Review

The role of environmental heavy metals and the risks for autoimmunity and related rheumatic diseases

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ABSTRACT

Heavy metal exposure has been associated with the development of autoimmune rheumatic diseases in susceptible individuals. We briefly reviewed the cellular and molecular mechanisms by which metals can affect auto proteins and convert them into neoantigens and analyse the potential integrin-dependent signalling pathways that result in the production of inflammatory cytokines and autoantibodies. We critically assess autoimmunity related to heavy metal exposure. We also discuss environmental measures to prevent environmental pollution and conclude that heavy metal environmental pollution is an unacceptable, yet preventable, problem.

Introduction

Exposure to heavy metals has been associated with the development or exacerbation of autoimmune rheumatic diseases in immunogenetically susceptible individuals, because these metals can induce autoreactive responses through the activation of integrins and their corresponding signalling pathways. This response results in the expression of inflammatory cytokines and autoantibody production, which constitutes a potential risk for autoimmunity and related rheumatic diseases.

Our specialty celebrates the *Journal of Environmental Rheumatology*, which publishes clinical and experimental findings about how environmental factors may induce rheumatic diseases (1). A prominent example is the emblematic case of toxic oil syndrome that appeared in 1981 in Spain as a consequence of contaminated oil ingestion, which affected thousands of subjects and was called "toxic oil syndrome" (TOS). Clinical and epidemiological observations, along with molecular investigations by Spaniards and other colleagues, revealed that the disease was caused by the consumption of contaminated rapeseed oil produced by a specific refinery and that two compounds, 1,2-di-oley ester (DEPAP) and oleic aniline, were responsible for triggering the disease. This case exemplifies the influence of environmental factors in eliciting a multiorgan rheumatic disease (2).

With respect to xenobiotics and rheumatology, pioneer studies in the early eighties drew our attention, especially the long-term work of Hultman and Pollard, who published diverse clinical and experimental findings related to mercury exposure and autoimmunity. In this review, we refer to their multiple contributions.

Human exposure to environmental pollutants is the result of anthropogenic industrial activities, particularly those related to heavy metals, which are, in most cases, a consequence of mining and related processes. In the past, mining waste contaminated air, soils, plants, water sources, and food, causing involuntary or accidental exposure in humans. With respect to rheumatology, there are diverse examples of how this type of environmental alteration may elicit autoimmunity, since multiple reports suggest that chronic exposure to heavy metal pollutants might elicit clinical symptoms with autoantibody production.

The specific aim of this review is to provide rheumatologists selected information about environmentally toxic risk factors for autoimmune rheumatic diseases (ARDs).

How do cells relate to the extracellular environment?

Integrins are heterodimeric glycoproteins that mediate cell adhesion and provide a molecular link between cells and the extracellular matrix (ECM). Integrins serve as bidirectional sensors that transmit signals from the extracellular environment to the interior of the cell and *vice versa*. A large amount of experimental evidence has demonstrated that transduction signals are mediated by one of the extracellular domains of integrins linked to the extracellular matrix. This domain is mechanically or chemically stimulated, which leads to a signalling event that results in specific modulation of some physiological action (3). Integrins are fundamental for tissue homeostasis, with functions that include the assembly of the extracellular matrix, cell adhesion, and immune cell trafficking. These molecules actively participate in inflammation and are involved in specific responses by acting at the immunological synapse level. The intracellular domain of integrins regulates the transduction cascades stimulating the serine/threonine kinases Raf-MEK or Raf-ERK; these molecules, according to their microenvironment, develop their own signalling dynamics depending on their specific interaction with different ligands, including metals and/or drugs (4).

Integrins are heterodimers formed by the α and β subunits; both subunits have an extracellular domain; the α subunit has approximately 700 residues; and the β subunit possesses ≈ 1000 residues. With the exception of α6β4 integrin, integrins possess extracellular domains that have a globular head that projects a transmembrane leg of alpha helices that ends in a short cytoplasmic tail, which activates membrane-bound kinases. The domain participates in cell-to-cell interactions, cell-to-matrix interactions, and matrix-to-matrix interactions, which promote adhesion during cell migration, morphogenesis, homeostasis, immunity, inflammation, and wound healing (5).

The extracellular head of the α-integrin has a structure of seven blades of α-helices that resemble a ship propeller. This structure allows intimate contact of the domain with the β-I domain. The nine α subunits (α1, α2, α10, α11, αD, αE, αL, αM, and αX) contain an additional conserved sequence named α-I, which is located between the two loops of the upper surface of the helix and plays an important role in binding. This invariant sequence or "I" domain is called the metal-ion-dependent binding site (5-7). The "I" domain functionally displays two conformational patterns. This domain is also present in all β subunits (I-like β I domain) and constitutes the principal structure of the ligand-binding pocket of integrins lacking α I (Fig. 1).

Metal binding cluster sites of integrins determine their interactions

The metal-ion-dependent adhesion site (MIDAS) motif is a coordinated motif composed of three loops of the "I" domains with residues prone to ligation, such as glutamic or aspartic acids, that build a transitory octagon surrounding the metal ion. The ligation ability of MIDAS depends on its conformational status, which also bestows affinity and functionality. If the conformation of the MIDAS motif is open, the affinity is high, and the integrin is active, resulting in a specific function. However, if the conformation is closed, the motif is inactive, and the integrin returns to a low-affinity state, stopping the function. In other words, the quaternary changes in the "I" domain affect the capacity of MIDAS for metal binding (6-8). Additionally, there is a Ca^{2+}-dependent cation-binding site adjacent to the MIDAS named AMIDAS that stabilizes the conformation of the integrin and is required to maintain the low-affinity conformation of the integrin head (9,10). Additionally, the ligand-associated metal-binding site (LIMBS) is a complementary region that enhances the activity of MIDAS (11). Metal binding to the cell surface is a complex event required for any cell response, and MIDAS motifs, AMIDAS, and LIMBS domains directly regulate the binding of metals to different cells. This interaction stereochemically modifies the shape of self-proteins to be recognized as "neoantigens" by antigen presenting cells (APCs).

Autoimmunity

The main role of the immune system is to protect the host from pathogens to maintain body homeostasis through the recognition of foreign antigens. This evolving ability of the vertebrate immune system is specific and is based on the complementary binding of "strange peptides" to their cognate T-cell receptors (TCRs); thus, by this mechanism, we can discriminate self-proteins from nonself proteins. T and B-cell receptor production is generated randomly by somatic rearrangements or by hypermutation; therefore, the possibility of self-reactive receptor production may arise. When this occurs, immunologic tolerance emerges as a mechanism to prevent tissue damage and self-harmful responses. This physiologic state of tolerance is maintained throughout life. For example, during ontogeny, self-reactive cells are avoided by deletion or receptor editing. $CD4^+$ T cells with autoreactive receptors are subjected to negative selection into the thymus to delete them. This action prevents the expansion of autoimmune clones. Additionally, the immune system uses another process that decreases signalling via a process of "anergy", which involves diverse costimulatory molecules, including CD28, CTLA-4 and their corresponding CD80 and CD86 ligands; additionally, an extra preventive mechanism exists at the medulla of the thymus, which is mediated by $CD4^+CD25^+Foxp3^+$ regulatory cells (tTregs) that can recognize autoantigens. These autoantigens are ectopically expressed by the transcriptional activity of the autoimmune regulator AIRE in thymic epithelial cells so that tTregs can attenuate the "self-reactive" immune response centrally. There is also a repertoire of peripheral tolerance mechanisms that include apoptosis, anergy, and peripheral $CD4^+Foxp3^+$ Tregs to prevent the activation or proliferation of autoreactive clones (12-17).

Autoimmune conditions are driven by abnormal T- and B-cell reactivity against normal or modified self-proteins or specific tissues. The pathophysiology of autoimmune conditions is complex and, in subjects exposed to metals, is linked to the major histo-

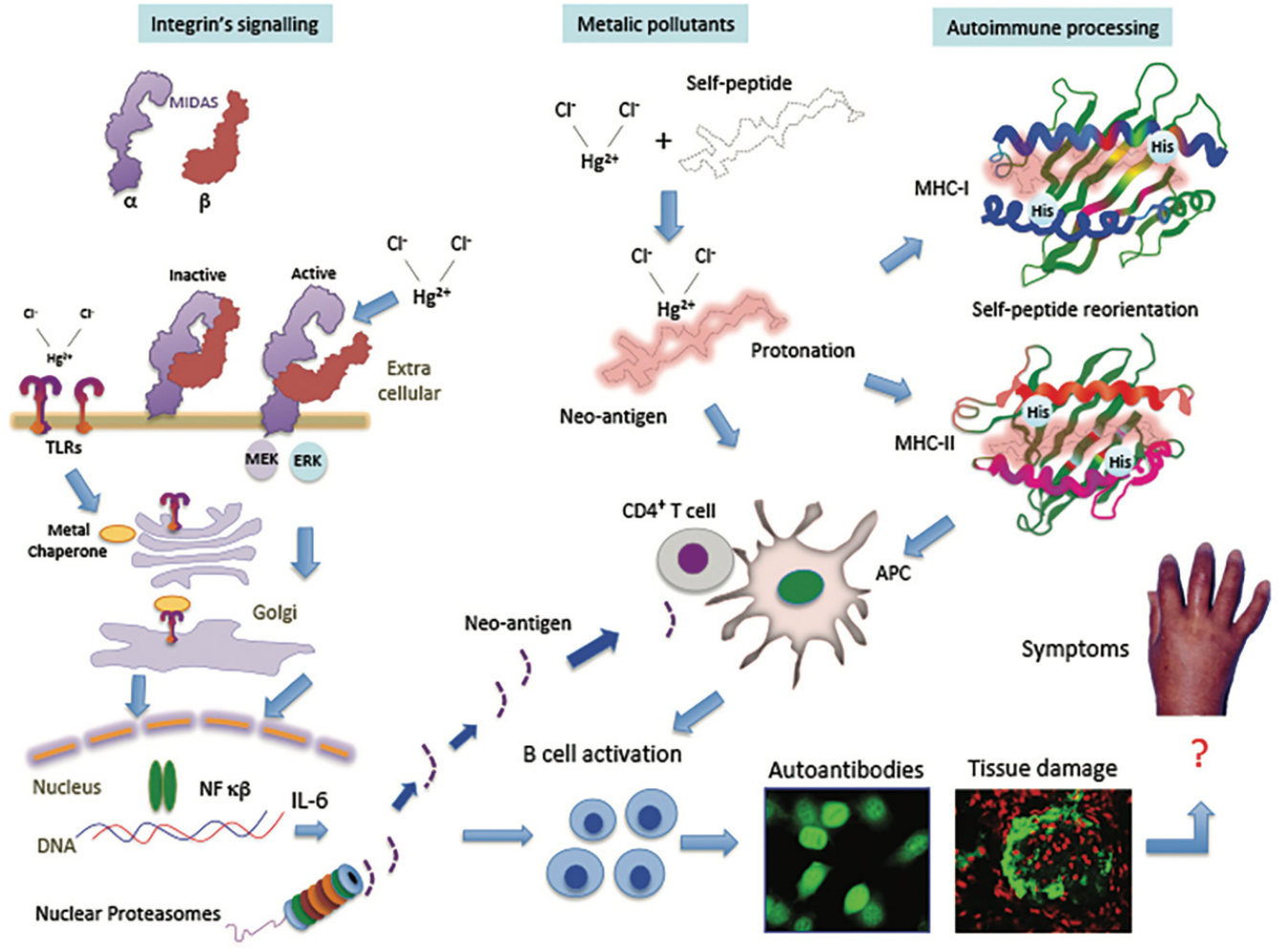

Fig. 1. Environmental pollutants, including metallic ions, may trigger an autoimmune response. One example in this figure is mercury chloride, which may reach the extracellular space and interact with integrins or TLRs and can be induced via Raf-MEK or Raf-ERK to promote the NF κβ pathway, resulting in IL-6 production, which in turn elicits autoantibody production. Additionally, metals may change the stereochemical conformation of normal peptides, transforming them into "neoantigens" through the protonation of histidine (His) residues and causing reorientation of peptides such that they are recognized by the MHC of APCs as autoantigens. In this way, autoimmunity is elicited via CD4+ T-cells, which in turn stimulate B-cells, which together cause inflammation and tissue damage, such as to the glomerulus. Eventually, some patients may display symptoms such as sclerodactyly or other clinical manifestations.

compatibility complex (MHC), and the repertoire of self-reactive responses includes the production of proinflammatory cytokines as well as cytotoxic mechanisms mediated by $CD8^+$ T-cells. In addition, autoimmune T-cells are, in most cases, responsible for autoreactive B-cell activation, which is reflected by autoantibody production. Autoantibodies are fundamental biomarkers for the clinical diagnosis and/or classification of autoimmune diseases.

From a clinical point of view, the autoimmune phenomenon is typically irrelevant; however, human autoimmune diseases (AIDs) are characterised by aberrant activation of autoreactive cells that produce diverse grades of tissue inflammation via diverse mechanisms that may result in transitory or permanent damage and organ dysfunction.

Autoimmune diseases are classified as follows: 1) organ-specific diseases that affect one organ, such as thyroiditis and pemphigus; 2) systemic diseases that evolve with diffuse or generalised manifestations, such as systemic lupus erythematosus (SLE) and related diseases, and 3) another "autoinflammatory" group of diseases that do not strictly fulfil the autoimmune criteria; however, these diseases, such as psoriasis and Crohn's disease, produce an inflammatory response and are included as part of this broad spectrum (18-22).

Many environmental factors have been linked to the development of autoimmune diseases, some of which may suggest possible pathogenic involvement, but in other cases, the link is uncertain. In this review, we focus on metals (22).

Autoimmune association with metal exposure

Clinical and experimental evidence suggests that chronic exposure to heavy metals results in autoimmune mechanisms that are not fully understood. It has been proposed that the interaction between metallic ions and cells is mediated via integrins, which chemically modify some self-proteins prone to being recognized as "autoantigens" by the class I or II molecules of APCs. In this context, metallic ions may af-

fect the behaviour of class I molecules that interact with self-peptides in an allele-specific mode as a consequence of this realignment. For example, the Cu^{2+} ions modify the conformation and orientation of self-peptides bound to class I molecules, creating "neo-antigens" with histidine (His) residues that are responsible for such reorientation. It seems that this modification also applies to certain class II molecules where changes in the protonation of the His residues of DR molecules may affect their interaction with specific ligands (self-proteins). Therefore, pH is a critical factor for this conformational transition that allows ligand exchange. In summary, normal proteins may be directly modified by their interaction with metallic ions or indirectly via protonation at His residues at MHC molecules (23-27).

Additionally, xenobiotics such as mercuric chloride and platinum salts may disturb proteolysis at the nuclear proteasomal level, which is followed by the recruitment of nuclear neoantigens, which seems to be important in scleroderma, as is the case for fibrillarin and DNA-topoisomerase I (28, 29).

Another possibility is that the interaction between metals and integrins triggers abnormal signalling that may stimulate the transcription factor NF-κβ pathway in immune cells, resulting in the production of autoantibodies. As previously mentioned, integrins regulate transduction signals via Raf-MEK or Raf-ERK cascades and serve as a link between excess Cu^{2+} and autoimmunity because copper chaperones (CCSs) increase Cu^{2+} binding to MEK1/2, which promotes the activation and proliferation of immune cells. Alternatively, the interaction between metals and integrins may trigger the type I IFN pathway via Toll-like receptors (TLRs), which induce NF-κβ signalling that promotes IL-6 synthesis, which in turn stimulates B-cells for autoantibody production (30, 31) (Fig. 1).

Experimental data of autoimmunity elicited by metallic ions

Metallic ions exist in nature in elemental, organic and inorganic forms and frequently form complexes because some of them are highly charged and susceptible to developing supramolecular clusters. These complexes result from bonding interactions between the metal ion and its neighbouring residues: the bond angle and torsion as well as the columbic and van der Waals (vdW) forces are involved in this process. Additionally, the noncovalent interactions are due to the attraction forces induced by the interchange of metallic ions established by the columbic and vdW forces. Thus, considering the aforementioned physicochemical properties, pollutants containing heavy metal ions are prone to interact with and modify soil or water compounds, so they present a potential risk to all living beings by interfering with their physiology (32).

There is extensive literature concerning the effects of heavy metals on the immune system. Among the best evidence of toxicity caused by mercury (Hg^{2+}) and its association with autoimmunity is the work of the Swedish investigators Hultman and Eneström, who injected BALB/c mice with $HgCl^2$/kg for 12 weeks; a significant number of animals developed antinuclear antibodies (ANAs) with nucleolar patterns and the autoantibodies were eluted from kidneys in a similar pattern to those found in sera (33). Later, the same investigators, in collaboration with Michel Pollard and Eng Tan from La Joya CA, clarified that the nucleolar pattern was fibrillarin autoantigen (34), which was important since fibrillarin is complexed with U3 small nucleolar RNAs, and such complexes are targets of autoantibodies of scleroderma patients. Furthermore, autoantibodies from experimental animals and patients recognize the same epitope encompassing residues 1-312 (35-44). Similarly, Arnett reported a causal association between anti-U3 fibrillarin autoantibodies and elevated Hg^{2+} levels measured in urine by atomic absorption, suggesting an association between mercury pollutants and scleroderma. Notably, the pathophysiology of this disease is enigmatic, multifactorial, and complex, and such an association does not necessarily indicate that this disease is caused by metal exposure (40, 41, 45). Hg^{2+}-induced nephrotoxicity was discovered in early 1978 by Roman-Franco *et al*., who reported the induction of anti-basement membrane antibodies and antigen-antibody complexes in an experimental model in rabbits injected with mercuric chloride (46). These observations were confirmed by other investigators, who demonstrated the role of T-cells in the induction of autoimmune glomerulonephritis in Brown-Norway rats. This susceptibility was also restricted to a strain, indicating a possible immunogenic role linked to the MHC genes for induced autoimmunity (46-49). Furthermore, inducers of autoimmunity extend to other metallic ions, some of which are capable of eliciting glomerulonephritis with the production of diverse antinuclear antibodies. We confirmed the previously mentioned findings and demonstrated that anti-DNA-elicited autoantibodies affect the glomerular filtration rate, which induces proteinuria because podocytes are sensitive to metallic ions that cause effacement and associated proteinuria (50) (Fig. 2).

From hypothesis in an animal to the clinical reality at the hospital

Clinical evidence of the impact of mine pollutant exposure and human health effects has been widely studied. In particular, the Lancet Commission identified the greatest number of environmental triggers and related diseases (51). Human exposure to the environment is a complex issue that includes geochemical, geographical, socioeconomic, and labour-related factors associated with a predisposition to environmental exposure. We understand this because our research institute is located near metallic ores from active mining activities. Incidentally, we note that most scleroderma patients recorded in our archives are residents of cities or small villages near active mines, and in many cases, the exploitation of these mines started 450 years ago and created almost permanent environmental pollutants that can now be traced in the human population (52).

Other conditions that must be considered in this matter are as follows: was the exposure to metallic ions occupa-

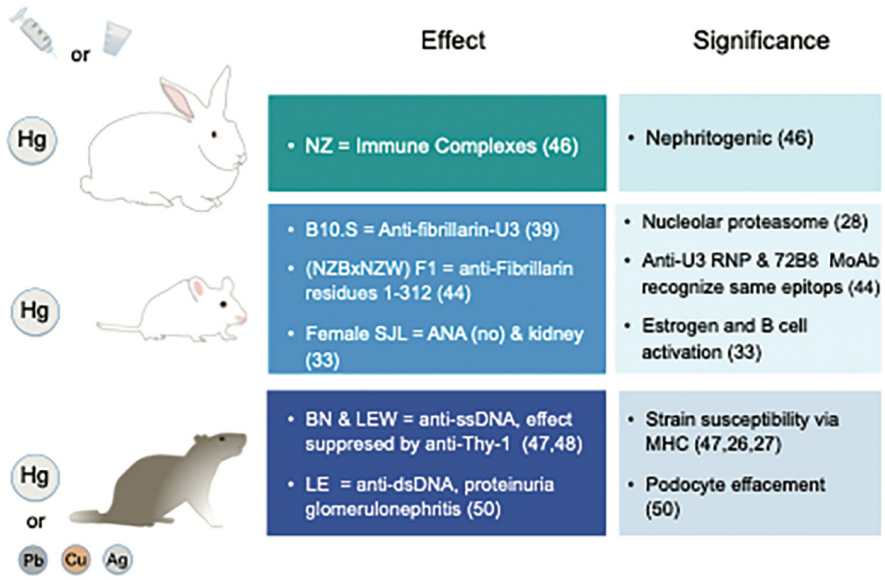

Fig. 2. Model autoimmunity induced by metals. The remaining strains were NZ (New Zealand rabbit). B10. S SJL is an inbred strain of mice with a specific MHC. F1 is a hybrid NZBxNZW prone to developing lupus. BN is a brown Norway rat. High susceptibility to mercury-induced glomerulonephritis. LEW is a Lewis rat that is highly sensitive to the induction of autoimmunity. LE is a Long Evans rat. The middle panel shows the main effect induced by the metal, and the right panel shows the possible meaning of this effect. (ANA(no) antinuclear antibodies with a nucleolar pattern.

tional? Accidental? Involuntary? Was it individual or collective exposure? Was it acute or chronic? All of these issues must be clarified (51, 53); we should consider that the progression from obtaining experimental data from animals or cell cultures to interpreting clinical data from humans is "a *long and winding road*" because many clinical records are limited, incomplete or lack epidemiologic studies, so most reports are not systematic and cannot be considered controlled clinical or epidemiological trials; thus, the analysis of clinical data often leads to more questions than answers (54). The aforementioned World Health Organization (WHO) task group analysed the relationship between environmental factors and autoimmunity. The product of this pioneering concern was drafted in 2002, and during various meetings at Bilthoven in the Netherlands. The task group finished a draft in November 2005 and published a formal document with the environmental health criteria in 2006. This remarkable effort contains a useful guide to identify autoimmune diseases linked to environmental factors (55). The proposal was revisited in 2012 by another group of studies led by Miller from the NIH and Pollard from La Joya, CA; in general, they were in agreement with the original hypothesis and noted "that by the identification of data to define the environmental risks for autoimmune disease, the epidemiological tools must be of help, and suggested that such associations would be followed by testing mechanisms using refined methods of confirmation before being considered criteria." In the same paper, Miller et al. indicated a critical issue: "the identification of the environmental agents capable of inducing autoimmune disease in individuals"; consequently, the reading and conceptualisation of the aforementioned documents are of crucial importance as a framework in environmental rheumatology (56).

Among the most toxic heavy metals for humans are mercury, lead, chromium, cadmium, and arsenic, as well as silver, gold and other possible triggers of autoimmunity (57-60). At the end of the last century, dental amalgams were identified as potential sources of mercury exposure in the general population, and many articles were published, arguing either for or against this hypothesis. As a result of this controversy, dental amalgams began to be substituted by other materials such as resins or porcelain, and amalgams and/or other metallic ions were speculated to be potential inducers of stomatitis, glomerulonephritis, thyroiditis, fibromyalgia, scleroderma, various types of nephropathy and other autoimmune clinical data not strictly related to rheumatology. However, the Achilles' heel of some reports was the lack of methods for identifying pollutants and specific biomarkers or molecular tissue changes induced by these pollutants (61-69). Interestingly, in a study of a large cohort of 5848 cases of dental amalgam filling in primary Sjögren's syndrome patients with their respective controls, there were no significant differences in the possible risk of developing Sjögren's syndrome; the aforementioned autoimmune risk can be explained by heterogeneous ethnic susceptibility (70).

Additionally, in Nordic countries, fish consumption during pregnancy has been reported to be associated with an increased risk of developing juvenile idiopathic arthritis, which is likely linked to contamination with heavy metals in the fish and therefore significantly increased concentrations of Al, Cd and Li in cord blood (71). Additionally, a mimicking case of SLE associated with mercury exposure was reported (72). Interestingly, delayed-type hypersensitivity to nickel and mercury was found in a cohort of 38 patients with connective tissue disease (73); in the same sense, patients with different autoimmune diseases have an increased risk of cutaneous metal hypersensitivity, especially nickel hypersensitivity, which improved after amalgam replacement (74, 75).

Currently, basic science and its relationship with clinical rheumatology has changed, and there are many better clinical, epidemiological and molecular tools, including transcriptomics, proteomics and other "multiomic" tools, that may reveal the toxic effects of metal contamination in biological samples or fluids, including those at the subcellular level, such as exosomes (76-82). The exposome reflects the influences of the environment at the cellular level and thus provides a better understanding of the effects of external pollutants. The exposome uses a mix-

ture of data that measure epigenetic modifications induced by pollutants and correlates this with data that measure environmental chemicals via convectional or refined methods to obtain a holistic understanding of the relationship between rheumatic autoimmunity and pollutants (83-85). Thus, our current tools, such as "the ANA patterns induced by xenobiotics", will be used in the near future as a conceptual arm of the reactome (86-89).

A final reflection on the mitigation of environmental impacts from mining

We must recognise that mining products contributed and are still contributing to the progress of humanity and have transformed the daily life of our society; however, mining activities have not been friendly to the environment, creating mineral waste or mineral deposits even after the closure of the mines. Many cities or small villages are located near mines, and in many cases, waste has been discharged into rivers or near water sources; however, according to international legislation, buffer zones have been designed to protect the environment (90-93). Additionally, there are many regulations designed to minimize the impact of mining, including the reclamation or regeneration of viable soils; biomining by microorganisms that oxidize some metals, allowing them to dissolve in water; soil treatment; water treatment; the prevention of acid rock drainage; and the control of gas emissions (94). Therefore, the current concept of environmental sustainability is a critical issue in modern mining. We must remember that this industrial activity uses non-renewable natural sources and that the healing of the planet is crucial (93, 94).

Concluding remarks

Finally, we must note that environmental pollution is a difficult issue tied to the economy and politics; however, overall, protecting the environment is critical for the survival of our planet, and actions to modify some paradigms. For example, the *planned obsolescence* of consumer goods towards a circular economy may be needed (95). As rheumatologists, our major interest is to identify and solve autoimmunity cases linked to environmental pollutants, but as common citizens, we must intensify efforts to clean the environment.

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As tribute to Manuel Macías-Patiño, an environmentalist.

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