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Oxidative Stress and Innate Immunity in the Early Pathogenesis of Environmental Toxicant Exposure

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ABSTRACT

Environmental toxicants, including heavy metals, particulate matter, pesticides, and industrial chemicals, constitute a major global health burden due to their ability to trigger oxidative stress and dysregulate innate immune responses. These early biological events play essential roles in determining susceptibility, severity, and progression of toxicant-induced diseases. Oxidative stress arises when the balance between the production of reactive oxygen species and the antioxidant defense system is disrupted, leading to macromolecular damage and altered cellular signalling. Simultaneously, innate immunity, which provides the first line of defense against harmful stimuli, responds to toxicant exposure through pattern-recognition receptors, inflammasome activation, cytokine release, and recruitment of inflammatory cells. The interplay between oxidative stress and innate immune pathways represents a critical early mechanism driving tissue injury, inflammatory diseases, metabolic dysfunction, carcinogenesis, and long-term systemic toxicity. This review synthesizes current understanding of how oxidative signalling, redox-sensitive transcription factors, mitochondrial dysfunction, and lipid peroxidation integrate with toll-like receptor activation, macrophage polarization, neutrophil responses, and inflammasome dynamics during the initial stages of toxicant exposure. Furthermore, it discusses emerging biomarkers, vulnerable populations, and potential therapeutic strategies targeting redox and immune pathways. Understanding these early events is key to improving environmental health assessments and designing effective preventive and therapeutic interventions.

Keywords: Oxidative stress, Innate immunity, Environmental toxicants, Inflammasome activation, Redox signaling

INTRODUCTION

Environmental toxicants contribute significantly to global morbidity by inducing chronic diseases, systemic inflammation, and organ dysfunction [1]. Inhalation of polluted air, ingestion of contaminated food and water, and occupational exposure to industrial chemicals all expose humans to harmful agents capable of disturbing cellular homeostasis [2]. Two interrelated mechanisms, oxidative stress and innate immune activation, are central to the early pathogenesis triggered by these environmental insults. Oxidative stress results from excessive formation of reactive oxygen species (ROS) such as superoxide anions, hydroxyl radicals, and hydrogen peroxide beyond the neutralizing capacity of the endogenous antioxidant systems [3]. Innate immunity, mediated by macrophages, neutrophils, dendritic cells, natural killer cells, and epithelial barriers, responds rapidly to foreign or harmful stimuli using pattern-recognition receptors. When toxicants enter the body, they often initiate oxidative damage and provoke innate immune responses long before any clinical disease becomes evident [4]. Understanding these early biological events is crucial, as they set the stage for downstream pathological consequences, influencing disease onset, progression, and severity [5]. This review provides a comprehensive discussion on how environmental toxicants induce oxidative stress and activate innate immunity, their mechanistic intersections, and implications for disease development.

2. Environmental Toxicants and Sources of Oxidative Stress

Environmental toxicants are a diverse group of chemical, physical, and biological substances present in air, water, soil, food, and manufactured products [6]. Despite differing structures and exposure routes, many toxicants initiate oxidative stress as an early and fundamental mechanism of toxicity. By altering redox homeostasis, they promote excessive production of reactive oxygen species, weaken antioxidant defenses, and trigger inflammatory cascades.

2.1 Heavy Metals

Heavy metals represent some of the most studied environmental pollutants known to induce oxidative stress [7]. Metals such as cadmium, arsenic, mercury, and lead do not directly participate in redox cycling, yet they exert

profound oxidative effects through indirect mechanisms. They bind sulfhydryl groups on glutathione and antioxidant enzymes, leading to significant depletion of intracellular glutathione pools. Many heavy metals accumulate in mitochondria where they inhibit electron transport chain complexes, resulting in electron leakage and ROS overproduction. Arsenic and cadmium disrupt mitochondrial membrane potential, promoting release of pro-oxidant molecules and impairing ATP synthesis. In contrast, transition metals like iron and copper directly catalyze redox reactions. Through Fenton and Haber–Weiss chemistry, they convert hydrogen peroxide into hydroxyl radicals, which are highly reactive and capable of damaging lipids, DNA, and proteins. This redox cycling property makes them potent drivers of oxidative injury, lipid peroxidation, and genomic instability [8].

2.2 Airborne Particulate Matter

Particulate matter, especially PM2.5 and ultrafine particles, is a major source of oxidative stress in urban and industrial environments [9]. These particles carry adsorbed organic pollutants, polyaromatic hydrocarbons, and transition metals on their surfaces, all of which contribute to ROS generation. Upon inhalation, they deposit deeply within the respiratory tract, reaching alveolar spaces where they are phagocytosed by macrophages. During phagocytosis, macrophages activate NADPH oxidase, generating superoxide as part of the respiratory burst. Particulate matter also damages epithelial cell membranes, disrupts mitochondrial function, and induces redox-sensitive signalling pathways [10]. Because ultrafine particles can translocate into the bloodstream, they exert systemic oxidative effects, contributing to cardiovascular and metabolic disturbances.

2.3 Pesticides and Organic Pollutants

Pesticides such as organophosphates and organochlorines, as well as organic pollutants like polycyclic aromatic hydrocarbons, exert oxidative effects primarily through metabolic activation [11]. These compounds enhance cytochrome P450 enzyme activity, leading to the formation of electrophilic metabolites that consume glutathione and other antioxidants [12]. Many of these metabolites undergo redox cycling, generating superoxide and hydrogen peroxide continuously. Pesticides may also inhibit antioxidant enzymes and disrupt mitochondrial respiration, compounding their oxidative impact on exposed tissues [13].

2.4 Industrial and Household Chemicals

A wide range of industrial solvents, plastic additives, cleaning agents, and endocrine-disrupting chemicals contribute to oxidative stress by disturbing mitochondrial bioenergetics [14]. For example, bisphenol A interferes with mitochondrial membrane potential, causing electron leakage from the electron transport chain. Similarly, solvents and surfactants impair metabolic enzymes, promote ROS formation, and sensitize cells to oxidative injury. Because these chemicals are common in homes and workplaces, they represent ubiquitous sources of redox imbalance across populations [15]. Overall, across all classes of environmental toxicants, oxidative stress emerges as a central early mechanism that precedes inflammation, apoptosis, tissue damage, and chronic disease.

3. Mechanisms of Oxidative Stress in Toxicant Exposure

3.1 Mitochondrial Dysfunction

Mitochondria are primary targets in toxicant-induced oxidative stress due to their central role in energy production and ROS generation. Many toxicants inhibit complexes I, III, or IV of the electron transport chain, preventing efficient electron transfer and promoting leakage of electrons that react with oxygen to form superoxide radicals [16]. Damaged mitochondria release pro-oxidant molecules, mitochondrial DNA, and cardiolipin, all of which act as intracellular danger signals. These signals amplify inflammation by activating pattern-recognition receptors and inflammasomes, linking oxidative injury directly to innate immune responses [17].

3.2 Disruption of Antioxidant Defense Systems

Cells possess multiple antioxidant systems to maintain redox balance, including enzymatic and non-enzymatic components such as glutathione, superoxide dismutase, catalase, and glutathione peroxidase [18]. Environmental toxicants often impair these systems by inhibiting enzyme activity, depleting antioxidant substrates, or interfering with their synthesis. When these protective mechanisms fail, cells become highly susceptible to ROS accumulation and oxidative damage [19].

3.3 Lipid Peroxidation

One of the hallmark consequences of toxicant-induced oxidative stress is lipid peroxidation, which occurs when ROS attack polyunsaturated fatty acids within cell membranes [20]. This process generates reactive aldehydes such as malondialdehyde and 4-hydroxynonenal. These secondary products form adducts with proteins and nucleic acids, altering their structure and function [21]. Lipid peroxidation not only compromises membrane integrity but also propagates further oxidative damage throughout the cell.

3.4 Activation of Redox-Sensitive Transcription Factors

Oxidative stress activates several transcription factors that regulate inflammatory and antioxidant responses. NF-kB and AP-1 promote pro-inflammatory cytokine production, while Nrf2 induces expression of detoxifying and antioxidant enzymes [22]. The balance between these pathways determines whether the cell adapts to oxidative stress or progresses toward injury and inflammation [23]. Toxicants can disturb this balance by persistently activating inflammatory pathways while suppressing protective Nrf2 responses.

3.5 ROS-Induced DNA Damage

Excess ROS cause a variety of DNA lesions including base oxidation, strand breaks, and cross-linking. Persistent DNA damage overwhelms repair pathways and may lead to mutations, genomic instability, and carcinogenesis. In addition to genetic consequences, DNA damage triggers cellular stress signaling and apoptosis, contributing to early tissue injury associated with toxicant exposure [24].

4. Innate Immune Activation in Early Toxicant Exposure

Innate immunity serves as the body's immediate defense system against harmful environmental exposures, responding within minutes to hours after toxicant entry [25]. Many environmental toxicants mimic pathogen-associated signals or induce cellular damage that releases endogenous danger molecules. These events activate innate immune pathways long before clinical symptoms become evident. The early innate response is shaped by the recognition of toxicants through specialized receptors, recruitment of immune cells, and initiation of inflammatory cascades that can become pathological if sustained [26].

4.1 Pattern Recognition Receptors

Pattern recognition receptors play a fundamental role in detecting environmental toxicants [27]. Toll-like receptors, NOD-like receptors, and scavenger receptors recognize structural motifs on pollutants or cellular debris generated by toxicant-induced damage. TLR4 has been extensively studied due to its strong activation by metals, organic pollutants, and particulate matter. Engagement of these receptors triggers intracellular signalling pathways such as NF-kB and MAPK, leading to transcription of pro-inflammatory cytokines, chemokines, and adhesion molecules [28]. This early signalling sets the stage for the recruitment of immune cells and the establishment of an inflammatory microenvironment.

4.2 Macrophage Responses

Macrophages are among the first responders to toxicant exposure and play pivotal roles in determining the nature of the early immune response. They engulf particulate toxicants, generate ROS through NADPH oxidase activation, and secrete cytokines including TNF-alpha, IL-1beta, and IL-6[29]. Although these actions are essential for containment of harmful agents, persistent exposure can push macrophages toward a chronic inflammatory phenotype. This results in prolonged tissue injury, fibrosis, and impaired resolution of inflammation [30].

4.3 Neutrophil Recruitment

Neutrophils are rapidly recruited to tissues following PRR activation. Their antimicrobial mechanisms, including ROS production, degranulation, and the release of extracellular traps, become excessive in the context of sterile chemical exposure [32]. These responses inadvertently damage surrounding tissues, disrupt epithelial barriers, and amplify inflammation. Repeated toxicant exposure can lead to persistent neutrophil infiltration, contributing to chronic inflammatory diseases of the lung, skin, and gastrointestinal tract.

4.4 Inflammasome Activation

A major feature of innate immune activation by toxicants is stimulation of the NLRP3 inflammasome. This cytosolic sensor detects a wide range of pollutants including silica, asbestos, heavy metals, and airborne particulates. Inflammasome activation requires signals such as lysosomal rupture, mitochondrial ROS production, and potassium efflux [33]. Once activated, NLRP3 drives maturation of IL-1beta and IL-18, potent inflammatory mediators that escalate tissue injury and attract more immune cells.

4.5 Epithelial Barrier Dysfunction

Epithelial cells lining the respiratory, gastrointestinal, and dermal surfaces act as both guards and detectors of toxicant exposure. Toxicants compromise tight junction proteins, weakening barrier integrity and increasing permeability. Damaged epithelial cells release cytokines, chemokines, and antimicrobial peptides, which alert nearby immune cells but also perpetuate inflammation [34]. Barrier dysfunction allows deeper penetration of toxicants, creating a continuous cycle of exposure, immune activation, and tissue remodeling.

CONCLUSION

Environmental toxicants initiate a cascade of interconnected biological responses where oxidative stress and innate immunity play central roles. These early events are crucial determinants of downstream disease development, affecting inflammatory responses, tissue integrity, metabolic pathways, and genomic stability. A deeper understanding of the cross-talk between redox dynamics and innate immune signaling is fundamental for early detection, improved risk assessments, and targeted interventions aimed at mitigating toxicant-associated disease burdens. Future research should focus on integrating multi-omics data, identifying sensitive biomarkers, and developing personalized strategies to protect vulnerable populations.

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