Unseen threats: The inflammatory pathways linking environmental pollutants to chronic diseases

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Abstract

Toxic environmental contaminants including airborne toxins, heavy metals, and endocrine-disrupting chemicals (EDCs) are among the key causes of the worldwide burden of chronic disease that involves shared mechanisms of inflammation leading to disease onset. These contaminants induce low-grade, chronic inflammation through numerous mechanisms, including the production of reactive oxygen species (ROS), activation of inflammatory signaling pathways, immune dysregulation, and epigenetics. Chronic inflammation has been linked with various conditions such as cardiovascular disease, diabetes, asthma, neurodegenerative disorders, autoimmune diseases, and certain cancers. The review describes how the pollutants trigger inflammatory mechanisms, that is, oxidative stress, immune alterations, and epigenetic alterations. It emphasizes raising awareness of this relationship to allow effective public health measures and regulation to control environmental health hazards.

Keywords: Chronic disease, epigenetic changes, environmental toxins, immune dysregulation, inflammation, oxidative stress

1. Introduction

Environmental toxins are now significant drivers of chronic disease burden globally, but short of being exceedingly valued for their role as causative agents of systemic inflammation. Massive exposure to harmful contaminants like particulate matter (PM), heavy metals, volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs), and EDCs through increased urbanization and industrialization over the years has impacted hundreds of millions of human beings around the globe (1). They contaminate air, water, earth, food, and consumer items and form chronic low-level exposure that

that generates disturbance in biological homeostasis. Chronic, low-grade inflammation is one of the most important mechanisms through which the pollutants cause disease pathology. Unlike the reversible protective response of acute inflammation, chronic inflammation results in tissue damage, cellular dysfunction, and disease progression (2). Pollutants may initiate and sustain such an inflammatory response through oxidative stress, activation of pro-inflammatory signaling pathways like Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) and Mitogen-Activated Protein Kinases (MAPKs), and immune suppression. They also regulate gene expression through epigenetic mechanisms and kill the mitochondria, further increasing inflammation (3). There is emerging evidence of environmental exposure linked with inflammatory conditions such as asthma, cardiovascular disease, diabetes, neurodegenerative disorders, autoimmune disorders, and certain cancers. Yet the molecular mechanism through which it happens has yet to be found (1,2). Understanding of the mechanisms by which environmental poisons cause and sustain inflammation will guide prevention and treatment strategies that are effective, and environmental health will become increasingly pertinent to the prevention of chronic disease as well as to public policy (3).

2. Types of environmental pollutants

The environmental pollutants expose human health and the environment to severe risks and effects through air, water, soil, and organism effects. The pollutants as particulate matter in microscopic form, to toxic chemicals, cause remote health effects by way of inflammation, endocrine balance disruption, and long-term disease induction (1).

2.1. Air and water contaminants

Air and water contaminants pose important public health dangers by exacerbating systemic as well as cellular-level chronic inflammation and oxidative stress. The four most dangerous air pollutants are fine particulate matter (PM2.5), nitrogen oxides (NOx), ground-level ozone (O_3), and carbon monoxide (CO). PM2.5 can infiltrate deep within the lungs, up to a level near alveoli, and into the blood, where it gets absorbed, and activate toll-like receptors (TLRs). This induces NF-κB signaling, which causes the release of pro-inflammatory cytokines like interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α). Prolonged inflammation induced by PM2.5 initiates respiratory disease like asthma and systemic cardiovascular disease (3). NOx gases contribute to smog formation and airway inflammation through MAPKs pathways. Ozone is a strong oxidant that causes damage to lung epithelial cells and enhances cytokine release, impairing lung function. CO has a high affinity for hemoglobin, which binds it to form carboxyhemoglobin and impairs oxygen transport and mitochondrial respiration, and leads to hypoxic injury (1).

In water bodies, toxins such as heavy metals (lead, mercury), pesticides, and drugs become deposited and damage the nervous system and endocrine functions. The toxins disrupt neurotransmitter and hormone receptor transduction of signals, cause mtROS, and maintain NF-κB activation. This causes chronic immune dysregulation and tissue damage and is associated with neurodevelopmental retardation, kidney damage, and hormonal interference in long-term exposure (4).

2.2. Endocrine-disrupting chemicals (EDCs)

Endocrine Disrupting Chemicals are outside chemicals that interfere with hormonal homeostasis through the mimicry or opposition of natural hormones. Bisphenol A (BPA), phthalates, and some pesticides are traditional EDCs, which directly bind to nuclear receptors such as estrogen receptors (ERα/β), androgen receptors (AR), and peroxisome proliferator-activated receptors (PPARs). Binding to the receptors causes the regulation of gene expression for reproduction, growth, and metabolism (5). BPA is an agonist on a subset of the estrogen receptor and induces aberrant gene transcription, causing precocious puberty, infertility, obesity, and hormone-sensitive cancer. . EDCs also induce epigenetic modifications such as DNA methylation and histone modification that lead to aberrant gene patterns and probable intergenerational transfer. Exposure elevates mtROS and activates inflammatory signaling (NF-κB, MAPKs), producing chronic low-grade inflammation with increased cytokines IL-6 and TNF-α,

suppressing immune function. Because of extensive application in plastics, cosmetics, and packaging, exposure to EDCs is ubiquitous, with their lipophilicity leading to bioaccumulation and augmented health impacts (2).

2.3. Persistent organic pollutants (POPs)

POPs such as polychlorinated biphenyls (PCBs) and DDT are chemically inert, degradation-resistant, and lipophilic chemicals. They are bioaccumulated by the food chain and globally dispersed through atmospheric transport, polluting remote regions. POPs interfere with endocrine systems by binding to receptors like the aryl hydrocarbon receptor (AhR) and thyroid hormone receptors, regulating gene expression for metabolism and immunity. POPs induce mitochondrial damage, increasing mtROS levels, and activating inflammatory signaling pathways like NF-κB and AP-1, leading to chronic inflammation. Long-term exposure to POPs has been linked to cardiovascular disease, diabetes, cancer, neurodevelopmental disorders, and immunotoxicity—dysfunctioning T cells and macrophages, and risking infection and autoimmunity. Far from eliminated despite international efforts such as the Stockholm Convention, POPs are a continuing environmental and health concern since they are stable and long-lasting (6).

3. Mechanisms of inflammation induced by pollutants

Environmental toxins play a significant role in the pathogenesis of chronic disease by a number of different biological mechanisms. Figure 1 shows the oxidative stress, induction of pro-inflammatory cascades, immune dysregulation, epigenetic modification, and mitochondrial damage culminating in inflammation and disease pathogenesis (2).

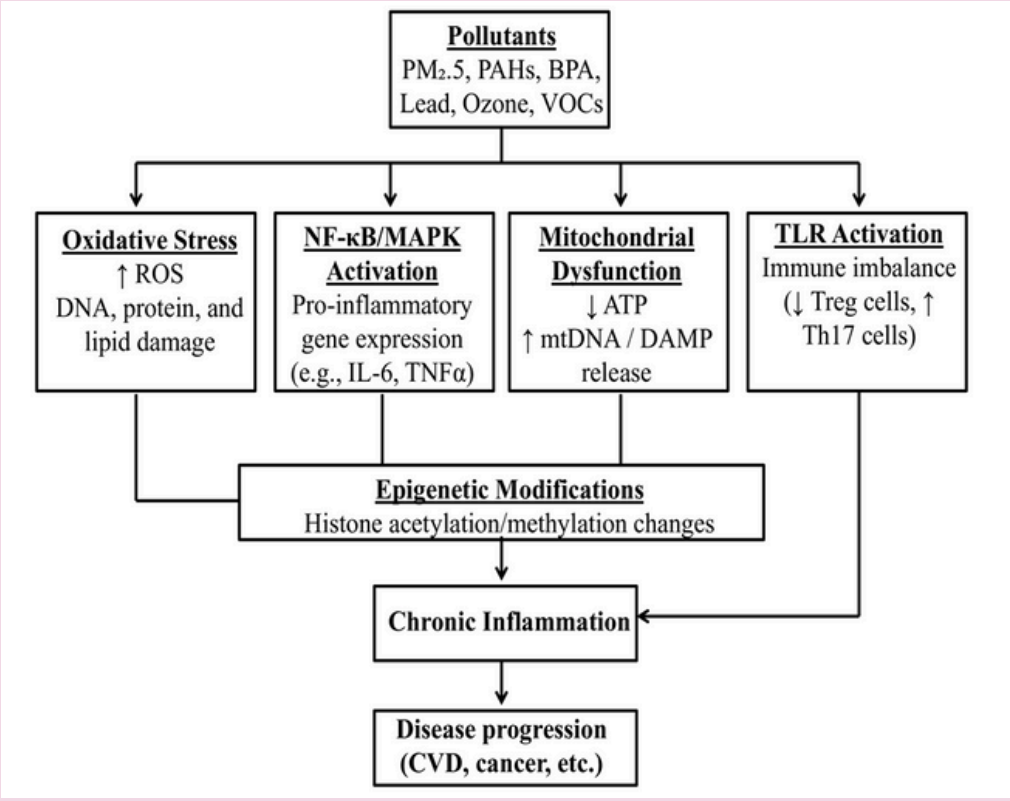

Figure 1. Mechanisms of inflammation induced by environmental pollutants

3.1. Oxidative stress and reactive oxygen species (ROS) production

We went on to study in more detail how the ambient air pollutants, such as particulate matter (PM), ozone, heavy metals, and polycyclic aromatic hydrocarbons (PAHs) form ROS. ROS are tightly regulated under resting physiological conditions through the antioxidant defense system. However, on exposure to pollutants, this balance is destroyed, and there is oxidative damage to DNA, lipids, and proteins. . This

triggers a cascade of inflammatory signaling and cytokine secretion. Chronic oxidative stress is highlighted now as a shared pathologic mechanism to explain cardiovascular, neurodegenerative, and metabolic disorders. Mitochondrial vulnerability to oxidative damage and resultant positive feedback vicious cycle of ROS production and inflammation were also addressed. Targeted antioxidant therapy is highlighted as an emerging therapy (4,5).

3.2. Activation of pro-inflammatory pathways

The section now contains a more elaborate molecular explanation of how pollution leads to NF-κB and MAPK signaling pathways. We explicitly described that activation of NF-κB is mediated through IκB degradation, thus enabling translocation to the nucleus and expression of inflammatory genes. We delineate cross-talk between MAPK cascades and NF-κB, which synergistically augment inflammatory responses. Pathological activation of pathways is linked to asthma pathogenesis, autoimmune diseases, and cancer (2,4,6).

3.3. Immune system dysregulation

We expanded the explanation of how toxicants disrupt immune system homeostasis. Heavy metals and PM over-activate immune cells like macrophages and dendritic cells and induce exaggerated cytokine production. We also describe how toxicants disrupt antigen presentation, reduce regulatory T cell (Treg) populations, and induce pathogenic T cell responses (Th17 and Th2) and amplify autoimmunity and allergic diseases. We also added information on how repeated activation of innate immune receptors, such as Toll-like receptors (TLRs), results in autoimmune and inflammatory disease conditions like asthma, rheumatoid arthritis, and multiple sclerosis (1,7).

3.4. Mitochondrial dysfunction

This subsection now explains in greater detail how mitochondrial toxicity due to such poisons as diesel exhaust and heavy metals results in dysfunctional electron transport, increased ROS, decreased ATP production, mtDNA release, and damage-associated molecular patterns (DAMPs). These stress signals from mitochondria activate immune receptors and initiate inflammation. We also observe how abnormal mitochondrial dynamics (fusion and fission) result in apoptosis and cellular stress. The interconnectedness of mitochondrial pathology, oxidative stress, and epigenetic deregulation is emphasized to underscore the system-wide impact of environmental toxicants (5,8).

4. Environmental pollutants and chronic diseases

Environmental pollutants are the culprits for toxin exposure, and this adds up to chronic inflammation, a major mediator of the disease pathogenesis of such conditions as cardiovascular disease, type 2 diabetes, asthma, Chronic Obstructive Pulmonary Disease (COPD), and neurodegenerative disorders. Table 1 shows the environmental toxins whose elevated inflammatory markers include C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), which are like pollutants PM2.5 (9). These inflammatory markers lead to endothelial dysfunction, insulin resistance, and tissue injury. Epidemiologic evidence indicates of higher chronic disease burden among exposed groups. Prevention of health risk due to long-term effects from environmental exposure includes decreasing the pollutant-induced inflammation and reasserting public health policy to curb these risks (7).

Table 1. Impact of environmental pollutants on chronic diseases: Unraveling the mechanisms of inflammation

S. N.	Environmental pollutant	Associated chronic diseases	Molecular mechanisms of inflammation	Ref.
1	Particulate matter (PM2.5)	Cardiovascular diseases (e.g., hypertension, atherosclerosis), asthma	ROS generation, oxidative stress, endothelial dysfunction, activation of NF-κB and MAPK pathways, cytokine production (IL-6, TNF-α), vascular inflammation	(8)

2	Ozone (O_3)	Asthma, COPD, and pulmonary fibrosis	Oxidative stress, lipid peroxidation, activation of NF-κB, neutrophilic airway inflammation, increased IL-8, GM-CSF	(9)
3	Tobacco smoke	COPD, lung cancer, cardiovascular diseases	Chronic oxidative stress, DNA adduct formation, pro-inflammatory cytokines (I1β, TNF-α), activation of MAPK/NF-κB, impaired macrophage function	(10)
4	Heavy metals (e.g., Lead, Cadmium, Mercury)	Neurodegenerative diseases,renal dysfunction,and cancer	Mitochondrial dysfunction, oxidative DNA damage, misfolded proteins, epigenetic modifications (histone deacetylation), Th17/Treg imbalance, microglial activation	(11)
5	Polycyclic aromatic hydrocarbons (PAHs)	Cardiovascular disease, lung cancer, and reproductive toxicity	Aryl hydrocarbon receptor (AhR) activation, ROS generation, DNA damage, NF-κB signaling, CYP450 enzyme induction, inflammation-driven carcinogenesis	(12)
6	Bisphenol A (BPA)	Obesity, type 2 diabetes, and hormone-dependent cancers	Estrogen receptor binding, insulin resistance, adipose inflammation, Th1/Th17 skewing, reduced Tregs, oxidative stress	(13)
7	Phthalates	Endocrine disorders, reproductive abnormalities, and obesity	PPAR-γ activation, epigenetic modulation, IL-6 and CRP elevation, macrophage infiltration into adipose tissue, and immune dysregulation	(14)
8	Dioxins	Cancer, autoimmune diseases, and developmental disorders	AhR activation, sustained TLR signaling, IL-6/IL-17 induction, Th17 polarization, immune suppression, and chronic inflammation	(15)
9	Arsenic	Diabetes, skin and lung cancer, cardiovascular disease	ROS overproduction, mitochondrial dysfunction, NF-κB/STAT3 activation, inflammasome (NLRP3) induction, apoptosis and chronic inflammation	(16)
10	Formaldehyde	Asthma, nasopharyngeal cancer, leukemia	Direct epithelial toxicity, protein cross-linking, DNA-protein adducts, ROS-mediated airway inflammation, activation of inflammatory transcription factors	(17)
11	Trichloroethylene (TCE)	Autoimmune diseases, liver and kidney toxicity, cancer	ROS generation, ER stress, hepatocellular inflammation, dysregulation of mitochondrial bioenergetics, altered immune tolerance	(18)
12	Tetrachloroethylene (PERC)	Hepatic injury, CNS toxicity, reproductive toxicity	Oxidative stress, glutathione depletion, mitochondrial respiration inhibition, cytokine release, disruption of neuronal homeostasis	(19)

5. Future perspective

Follow-up research will attempt to elucidate the intricate molecular mechanisms by which toxins induce chronic inflammation. Biomarkers for previous-in-time exposure will enable improved surveillance and targeted intervention (20). Combining environmental exposure with genetic data can enable precision medicine to inform the prevention of disease. New treatments, such as inflammasome inhibitors and mitochondrial protectants, have the potential to reverse damage from contaminants (21). Increased control of polluting emissions and promotion of clean technology are necessary now more than ever. Special attention has to be paid to vulnerable populations under increased risk of exposure. There has to be public health action in the form of prevention, education, and awareness of environmental health. Increased global collaborative action in science, policy, and community is required to reduce long-term health consequence that goes hand in hand with environmental pollutants (22).

6. Conclusion

Environmental toxins are insidious initiators of chronic disease and inflammation everywhere in the world. Through induction of oxidative stress, immune dysregulation, epigenetic modification, and mitochondrial damage, toxins initiate and perpetuate inflammation and cause cardiovascular disease, diabetes, respiratory disease, neurodegenerative disease, autoimmune disease, and cancer. Understanding the toxin-inflammation link redirects our approach to disease prevention, catalyzing a paradigm shift from treatment of symptoms to treatment of environmental causatives. Action next year has to include the integration of scientific knowledge, protection of the environment, health reform, and education to mitigate this pressing global threat. An all-out, interdisciplinary assault on protecting human health and avoiding a disastrous future must be undertaken.

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