Summer 2025, Volume 10, Issue 38 (34- 47) DOI: 10.22034/pmj.2025.728531

Personalized & Precision Medicine Journal

Homepage: www.pmjournal.ir

Autoimmune Diseases and Their Relationship with Environmental Pollution

Farnaz Eghbalpour [1,*], **Mahnaz Saremi** [2]

[1]**Department of Molecular Medicine, Golestan University of Medical Sciences, Gorgan, Iran.**
[2] **Reference Health Laboratory, Ministry of Health and Medical Education, Tehran, Iran.**

ARTICLE INFO

Paper Type: Review Article

Submitted: 2025-04-25
Accepted: 2025-08-16

Keywords:
Autoimmune diseases
Environmental pollution
Heavy metals
Airborne particulate matter
Oxidative stress

Corresponding author:
Farnaz Eghbalpour
Email: F.eghbalpour@goums.ac.ir

ABSTRACT

Autoimmune diseases (AIDs) are characterized by the immune system's maladaptive response against self-antigens, culminating in chronic inflammation and progressive tissue damage. Although genetic predisposition establishes baseline susceptibility, environmental pollutants—such as heavy metals, pesticides, fine particulate matter (PM2.5), and industrial chemicals—are increasingly recognized as pivotal triggers of immune dysregulation. These xenobiotics induce oxidative stress, disrupt immune tolerance by impairing regulatory T-cell function, and modulate critical signaling pathways including NF-κB, MAPK, and JAK-STAT. Epidemiological studies corroborate associations between pollutant exposure and heightened incidence or severity of conditions such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and type 1 diabetes. This review synthesizes molecular, cellular, and population-based evidence to elucidate the mechanisms by which environmental pollution contributes to the onset and progression of AIDs.

How to Cite this Article:

F. Eghbalpour, M. Saremi. "Autoimmune Diseases and Their Relationship with Environmental Pollution" Personalized & Precision Medicine Journal, Vol. 10, no. 38, pp. 34- 47.

INTRODUCTION

Autoimmune diseases (AIDs) encompass a diverse group of disorders in which the immune system mistakenly attacks the body's own cells and tissues, leading to chronic inflammation, functional impairment, and often irreversible damage (1, 2). The clinical manifestations vary widely from organ-specific conditions like Hashimoto's thyroiditis to systemic diseases such as systemic lupus erythematosus (3), rheumatoid arthritis (RA), multiple sclerosis (4), and type 1 diabetes (T1D) (5). Collectively, these diseases affect millions of individuals worldwide, and their prevalence is rising across both developed and developing nations (6).

Although genetic predisposition particularly involving human leukocyte antigen (HLA) genes and other immune-regulatory loci plays a foundational role in determining individual susceptibility, it does not fully account for disease onset. Increasingly, environmental exposures are recognized as necessary cofactors that trigger autoimmunity in genetically susceptible hosts (7).

Among these environmental factors, pollution has emerged as a major contributor. Industrial expansion, urbanization, and modern agricultural practices have led to elevated levels of airborne and waterborne toxins, including heavy metals (e.g., lead, mercury, cadmium), fine particulate matter ($PM_{2.5}$), gaseous pollutants (NO_2, O_3, SO_2), and synthetic pesticides (8). These pollutants are capable of disrupting immune homeostasis by inducing oxidative stress, damaging cellular components, impairing regulatory T-cell (Treg)

function, and modulating key signaling pathways involved in inflammation and immune surveillance—such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), mitogen-activated protein kinase (MAPK), and Janus kinase/signal transducer and activator of transcription (JAK-STAT) pathways (9).

This dysregulation compromises immune tolerance, leading to aberrant immune responses and loss of self-recognition. The ensuing proinflammatory state not only increases the likelihood of developing autoimmune diseases but also exacerbates allergic responses and susceptibility to infections (10).

As the interplay between genetic and environmental risk factors becomes more evident, it emphasizes the need for integrated prevention strategies. This includes both personalized medicine approaches—taking into account individual genetic profiles—and public health policies aimed at reducing environmental toxin exposure. Raising public awareness, enhancing early detection, and implementing regulatory interventions are essential steps toward reducing the global burden of autoimmune diseases (11).

Environmental Pollutants and Their Impact on Immune System Function

Environmental pollutants exert profound effects on immune system function through multiple interconnected mechanisms. Various toxicants including heavy metals (e.g., lead, mercury, cadmium, arsenic), pesticides, industrial chemicals, and airborne particulate matter can modulate both innate and adaptive immune responses (12). These contaminants influence the activity and behavior of immune cells such as dendritic cells, macrophages, T lymphocytes, and B lymphocytes, all of which are essential for maintaining immune homeostasis and orchestrating effective responses to pathogens (13).

One of the primary ways pollutants impact immune regulation is through the alteration of cytokine production. Cytokines are pivotal signaling molecules that mediate immune cell communication and coordinate inflammation, immune activation, and resolution processes. Exposure to environmental toxins can lead to aberrant cytokine profiles, characterized by either exaggerated proinflammatory responses or impaired anti-inflammatory signaling, thereby contributing to immune dysregulation (14).

Moreover, many pollutants induce oxidative stress by generating excessive reactive oxygen species (ROS), which overwhelm the body's endogenous antioxidant defense systems. This redox imbalance compromises the integrity of immune cells and tissues, leading to chronic inflammation, DNA damage, and impaired immunoregulation (15). Persistent oxidative stress not only weakens host defenses against infections but also promotes the development of autoimmunity through mechanisms such as antigen modification, loss of tolerance, and sustained immune activation (16).

At the molecular level, several key signaling pathways are implicated in pollutant-induced immune dysfunction. These include

- **Nuclear factor kappa B (NF-κB)**: A central regulator of inflammation and immune responses, frequently activated by environmental stressors.
- **Mitogen-activated protein kinases (MAPKs)**: Involved in cellular responses to oxidative stress, cytokine production, and apoptosis.
- **Janus kinase/signal transducer and activator of transcription (JAK-STAT)**: Modulates cytokine signaling and immune cell differentiation.
- **Nuclear factor erythroid 2–related factor 2 (Nrf2)**: A master regulator of antioxidant defense mechanisms.

Among these, Nrf2 plays a particularly vital role in cellular defense by regulating the expression of genes involved in antioxidant production and detoxification. Activation of the Nrf2 pathway has emerged as a promising therapeutic strategy to counteract pollutant-induced oxidative damage. Enhancing Nrf2 signaling may bolster immune resilience by attenuating oxidative stress and reducing chronic inflammation (17).

Understanding the interaction between environmental pollutants and these signaling pathways is critical for the development of targeted therapeutic interventions. By modulating these pathways, researchers aim to create innovative strategies that mitigate the immunotoxic effects of environmental exposures and restore immune balance (18). For instance, pharmacologic Nrf2 activators, anti-inflammatory agents, and immune-modulating compounds are being investigated for their potential to enhance immune defense mechanisms in polluted environments (1).

Pollutants also exert epigenetic effects by altering gene expression through DNA methylation, histone modification, and microRNA regulation. These changes may dysregulate immune function and contribute to the development of autoimmune diseases such as multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis (19). Identifying pollutant-induced epigenetic markers and immune biomarkers may facilitate early diagnosis and personalized treatment strategies tailored to individuals with environmental exposure histories (20).

Immune Activation and the Role of Inflammation in Autoimmune Diseases

Chronic inflammation is a central hallmark of autoimmune diseases, stemming from the immune system's inability to distinguish self-antigens from foreign pathogens. This loss of immunological tolerance leads to sustained activation of both innate and adaptive immune responses, resulting in localized or

systemic tissue damage (21). Environmental pollutants such as airborne particulates, heavy metals, and agricultural chemicals—have been shown to intensify these immune processes by stimulating the production of key pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and interleukin-17 (IL-17). These cytokines are critical mediators of inflammatory cascades and play pivotal roles in the pathogenesis of various autoimmune disorders (22).

Pollutant-induced immune activation occurs through several mechanisms. Environmental toxins stimulate antigen-presenting cells, such as dendritic cells and macrophages, which in turn promote the differentiation of pro-inflammatory T helper (Th) cell subsets particularly Th1, Th17, and T follicular helper (Tfh) cells. These cells secrete cytokines that perpetuate the inflammatory milieu, recruit additional effector immune cells to target tissues, and exacerbate tissue injury (22). For example, IL-17 produced by Th17 cells enhances neutrophil recruitment, disrupts epithelial and endothelial barriers, and increases tissue permeability, contributing to the pathophysiology of diseases such as multiple sclerosis (4). Similarly, Th1 cells, through the release of interferon-gamma (IFN-γ) and TNF-α, are implicated in the destruction of pancreatic β-cells in type 1 diabetes (T1D) (23).

This aberrant immune activity often establishes a self-perpetuating inflammatory cycle: tissue damage leads to the release of self-antigens, which further activate immune responses and sustain chronic inflammation. This cycle not only drives disease progression but also contributes to increased severity, comorbidities, and treatment resistance in autoimmune conditions (23).

Given the central role of inflammatory cytokines in disease pathogenesis, they have become prime targets for therapeutic intervention. Biologic agents that block TNF-α, IL-6, IL-17, or their receptors have shown significant clinical efficacy in managing autoimmune diseases such as rheumatoid arthritis, psoriasis, ankylosing spondylitis, and MS (24). These targeted therapies help modulate the immune response, reduce inflammation, and minimize tissue destruction, thereby improving patient outcomes and quality of life (25).

Nonetheless, pharmacologic therapy alone may not suffice for optimal disease control. An integrative approach that combines immunomodulatory treatments with lifestyle modifications such as adopting anti-inflammatory diets, reducing environmental toxin exposure, managing stress, and engaging in regular physical activity can significantly improve therapeutic outcomes. Psychological support and patient education are also critical, as psychosocial stressors are known to influence immune regulation and disease activity (26).

Emerging advances in precision medicine hold promise for individualized therapeutic strategies. By profiling patients' cytokine signatures, genetic susceptibilities, environmental exposures, and immune cell phenotypes, clinicians can tailor interventions that specifically target dysregulated pathways. Such personalized approaches may not only enhance efficacy but also reduce the risk of adverse effects and improve long-term disease management (27).

Pollution and Immune Tolerance: Disrupting the Balance

Maintaining immune tolerance that is, avoiding the immune system from attacking its cells and tissues is a fundamental component of immune system operation. Environmental pollution can disturb this delicate balance by triggering immune system malfunction. Immune tolerance is preserved by Tregs; thus, their absence or malfunction has been linked to the beginning of autoimmune diseases (28). A Treg imbalance causes an improper immune response that might see the body's tissues as foreign invaders. Knowing the causes of Treg loss will help one to develop new approaches for the management of autoimmune diseases. Knowing the mechanisms behind Treg loss will help to find new therapeutic approaches for autoimmune diseases (29). By looking at the environmental elements causing Treg issues, researchers will be able to design tailored treatments meant to restore the balance of the immune system and increase the body's ability to distinguish it from foreign invaders. Reducing the consequences of autoimmune diseases depends on this immune balance restoration, which also may generate creative treatments enhancing the body's natural regulating systems (30).

Ultimately, a more profound understanding of Treg dynamics could offer the tools for personalized therapeutic approaches that meet the specific needs of individual patients. This knowledge helps one control autoimmune diseases. Good control of autoimmune diseases helps medical systems to lower their load and significantly raise patients' quality of life (31). By means of targeted treatments and Treg cells, researchers hope to generate more exact interventions, so mitigating symptoms and addressing the fundamental causes of these difficult disorders. These developments provide improved therapy results and long-term remission for those suffering from autoimmune diseases (32). Including these novel concepts into clinical practice as research develops could transform patient treatment in this demanding sector. By matching treatments to individual patient profiles, customized medicine approaches arising from this revolution may improve safety and efficacy. Giving Treg cell modulation top attention will help doctors to identify fresh approaches to restore immune balance and enhance the quality of life for patients with these terrible diseases (33).

By including lifestyle, environmental, and genetic

elements into treatment plans, doctors can maximize therapeutic results and improve patients quality of life. Treg function is interfered interfered with by environmental toxins, including heavy metals and pesticides, so compromising immune control and raising sensitivity to autoimmune reactions (34). Furthermore, compromising immune tolerance is epigenetic modifications induced by environmental toxins. Environmental toxins change how DNA is marked, how proteins around DNA are modified, and how certain small RNA molecules are expressed, which affects how immune cells work and how genes are expressed, making people more likely to develop autoimmune diseases (35). This complex interaction of environmental elements with genetic inclination emphasizes the need to understand how toxins affect immune system control. By addressing environmental triggers, treatment and prevention of autoimmune diseases may find new pathways and so support better health outcomes. Better health outcomes can be achieved through a multifaceted approach that includes reducing exposure to harmful substances, promoting a healthy lifestyle, and tailoring interventions based on an individual's genetic predisposition (36). This holistic perspective enhances our understanding of autoimmune diseases and paves the way for innovative therapeutic strategies. These strategies not only aim to mitigate the effects of toxins but also empower individuals to take charge of their health through education and awareness. By fostering a collaborative approach among healthcare providers, researchers, and patients, we can drive advancements in the management and treatment of autoimmune conditions (37).

Environmental Factors in Autoimmune Disease Susceptibility: A Genetic Perspective

While environmental pollution is mostly responsible for the start of autoimmune diseases, genetic inclination is rather crucial. Some people may have hereditary variations that increase their sensitivity to environmental toxins. Environmental toxins can alter genes that influence the immune system's performance, including those related to cytokine generation, immune receptor signaling, and responses to oxidative stress, thereby increasing an individual's risk of developing autoimmune diseases (38). Therefore, awareness of how genes and the surroundings interact determines better strategies to avoid and treat autoimmune diseases. In autoimmune diseases, effective preventive and therapeutic interventions are quite essential. Furthermore, by means of tailored medicine and focused treatments derived from the analysis of the particular genetic markers linked to these diseases, patient outcomes can be improved and the effects of these diseases on individuals and healthcare systems can be minimized (39). Researchers can identify new therapeutic targets and improve present treatment plans by using developments in biotechnology and genetics, thus improving patient quality of life. Furthermore, including environmental strategies and lifestyle modifications in therapy plans helps reduce the effects of autoimmune diseases and enhances general health (40). This data guides public health campaigns meant to lower exposure to hazardous pollutants and helps to identify vulnerable populations. By means of an analysis of the interactions between genes and environmental elements, scientists can better plan treatments and direct society toward reduced risks related to environmental pollutants (41). This proactive approach helps people to control their health and advance general society. Individuals who combine more environmental pollution exposure with a genetic inclination are likely to have autoimmune issues since the interaction between genetic elements and environmental exposure is complex (42).

Environmental Pollutants and Their Immunotoxicity

Heavy Metals and Autoimmune Disease Development

Over time, highly toxic heavy metals, including lead (Pb), cadmium (Cd), mercury (Hg), and arsenic (As), can accumulate in the body and fundamentally alter immune systems. Since these metals interfere with the normal immune system and might raise susceptibility to diseases and infections, this accumulation can cause several health problems. Long-term exposure thus clearly jeopardizes general health and well-being (43). These metals reduce immune tolerance, cause inflammation, and alter immune cell behavior, thus raising a person's susceptibility to autoimmune diseases. Lead: Pb; lead exposures compromise immune system performance via many routes. Pb disrupts the operation of T cells, B cells, and natural killer (NK) cells all of which are important components of immune surveillance and response (44). Studies reveal that Pb exposure can upset the equilibrium between Th1 and Th2 immune responses, thus aggravating Th2-related inflammation. Pb also causes reactive oxygen species (ROS) generation and oxidative stress, which damages tissue and activates the immune system. At the molecular level, Pb stimulates important controllers of inflammation, NF-κB and MAPK signaling pathways (45). Linked to autoimmune diseases including lupus and rheumatoid arthritis, these pathways downregulate pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6. Pb also stimulates T follicular helper (Tfh) cells, which support B cell differentiation, so fostering autoantibody production a feature of many autoimmune diseases (46). A strong neurotoxin influencing the immune system as well is mercury (Hg). Mercury increases macrophage activity that generates pro-inflammatory cytokines and chemokines. Mercury exposure is well known to activate the NF-κB

pathway, thus boosting tissue damage and aggravating the inflammatory response (47). Mercury also stimulates Th17 cells, a type of T helper cell crucial for autoimmune inflammation, especially in diseases like rheumatoid arthritis and systemic lupus erythematosus (3). Oxidative stress brought on by mercury sets off the Nrf2 antioxidant pathway, producing ROS. This therefore, fuels immune dysregulation and damages cellular structures (48). Cadmium (Cd) exposure results in the accumulation of this metal in the kidneys, liver, and lungs, where it induces notable immune dysregulation. Cd stimulates inflammation by triggering the synthesis of nitric oxide (NO) and ROS, so compromising immune cell performance (49). Cd exposure causes Th1 responses that generate IFN-γ and TNF-α, so throwing off the ratio of pro- to anti-inflammatory cytokines. Cadmium exposure has been shown at the cellular level to influence dendritic cell maturation, so distorting the immune response towards inflammation (50). Furthermore, by influencing T regulatory cells (Tregs), Cd compromises immune tolerance systems and fuels the development of autoimmune diseases. Arsenic (As) exposure has been linked to rheumatoid arthritis and systemic lupus erythematosus, among several autoimmune diseases (51). Arsenic promotes Th1/Th17 polarization, which is linked to autoimmune inflammation and modulates T cell differentiation. The arrangement of arsenic also helps generate autoantibodies, which target self-antigens and set off autoimmune reactions. Arsenic interacts at the molecular level with the JAK-STAT pathway, which is essential for immune cell signaling and activates inflammatory genes. Additionally causing ROS and oxidative stress, it further disturbs the immune system and accelerates the course of autoimmune diseases (52).

Air Pollution and Autoimmune Disease

Air pollution is one often occurring environmental hazards that seriously compromises immune system performance, among other aspects of human health. Autoimmune diseases have been most connected among all the components of air pollution to ozone (O_3), nitrogen dioxide (NO_2), and fine particulate matter ($PM_{2.5}$) (53). Important elements in the beginning and aggravation of autoimmune diseases, these toxins can enter the bloodstream via the respiratory system and cause oxidative stress, systematic inflammation, and immune dysregulation. Autoimmune diseases, including type 1 diabetes (T1D), multiple sclerosis (4), rheumatoid arthritis (RA), and systemic lupus erythematosus (3), have been linked to air pollution (54). Comprising many immune cell types, signaling pathways, and molecular mechanisms, the immune system's sophisticated response to air pollutants is environmental toxins can induce tissue damage, autoimmunity, and chronic inflammation by means of specific immune system activation (55). Starting a vicious cycle that might lead to the development of chronic diseases, tissue damage can aggravate the inflammatory response even more. Public health campaigns and targeted treatments meant to reduce the effects of pollution on immune system performance depend on an awareness of these processes.Air pollution is one often occurring environmental hazard that seriously compromises human health including immune system performance (56). Among all the components of air pollution, autoimmune diseases have been most linked to ozone (O_3), nitrogen dioxide (NO_2), and fine particulate matter ($PM_{2.5}$). Important components in the beginning and aggravation of autoimmune diseases, these toxins can enter the bloodstream via the respiratory system and induce oxidative stress, systemic inflammation, and immune dysregulation (3). Autoimmune diseases, including type 1 diabetes (T1D), multiple sclerosis (4), rheumatoid arthritis (RA), and systemic lupus erythematosus (3), have been linked to air pollution. Comprising many immune cell types, signaling pathways, and molecular mechanisms, the immune system's sophisticated response to air pollutants is by means of specific immune system activation, environmental toxins can cause tissue damage, autoimmunity, and chronic inflammation (3). Tissue damage can further aggravate the inflammatory response, potentially initiating a vicious cycle that may lead to the development of chronic diseases. Public health campaigns and targeted treatments meant to reduce the effects of pollution on immune system performance depend on being aware of these processes (57).

Molecular Mechanisms of Air Pollution-Induced Autoimmune Diseases

The immune system is equipped with pattern recognition receptors (PRRs) that recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). These receptors are crucial in detecting external and internal threats and initiating an immune response. Airborne pollutants, such as PM2.5, NO2, and O3, are capable of activating these PRRs, leading to a cascade of immune responses that contribute to inflammation and immune dysfunction (58).

1.Activation of Pattern Recognition Receptors (PRRs)

Pollutants in the air are recognized by Toll-like receptors (TLRs), which are a key subset of PRRs. TLRs are present on macrophages, dendritic cells, and epithelial cells, all of which are involved in initiating immune responses. Upon binding to air pollution components, TLRs activate downstream signaling

pathways that promote an inflammatory response. The most commonly involved TLRs in air pollution-induced inflammation are TLR4 and TLR2, which recognize particulate matter, and TLR9, which can be activated by the DNA fragments found in pollutants (59).

The activation of these receptors triggers several intracellular signaling pathways, most notably the NF-κB (nuclear factor kappa B) and MAPK (mitogen-activated protein kinase) pathways. These pathways are critical for regulating immune cell function, inflammatory cytokine production, and the survival of immune cells (60).

2.NF-κB Pathway and Cytokine Production

Once TLRs are activated, NF-κB quickly produces TNF-α, IL-1β, IL-6, and IL-12. These cytokines are mostly responsible for the inflammatory reaction and also significantly help autoimmune diseases to develop. Involved in inflammation, TNF-α is crucial for the development of T helper 17 (Th17) cells, which abound in autoimmune diseases including rheumatoid arthritis (RA) and multiple sclerosis (4, 61). Higher TNF-α levels also promote the synthesis of autoantibodies and B cell development, which may produce immune complexes possibly damaging tissues. More inflammatory reactions triggered by these immune complexes can aggravate tissue damage and support the progression of autoimmune diseases (62). Consequently, concentrating on TNF-α and associated cytokines has become a primary objective in the development of treatments for several diseases. Although TNF-α targeting helps some autoimmune diseases under control, some studies indicate that blocking this cytokine might cause other issues, including more susceptibility to infections (63). Moreover, there are other therapeutic modalities that concentrate on changing the immune response without particularly aiming at TNF-α, so providing a more balanced course of treatment. Another necessary cytokine causing immune cell activation and inflammation continuation is IL-1β (64). Understanding how IL-1β generates inflammation has helped to design targeted treatments meant to stop its activity. These treatments provide a better way to treat autoimmune diseases since they could lower the risk of infections related to TNF-α inhibitors and so decrease inflammation. Rising IL-1β levels in the joints and other tissues help to explain the advancement in RA and other autoimmune diseases. Essential in the transition from acute to chronic inflammation, IL-6 is a multifarious cytokine (65). This shift is significant because of changes in the body's immune response: acute inflammation, meant to react to immediate threats, can become chronic and contribute to driving continuous tissue damage and disease progression. Targeting cytokines such as IL-1β and IL-6 could help therapies break this cycle and provide better control of autoimmune diseases (66). Targeting T follicular helper (Tfh) cells and T helper 17 (Th17) cells will help encourage their differentiation since both of these cells are essential for the onset of autoimmune diseases (67). IL-6 also produces autoantibodies, so it helps B cells to proliferate and activate. In diseases including rheumatoid arthritis, lupus, and multiple sclerosis, the sustained presence of these cytokines aggravates the autoimmune process by causing tissue damage, synovial inflammation, and neuronal damage (68). Once TLRs are activated, NF-κB quickly reacts to create several substances that promote inflammation, such as TNF-α (tumor necrosis factor-alpha), IL-1β (interleukin-1 beta), IL-6, and IL-12. The inflammatory response is mostly dependent on these cytokines, which also greatly contribute to the development of autoimmune diseases (69). Involved in inflammation, TNF-α is essential for the development of T helper 17 (Th17) cells, which are present in autoimmune diseases including rheumatoid arthritis (RA) and multiple sclerosis (4). Higher TNF-α levels also stimulate B cell development and the synthesis of autoantibodies, which could lead to immune complexes maybe harm tissues (70). More inflammatory reactions triggered by these immune complexes can aggravate tissue damage and support the progression progression of autoimmune diseases. Thus, focusing on TNF-α and related cytokines has become a main goal in developing treatments for several diseases. While some autoimmune diseases may be controlled with TNF-α targeting, some studies show that blocking this cytokine may lead to other problems, including more susceptibility to infections (71). Moreover, there are other therapeutic approaches that focus on altering the immune response without especially aiming at TNF-α, so offering a more balanced course of therapy. IL-1β is another indispensable cytokine driving immune cell activation and inflammation continuation (72). Understanding how IL-1β generates inflammation has helped to design targeted treatments meant to stop its activity. These therapies offer a better approach to treating autoimmune diseases since they could reduce inflammation and lower the risk of infections connected with TNF-α inhibitors (73). Rising IL-1β levels in the joints and other tissues help to explain the advancement in RA and other autoimmune diseases. Essential in the transition from acute to chronic inflammation, IL-6 is a multifarious cytokine. This is significant because of changes in the body's immune response: acute inflammation, meant to react to immediate threats, can become chronic and contribute to the continuous tissue damage and disease progression (74). Targeting cytokines such as IL-1β and IL-6 could help therapies maybe break this cycle and provide better control of autoimmune diseases. Targeting T follicular helper

(Tfh) cells and T helper 17 (Th17) cells will help encourage their differentiation since both of these cells are essential for the onset of autoimmune diseases (75). IL-6 also produces autoantibodies, so it helps B cells to proliferate and activate. In diseases including rheumatoid arthritis, lupus, and multiple sclerosis, the sustained presence of these cytokines aggravates the autoimmune process by causing tissue damage, synovial inflammation, and neuronal damage (46).

3.MAPK Pathway and Immune Cell Activation

The MAPK pathway is another important signaling cascade activated by TLR engagement. This pathway influences various cellular processes, including cell proliferation, differentiation, survival, and immune cell activation. In the context of air pollution, the MAPK pathway plays a role in macrophage activation and the production of reactive oxygen species (ROS), which contribute to oxidative stress and further inflammation (76).

•p38 MAPK is particularly important in the activation of pro-inflammatory cytokines and immune cell differentiation. Activation of this pathway in response to pollutants has been shown to promote the expression of IL-6, TNF-α, and IL-1β in immune cells, further perpetuating inflammatory cycles (77).

4.Oxidative Stress and Immune Dysregulation

One of the key consequences of air pollution exposure is oxidative stress, which occurs due to the excessive production of reactive oxygen species (ROS), such as superoxide radicals, hydrogen peroxide, and hydroxyl radicals. These ROS can directly damage cellular components, including DNA, lipids, and proteins, leading to cell death and the activation of immune responses (78).

The accumulation of ROS in immune cells such as macrophages, dendritic cells, and T cells can enhance the production of pro-inflammatory cytokines and trigger cellular signaling pathways like NF-κB, further promoting immune system activation. Moreover, oxidative stress can disrupt Treg (regulatory T cell) function, impairing immune tolerance and facilitating the development of autoimmune responses (79).

Oxidative stress can also lead to epigenetic modifications, such as changes in DNA methylation and histone modification, which can result in long-lasting changes in immune cell function and gene expression, further enhancing susceptibility to autoimmune diseases (80).

Molecular Mechanisms Linking Pollution to Autoimmune Diseases

Environmental pollutants, through a variety of molecular mechanisms, significantly contribute to the pathogenesis of autoimmune diseases. These mechanisms involve the activation of key inflammatory pathways, induction of oxidative stress, and disruption of immune tolerance (81). The interaction between pollutants and the immune system can lead to immune activation, an imabalance in immune cell populations, and the generation of autoreactive antibodies. In this section, we will explore the molecular pathways through which pollutants, such as heavy metals, air pollution, and other environmental toxins, contribute to the development of autoimmune diseases (82).

Inflammatory Pathways

Inflammation is a hallmark of autoimmune diseases, and many environmental pollutants contribute to immune system dysregulation through the activation of inflammatory signaling pathways. These pathways not only promote local inflammation but also perpetuate systemic immune activation, setting the stage for autoimmune responses (83).

1.NF-κB Pathway: A Key Regulator of Immune Inflammation

The NF-κB (nuclear factor kappa B) signaling pathway is one of the most critical regulators of the immune response. This pathway is activated by a variety of environmental pollutants, including heavy metals (like lead and mercury), airborne particulate matter, and pesticides (84). Under normal conditions, NF-κB is kept inactive in the cytoplasm by binding to IκB (inhibitory κB) proteins. Upon exposure to pollutants, IκB proteins are phosphorylated and degraded, releasing NF-κB dimers (usually p65/p50) to translocate to the nucleus, where they initiate the transcription of genes involved in inflammation, immune response, and cell survival (85).

Pollutants trigger NF-κB activation through various receptors, including pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs). The activation of NF-κB leads to the expression of key pro-inflammatory cytokines like TNF-α, IL-1β, IL-6, and IL-8, which are crucial in the development and progression of autoimmune diseases (86). These cytokines promote the recruitment and activation of immune cells like macrophages, T cells, and B cells, further amplifying the inflammatory response. Additionally, NF-κB also promotes angiogenesis and tissue remodeling, which can contribute to autoimmune-mediated tissue damage (87).

Recent Findings: Studies have shown that exposure to air pollution increases NF-κB activation in the lungs and synovial joints, contributing to diseases like rheumatoid arthritis (RA) and systemic lupus erythematosus (3). Chronic activation of NF-κB by environmental toxins can lead to sustained inflammation, which plays a critical role in autoimmune pathogenesis (88).

2.MAPK (Mitogen-Activated Protein Kinase) Pathway

The MAPK (Mitogen-Activated Protein Kinase) signaling pathway includes several key members, such as JNK (c-Jun N-terminal kinase), ERK (extracellular signal-regulated kinase), and p38 MAPK. These pathways regulate a wide range of cellular processes, including cell proliferation, apoptosis, immune cell activation, and inflammation (89). Many environmental pollutants, such as heavy metals, pesticides, and airborne particulate matter (PM2.5), activate MAPK pathways by engaging PRRs, cytokine receptors, and cellular stress responses (90).

MAPK pathways play an important role in immune cell differentiation and the activation of transcription factors like AP-1 (activator protein 1), which are involved in the production of inflammatory cytokines. For example, JNK activation promotes the expression of pro-inflammatory cytokines such as TNF-α and IL-6, which drive inflammation and autoimmune responses (91). Similarly, p38 MAPK is implicated in the regulation of T cell differentiation, particularly in the promotion of Th17 cells, which are associated with autoimmune diseases like multiple sclerosis (4) and rheumatoid arthritis (RA) (92).

Furthermore, ERK signaling is involved in regulating T cell activation and B cell differentiation, both of which are critical for the development of autoimmune diseases. The activation of the MAPK pathway by pollutants not only drives the inflammatory response but also enhances the ability of the immune system to mount inappropriate attacks against self-tissues (93).

Recent Findings: Studies indicate that exposure to particulate matter (PM2.5) from air pollution can activate MAPK signaling in dendritic cells and macrophages, enhancing the production of inflammatory cytokines and promoting the differentiation of autoreactive T helper cells. This activation contributes to the exacerbation of diseases such as asthma, rheumatoid arthritis, and systemic lupus erythematosus (94).

3.JAK-STAT Pathway: Key Modulator of Immune Responses

The JAK-STAT (Janus kinase-signal transducer and activator of transcription) signaling pathway is a crucial regulator of immune cell function and inflammation. It is activated by cytokines and growth factors, and it plays an essential role in the differentiation and activation of **T** cells, B cells, and myeloid cells (95). Pollutants, including arsenic, mercury, and airborne particulate matter, can activate the JAK-STAT pathway, leading to the production of pro-inflammatory cytokines, especially those involved in the Th1 and Th17 immune responses, which are implicated in autoimmune diseases (96).

When pollutants bind to their respective cytokine receptors, they activate JAKs, which then phosphorylate STAT proteins. Phosphorylated STATs translocate to the nucleus, where they induce the transcription of genes involved in immune activation, inflammation, and autoimmunity (97). For example, STAT1 is a key mediator of the Th1 response, which is involved in autoimmune diseases like multiple sclerosis (4) and type 1 diabetes (T1D). STAT3, on the other hand, is critical for the development of Th17 cells, which are involved in autoimmune diseases like rheumatoid arthritis and psoriasis (98).

Pollutants like arsenic and mercury have been shown to specifically activate JAK-STAT signaling, leading to an overproduction of Th1 and Th17 cytokines such as IFN-γ and IL-17, which contribute to the chronic inflammation and tissue damage seen in autoimmune diseases (99).

Recent Findings: Research has demonstrated that arsenic exposure can increase the expression of IL-6 and IL-17 through the activation of the JAK-STAT pathway in T cells and macrophages, leading to increased susceptibility to diseases such as rheumatoid arthritis and systemic lupus erythematosus. Furthermore, mercury exposure has been associated with the induction of a Th17 response through STAT3 activation, further implicating the JAK-STAT pathway in pollutant-induced autoimmunity (100).

Other Cellular and Molecular Mechanisms

While the activation of inflammatory pathways like NF-κB, MAPK, and JAK-STAT plays a pivotal role in pollutant-induced autoimmune diseases, additional mechanisms contribute to immune dysregulation. These include

- **Oxidative Stress and ROS Production**: Pollution-induced oxidative stress is a key mechanism through which pollutants contribute to autoimmune disease development. ROS activate NF-κB and MAPK pathways, leading to inflammation and tissue damage (101).
- **Disruption of Immune Tolerance**: Environmental pollutants may interfere with the development and function of regulatory T cells (Tregs), which are essential for maintaining immune tolerance and preventing autoimmunity. Pollutants such as heavy metals and air pollution have been shown to impair Treg function, promoting autoimmunity (102).
- **Epigenetic Modifications**: Exposure to environmental pollutants can lead to epigenetic changes, including DNA methylation, histone modifications, and the expression of non-coding RNAs, all of which can influence immune cell function and predispose individuals to autoimmune diseases (103).

3. Pathways Activated by Oxidative Stress

Oxidative stress activates several cellular

signaling pathways that exacerbate inflammation and autoimmunity. These pathways play a crucial role in immune cell activation, differentiation, and tissue damage (104).

•**NF-κB Pathway**: As mentioned earlier, oxidative stress can activate the NF-κB signaling pathway, leading to the upregulation of pro-inflammatory cytokines and chemokines that drive the inflammatory response. In T cells, macrophages, and other immune cells, NF-κB activation promotes the expression of cytokines like TNF-α, IL-6, and IL-1β, which contribute to chronic inflammation seen in autoimmune diseases (105).

•MAPK Pathway: Oxidative stress activates various MAPK signaling pathways, including JNK, ERK, and p38 MAPK. These pathways play a key role in regulating inflammation and immune cell activation. For example, JNK activation can enhance the production of IL-17 and IFN-γ in Th17 and Th1 cells, respectively, both of which are critical drivers of autoimmunity (4). Additionally, p38 MAPK activation promotes the secretion of pro-inflammatory cytokines and enhances the survival of activated immune cells (106).

•Nrf2 Pathway: The Nrf2 (nuclear factor erythroid 2-related factor 2) pathway is a key cellular defense mechanism against oxidative stress. Nrf2 regulates the expression of antioxidant genes, such as heme oxygenase-1 (HO-1) and superoxide dismutase (SOD), which protect cells from ROS-induced damage (107). However, prolonged oxidative stress can lead to the failure of the Nrf2 pathway, resulting in reduced cellular protection and increased susceptibility to immune dysregulation and autoimmune diseases (108).

•Aryl Hydrocarbon Receptor: The AhR is a ligand-activated transcription factor that responds to environmental pollutants, such as dioxins and polyaromatic hydrocarbons. AhR activation by pollutants increases ROS production and induces inflammation (109). Additionally, AhR signaling can disrupt the function of Tregs, impairing immune tolerance and promoting autoimmunity. AhR has been implicated in diseases such as rheumatoid arthritis and multiple sclerosis, where oxidative stress and dysregulated AhR signaling contribute to disease progression (110).

Genetic Mechanisms and Epigenetic Modifications

Oxidative stress, which is triggered by environmental pollutants such as heavy metals and air pollution, not only induces cellular damage but also plays a critical role in shaping genetic and epigenetic responses that influence the development of autoimmune diseases. These pollutants can lead to DNA damage, causing mutations and alterations in gene expression, which, in turn, can activate pathological immune responses and increase susceptibility to autoimmune diseases (111). Furthermore, epigenetic modifications including changes in DNA methylation, histone modifications, and non-coding RNA regulation have emerged as key mechanisms through which oxidative stress modulates the immune system and contributes to the pathogenesis of autoimmune disorders (112).

RECENT FINDINGS AND FUTURE DIRECTIONS

Recent studies have highlighted the growing concern over the role of epigenetics in autoimmune diseases triggered by environmental factors. Research on epigenetic biomarkers for autoimmune diseases, such as DNA methylation profiles and histone modifications, is expanding, with a focus on identifying early biomarkers of autoimmune disease onset (113). In addition, the interactions between epigenetic changes and immune cell plasticity are being increasingly recognized as critical mechanisms in the development of autoimmune diseases (114).

As research continues, future studies should focus on the long-term effects of pollutants on epigenetic modifications, particularly in genetically predisposed individuals. Investigating the reversibility of these epigenetic changes through interventions such as dietary modifications, antioxidant therapies, or epigenetic drugs could provide new strategies for preventing or treating autoimmune diseases associated with environmental pollution (115).

CONCLUSION

Environmental pollution plays a significant role in the development and exacerbation of autoimmune diseases. Pollutants such as heavy metals, air pollution, pesticides, and industrial chemicals can activate inflammatory pathways, induce oxidative stress, and impair immune tolerance, all of which contribute to immune dysfunction and autoimmune disease progression. The molecular mechanisms underlying these effects involve complex interactions between immune cells, signaling pathways, and genetic predisposition. Further research is needed to fully understand the genetic, molecular, and cellular mechanisms through which environmental pollutants influence autoimmune diseases. Additionally, public health initiatives aimed at reducing environmental exposure to harmful pollutants are essential to mitigate their impact on immune health.

Authors' Contribution

Farnaz Eghbalpour: data curation; editing and review. Mahnaz Saremi: investigation and writing. The authors read and confirmed the final manuscript.

Funding

This study is the outcome of self-directed research carried out without any financial assistance.

Ethics approval and consent to participate

Not applicable.

Conflict of Interest

The authors declared no conflict of interest. The author is the Editor-in-Chief of this journal; however, the review and editorial processes for this manuscript were conducted independently.

Consent for publication

Not Applicable.

REFERENCE

1. Yasmeen F, Pirzada RH, Ahmad B, Choi B, Choi S. Understanding Autoimmunity: Mechanisms, Predisposing Factors, and Cytokine Therapies. International journal of molecular sciences. 2024;25(14).
2. Goswami TK, Singh M, Dhawan M, Mitra S, Emran TB, Rabaan AA, et al. Regulatory T cells (Tregs) and their therapeutic potential against autoimmune disorders - Advances and challenges. Human vaccines & immunotherapeutics. 2022;18(1):2035117.
3. 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. Environmental research. 2015;140:474-8.
4. Kubatka P, Bojkova B, Nosalova N, Huniadi M, Samuel SM, Sreenesh B, et al. Targeting the MAPK signaling pathway: implications and prospects of flavonoids in 3P medicine as modulators of cancer cell plasticity and therapeutic resistance in breast cancer patients. EPMA Journal. 2025;16(2):437-63.
5. Frazzei G, van Vollenhoven RF, de Jong BA, Siegelaar SE, van Schaardenburg D. Preclinical Autoimmune Disease: a Comparison of Rheumatoid Arthritis, Systemic Lupus Erythematosus, Multiple Sclerosis and Type 1 Diabetes. Frontiers in immunology. 2022;13:899372.
6. Lee CE, Singleton KS, Wallin M, Faundez V. Rare Genetic Diseases: Nature's Experiments on Human Development. iScience. 2020;23(5):101123.
7. Medhasi S, Chantratita N. Human Leukocyte Antigen (HLA) System: Genetics and Association with Bacterial and Viral Infections. Journal of immunology research. 2022;2022:9710376.
8. Shetty SS, D D, S H, Sonkusare S, Naik PB, Kumari N S, et al. Environmental pollutants and their effects on human health. Heliyon. 2023;9(9):e19496.
9. Cheng Y, Yang Y, Bai L, Cui J. Microplastics: an often-overlooked issue in the transition from chronic inflammation to cancer. Journal of translational medicine. 2024;22(1):959.
10. Song Y, Li J, Wu Y. Evolving understanding of autoimmune mechanisms and new therapeutic strategies of autoimmune disorders. Signal Transduction and Targeted Therapy. 2024;9(1):263.
11. Stefanicka-Wojtas D, Kurpas D. Personalised Medicine-Implementation to the Healthcare System in Europe (Focus Group Discussions). Journal of personalized medicine. 2023;13(3).
12. Drago G, Aloi N, Ruggieri S, Longo A, Contrino ML, Contarino FM, et al. Guardians under Siege: Exploring Pollution's Effects on Human Immunity. International journal of molecular sciences [Internet]. 2024; 25(14).
13. Alotiby A. Immunology of Stress: A Review Article. Journal of clinical medicine. 2024;13(21).
14. Harshitha P, Bose K, Dsouza HS. Influence of lead-induced toxicity on the inflammatory cytokines. Toxicology. 2024;503:153771.
15. Chandimali N, Bak SG, Park EH, Lim H-J, Won Y-S, Kim E-K, et al. Free radicals and their impact on health and antioxidant defenses: a review. Cell Death Discovery. 2025;11(1):19.
16. Kowalczyk P, Sulejczak D, Kleczkowska P, Bukowska-Ośko I, Kucia M, Popiel M, et al. Mitochondrial Oxidative Stress-A Causative Factor and Therapeutic Target in Many Diseases. International journal of molecular sciences. 2021;22(24).
17. Kanwugu ON, Glukhareva TV. Activation of Nrf2 pathway as a protective mechanism against oxidative stress-induced diseases: Potential of astaxanthin. Archives of Biochemistry and Biophysics. 2023;741:109601.
18. Goshtasbi H, Hashemzadeh N, Fathi M, Movafeghi A, Barar J, Omidi Y. Mitigating oxidative stress toxicities of environmental pollutants by antioxidant nanoformulations. Nano TransMed. 2025;4:100087.
19. Danieli MG, Casciaro M, Paladini A, Bartolucci M, Sordoni M, Shoenfeld Y, et al. Exposome: Epigenetics and autoimmune diseases. Autoimmunity Reviews. 2024;23(6):103584.
20. Mukherjee S, Dasgupta S, Mishra PK, Chaudhury K. Air pollution-induced epigenetic changes: disease development and a possible link with hypersensitivity pneumonitis. Environmental science and pollution research international. 2021;28(40):55981-6002.
21. Xiang Y, Zhang M, Jiang D, Su Q, Shi J. The role of inflammation in autoimmune disease: a therapeutic target. Frontiers in immunology. 2023;14:1267091.
22. Trivadila T, Iswantini D, Rahminiwati M, Rafi M, Salsabila AP, Sianipar RN, et al. Herbal Immunostimulants and Their Phytochemicals: Exploring Morinda citrifolia, Echinacea purpurea, and Phyllanthus niruri. Plants [Internet]. 2025; 14(6).
23. Lai S, Wu X, Liu Y, Liu B, Wu H, Ma K.Interaction between Th17 and central nervous system in multiple sclerosis. Brain, Behavior, & Immunity - Health. 2025;43:100928.

24.Abianeh HS, Kesharwani P, Sahebkar A. The use of aptamers as therapeutic inhibitors and biosensors of TNF-alpha. International Journal of Biological Macromolecules. 2025;306:141202.
25.Jang DI, Lee AH, Shin HY, Song HR, Park JH, Kang TB, et al. The Role of Tumor Necrosis Factor Alpha (TNF-α) in Autoimmune Disease and Current TNF-α Inhibitors in Therapeutics. International journal of molecular sciences. 2021;22(5).
26.Antar SA, Ashour NA, Sharaky M, Khattab M, Ashour NA, Zaid RT, et al. Diabetes mellitus: Classification, mediators, and complications; A gate to identify potential targets for the development of new effective treatments. Biomedicine & Pharmacotherapy. 2023;168:115734.
27.Jagirdhar GSK, Perez JA, Perez AB, Surani S. Integration and implementation of precision medicine in the multifaceted inflammatory bowel disease. World journal of gastroenterology. 2023;29(36):5211-25.
28.Pondman K, Le Gac S, Kishore U. Nanoparticle-induced immune response: Health risk versus treatment opportunity? Immunobiology. 2023;228(2):152317.
29.Mashayekhi K, Khazaie K, Faubion WA, Kim GB. Biomaterial-enhanced treg cell immunotherapy: A promising approach for transplant medicine and autoimmune disease treatment. Bioactive Materials. 2024;37:269-98.
30.Schlöder J, Shahneh F, Schneider F-J, Wieschendorf B. Boosting regulatory T cell function for the treatment of autoimmune diseases – That's only half the battle! 2022;Volume 13 - 2022.
31.Hassan M, Elzallat M, Mohammed DM, Balata M, El-Maadawy WH. Exploiting regulatory T cells (Tregs): Cutting-edge therapy for autoimmune diseases. International Immunopharmacology. 2025;155:114624.
32.Li Y, Liu H, Yan H, Xiong J. Research advances on targeted-Treg therapies on immune-mediated kidney diseases. Autoimmunity Reviews. 2023;22(2):103257.
33.Marques L, Costa B, Pereira M, Silva A, Santos J, Saldanha L, et al. Advancing Precision Medicine: A Review of Innovative In Silico Approaches for Drug Development, Clinical Pharmacology and Personalized Healthcare. Pharmaceutics. 2024;16(3).
34.Alengebawy A, Abdelkhalek ST, Qureshi SR, Wang MQ. Heavy Metals and Pesticides Toxicity in Agricultural Soil and Plants: Ecological Risks and Human Health Implications. Toxics. 2021;9(3).
35.Abdulraheem MI, Xiong Y, Moshood AY, Cadenas-Pliego G, Zhang H, Hu J. Mechanisms of Plant Epigenetic Regulation in Response to Plant Stress: Recent Discoveries and Implications. Plants (Basel, Switzerland). 2024;13(2).
36.Unar A, Qureshi M, Afridi HI, Wassan S. The Role of Bacterial Toxins and Environmental Factors in the Development of Food Allergies. Allergies [Internet]. 2024; 4(4):[192-217 pp.].
37.Parvin N, Joo SW, Mandal TK. Biodegradable and Stimuli-Responsive Nanomaterials for Targeted Drug Delivery in Autoimmune Diseases. Journal of functional biomaterials. 2025;16(1).
38.Kharrazian D. Exposure to Environmental Toxins and Autoimmune Conditions. Integrative medicine (Encinitas, Calif). 2021;20(2):20-4.
39.Danieli MG, Brunetto S, Gammeri L, Palmeri D, Claudi I, Shoenfeld Y, et al. Machine learning application in autoimmune diseases: State of art and future prospectives. Autoimmunity Reviews. 2024;23(2):103496.
40.Su J, Yang L, Sun Z, Zhan X. Personalized Drug Therapy: Innovative Concept Guided With Proteoformics. Molecular & cellular proteomics : MCP. 2024;23(3):100737.
41.Li Y, Chen B, Yang S, Jiao Z, Zhang M, Yang Y, et al. Advances in environmental pollutant detection techniques: Enhancing public health monitoring and risk assessment. Environment International. 2025;197:109365.
42.Mpakosi A, Cholevas V, Tzouvelekis I, Passos I, Kaliouli-Antonopoulou C, Mironidou-Tzouveleki M. Autoimmune Diseases Following Environmental Disasters: A Narrative Review of the Literature. Healthcare (Basel, Switzerland). 2024;12(17).
43.Mitra S, Chakraborty AJ, Tareq AM, Emran TB, Nainu F, Khusro A, et al. Impact of heavy metals on the environment and human health: Novel therapeutic insights to counter the toxicity. Journal of King Saud University - Science. 2022;34(3):101865.
44.Yasmeen F, Pirzada RH, Ahmad B, Choi B, Choi S. Understanding Autoimmunity: Mechanisms, Predisposing Factors, and Cytokine Therapies. International journal of molecular sciences [Internet]. 2024; 25(14).
45.Metryka E, Chibowska K, Gutowska I, Falkowska A, Kupnicka P, Barczak K, et al. Lead (Pb) Exposure Enhances Expression of Factors Associated with Inflammation. International journal of molecular sciences. 2018;19(6).
46.Christodoulou M, Moysidou E, Lioulios G, Stai S, Lazarou C, Xochelli A, et al. T-Follicular Helper Cells and Their Role in Autoimmune Diseases. Life (Basel, Switzerland). 2025;15(4).
47.Haidar Z, Fatema K, Shoily SS, Sajib AA. Disease-associated metabolic pathways affected by heavy metals and metalloid. Toxicology reports. 2023;10:554-70.
48.Hemdan NY, Abu El-Saad AM, Sack U. The role of T helper (TH)17 cells as a double-edged sword in the interplay of infection and autoimmunity with a focus

on xenobiotic-induced immunomodulation. Clinical & developmental immunology. 2013;2013:374769.
49.Rasin P, V AA, Basheer SM, Haribabu J, Santibanez JF, Garrote CA, et al. Exposure to cadmium and its impacts on human health: A short review. Journal of Hazardous Materials Advances. 2025;17:100608.
50.Knoell DL, Wyatt TA. The adverse impact of cadmium on immune function and lung host defense. Seminars in cell & developmental biology. 2021;115:70-6.
51.Rajendeeran A, Tenbrock K. Regulatory T cell function in autoimmune disease. Journal of translational autoimmunity. 2021;4:100130.
52.Duan X, Xu G, Li J, Yan N, Li X, Liu X, et al. Arsenic Induces Continuous Inflammation and Regulates Th1/Th2/Th17/Treg Balance in Liver and Kidney In Vivo. Mediators of inflammation. 2022;2022:8414047.
53.Serafini MM, Maddalon A, Iulini M, Galbiati V. Air Pollution: Possible Interaction between the Immune and Nervous System? International journal of environmental research and public health. 2022;19(23).
54.Moudgil KD, Venkatesha SH. The Anti-Inflammatory and Immunomodulatory Activities of Natural Products to Control Autoimmune Inflammation. International journal of molecular sciences [Internet]. 2023; 24(1).
55.Glencross DA, Ho T-R, Camiña N, Hawrylowicz CM, Pfeffer PE. Air pollution and its effects on the immune system. Free Radical Biology and Medicine. 2020;151:56-68.
56.Nasb M, Li F, Dayoub L, Wu T, Wei M, Chen N. Bridging the gap: Integrating exercise mimicry into chronic disease management through suppressing chronic inflammation. Journal of Advanced Research. 2025;70:307-22.
57.Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2018;9(6):7204-18.
58.Amarante-Mendes GP, Adjemian S, Branco LM, Zanetti LC, Weinlich R, Bortoluci KR. Pattern Recognition Receptors and the Host Cell Death Molecular Machinery. Frontiers in immunology. 2018;9:2379.
59.Xuan S, Ma Y, Zhou H, Gu S, Yao X, Zeng X. The implication of dendritic cells in lung diseases: Immunological role of toll-like receptor 4. Genes & Diseases. 2024;11(6):101007.
60.Zhang P, Martin M, Michalek SM, Katz J. Role of mitogen-activated protein kinases and NF-kappaB in the regulation of proinflammatory and anti-inflammatory cytokines by Porphyromonas gingivalis hemagglutinin B. Infection and immunity. 2005;73(7):3990-8.
61.Andretto V, Dusi S, Zilio S, Repellin M, Kryza D, Ugel S, et al. Tackling TNF-α in autoinflammatory disorders and autoimmune diseases: From conventional to cutting edge in biologics and RNA-based nanomedicines. Advanced Drug Delivery Reviews. 2023;201:115080.
62.Richter P, Macovei LA, Mihai IR, Cardoneanu A, Burlui MA, Rezus E. Cytokines in Systemic Lupus Erythematosus—Focus on TNF-α and IL-17. International journal of molecular sciences [Internet]. 2023; 24(19).
63.Lopetuso LR, Cuomo C, Mignini I, Gasbarrini A, Papa A. Focus on Anti-Tumour Necrosis Factor (TNF)-α-Related Autoimmune Diseases. International journal of molecular sciences [Internet]. 2023; 24(9).
64.Hung AL, Lim M, Doshi TL. Targeting cytokines for treatment of neuropathic pain. Scandinavian journal of pain. 2017;17:287-93.
65.Tylutka A, Walas Ł, Zembron-Lacny A. Level of IL-6, TNF, and IL-1β and age-related diseases: a systematic review and meta-analysis. 2024;Volume 15 - 2024.
66.Nie J, Zhou L, Tian W, Liu X, Yang L, Yang X, et al. Deep insight into cytokine storm: from pathogenesis to treatment. Signal Transduction and Targeted Therapy. 2025;10(1):112.
67.Quinn JL, Kumar G, Agasing A, Ko RM, Axtell RC. Role of TFH Cells in Promoting T Helper 17-Induced Neuroinflammation. 2018;Volume 9 - 2018.
68.Xie G, Chen X, Gao Y, Yang M, Zhou S, Lu L, et al. Age-Associated B Cells in Autoimmune Diseases: Pathogenesis and Clinical Implications. Clinical Reviews in Allergy & Immunology. 2025;68(1):18.
69.Wei J, Zhang Y, Li H, Wang F, Yao S. Toll-like receptor 4: A potential therapeutic target for multiple human diseases. Biomedicine & Pharmacotherapy. 2023;166:115338.
70.Wang G, Su Z, Li H, Xiao L, Li C, Lian G. The role of metabolism in Th17 cell differentiation and autoimmune diseases. International Immunopharmacology. 2022;103:108450.
71.Jang D-i, Lee AH, Shin H-Y, Song H-R, Park J-H, Kang T-B, et al. The Role of Tumor Necrosis Factor Alpha (TNF-α) in Autoimmune Disease and Current TNF-α Inhibitors in Therapeutics. International journal of molecular sciences [Internet]. 2021; 22(5).
72.Strzelec M, Detka J, Mieszczak P, Sobocińska MK, Majka M. Immunomodulation-a general review of the current state-of-the-art and new therapeutic strategies for targeting the immune system. Frontiers in immunology. 2023;14:1127704.
73.Dinarello CA, van der Meer JW. Treating inflammation by blocking interleukin-1 in humans. Seminars in immunology. 2013;25(6):469-84.
74.Favalli EG. Understanding the Role of Interleukin-6 (IL-6) in the Joint and Beyond: A Comprehensive

Review of IL-6 Inhibition for the Management of Rheumatoid Arthritis. Rheumatology and therapy. 2020;7(3):473-516.
75.Bi Y, Yang R. Direct and Indirect Regulatory Mechanisms in TH17 cell Differentiation and Functions. 2012;75(6):543-52.
76.Soares-Silva M, Diniz FF, Gomes GN, Bahia D. The Mitogen-Activated Protein Kinase (MAPK) Pathway: Role in Immune Evasion by Trypanosomatids. 2016;Volume 7 - 2016.
77.Ahmadi A, Ahrari S, Salimian J, Salehi Z, Karimi M, Emamvirdizadeh A, et al. p38 MAPK signaling in chronic obstructive pulmonary disease pathogenesis and inhibitor therapeutics. Cell communication and signaling : CCS. 2023;21(1):314.
78.Vilas-Boas V, Chatterjee N, Carvalho A, Alfaro-Moreno E. Particulate matter-induced oxidative stress – Mechanistic insights and antioxidant approaches reported in in vitro studies. Environmental Toxicology and Pharmacology. 2024;110:104529.
79.Canton M, Sánchez-Rodríguez R, Spera I, Venegas FC, Favia M, Viola A, et al. Reactive Oxygen Species in Macrophages: Sources and Targets. Frontiers in immunology. 2021;12:734229.
80.Zheng X, Sawalha AH. The Role of Oxidative Stress in Epigenetic Changes Underlying Autoimmunity. Antioxidants & redox signaling. 2022;36(7-9):423-40.
81.Khan MF, Wang H. Environmental Exposures and Autoimmune Diseases: Contribution of Gut Microbiome. Frontiers in immunology. 2019;10:3094.
82.Zhao C-N, Xu Z, Wu G-C, Mao Y-M, Liu L-N, Qian W, et al. Emerging role of air pollution in autoimmune diseases. Autoimmunity Reviews. 2019;18(6):607-14.
83.Jee Y-M, Lee J-Y, Ryu T. Chronic Inflammation and Immune Dysregulation in Metabolic-Dysfunction-Associated Steatotic Liver Disease Progression: From Steatosis to Hepatocellular Carcinoma. Biomedicines [Internet]. 2025; 13(5).
84.Rio P, Gasbarrini A, Gambassi G, Cianci R. Pollutants, microbiota and immune system: frenemies within the gut. Frontiers in public health. 2024;12:1285186.
85.Zinatizadeh MR, Schock B, Chalbatani GM, Zarandi PK, Jalali SA, Miri SR. The Nuclear Factor Kappa B (NF-kB) signaling in cancer development and immune diseases. Genes Dis. 2021;8(3):287-97.
86.Bauer RN, Diaz-Sanchez D, Jaspers I. Effects of air pollutants on innate immunity: the role of Toll-like receptors and nucleotide-binding oligomerization domain-like receptors. The Journal of allergy and clinical immunology. 2012;129(1):14-24; quiz 5-6.
87.Kany S, Vollrath JT, Relja B. Cytokines in Inflammatory Disease. International journal of molecular sciences. 2019;20(23).
88.Galeano-Sánchez D, Morales-González V, Monsalve DM, Ramırez-Santana C, Acosta-Ampudia Y. Airborne culprits: A comprehensive review of PM, silica, and TCDD in autoimmune diseases. Journal of translational autoimmunity. 2024;9:100253.
89.Zhang W, Liu HT. MAPK signal pathways in the regulation of cell proliferation in mammalian cells. Cell Research. 2002;12(1):9-18.
90.Zhang K. Environmental PM(2.5)-triggered stress responses in digestive diseases. eGastroenterology. 2024;2(2).
91.Lin F-x, Gu H-y, He W. MAPK signaling pathway in spinal cord injury: Mechanisms and therapeutic potential. Experimental Neurology. 2025;383:115043.
92.Alam MS, Gaida MM, Ogawa Y, Kolios AG, Lasitschka F, Ashwell JD. Counter-regulation of T cell effector function by differentially activated p38. The Journal of experimental medicine. 2014;211(6):1257-70.
93.Liu Z, Liang Q, Ren Y, Guo C, Ge X, Wang L, et al. Immunosenescence: molecular mechanisms and diseases. Signal Transduction and Targeted Therapy. 2023;8(1):200.
94.Singh N, Sharma S. Molecular and Immunological Mechanisms Associated with Diesel Exhaust Exposure. Targets [Internet]. 2025; 3(2).
95.Xue C, Yao Q, Gu X, Shi Q, Yuan X, Chu Q, et al. Evolving cognition of the JAK-STAT signaling pathway: autoimmune disorders and cancer. Signal Transduction and Targeted Therapy. 2023;8(1):204.
96.Zhou X, Dai H, Jiang H, Rui H, Liu W, Dong Z, et al. MicroRNAs: Potential mediators between particulate matter 2.5 and Th17/Treg immune disorder in primary membranous nephropathy. 2022;Volume 13 - 2022.
97.Hu Q, Bian Q, Rong D, Wang L, Song J, Huang H-S, et al. JAK/STAT pathway: Extracellular signals, diseases, immunity, and therapeutic regimens. 2023;Volume 11 - 2023.
98.Sun L, Su Y, Jiao A, Wang X, Zhang B. T cells in health and disease. Signal Transduction and Targeted Therapy. 2023;8(1):235.
99.Mourik BC, Lubberts E, de Steenwinkel JEM, Ottenhoff THM, Leenen PJM. Interactions between Type 1 Interferons and the Th17 Response in Tuberculosis: Lessons Learned from Autoimmune Diseases. 2017;Volume 8 - 2017.
100.Woś I, Tabarkiewicz J. Effect of interleukin-6, -17, -21, -22, and -23 and STAT3 on signal transduction pathways and their inhibition in autoimmune arthritis. Immunologic research. 2021;69(1):26-42.
101.Jomova K, Raptova R, Alomar SY, Alwasel SH, Nepovimova E, Kuca K, et al. Reactive oxygen

species, toxicity, oxidative stress, and antioxidants: chronic diseases and aging. Archives of toxicology. 2023;97(10):2499-574.
102.Honing DY, Luiten RM, Matos TR. Regulatory T Cell Dysfunction in Autoimmune Diseases. International journal of molecular sciences [Internet]. 2024; 25(13).
103.Mijač S, Banić I, Genc A-M, Lipej M, Turkalj M. The Effects of Environmental Exposure on Epigenetic Modifications in Allergic Diseases. Medicina [Internet]. 2024; 60(1).
104.Ramos-González EJ, Bitzer-Quintero OK, Ortiz G, Hernández-Cruz JJ, Ramírez-Jirano LJ. Relationship between inflammation and oxidative stress and its effect on multiple sclerosis. Neurología. 2024;39(3):292-301.
105.Liu T, Zhang L, Joo D, Sun SC. NF-κB signaling in inflammation. Signal Transduct Target Ther. 2017;2:17023-.
106.Canovas B, Nebreda AR. Diversity and versatility of p38 kinase signalling in health and disease. Nature Reviews Molecular Cell Biology. 2021;22(5):346-66.
107.He F, Ru X, Wen T. NRF2, a Transcription Factor for Stress Response and Beyond. International journal of molecular sciences. 2020;21(13).
108.Pant T, Uche N, Juric M, Zielonka J, Bai X. Regulation of immunomodulatory networks by Nrf2-activation in immune cells: Redox control and therapeutic potential in inflammatory diseases. Redox Biology. 2024;70:103077.
109.Vogel CFA, Van Winkle LS, Esser C, Haarmann-Stemmann T. The aryl hydrocarbon receptor as a target of environmental stressors - Implications for pollution mediated stress and inflammatory responses. Redox Biol. 2020;34:101530.
110.Bahman F, Choudhry K, Al-Rashed F, Al-Mulla F, Sindhu S, Ahmad R. Aryl hydrocarbon receptor: current perspectives on key signaling partners and immunoregulatory role in inflammatory diseases. 2024;Volume 15 - 2024.
111.Vogel CFA, Van Winkle LS, Esser C, Haarmann-Stemmann T. The aryl hydrocarbon receptor as a target of environmental stressors – Implications for pollution mediated stress and inflammatory responses. Redox Biology. 2020;34:101530.
112.Wu Y-L, Lin Z-J, Li C-C, Lin X, Shan S-K, Guo B, et al. Epigenetic regulation in metabolic diseases: mechanisms and advances in clinical study. Signal Transduction and Targeted Therapy. 2023;8(1):98.
113.Mei X, Zhang B, Zhao M, Lu Q. An update on epigenetic regulation in autoimmune diseases. Journal of translational autoimmunity. 2022;5:100176.
114.Eghbalpour F, Aghaei M, Ebrahimi M, Tahsili M, Golalipour M, Mohammadi S, et al. Effect of indole-3-carbinol on transcriptional profiling of wound-healing genes in macrophages of systemic lupus erythematosus patients: an RNA sequencing assay. Lupus. 2020;29:954-63.
115.Rider CF, Carlsten C. Air pollution and DNA methylation: effects of exposure in humans. Clinical Epigenetics. 2019;11(1):131.