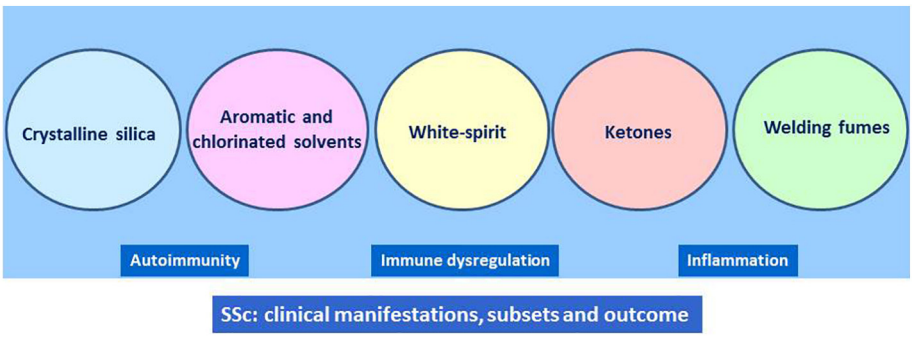

Fig. 2. Occupational influences on the onset of SSc.

T cells and regulatory T cells [31–33]. These activated responder T cells enter the peripheral CD4 + 25 + fraction and activated regulatory T cells, which may lead to decreased inhibitory function of regulatory T cells [31–33]. Furthermore, persistently activated responder T cells may further express Fas-mediated apoptosis inhibitory molecules such as soluble Fas and survive longer, contributing to progression of SSc [31–33];
- autoimmunity related to apoptosis with autoantigen alterations [34]. Indeed, when neutrophils undergo apoptosis, primary granule constituents translocate to the cell surface, leading to both generation of self antigens and tolerance breakdown [35];
- and activation of fibroblast proliferation, with increased synthesis of collagen and other components of extracellular matrix (fibronectin, glycosaminoglycans) [29,36].

- **Organic solvents** are compounds that can be dichotomized into aliphatic-chain compounds (n-hexane), aromatic compounds (benzene, xylene), and chlorinated compounds. Common uses for organic solvents are: dry cleaning (tetrachloroethylene), paint thinners (toluene), nail polish removers and glue solvents (acetone, methyl acetate, ethyl acetate) and spot removers (hexane) [29]. To date, the applications of organic solvents are increasingly diversified in both developed and developing countries. The association between SSc and organic solvent exposure was first described by Reinl [37]. Such an association between organic solvent exposure and increased risk of SSc has further been found [27,38–40]. A large case-control study also showed the marked association between SSc and organic solvents for white spirit (OR 7.69, 95% CI 4.11–14.7), aromatic solvents (OR 8.17, 95%CI 2.29–36.5), chlorinated solvents (OR 2.46, 95% CI 1.12–5.32), trichloroethylene (OR 2.26, 95% CI 0.95–5.26), and ketones (OR 3.37, 95% CI 1.51–7.53) [29]. Additionally, occupational exposure to organic solvents seems to be a predictive parameter of SSc severity [30]. Thus, SSc patients who were exposed to organic solvents, compared to non-exposed patients, more often exhibited: 1) diffuse cutaneous SSc (P = .001); 2) severe microangiopathy as shown by higher prevalence of digital ulcers (P = .01) and lower median value of left ventricular ejection fraction (P = .04); 3) ILD (P = .02), which was more severe in exposed patients with lower median values of FVC (P = .005) and DLCO (P = .02) on pulmonary function tests; 4) cancer (P = .003); and 5) positivity of anti-Scl70 antibody (P = .04) [30]. Interestingly, in this latter series, the authors have found that patients who were exposed to chlorinated solvents, compared to those exposed to white spirit, aromatic solvents, or ketones, exhibited the more severe pattern of SSc, including higher median values of Rodnan score (P = .037) and lower median values of left ventricular ejection fraction (P = .04), VC (P = .04), FVC (P = .03), and DLCO (P = .009) [30].

The pathogenic mechanisms of organic solvents remain unclear in the onset of SSc. Previous authors have speculated that organic solvents may link with nucleic acids and proteins, leading to immune disruptors and increased risk of SSc [36]. MRL+/+ mice, when exposed to trichloroethylene, developed higher levels of overall serum IgG and increased prevalence of antinuclear antibodies [41]. Other experimental models have shown that exposure to trichloroethylene resulted in:

- protein modifications [42–46];
- increased synthesis of IL-17 and IL-21 by splenocytes in trichloroethylene-treated mice [47];
- production of reactive oxygen species and increased nitric oxide by nitric oxide synthase in cultured human epidermal keratinocytes [48];
- Th1 T cell activation and inhibition of cellular apoptosis of naïve CD4+ and CD8+ T cells in MRL+/+ mice [49,50];
- and DNA hypermethylation on rat cardiac myoblasts [51].

In addition, other experimental studies have demonstrated that exposure to benzene led to: 1) decreased number of CD4+/CD8+ T cells and B cells in exposed workers [52]; 2) higher reactive oxygen species and induction of DNA fragmentation in pump workers [53]; and 3) changes in gene transcription involved in apoptosis, oxidative stress, cellular cycle, and cytokine production in benzene-treated mice [54].

- **Welding fumes**: One case-control series has found higher OR in SSc for welding fumes (OR 3.74, 95% CI 1.06–13.18) [27]. Another larger case-report study (100 SSc patients, 300 controls) showed a significant association between SSc and occupational exposure to welding fumes (OR 2.60, 95% CI 1.15 to 5.81) [29]. This latter study has demonstrated that the risk of SSc was increased in patients with a higher level exposure (OR 4.70, 95% CI 1.09–23.14) for welding fumes [29].

2.2. Physical agents

Physical agents include ionizing radiation, ultraviolet radiation, electric and magnetic fields. To date, there is growing evidence for: 1) an association between ionizing radiation and risk of autoimmune thyroiditis and Graves' disease; and 2) an inverse relationship between ultraviolet exposure and risk of multiple sclerosis [3]. However, no investigators have yet assessed the risk of SSc in patients exposed to ionizing radiation, ultraviolet radiation, as well as electric and magnetic fields.

2.3. Air pollutants

In 2016, among 14,000 male rescue/recovery workers enrolled in the Fire Department of the City of World Trade Center (WTC), acute and high level exposure to dusts has been linked to increased risk of systemic autoimmune disorders; the higher WTC exposure group had, in fact, 7.7 excess cases of systemic autoimmune diseases [55]. Among the 97 patients who developed autoimmune diseases, two had SSc [55]. In the patients exposed to dust, in whom interstitial lung inflammation and disease developed, histological analyses of lung biopsy specimens revealed the presence of aluminum and magnesium silicates, chrysotile asbestos, calcium phosphate and calcium sulfate, small shards of glass and carbon nanotubes of various sizes and lengths [56]. In experimental models, such dust exposure was also found to be related to changes in markers of pulmonary inflammation, oxidative stress and epigenetic changes [56,57].

Furthermore, particulate air pollution has been speculated to be associated with onset of autoimmune diseases, including SSc, although the extent to which such exposure increases susceptibility to SSc requires further assessment [58,59]. In addition, particulate emission from diesel exhaust engines has also been associated with fibrosis [60,61]. Diesel exhaust nanoparticles have been shown to be internalized by monocyte-derived macrophages and keratinocytes from healthy subjects, resulting in oxidative, pro-fibrotic, and pro-inflammatory processes in normal human skin [60,61]. In fact, diesel exhaust nanoparticles have been found, *in vitro*, to result in:

- increased mRNA gene expression of: metalloproteases 2, 7, 9, and 12; collagen I and III;
- higher levels of vascular endothelial growth factor (VEGF) in SSc fibroblasts than in controls [3];
- and activation of keratinocytes in patients with diffuse cutaneous SSc with elevated levels of pro-fibrotic cytokines: IL-1α, IL-8, and IL-6 mRNA levels [62]. Interestingly, IL-1α has been reported to be strongly elevated in SSc epidermis, which may be responsible for keratinocyte–fibroblast interactions, contributing to fibroblast activation [63].

2.4. Infections

Infections have been speculated to play a role in SSc onset. Numerous mechanisms of infections have been proposed, such as endothelial cell damage, molecular mimicry and self-reactive antibodies [64]. The following pathogen micro-organisms have been incriminated in SSc genesis:

- Parvovirus B19. The presence of the parvovirus B19 has further been observed in bone marrow biopsy specimens of 57% of SSc patients [65], suggesting that the bone marrow may represent a reservoir from which the parvovirus B19 virus spreads to SSc tissues [66]. Endothelial injury in patients with parvovirus B19 has been speculated to reflect a combination of direct viral cytotoxicity and humoral immunity [67]. It has also been reported that parvovirus B19 exerts a cytotoxic effect on infected cells through a non-structural protein NS-1 [68]. The ability of parvovirus B19 to persistently infect SSc fibroblasts might result in marked cell alterations [69].
- Cytomegalovirus: Cytomegalovirus may play a role in SSc onset due to its ability to infect both endothelial cells and monocytes/macrophages and through the upregulation of fibrogenic cytokines and induction of immune dysregulation [70]. Infection of endothelial cells by cytomegalovirus may alter the expression of different integrins and be responsible for the expression of fibrogenic cytokines and dysregulation of different antibodies, especially anti-Scl70 antibody [70,71]; anti-Scl70 antibody could cross-react with a peptide sequence of the UL-70 protein of cytomegalovirus [70,71].
- Helicobacter pylori (*H. pylori*). Previous authors have found higher prevalence of *H. pylori* in SSc patients, compared with healthy subjects [72,73]. It has been suggested that *H. pylori* may shed extracellular products, principally heat shock protein 60 (HSP 60) eliciting local and systemic immune responses, leading subsequently to tissue damage [74].

2.5. Diet, foods and dietary contaminants

Regarding dietary factors in autoimmune diseases, the gold standard is the causation of celiac disease by gluten ingestion [36]. Nutritional sources may also provide the methyl donors and cofactors (folic acid, vitamin B12, and pyridoxal phosphate) crucial for DNA and histone methylation. There are reports of diet-induced epigenetic changes in adults [3]. However, the association between dietary factors and Sc has not yet been evaluated.

3. Heavy metals and SSc

In 1988, Pedersen et al. [75] have first mentioned that four great masters suffered from rheumatoid arthritis (Duffy, Renoir, Rubens) and SSc (Klee). Because these painters used significantly more bright and clear colors based on toxic heavy metals and fewer earth colors, it has been suggested that they may have been markedly exposed to the following heavy metals: antimony, arsenic, cadmium, chromium, cobalt, lead, manganese, mercury and tin [75].

In 2017, the role of heavy metals has been, to our knowledge, underscored for the first time in SSc pathogenesis (Fig. 3) [76]. The investigators have conducted a prospective case-control study, in order to assess the risk of SSc related to occupational exposure to heavy metals, in 100 patients with a definite diagnosis of SSc and 300 controls; 3 age (± 5 years), gender, and smoking habit matched controls were selected for each patient [76]. All SSc patients and controls underwent detection and quantification of heavy metal traces in hair samples, using multi-element inductively coupled plasma mass spectrometry (ICP-MS): aluminum, antimony, arsenic, barium, beryllium, bismuth, boron, cadmium, chromium, cobalt, copper, germanium, lead, lithium, manganese, mercury, molybdenum, nickel, palladium, platinum, rubidium, selenium, silver, strontium, tellurium, thallium, tin, tungsten, uranium,

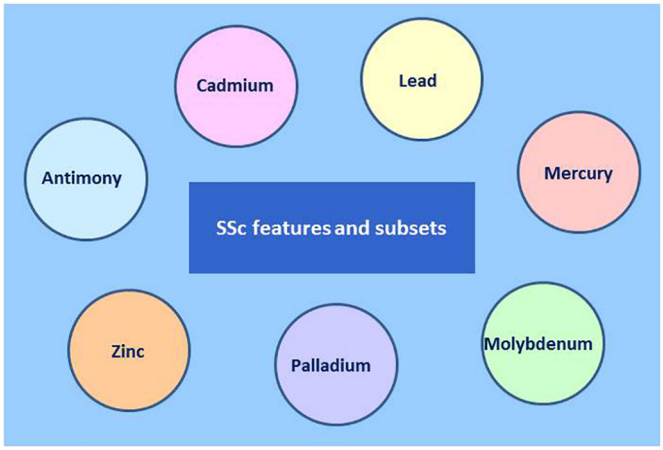

Fig. 3. Association between heavy metal exposure and development of SSc.

vanadium, and zinc [76]. Interestingly, this study has demonstrated that SSc patients exhibited higher median levels of the following metals in hair samples: antimony ($p = .001$), cadmium ($p = .0003$), lead ($p = .02$), mercury ($p = .02$), molybdenum ($p = .04$), palladium ($p < .0001$) and zinc ($p = .0003$). The authors have therefore pointed out that occupational exposure should be systematically checked at initial evaluation of patients with SSc [76]. They have also suggested that exposure to such heavy metals may play a role in development of SSc [76].

3.1. Antimony

Studies in the US general population have found a correlation between higher levels of antimony and peripheral arterial diseases, as well as cardiovascular and cerebral diseases and diabetes [77,78]. Furthermore, another study showed that antimony was associated with cardiovascular endpoints in smelter workers [79,80]. The 2017 case-control study adds SSc to the health outcomes, which may be associated with antimony exposure. In this latter case-control study, a significant association between SSc and antimony exposure was observed in both male and female patients; most cases exposed to antimony were workers in manufactures of semi-conductors, infrared detectors and diodes, lead storage batteries, fire-retardant formulations for plastics, rubbers and paints, and electronics [76]. In fact, antimony is released in: 1) producing of semi-conductors, infrared detectors and diodes, lead storage batteries, solder, sheet and pipe metal bearings, castings, pewter, metal alloys, fire-retardant formulations for plastics, rubbers, textiles, paper and paints, and explosives; and 2) manufacturing of electronics [81,82].

The pathogenic mechanisms of antimony remain unclear in the onset of SSc. Antimony has been reported to induce enhanced autophagy, leading to radical oxygen species generation and cell death [83]. Basic science series have suggested that antimony may alter the epigenome [80,81,84,85], leading to (Fig. 4): 1) chromosomal aberration tests in cultured mammalian cells; and 2) excess production of active oxygen species and interference with DNA repair system [84]. In another series, oxidative DNA damage were more often observed in mall workers, who handled materials containing antimony, than in controls [86]. Furthermore, antimony may deplete glutathione and protein-bound sulfhydryl groups, leading to the production of reactive oxygen species (superoxide anion, hydrogen peroxide, hydroxyl radicals) [87].

3.2. Cadmium

Cadmium is a widespread metal [88]. Cadmium excretion is slow, resulting in a gradual accumulation in the whole body with a half life being as long as 45 years [76]. The association between cadmium

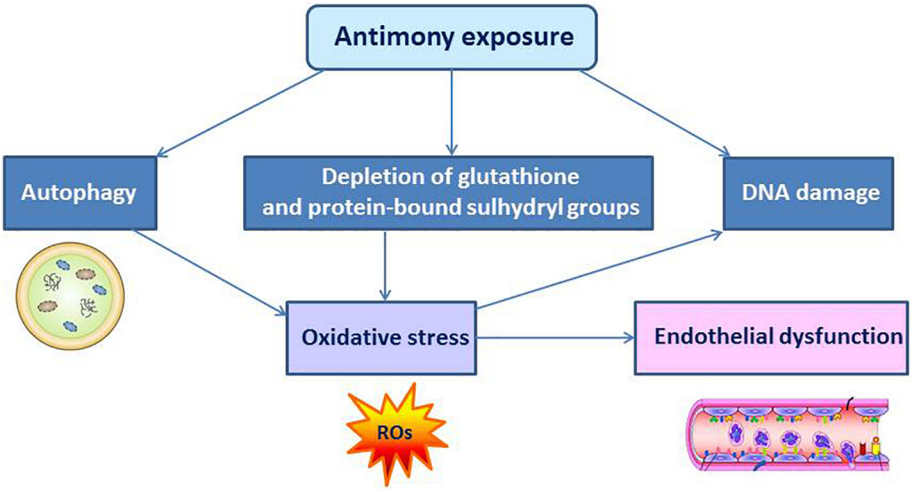

Fig. 4. Putative pathogenic mechanisms of antimony in the onset of SSc.

exposure and elevated risk of cardiovascular diseases, including ischemic heart disease, heart failure, stroke, peripheral arterial disease, diabetes and lung cancer has been described [89–95]. In a case-control series, a correlation was found between cadmium and rheumatoid arthritis; indeed, patients with rheumatoid arthritis exhibited higher levels of cadmium within hair samples [96]. In the 2017 case-control study, the investigators have observed a marked association between SSc and cadmium exposure [76]. They further found that the association between SSc and cadmium exposure was stronger in females than in males. This finding was explained, in part, by the occupational differences between male and female SSc patients [76]. In fact, exposure to cadmium was observed in patients producing batteries, pigments, coatings and platings, stabilizers for plastics and nonferrous alloys, and photovoltaic devices, as described previously [76].

The pathogenic mechanisms of cadmium remain unknown in the development of SSc. Murine series have indicated that cadmium may result in immune dysfunction, and notably in:

- increased neutrophil recruitment, resulting in synthesis of radical oxygen species [97];
- macrophage immune dysfunction, with altered phagocytic activity and migration, through: 1) inhibition of NF-κB pathway, specifically through inhibition of IKKβ; and 2) alteration of macrophage programming with predominant M2 macrophages that elicit a cytokine profile designed to promote humoral-mediated Th2 immune response, leading to release of matrix metalloproteases and damage-associated molecular patterns recruiting more macropahges [98].
- activation and proliferation of T and B lymphocytes, leading to up-regulation of: 1) pro-inflammatory cytokines (*e.g.*: TNFα, IL-1, IL-6 and IL-8), activating inflammatory cells to release reactive oxygen species; and 2) adhesion cell molecules (such as ICAM-1, VCAM-1, PECAM-1 and VE cadherines), prostaglandin E2 and cyclooxygenase 2 with impairment of the metalloproteinase 9/TIMP-1 balance and elevated endothelial cell permeability and death [99,100];
- synthesis of antinuclear antibodies and non-specific antibodies, as well as impairment of immunoglobulin profile with decreased circulating IgG and IgA [101–103] (Fig. 5);
- impairment of natural killer cell activity [104].
- vascular damages, especially by oxidative stress [105,106]. In fact, cadmium can induce: 1) disruption of: normal calcium-channel function and endothelial barrier functions; 2) apoptosis of endothelial cells, inhibition of vasodilator substances such as NO [102]; 3) elevation of lipid peroxidation by competition with zinc for binding to metallothioneins and glutathione, ROS-generating Fenton reactions, antioxidant depletion and enzyme detoxification [102,105]; and 4) platelet activation and vascular remodelling [107]. Interestingly, cadmium has also been reported to be associated with higher serum levels of galetin-3 which is a biomarker of myocardial fibrosis [107] (Fig. 6).

Furthermore, cadmium has also been found to exert effects on the epigenome, resulting in: 1) DNA strand breaks, sister chromatid exchange and chromosomal aberrations; and 2) increased expression of death receptor marker TNFα (marker of cellular apoptotic activity), executor caspase-8 and pro-apoptotic Bax gene 2 [108–112] (Fig. 5).

3.3. Lead

The association between autoimmune diseases and lead exposure has been described. A case-control study found a correlation between rheumatoid arthritis and lead exposure; indeed, the authors have reported that lead levels were higher in hair samples of patients with rheumatoid arthritis than in controls [113]. In the 2017 case-control study, an association between SSc and lead exposure was found [76]. Among the SSc patients exposed to lead, most cases were workers in manufactures of production/recycling of storage batteries; the differences between the occupational exposure to lead may explain, in part, the fact that the relationship between SSc and lead exposure was stronger in female patients SSc.

The pathogenic mechanisms of lead are not established in the onset of SSc. Animal and basic science series in autoimmune diseases indicated that lead may interact with different cells, leading to: 1) activation of T and B lymphocytes, responsible for cytokine synthesis [114]; 2) NF-κB activation *via* increased oxidative stess, resulting in oxidation of low-density lipoprotein, increased expression of adhesive molecules on monocytes and increased foam cell formation [115]. Lead also promotes vascular damages, including: 1) oxidative stress, endothelial dysfunction and proliferation of vascular smooth muscle cells and fibroblasts [105,116,117]; 2) downregulation of NO and soluble gualylate cyclase, resulting subsequently in sodium retention, vasoconstriction and increased adrenergic tone [105]; 3) stimulation of the renin-angiotensin system and the sympathetic nervous system [105] (Fig. 7). Furthermore, in lead-exposed rodents, aortic media thickness and tissue collagen deposits were increased compared with untreated controls [118]. Finally, in US studies, lead has been reported to alter the epigenome, resulting in: 1) DNA hypomethylation; 2) decreased methylation of cpG site in the promoter of the COL1A2 gene; and 3) increased expression of microRNAs that are involved in oxidative stress and inflammation [118–121].

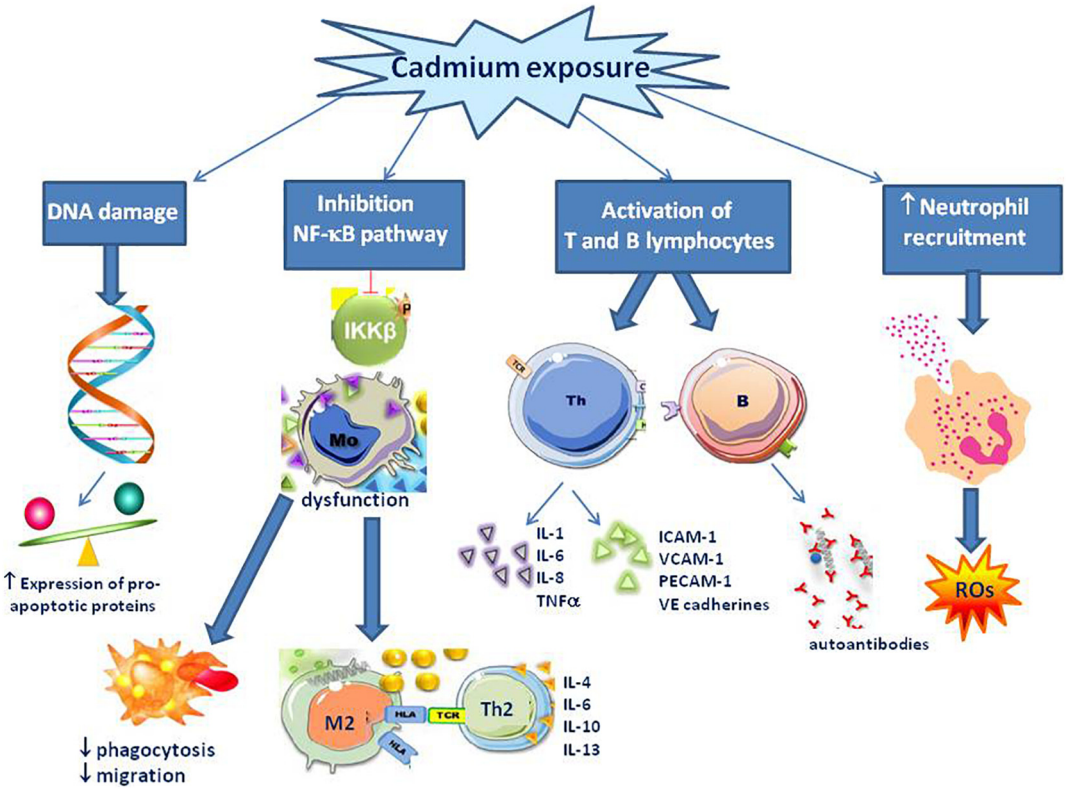

Fig. 5. Putative pathogenic mechanisms of cadmium in the onset of SSc.

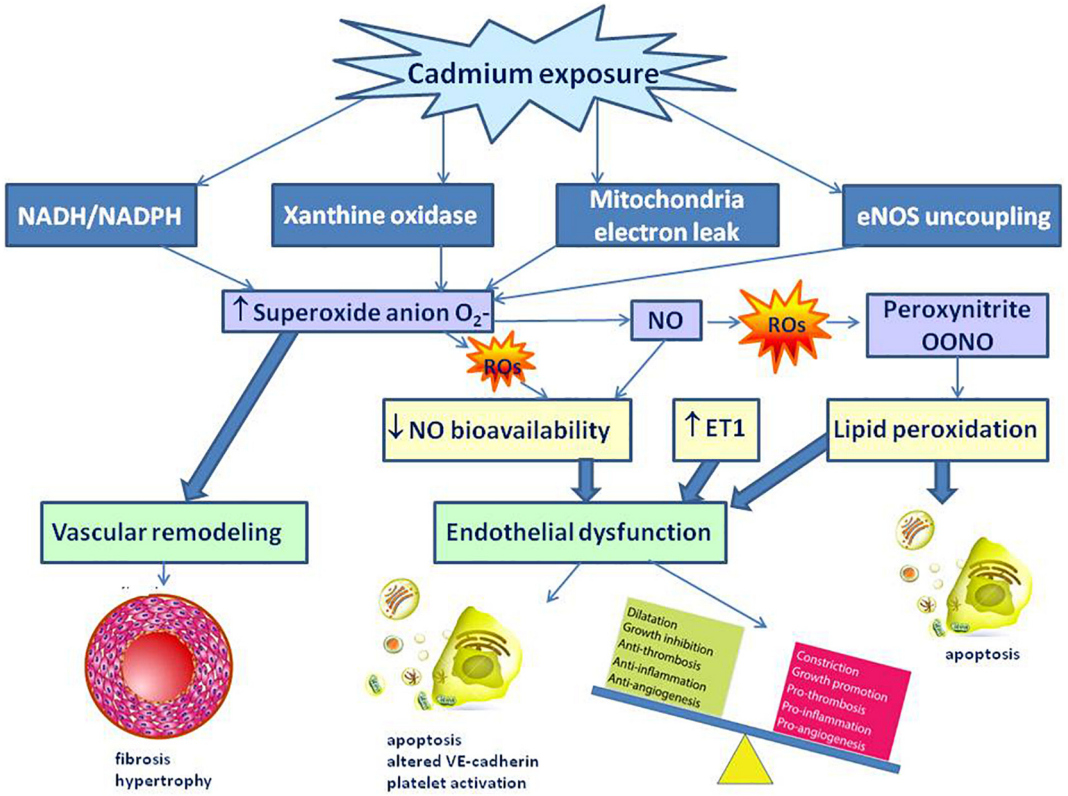

Fig. 6. Putative pathogenic mechanisms of cadmium in the onset of vascular damage in SSc.

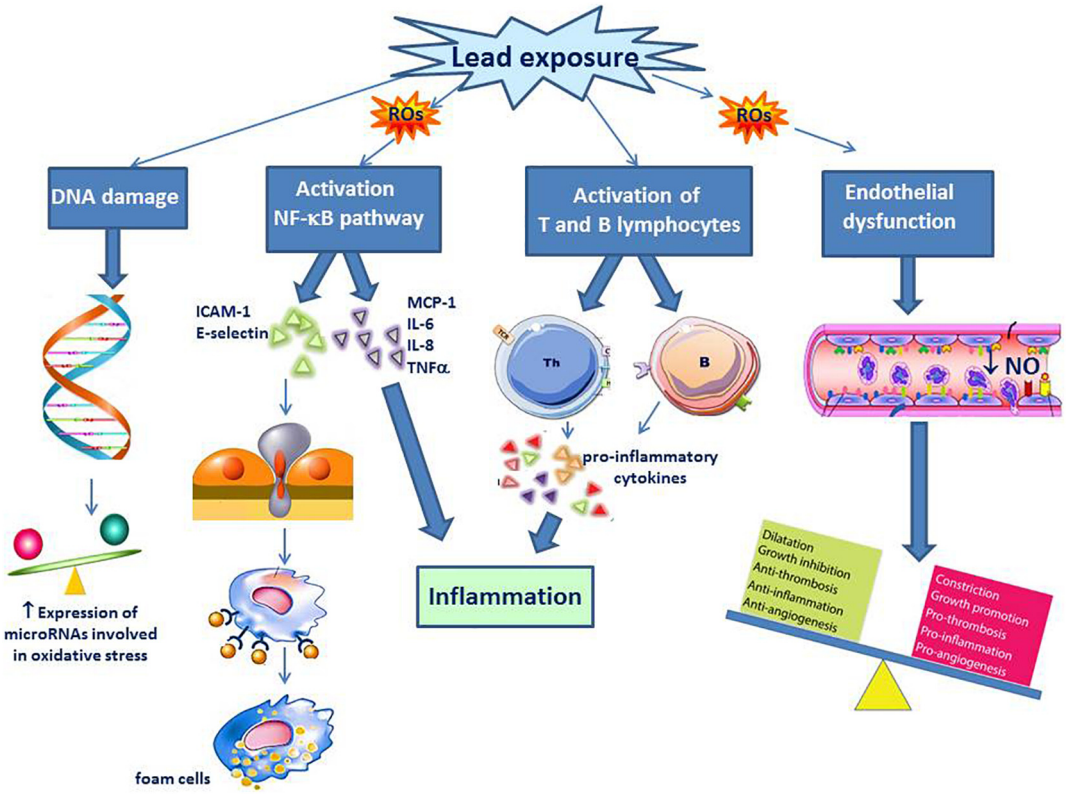

Fig. 7. Putative pathogenic mechanisms of lead in the development of SSc.

3.4. Mercury

The relationship between exposure to metallic mercury and autoimmunity is well established. Mercury-exposed gold miners have been found to exhibit higher prevalence of detectable antinuclear antibodies (OR: 8.6 [95% CI: 4.1–18.0]) and antinucleolar antibodies (OR: 30.6 [95% CI: 7.1–131.9]) as compared to diamond/emerald miners [122]. In the 2017 case-control study, an association between SSc and metallic mercury exposure has been found [76]. SSc patients exposed to mercury were principally workers in electronic devices, batteries and fluorescent lights; the differences between the occupational exposure to mercury of male and female SSc patients likely explained the fact that the relationship between mercury exposure and SSc was stronger in females.

The pathogenic mechanisms of mercury remain unclear in the development of SSc. Experimental models have demonstrated that exposure to mercury led to:

- autoimmunity [122–125]. In susceptible murine models, mercury exposure has been shown to result in immune complex mediated glomerulonephritis and autoantibody synthesis [126]; such autoantigens might be laminin-1 and fibrillarin [127]. Mercury may alter self proteins, especially fibrillarin through mercuric-thiol interactions leading to auto-antigenicity [128];
- polyclonal activation of T and B lymphocytes [122,129–131]. Mercury-exposed gold miners, as compared to diamond/emerald miners have also been found to exhibit higher levels of pro-inflammatory cytokines (IL-1β, IL-17, TNF-α, IFN-γ) and lower levels of anti-inflammatory cytokines (IL-1Ra and IL-10) in serum [122,132];
- alterations in mitochondrial function and glutathione depletion in human T lymphocytes, leading to reactive oxygen species' generation and activation of apoptotic signalling pathways [133,134]. Another recent series has also demonstrated that mercury-exposed gold miners had higher serum titers of anti-glutathione S-transferase alpha (OR: 89.6; 95% CI: 27.2–294.6) compared to emerald miners [131]. These latter data suggest that glutathione S-transferases may play a role in immune dysfunction, resulting in oxidative stress and synthesis of pro-inflammatory cytokines (Fig. 8) [135,136].
- increased radical oxygen species production related to the increase in both nicotinamide adenine dinucleotide phosphate oxidase: NOX-1 and NOX-4 subunits, resulting in alterations in the structure and function of vascular endothelium and less endothelium-dependent relaxation [137].

Finally, mercury exposure may also interact with the epigenome. In fact, mercury may induce overexpression of the detoxification protein peroxisome proliferation-activated receptor gamma, co-activator-related 1LPPR01, resulting in activation of Nrf1 and Nrf2 (which regulates glutathione genes) [132].

3.5. Molybdenum

The 2017 case-control study has shown an association between SSc and molybdenum exposure [76]. The pathogenic effects of molybdenum are unclear in SSc development. Although, previous authors have described that exposure to molybdenum resulted in: 1) autoimmunity triggering with synthesis of antinuclear antibodies [138]; and 2) activation of T cells, increased production of IL1-β and induction of Th17 response characterized by high levels of IL-17-triggered or mediated by other cytokines [139,140]. Interestingly, Th17 responses have been implicated in the pathogenesis of SSc [76]. Furthermore, molybdenum has been reported to induce oxidative stress with generation of free radical processes and reactive species, resulting in alteration of malondialdehyde [141]. Finally, molybdenum has also been shown to lead to alterations of the epigenome with overexpression of the pro-apoptotic protein Bak-1 gene and caspase-3 (that plays a role in mediating apoptosis in mitochondrial pathways [141].

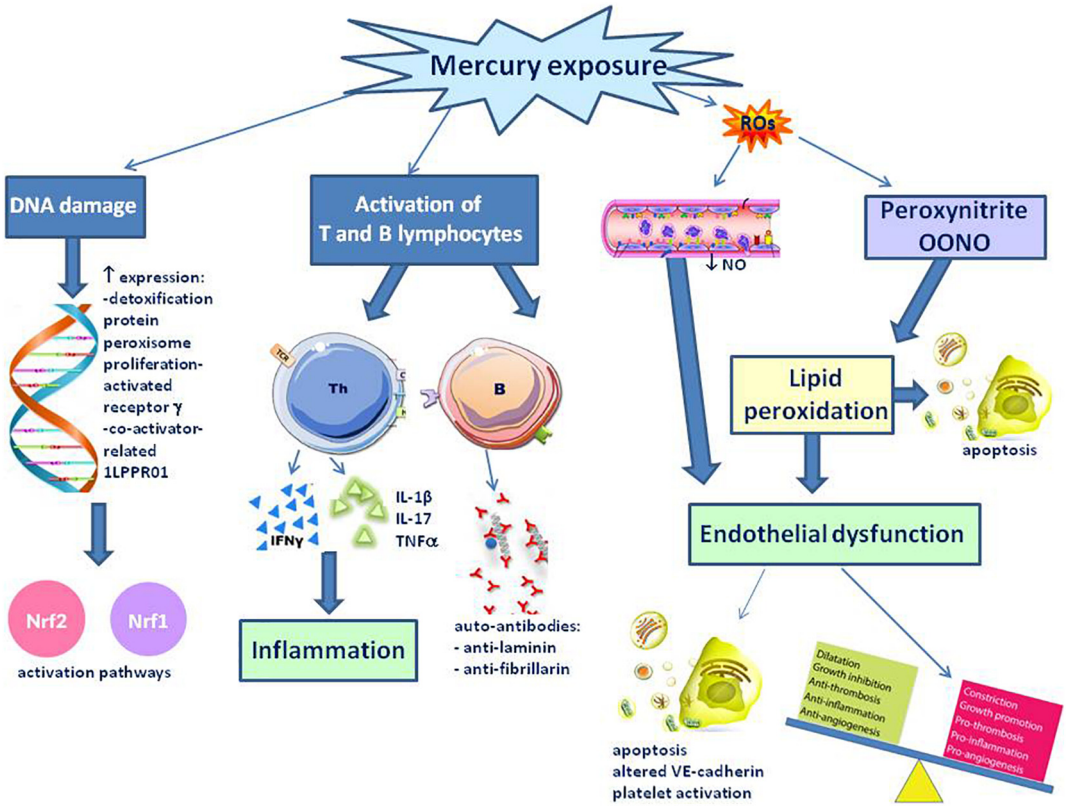

Fig. 8. Putative pathogenic mechanisms of mercury in the developmen of SSc.

3.6. Palladium

In the 2017 case-control study, a significant association has been found between SSc and palladium exposure in female patients [76]. SSc patients exposed to palladium were mainly workers in chemical industries [76]. The effects of palladium are unknown in SSc onset. Nevertheless, palladium is known to lead to immune dysfunction [142–144]. In fact, *in vitro* series have demonstrated that exposure to palladium resulted in: 1) maturation of antigen presenting cells, synthesis of pro-inflammatory cytokines (IL-8) *via* binding to the endotoxin receptor TLR4 [145,146]; and 2) inactivation of C5a in human neutrophils [147].

3.7. Zinc

The 2017 case-control study showed an association between SSc and zinc exposure in female patients [76]. Interestingly, *in vitro* studies and experimental models, exposure to zinc has been described to lead to: 1) formation of neutrophilic and activated lymphocyte infiltrates with synthesis of pro-inflammatory cytokines and release of free radicals [148]; 2) high expression on monocytes of the IL-6 receptor [149]; 3) dysfunction of endothelial cells, with upregulation of cellular molecules, that are ICAM-1 and VCAM-1 [148]; and 4) elevated cell oxidant concentrations and alteration of transcription factors [116,150]. Furthermore, zinc exposure has also been found, *in vitro*, to result in downregulation of cardiovascular associated genes, including AGTR1 which may be responsible for impairment of endothelium-dependent and independent vascular release [151].

3.8. Germanium

In the 2017 case-control study, SSc patients have been found to exhibit lower levels of germanium within hair samples [76]. The role of this decreased level of germanium levels is still unknown in SSc. However, previous investigators have mentioned that germanium plays a role in the inhibition of tumor growth [152]; this activity seems to be linked with stimulating production of gamma interferon and activation of macrophages and NK lymphocytes [153,154]. These findings are relevant, as SSc patients have a 1.5- to 5-fold risk of malignancies [155,156]. In patients with SSc, many mechanisms have been speculated as contributing to cancer onset, including impaired clearance of carcinogens and DNA damage induced by reactive oxygen species [76]. The data of the 2017 case-control also suggest that lower median levels of germanium may be a contributing parameter of cancer in SSc. Nevertheless, further investigations are warranted to confirm these data.

4. Conclusion

As a mirror image of the Roman god Janus Bifrons, the environment has a hidden face. To highlight this hidden face of the environment in the field of SSc will allow to identify responsible agents emerging in the future. To date, there is, in fact, a growing scientific evidence that environmental factors have a crucial impact on both alterations and modulation of epigenetic determinants, resulting in SSc onset and progression. Interestingly, a marked correlation has been found between SSc onset and occupational exposure to crystalline silica, organic solvents and more recently to heavy metals that are: antimony, cadmium, lead, mercury. Altogether, occupational exposure should be systematically checked in all SSc patients at diagnosis, as the identification of the occupational toxic agent will allow its interruption, which may result in potential improvement of SSc outcome.

Acknowledgement

This study was supported by a grant of the French Ministry of Health (PHRCIR 2003-0549) and was sponsored by Rouen University Hospital (Etude TOSCAN, 2002-039HP).

References

[1] Fischer A, Zimovetz E, Ling C, Esser D, Schoof N. Humanistic and cost burden of systemic sclerosis: a review of the literature. Autoimmun Rev 2017;16:1147–54.
[2] Giuggioli D, Manfredi A, Lumetti F, Colaci M, Ferri C. Scleroderma skin ulcers definition, classification and treatment strategies our experience and review of the literature. Autoimmun Rev 2018;17:155–64.
[3] Marie I, Gehanno JF. Environmental risk factors of systemic sclerosis. Semin Immunopathol 2015;37:463–73.
[4] Rossi D, Zanatta E, Marson P, Sciascia S, Polito P, Roccatello D, et al. How I treat patients with systemic sclerosis in clinical practice. Autoimmun Rev 2017;16:1024–8.
[5] Soulaidopoulos S, Triantafyllidou E, Garyfallos A, Kitas GD, Dimitroulas T. The role of nailfold capillaroscopy in the assessment of internal organ involvement in systemic sclerosis: a critical review. Autoimmun Rev 2017;16:787–95.
[6] Ciechomska M, van Laar JM, O'Reilly S. Emerging role of epigenetics in systemic sclerosis pathogenesis. Genes Immun 2014;15:433–9.
[7] Forestier A, Guerrier T, Jouvray M, Giovannelli J, Lefèvre G, Sobanski V, et al. Altered B lymphocyte homeostasis and functions in systemic sclerosis. Autoimmun Rev 2018;17:244–55.
[8] Marie I, Bény JL. Endothelial dysfunction in murine model of systemic sclerosis: tight-skin mice 1. J Invest Dermatol 2002;119:1379–87.
[9] Mostmans Y, Cutolo M, Giddelo C, Decuman S, Melsens K, Declercq H, et al. The role of endothelial cells in the vasculopathy of systemic sclerosis: a systematic review. Autoimmun Rev 2017;16:774–86.
[10] Murdaca G, Contatore M, Gulli R, Mandich P, Puppo F. Genetic factors and systemic sclerosis. Autoimmun Rev 2016;15:427–32.
[11] Scherlinger M, Guillotin V, Truchetet ME, Contin-Bordes C, Sisirak V, Duffau P, et al. Systemic lupus erythematosus and systemic sclerosis: all roads lead to platelets. Autoimmun Rev 2018;17:625–35.
[12] Luo Y, Wang Y, Wang Q, Xiao R, Lu Q. Systemic sclerosis: genetics and epigenetics. J Autoimmun 2013;41:161–7.
[13] Lu Q. The critical importance of epigenetics in autoimmunity. J Autoimmun 2013;41:1–5.
[14] Lei W, Luo Y, Lei W, Luo Y, Yan K, Zhao S, et al. Abnormal DNA methylation in CD4+ T cells from patients with systemic lupus erythematosus, systemic sclerosis, and dermatomyositis. Scand J Rheumatol 2009;38:369–74.
[15] Lian X, Xiao R, Hu X, Kanekura T, Jiang H, Li Y, et al. DNA demethylation of CD40l in CD4+ T cells from women with systemic sclerosis: a possible explanation for female susceptibility. Arthritis Rheum 2012;64:2338–45.
[16] Wang Y, Kahaleh B. Epigenetic repression of bone morphogenetic protein receptor II expression in scleroderma. J Cell Mol Med 2013;17:1291–9.
[17] Ghosh AK, Bhattacharyya S, Lafyatis R, Farina G, Yu J, Thimmapaya B, et al. p300 is elevated in systemic sclerosis and its expression is positively regulated by TGF-β: epigenetic feed-forward amplification of fibrosis. J Invest Dermatol 2013;133:1302–10.
[18] Wei J, Ghosh AK, Chu H, Fang F, Hinchcliff ME, Wang J, et al. The histone deacetylase sirtuin 1 is reduced in systemic sclerosis and abrogates fibrotic responses by targeting transforming growth factor β signaling. Arthritis Rheumatol 2015;67:1323–34.
[19] Altorok N, Kahaleh B. Epigenetics and systemic sclerosis. Semin Immunopathol 2015;37:453–62.
[20] Selmi C, Leung PS, Sherr DH, Diaz M, Nyland JF, Monestier M, et al. Mechanisms of environmental influence on human autoimmunity: a National Institute of Environmental Health Sciences expert panel workshop. J Autoimmun 2012;39:272–84.
[21] Takemoto R, Jinnin M, Wang Z, Kudo H, Inoue K, Nakayama W, et al. Hair miR-29a levels are decreased in patients with scleroderma. Exp Dermatol 2013;22:832–3.
[22] Tsou PS, Sawalha AH. Unfolding the pathogenesis of scleroderma through genomics and epigenomics. J Autoimmun 2017;83:73–94.
[23] Nakashima T, Jinnin M, Yamane K, Honda N, Kajihara I, Makino T, et al. Impaired IL-17 signaling pathway contributes to the increased collagen expression in scleroderma fibroblasts. J Immunol 2012;188:3573–83.
[24] Bramwell B. Diffuse scleroderma: its frequency and occurrence in stonemasons; its treatment by fibrinolysin: elevations of temperature due to fibrinolysin injections. Edinburg Med J 1914;12:387.
[25] Erasmus LD. Scleroderma in goldminers on the Witwatersrand with particular reference to pulmonary manifestations. S Afr Lab Clin Med 1957;3:209–31.
[26] Calvert GM, Rice FL, Boiano JM, Sheehy JW, Sanderson WT. Occupational silica exposure and risk of various diseases: an analysis using death certificates from 27 states of the United States. Occup Environ Med 2003;60:122–9.
[27] Diot E, Lesire V, Guilmot JL, Metzger MD, Pilore R, Rogier S, et al. Systemic sclerosis and occupational risk factors: a case–control study. Occup Environ Med 2002;59:545–9.
[28] Silman AJ, Jones S. What is the contribution of occupational environmental factors to the occurrence of scleroderma in men? Ann Rheum Dis 1992;51:1322–4.
[29] Marie I, Gehanno JF, Bubenheim M, Duval-Modeste AB, Joly P, Dominique S, et al. Prospective study to evaluate the association between systemic sclerosis and occupational exposure and review of the literature. Autoimmun Rev 2014;13:151–6.
[30] Marie I, Menard JF, Duval-Modeste AB, Joly P, Dominique S, Bravard P, et al. Association of occupational exposure with features of systemic sclerosis. J Am Acad Dermatol 2015;72:456–64.
[31] Maeda M, Nishimura Y, Kumagai N, Hayashi H, Hatayama T, Katoh M, et al. Dysregulation of the immune system caused by silica and asbestos. J Immunotoxicol 2010;7:268–78.
[32] Otsuki T, Hayashi H, Nishimura Y, Hyodo F, Maeda M, Kumagai N, et al. Dysregulation of autoimmunity caused by silica exposure and alteration of Fas-mediated apoptosis in T lymphocytes derived from silicosis patients. Int J Immunopathol Pharmacol 2011;24. (11S-6S).
[33] Pfau JC, Serve KM, Noonan CW. Autoimmunity and asbestos exposure. Autoimmune Dis 2014;3014:782045.
[34] Otsuki T, Maeda M, Murakami S, Hayashi H, Miura Y, Kusaka M, et al. Immunological effects of silica and asbestos. Cell Mol Immunol 2007;4:261–8.
[35] Lee S, Hayashi H, Maeda M, Chen Y, Matsuzaki H, Takei-Kumagai N, et al. Environmental factors producing autoimmune dysregulation—chronic activation of T cells caused by silica exposure. Immunobiology 2012;17:743–8.
[36] Miller FW, Alfredsson L, Costenbader KH, Kamen DL, Nelson LM, Norris JM, et al. Epidemiology of environmental exposures and human autoimmune diseases: findings from a National Institute of Environmental Health Sciences Expert Panel Workshop. J Autoimmun 2012;39:25971.
[37] Reinl W. Sklerodermie durch trichloräthylen-einwirkung? Zent F Arbeitsmd u Arbettsschutz 1957;7:58–60.
[38] Garabrant DH, Lacey Jr. JV, Laing TJ, Gillepsie BW, Mayes MD, Cooper BC. Scleroderma and solvent exposure among women. Am J Epidemiol 2003;157:493–500.
[39] Kettaneh A, Al Moufti O, Tiev KP, Chayet C, Toledano C, Fabre B, et al. Occupational exposure to solvents and gender-related risk of systemic sclerosis: a metaanalysis of case–control studies. J Rheumatol 2007;34:97–103.
[40] Nietert PJ, Sutherland SE, Silver RM, Pandey JP, Knapp RG, Hoel DG, et al. Is occupational organic solvent exposure a risk factor for scleroderma? Arthritis Rheum 1998;41:1111–8.
[41] Cai P, König R, Khan MF, Kaphalia BS, Ansari GA. Differential immune responses to albumin adducts of reactive intermediates of trichloroethene in MRL+/+ mice. Toxicol Appl Pharmacol 2007;220:278–83.
[42] Grune T, Michel P, Sitte N, Eggert W, Albrecht-Nebe H, Esterbauer H, et al. Increased levels of 4-hydroxynonenal modified proteins in plasma of children with autoimmune diseases. Free Radic Biol Med 1997;23:357–60.
[43] Halmes NC, Perkins EJ, McMillan DC, Pumford NR. Detection of trichloroethylene-protein adducts in rat liver and plasma. Toxicol Lett 1997;92:187–94.
[44] Wang G, Ansari GA, Khan MF. Involvement of lipid peroxidation-derived aldehyde-protein adducts in autoimmunity mediated by trichloroethene. J Toxicol Environ Health 2007;70:1977–85.
[45] Wang G, König R, Ansari GA, Khan MF. Lipid peroxidation-derived aldehyde-protein adducts contribute to trichloroethene-mediated autoimmunity via activation of CD4+ T cells. Free Radic Biol Med 2008;44:1475–82.
[46] Wang G, Wang J, Fan X, Ansari GA, Khan MF. Protein adducts of malondialdehyde and 4-hydroxynonenal contribute to trichloroethene-mediated autoimmunity via activating Th17 cells: dose- and time-response studies in female MRL+/+ mice. Toxicology 2012;292:113–22.
[47] Shen T, Zhu QX, Yang S, Ding R, Ma T, Ye LP, et al. Trichloroethylene induce nitric oxide production and nitric oxide synthase mRNA expression in cultured normal human epidermal keratinocytes. Toxicology 2007;239:186–94.
[48] Griffin JM, Blossom SJ, Jackson SK, Gilbert KM, Pumford NR. Trichloroethylene accelerates an autoimmune response by Th1 T cell activation in MRL +/+ mice. Immunopharmacology 2000;46:123–37.
[49] Blossom SJ, Doss JC. Trichloroethylene alters central and peripheral immune function in autoimmune-prone MRL(+/+) mice following continuous developmental and early life exposure. J Immunotoxicol 2007;4:129–41.
[50] Palbykin B, Borg J, Caldwell PT, Rowles J, Papoutsis AJ, Romagnolo DF, et al. Trichloroethylene induces methylation of the Serca2 promoter in H9c2 cells and embryonic heart. Cardiovasc Toxicol 2011;11:204–14.
[51] Olsgard ML, Bortolotti GR, Trask BR, Smits JE. Effects of inhalation exposure to a binary mixture of benzene and toluene on vitamin a status and humoral and cell-mediated immunity in wild and captive American kestrels. J Toxicol Environ Health 2008;71:1100–8.
[52] Emara AM, El-Bahrawy H. Green tea attenuates benzene-induced oxidative stress in pump workers. J Immunotoxicol 2008;5:69–80.
[53] Park HJ, Oh JH, Yoon S, Rana SV. Time dependent gene expression changes in the liver of mice treated with benzene. Biomark Insights 2008;3:191–201.
[54] Cooper GS, Parks CG, Treadwell EL, St Clair EW, Gilkeson GS, Dooley MA. Occupational risk factors for the development of systemic lupus erythematosus. J Rheumatol 2004;31:1928–33.
[55] Webber MP, Moir W, Crowson CS, Cohen HW, Zeig-Owens R, Hall CB, et al. Post-September 11, 2001, Incidence of Systemic Autoimmune Diseases in World Trade Center-Exposed Firefighters and Emergency Medical Service Workers. Mayo Clin Proc 2016;91:23–32.
[56] Wu M, Gordon RE, Herbert R, Padilla M, Moline J, Mendelson D, et al. Case report: lung disease in world trade center responders exposed to dust and smoke: carbon nanotubes found in the lungs of world trade center patients and dust samples. Environ Health Perspect 2010;118:499–504.
[57] Kazeros A, Zhang E, Cheng X, Shao Y, Liu M, Qian M, et al. Systemic inflammation associated with world trade center dust exposures and airway abnormalities in the local community. J Occup Environ Med 2015;57:610–6.
[58] Bernatsky S, Smargiassi A, Johnson M, Kaplan GG, Barnabe C, Svenson L, et al. Fine particulate air pollution, nitrogen dioxide, and systemic autoimmune rheumatic disease in Calgary, Alberta. Environ Res 2015;140:474–8.
[59] Bernatsky S, Smargiassi A, Barnabe C, Svenson LW, Brand A, Martin RV, et al. Fine particulate air pollution and systemic autoimmune rheumatic disease in two Canadian provinces. Environ Res 2016;146:85–91.
[60] Fiorito S, Mastrofrancesco A, Cardinali G, Rosato E, Salsano F, Su DS, et al. Effects

of carbonaceous nanoparticles from low-emission and older diesel engines on human skin cells. Carbon 2011;49:5038–48.
[61] Mastrofrancesco A, Alfè M, Rosato E, Gargiulo V, Beatrice C, Di Blasio G, et al. Proinflammatory effects of diesel exhaust nanoparticles on scleroderma skin cells. J Immunol Res 2014;2014:138751.
[62] Aden N, Nuttall A, Shiwen X, de Winter P, Leask A, Black CM, et al. Epithelial cells promote fibroblast activation via IL-1alpha in systemic sclerosis. J Invest Dermatol 2010;30:2191–200.
[63] Chaudhary P, Chen X, Assassi S, Gorlova O, Draeger H, Harper BE, et al. Cigarette smoking is not a risk factor for systemic sclerosis. Arthritis Rheum 2011;63:3098–102.
[64] Yoto Y, Kudoh T, Haseyama K, Suzuki N, Oda T, Katoh T, et al. Incidence of human parvovirus B19 DNA detection in blood donors. Br J Haematol 1995;91:1017–8.
[65] Cassinotti P, Burtonboy G, Fopp M, Siegl G. Evidence for persistence of human parvovirus B19 DNA in bone marrow. J Med Virol 1997;53:229–32.
[66] Magro CM, Nuovo G, Ferri C, Crowson AN, Giuggioli D, Sebastiani M. Parvoviral infection of endothelial cells and stromal fibroblasts: a possible pathogenetic role in scleroderma. J Cutan Pathol 2004;31:43–50.
[67] Sol N, Le Junter J, Vassias I, Freyssinier JM, Thomas A, Prigent AF, et al. Possible interactions between the NS-1 protein and tumor necrosis factor alpha pathways in erythroid cell apoptosis induced by human parvovirus B19. J Virol 1999;73:8762–70.
[68] Ferri C, Giuggioli D, Sebastiani M, Panfilo S, Abatangelo G, Zakrzewska K, et al. Parvovirus B19 infection of cultured skin fibroblasts from systemic sclerosis patients: comment on the article by Ray et al. Arthritis Rheum 2002;46:2262–3.
[69] Pandey JP, Leroy EC. Human cytomegalovirus and the vasculopathies of autoimmune diseases (especially scleroderma), allograft rejection, and coronary restenosis. Arthritis Rheum 1998;41:10–5.
[70] Vaughan JH, Shaw PX, Nguyen MD, Medsger Jr. TA, Wright TM, Metcalf JS, et al. Evidence of activation of 2 herpesviruses, Epstein-Barr virus and cytomegalovirus, in systemic sclerosis and normal skins. J Rheumatol 2000;27:821–3.
[71] Magen E, Delgado JS. Helicobacter pylori and skin autoimmune diseases. World J Gastroenterol 2014;20:1510–6.
[72] Danese S, Zoli A, Cremonini F, Gasbarrini A. High prevalence of Helicobacter pylori type I virulent strains in patients with systemic sclerosis. J Rheumatol 2000;27:1568–9.
[73] Radić M, Martinović Kaliterna D, Bonacin D, Morović Vergles J, Radić J. Correlation between Helicobacter pylori infection and systemic sclerosis activity. Rheumatology (Oxford) 2010;49:1784–5.
[74] Alonso-Ruiz A, Calabozo M, Perez-Ruiz F, Mancebo L. Toxic oil syndrome. A long-term follow-up of a cohort of 332 patients. Medicine (Baltimore) 1993;72:285–95.
[75] Pedersen LM. Permin H. heumatic disease, heavy-metal pigments, and the Great Masters. Lancet 1988;1:1267–9.
[76] Marie I, Gehanno JF, Bubenheim M, Duval-Modeste AB, Joly P, Dominique S, et al. Systemic sclerosis and exposure to heavy metals: a case control study of 100 patients and 300 controls. Autoimmun Rev 2017;16:223–30.
[77] Agarwal S, Zaman T, Tuzcu EM, Kapadia SR. Heavy metals and cardiovascular disease: results from the National Health and Nutrition Examination Survey (NHANES) 1999–2006. Angiology 2011;62:422–9.
[78] Navas-Acien A, Silbergeld EK, Sharrett R, Calderon-Aranda E, Selvin E, Guallar E. Metals in urine and peripheral arterial disease. Environ Health Perspect 2005;113:164–9.
[79] Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for antimony. Altanta, GA: U.S. Public Health Service, U.S. Department of Health and Human Services; 1992.
[80] Schnorr TM, Steenland K, Thun MJ, Rinsky RA. Mortality in a cohort of antimony smelter workers. Am J Ind Med 1995;27:759–70.
[81] Sundar S, Chakravarty J. Antimony toxicity. Int J Environ Res Public Health 2010;7:4267–77.
[82] Winship KA. Toxicity of antimony and its compounds. Adverse Drug React Acute Poisoning Rev 1987;6:67–90.
[83] Zhao X, Xing F, Cong Y, Zhuang Y, Han M, Wu Z, et al. Antimony trichloride induces a loss of cell viability via reactive oxygen species-dependent autophagy in A549 cells. Int J Biochem Cell Biol 2017;93:32–40.
[84] Asakura K, Satoh H, Chiba M, Okamoto M, Serizawa K, Nakano M, et al. Genotoxicity studies of heavy metals: lead, bismuth, indium, silver and antimony. J Occup Health 2009;51:498–512.
[85] Wu F, Fu Z, Liu B, Mo C, Chen B, Corns W, et al. Health risk associated with dietary co-exposure to high levels of antimony and arsenic in the world's largest antimony mine area. Sci Total Environ 2011;409:3344–51.
[86] Cavallo D, Iavicoli I, Setini A, Marinaccio A, Perniconi B, Carelli G, et al. Genotoxic risk and oxidative DNA damage in workers exposed to antimony trioxide. Environ Mol Mutagen 2002;40:184–9.
[87] Stohs SJ, Bagchi D. Oxidative mechanisms in the toxicity of metal ions. Free Radic Biol Med 1995;18:321–36.
[88] Faroon O, Ashizawa A, Wright S, Tucker P, Jenkins K, Ingerman L, et al. Toxicological profile for cadmium. Atlanta (GA): Agency for Toxic Substances and Disease Registry (US); Sep. 2012.
[89] Fagerberg B, Bergstrom G, Boren J, Barregard L. Cadmium exposure is accompanied by increased prevalence and future growth of atherosclerotic plaques in 64-yearold women. J Intern Med 2012;272:601–61.
[90] Menke A, Guallar E, Cowie CC. Metals in urine and diabetes in U.S. adults. Diabetes 2016;65:164–71.
[91] Navas-Acien A, Selvin E, Sharrett AR, Calderon-Aranda E, Silbergeld E, Guallar E. Lead, cadmium, smoking, and increased risk of peripheral arterial disease. Circulation 2004;109:3196–201.
[92] Nawrot TS, Van Hecke E, Thijs L, Richart T, Kuznetsova T, Jin Y, et al. Cadmiumrelated mortality and long-term secular trends in the cadmium body burden of an environmentally exposed population. Environ Health Perspect 2008;116:1620–8.
[93] Peters JL, Perlstein TS, Perry MJ, McNeely E, Weuve J. Cadmium exposure in association with history of stroke and heart failure. Environ Res 2010;110:199–206.
[94] Tellez-Plaza M, Guallar E, Howard B, Umans JG, Francesconi KA, Goessler W, et al. Cadmium exposure and incident cardiovascular disease. Epidemiology 2013;24:421–9.
[95] Tellez-Plaza M, Navas-Acien A, Menke A, Crainiceanu CM, Pastor-Barriuso R, Guallar E. Cadmium exposure and all-cause and cardiovascular mortality in the U.S. general population. Environ Health Perspect 2012;120:1017–22.
[96] Afridi HI, Kazi TG, Brabazon D, Naher S. Interaction between zinc, cadmium, and lead in scalp hair samples of Pakistani and Irish smokers rheumatoid arthritis subjects in relation to controls. Biol Trace Elem Res 2012;148:139–47.
[97] Ansari MM, Neha Khan HA. Effect of cadmium chloride exposure during the induction of collagen induced arthritis. Chem Biol Interact 2015;238:55–65.
[98] Cox JN, Rahman MA, Bao S, Liu M, Wheeler SE, Knoell DL. Cadmium attenuates the macrophage response to LPS through inhibition of the NF-κB pathway. Am J Physiol Lung Cell Mol Physiol 2016;311:L754–65.
[99] Messner B, Bernhard D. Cadmium and cardiovascular diseases: cell biology, pathophysiology, and epidemiological relevance. Biometals 2010;23:811–22.
[100] Olszowski T, Gutowska I, Baranowska-Bosiacka I, Łukomska A, Drozd A, Chlubek D. Cadmium Alters the Concentration of Fatty Acids in THP-1 Macrophages. Biol Trace Elem Res 2018;182:29–36.
[101] Mohajeri M, Rezaee M, Sahebkar A. Cadmium-induced toxicity is rescued by curcumin: a review. Biofactors 2017;43:645–61.
[102] Ohsawa M, Takahashi K, Otsuka F. Induction of anti-nuclear antibodies in mice orally exposed to cadmium at low concentrations. Clin Exp Immunol 1988;73:98–102.
[103] Svensson S, Trobos M, Hoffman M, Norlindh B, Petronis S, Lausmaa J, et al. A novel soft tissue model for biomaterial-associated infection and inflammation - bacteriological, morphological and molecular observations. Biomaterials 2015;41:106–21.
[104] Fortier M, Omara F, Bernier J, Brousseau P, Fournier M. Effects of physiological concentrations of heavy metals both individually and in mixtures on the viability and function of peripheral blood human leukocytes in vitro. J Toxicol Environ Health A 2008;71:1327–37.
[105] Cosselman KE, Navas-Acien A, Kaufman JD. Environmental factors in cardiovascular disease. Nat Rev Cardiol 2015;12:627–42.
[106] KnoflachM Messner B, Shen YH, Frotschnig S, Liu G, Pfaller K, et al. Non-toxic cadmium concentrations induce vascular inflammation and promote atherosclerosis. Circ J 2011;75:2491–5.
[107] Burroughs Peña MS, Rollins A. Environmental exposures and cardiovascular disease: a challenge for health and development in low- and middle-income countries. Cardiol Clin 2017;35:71–86.
[108] Kiran Kumar KM, Naveen Kumar M, Patil RH, Nagesh R, Hegde SM, Kavya K, et al. Cadmium induces oxidative stress and apoptosis in lung epithelial cells. Toxicol Mech Methods 2016;26:658–66.
[109] Saplakoğlu U, Işcan M. Sister chromatid exchanges in human lymphocytes treated in vitro with cadmiumin G(o) and S phase of their cell cycles. Mutat Res 1998;412:109–14.
[110] Vaziri ND, Ding Y, Ni Z. Compensatory up-regulation of nitric-oxide synthase isoforms in lead-induced hypertension; reversal by a superoxide dismutase-mimetic drug. J Pharmacol Exp Ther 2001;298:679–85.
[111] Wadhwa SK, Kazi TG, Afridi HI, Talpur FN, Naeemullah. Interaction between carcinogenic and anti-carcinogenic trace elements in the scalp hair samples of different types of Pakistani female cancer patients. Clin Chim Acta 2015;439:178–84.
[112] Wang B, Li Y, Shao C, Tan Y, Cai L. Cadmium and its epigenetic effects. Curr Med Chem 2012;19:2611–20.
[113] [15] Miekeley N, Dias Carneiro MT, da Silveira CL. How reliable are human hair reference intervals for trace elements? Sci Total Environ 1998;218:9–17.
[114] Heo Y, Parsons PJ, Lawrence DA. Lead differentially modifies cytokine production in vitro and in vivo. Toxicol Appl Pharmacol 1996;138:149–57.
[115] Vaziri ND. Mechanisms of lead-induced hypertension and cardiovascular disease. Am J Physiol Heart Circ Physiol 2008;295:H454–65.
[116] Afridi HI, Brabazon D, Kazi TG, Naher S, Nesterenko E. Comparative metal distribution in scalp hair of Pakistani and Irish referents and hypertensive patients. Biol Trace Elem Res 2011;143:1367–82.
[117] Navas-Acien A, Guallar E, Silbergeld EK, Rothenberg SJ. Lead exposure and cardiovascular disease–a systematic review. Environ Health Perspect 2007;115:472–82.
[118] Hanna CW, Bloom MS, Robinson WP, Kim D, Parsons PJ, Vom Saal FS, et al. DNA methylation changes in whole blood is associated with exposure to the environmental contaminants, mercury, lead, cadmium and bisphenol A, in women undergoing ovarian stimulation for IVF. Hum Reprod 2012;27:1401–10.
[119] Bollati V, Marinelli B, Apostoli P, Bonzini M, Nordio F, Hoxha M, et al. Exposure to metal-rich particulate matter modifies the expression of candidate microRNAs in peripheral blood leukocytes. Environ Health Perspect 2010;118:763–8.
[120] Li C, Yang X, Xu M, Zhang J, Sun N. Epigenetic marker (LINE-1 promoter) methylation level was associated with occupational lead exposure. Clin Toxicol (Phila) 2013;51:225–9.
[121] Wright RO, Schwartz J, Wright RJ, Bollati V, Tarantini L, Park SK, et al. Biomarkers of lead exposure and DNA methylation within retrotransposons.

Environ Health Perspect 2010;118:790–5.
[122] Gardner RM, Nyland JF, Silva IA, Ventura AM, de Souza JM, Silbergeld EK. Mercury exposure, serumantinuclear/antinucleolar antibodies, and serumcytokine levels in mining populations in Amazonian Brazil: a cross-sectional study. Environ Res 2010;110:345–54.
[123] Abedi-Valugerdi M. Mercury and silver induce B cell activation and anti-nucleolar autoantibody production in outbred mouse stocks: are environmental factors more important than the susceptibility genes in connection with autoimmunity? Clin Exp Immunol 2009;155:117–24.
[124] de Vos G, Abotaga S, Liao Z, Jerschow E, Rosenstreich D. Selective effect of mercury on Th2-type cytokine production in humans. Immunopharmacol Immunotoxicol 2007;29:537–48.
[125] Via CS, Nguyen P, Niculescu F, Papadimitriou J, Hoover D, Silbergeld EK. Low-dose exposure to inorganic mercury accelerates disease and mortality in acquired murine lupus. Environ Health Perspect 2003;111:1273–7.
[126] Hanley GA, Schiffenbauer J, Sobel ES. Resistance to HgCl2-induced autoimmunity in haplotype-heterozygous mice is an intrinsic property of B cells. J Immunol 1998;161:1778–85.
[127] Pollard KM, Lee DK, Casiano CA, Bluthner M, Johnston MM, Tan EM. The autoimmunity-inducing xenobiotic mercury interacts with the autoantigen fibrillarin and modifies its molecular and antigenic properties. J Immunol 1997;158:3521–8.
[128] Hess EV. Environmental chemicals and autoimmune disease: cause and effect. Toxicology 2002;181–182:65–70.
[129] Gardner RM, Nyland JF, Evans SL, Wang SB, Doyle KM, Crainiceanu CM, et al. Mercury induces an unopposed inflammatory response in human peripheral blood mononuclear cells in vitro. Environ Health Perspect 2009;117:1932–8.
[130] Hemdan NY, Lehmann I, Wichmann G, Lehmann J, Emmrich F, Sack U. Immunomodulation by mercuric chloride in vitro: application of different cell activation pathways. Clin Exp Immunol 2007;148:325–37.
[131] Motts JA, Shirley DL, Silbergeld EK, Nyland JF. Novel biomarkers of mercuryinduced autoimmune dysfunction: a cross-sectional study in Amazonian Brazil. Environ Res 2014;132:12–8.
[132] Crowe W, Allsopp PJ, Watson GE, Magee PJ, Strain JJ, Armstrong DJ, et al. Mercury as an environmental stimulus in the development of autoimmunity - a systematic review. Autoimmun Rev 2017;16:72–80.
[133] Ercal N, Gurer-Orhan H, Aykin-Burns N. Toxic metals and oxidative stress part I: mechanisms involved in metal-induced oxidative damage. Curr Top Med Chem 2001;1:529–39.
[134] Grotto D, Valentini J, Fillion M, Passos CJ, Garcia SC, Mergler D, et al. Mercury exposure and oxidative stress in communities of the Brazilian Amazon. Sci Total Environ 2010;408:806–11.
[135] Hayes JD, Flanagan JU, Jowsey IR. Glutathione transferases. Annu Rev Pharmacol Toxicol 2005;45:51–88.
[136] Liang FQ, Alssadi R, Morehead P, Awasthi YC, Godley BF. Enhanced expression of glutathione-S-transferase A1-1 protects against oxidative stress in human retinal pigment epithelial cells. Exp Eye Res 2005;80:113–9.
[137] Omanwar S, Fahim M. Mercury exposure and endothelial dysfunction: an interplay between nitric oxide and oxidative stress. Int J Toxicol 2015;34:300–7.
[138] Federmann M, Morell B, Graetz G, Wyss M, Elsner P, von Thiessen R, et al. Hypersensitivity to molybdenumas a possible trigger of ANA-negative systemic lupus erythematosus. Ann Rheum Dis 1994;53:403–5.
[139] Caicedo MS, Samelko L, McAllister K, Jacobs JJ, Hallab NJ. Increasing both CoCrMoalloy particle size and surface irregularity induces increased macrophage inflammasome activation in vitro potentially through lysosomal destabilization mechanisms. J Orthop Res 2013;31:1633–42.
[140] Pearson MJ, Williams RL, Floyd H, Bodansky D, Grover LM, Davis ET, et al. The effects of cobalt-chromium-molybdenum wear debris in vitro on serum cytokine profiles and T cell repertoire. Biomaterials 2015;67:232–9.
[141] Dai X, Xing C, Cao H, Luo J, Wang T, Liu P, et al. Alterations of mitochondrial antioxidant indexes and apoptosis in duck livers caused by Molybdenum or/and cadmium. Chemosphere 2018;193:574–80.
[142] Hansen PA, West LA. Allergic reaction following insertion of a Pd-Cu-Au fixed partial denture: a clinical report. J Prosthodont 1997;6:144–8.
[143] Helm D. Association between palladium urinary concentrations and diseases of the thyroid and the immune system. Sci Total Environ 2002;299:247–9.
[144] Stejskal J, Stejskal VD. The role of metals in autoimmunity and the link to neuroendocrinology. Neuro Endocrinol Lett 1999;20:351–64.
[145] Rachmawati D, Bontkes HJ, Verstege MI, Muris J, von Blomberg BM, Scheper RJ, et al. Transition metal sensing by Toll-like receptor-4: next to nickel, cobalt and palladium are potent human dendritic cell stimulators. Contact Dermatitis 2013;68:331–8.
[146] Rachmawati D, Muris J, Scheper RJ, Rustemeyer T, Kleverlaan CJ, Feilzer AJ, et al. Continuing the quest for autoimmunity due to oral metal exposure. Autoimmunity 2015;48:494–501.
[147] Fickl H, Theron AJ, Anderson R, Mitchell TJ, Feldman C. Palladium attenuates the pro-inflammatory interactions of C5a, interleukin-8 and pneumolysin with human neutrophils. J Immunotoxicol 2007;4:247–52.
[148] Chuang HC, Juan HT, Chang CN, Yan YH, Yuan TH, Wang JS, et al. Cardiopulmonary toxicity of pulmonary exposure to occupationally relevant zinc oxide nanoparticles. Nanotoxicology 2014;8:593–604.
[149] Bengalli R, Gualtieri M, Capasso L, Urani C, Camatini M. Impact of zinc oxide nanoparticles on an in vitro model of the human air-blood barrier. Toxicol Lett 2017;279:22–32.
[150] Bonaventura P, Benedetti G, Albarède F, Miossec P. Zinc and its role in immunity and inflammation. Autoimmun Rev 2015;14:277–85.
[151] Chuang KJ, Lee KY, Pan CH, Lai CH, Lin LY, Ho SC, et al. Effects of zinc oxide nanoparticles on human coronary artery endothelial cells. Food Chem Toxicol 2016;93:138–44.
[152] Sato I, Yuan BD, Nishimura T, Tanaka N. Inhibition of tumor growth and metastasis in association with modification of immune response by novel organic germanium compounds. J Biol Response Mod 1985;4:159–68.
[153] Aso H, Suzuki F, Yamaguchi T, Hayashi Y, Ebina T, Ishida N. Induction of interferon and activation of NK cells and macrophages in mice by oral administration of Ge-132, an organic germanium compound. Microbiol Immunol 1985;29:65–74.
[154] Nakamura T, Saito M, Aso H. Effects of a lactobacilli, oligosaccharide and organic germanium intake on the immune responses of mice. Biosci Biotechnol Biochem 2012;76:375–7.
[155] Bernal-Bello D, de Tena JG, Guillén-Del Castillo A, Selva-O'Callaghan A, Callejas-Moraga EL, Marín-Sánchez AM, et al. Novel risk factors related to cancer in scleroderma. Autoimmun Rev 2017;16:461–8.
[156] Giat E, Ehrenfeld M, Shoenfeld Y. Cancer and autoimmune diseases. Autoimmun Rev 2017;16:1049–57.