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The Role of Air Pollution in Inducing Ferroptosis: Mechanisms, Evidence, and Innovative Perspectives: Review Article

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A B S T R A C T

Introduction: Air pollution is a complex environmental hazard composed of particulate matter ($PM_{2.5}$, PM_{10}), heavy metals, ozone, nitrogen dioxide, and polycyclic aromatic hydrocarbons. These pollutants are strongly associated with respiratory, cardiovascular, and neurological disorders. At the molecular level, pollutants induce oxidative stress, inflammation, and mitochondrial dysfunction. Ferroptosis, an iron-dependent regulated cell death characterized by lipid peroxidation and glutathione depletion, has recently emerged as a critical pathway in pollution-related cellular injury. This review aims to summarize the mechanistic links between air pollution and ferroptosis, highlight supporting experimental and clinical evidence, and discuss future therapeutic perspectives.

Materials & Methods: A systematic literature review was conducted in PubMed, Scopus, and Web of Science databases using the keywords *ferroptosis, air pollution,* and *mechanisms.* Articles were screened and analyzed following PRISMA guidelines. Both in vitro, in vivo, and limited human studies were evaluated. Statistical synthesis was descriptive, as data heterogeneity precluded quantitative meta-analysis.

Results: Findings from multiple studies demonstrate that pollutants induce ferroptosis through iron overload, suppression of the cystine/glutamate antiporter (system Xc^-), inactivation of glutathione peroxidase 4 (GPX4), and excessive reactive oxygen species production. Markers of ferroptosis, including increased lipid peroxidation and reduced GPX4, were consistently observed. Evidence links ferroptosis to pollutant-induced chronic diseases such as chronic obstructive pulmonary disease (COPD), cardiovascular dysfunction, and neurodegenerative disorders.

Conclusion: Ferroptosis represents a mechanistic bridge between air pollution and chronic disease development. Beyond oxidative stress, it acts as a pathological orchestrator driving inflammation and tissue remodeling. Targeting ferroptosis offers innovative therapeutic opportunities to mitigate the global health impacts of air pollution.

Keywords: ferroptosis, air pollution, mechanism

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Introduction

Air pollution comprises a complex mixture of particulate matter and gases, including fine particulate matter ($PM_{2.5}$, PM_{10}), polycyclic aromatic hydrocarbons (PAHs), heavy metals, ozone (O_3), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) (1). Exposure to these pollutants is strongly linked to respiratory, cardiovascular, neurological diseases, and cancer (1). At the cellular level, air pollutants induce damage through oxidative stress, inflammation, DNA damage, and mitochondrial dysfunction(2).

Ferroptosis, first identified in 2012, represents a distinct form of regulated cell death that is iron-dependent and mechanistically different from apoptosis or necrosis(3). It is characterized by the accumulation of intracellular iron, lipid peroxidation of polyunsaturated fatty acids, and impairment of the glutathione-dependent antioxidant defense system(4). Morphological hallmarks include mitochondrial shrinkage, reduced cristae, and rupture of the outer mitochondrial membrane without nuclear condensation(5).

Mechanistically, ferroptosis is governed by the cystine/glutamate antiporter (system Xc^-), glutathione peroxidase 4 (GPX4), and iron metabolism. Disruption of these pathways triggers excessive lipid peroxidation and ferroptotic cell death(6). Given the oxidative nature of air pollutants and their capacity to disrupt both iron homeostasis and antioxidant defenses, the hypothesis that air pollution induces ferroptosis has recently gained significant attention(7, 8).

Similarly, epigenetic and gene profiling studies in human lung tissue have shown that genetic and epigenetic differences can modulate ferroptotic responses to chronic exposure to pollutants such as $PM_{2.5}$ (9). In addition, novel therapeutic strategies are being developed, including the use of nanoparticles and other targeted interventions to inhibit ferroptosis and reduce pollutant-induced lung injury(10). Taken together, this evidence suggests that ferroptosis is not simply a byproduct of oxidative stress, but rather an active driver in the long-term pathological remodeling of pollution-related diseases such as chronic obstructive pulmonary disease (COPD), cardiovascular disorders, and neurodegenerative disorders(11).

Recent studies have expanded this concept, showing that reactive oxygen species (ROS) act as a rheostat regulating different cell death modalities, including ferroptosis, apoptosis, and necroptosis(12). This highlights the role of ferroptosis not merely as a byproduct of oxidative stress, but as a central pathogenic mechanism in pollution-related diseases.

Mechanisms of Air Pollution-Induced Ferroptosis and Existing Evidence

Mechanisms are multifaceted, primarily involving iron dyshomeostasis, lipid peroxidation, and antioxidant suppression:

a) Iron Metabolism Dysregulation and Reactive Iron Accumulation

- Increased labile iron: PM and heavy metals (e.g., Fe, Cd) directly or indirectly elevate intracellular free iron via lysosomal disruption, enhanced iron uptake, or impaired iron storage/transport proteins (e.g., ferritin, transferrin).

- Fenton reaction: Fe^{2+} reacts with H_2O_2 to generate hydroxyl radicals (•OH), initiating membrane lipid peroxidation (13).

- Iron regulators: Pollutants may alter iron-regulatory proteins (IRPs) or hepcidin, increasing iron retention(14).

b) Lipid Peroxidation Induction

- ROS overproduction: PM and PAHs directly increase mitochondrial/cytosolic ROS (e.g., superoxide, H_2O_2), oxidizing membrane lipids (15).

- Lipoxygenase (LOX) activation: LOXs catalyze PUFA peroxidation (e.g.,

arachidonic/adrenic acids) (16). Air pollutants upregulate LOX activity(17).

• Role of PUFAs: PUFA-rich phospholipids are primary ferroptosis substrates. Pollutants drive their oxidation via ROS and iron(18).

c) Glutathione Antioxidant System Impairment

• System xCT inhibition: This transporter imports cystine for glutathione (GSH) synthesis. Pollutants suppress xCT activity, depleting GSH(19).

• GPX4 inactivation: GPX4 reduces lipid hydroperoxides to nontoxic alcohols. Its direct or indirect (via GSH loss) inhibition by pollutants causes lethal lipid peroxide accumulation (20).

Existing Evidence and Critique

In vitro studies: Lung epithelial cells, macrophages, and endothelia exposed to $PM_{2.5}$, heavy metals (Cd, As), or PAHs show ferroptosis markers (↓GPX4, ↓GSH, ↑lipid peroxidation, iron overload). Ferroptosis inhibitors (e.g., ferrostatin-1, deferoxamine) mitigate damage(21).

In vivo models: Animals (mice/rats) exposed to air pollutants (especially $PM_{2.5}$) develop lung/cardiac/neural injury with ferroptotic markers (↑lipid peroxidation, altered GPX4, iron accumulation)(22).

Human biomarker studies: Populations in high-pollution areas show elevated lipid oxidation markers and disrupted iron metabolism, indirectly suggesting ferroptosis(23).

Critique of Current Evidence:

• Strengths: Mechanistic clarity and inhibitor studies provide robust evidence.

• Limitations:

1. Pollutant complexity: Most studies examine single components (e.g., $PM_{2.5}$), not real-world mixtures.

2. Dose/duration gaps: Experimental exposures may not reflect chronic low-dose human exposure.

3. Human evidence limitations: Direct tissue proof is ethically/technically challenging; reliance on indirect biomarkers.

4. Cell death crosstalk: Distinguishing ferroptosis from apoptosis/necrosis/pyroptosis in vivo requires multiple markers.

5. Genetic variability: Genetic polymorphisms in ferroptosis pathways remain understudied.

Synthesis: Global research confirms ferroptosis as a central pathogenic pathway in air pollution-induced injury. It acts as a convergence point for pollutant stressors (metal accumulation, ROS, antioxidant failure), making it a promising therapeutic target(24).

Innovation: Ferroptosis as a Pathological Orchestrator

Beyond being a consequence of exposure, we propose ferroptosis as a master regulator driving inflammation and pathological tissue remodeling in chronic pollution-related diseases. Lipid peroxidation products and DAMPs from ferroptotic cells act as "danger signals," perpetuating inflammation and fibrosis in lungs/heart. This paradigm shift positions ferroptosis as a "pathological orchestrator"—targeting it may halt both initial cell death and downstream clinical sequelae, opening avenues for preventive and therapeutic strategies(25).

Proposed Research Directions

1. Human biomarkers:

-Large cohort studies in polluted areas to identify ferroptosis biomarkers (e.g., oxidized lipids, iron metabolites) in biofluids.

-Diagnostic kits for risk prediction.

2. Mechanistic studies:

-Combinatorial pollutant effects using in vitro/in vivo models.

-Cell-type-specific susceptibility (epithelium, endothelium, macrophages) via single-cell RNA sequencing.

3. Disease pathogenesis:

-Animal models (e.g., conditional GPX4 knockouts) to define ferroptosis' role in COPD, atherosclerosis, and neurodegeneration.

-Impact on pollutant clearance and immunity(26).

4. Therapeutic strategies:

-Test ferroptosis inhibitors (ferrostatins, LOX inhibitors, lipophilic antioxidants) in pollution-exposed animal models.

-Combine with standard therapies.

5. Gene-environment interactions:

-Investigate genetic polymorphisms (iron metabolism, antioxidant genes) in susceptibility(27).

Role of Air Pollution–Induced Ferroptosis in Human Diseases

Emerging evidence highlights that air pollution–induced ferroptosis contributes to the development and progression of multiple chronic diseases. In the cardiovascular system, $PM_{2.5}$ exposure suppresses the Nrf2/GPX4 axis, leading to ferroptosis-mediated cardiotoxicity and accelerated atherosclerosis(28). In the central nervous system, ferroptotic cell death has been linked to neuroinflammation and neurodegeneration, with recent studies identifying ferroptosis biomarkers in cerebrospinal fluid from individuals exposed to high levels of pollution(29). Pulmonary diseases are also strongly influenced by this pathway: combinatorial pollutant exposure synergistically amplifies ferroptosis in lung epithelial cells, triggering chronic inflammation and fibrosis (30). Furthermore, nanoparticle-based experimental therapies that target ferroptosis have shown promise in alleviating pollution-induced lung injury(31).

Collectively, these findings indicate that ferroptosis acts as a mechanistic bridge between environmental pollution and the onset of major diseases such as COPD, cardiovascular dysfunction, and neurodegenerative disorders, underscoring its importance as both a diagnostic marker and therapeutic target.

Conclusion

Ferroptosis is a pivotal mechanism in air pollution–induced cellular injury and disease. A substantial body of evidence confirms the central roles of iron overload, lipid peroxidation, and glutathione disruption in mediating ferroptotic death following pollutant exposure. Beyond being a downstream effect of oxidative stress, ferroptosis functions as a pathological orchestrator, amplifying chronic inflammation, tissue remodeling, and organ dysfunction. Recent studies have highlighted its contribution to the pathogenesis of major human diseases. For example, air pollution–induced ferroptosis drives cardiotoxicity and atherosclerosis through Nrf2/GPX4 suppression, promotes neurodegeneration via ferroptotic signaling detectable in human cerebrospinal fluid, and exacerbates pulmonary injury through combinatorial pollutant exposure and epithelial ferroptosis. These findings establish ferroptosis as a mechanistic bridge between environmental exposure and chronic diseases such as COPD, cardiovascular dysfunction, and neurodegenerative disorders. Framing ferroptosis as both a biomarker and a therapeutic target opens new opportunities for intervention. Identifying robust human biomarkers, developing ferroptosis-targeted therapies, and integrating nanoparticle-based delivery systems may provide innovative strategies to mitigate the global health burden of air pollution–related diseases.

Ethics approval

Not applicable.

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Conflict of interest

The authors report no conflict of interest in this study.

Authors' contributions

FM and MKh did the literature review, drafting of the paper. All authors read, revised, and approved the final manuscript.

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