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Mini Review

Inhaled Nanoparticles and Respiratory Diseases: A Study on The Mechanisms of Mitochondrial Dysfunction in Pulmonary Fibrosis and Asthma

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Abstract

The rapid advancement of nanotechnology has markedly increased the potential for human exposure to inhaled nanoparticles (NPs), raising growing concerns regarding their adverse respiratory effects. Owing to their ultrafine aerodynamic size and high surface reactivity, inhaled NPs can readily penetrate deep into the pulmonary alveoli, where they interact with epithelial and immune cells to trigger oxidative stress, inflammatory responses, and fibrotic remodeling. Among the various pathogenic mechanisms, mitochondrial dysfunction has emerged as a central mediator linking NP exposure to the onset and progression of pulmonary fibrosis and asthma. This mini-review provides an overview of the physicochemical characteristics, cellular interactions, and molecular pathways underlying NP-induced pulmonary toxicity, with a particular emphasis on carbon nanotubes (CNTs) and their mitochondria-targeted toxicity that contributes to both fibrotic and allergic airway remodeling.

Keywords: Nanotoxicology; Pulmonary Fibrosis; Asthma; Mitochondrial Dysfunction; Carbon Nanotubes; Oxidative Stress

Introduction

Inhaled nanoparticles (NPs) constitute a major route of both environmental and occupational exposure. Their nanoscale dimensions allow them to evade mucociliary and phagocytic clearance mechanisms, facilitating deep deposition within the alveolar regions of the lung. Once deposited, NPs can directly interact with macrophages, epithelial cells, and fibroblasts, leading to a cascade of cellular and molecular perturbations. Epidemiological and experimental investigations have consistently associated chronic NP exposure with respiratory pathologies such as pulmonary fibrosis and asthma [1]. Although the pulmonary defense system effectively removes most inhaled particles through mucociliary transport and macrophage-mediated phagocytosis, continuous or high-dose exposure can overwhelm these protective barriers, resulting in persistent inflammation, epithelial–mesenchymal transition (EMT), and extracellular matrix (ECM) remodeling. Recent findings highlight mitochondrial injury as a central mechanism integrating oxidative stress, inflammatory signaling, and fibrogenic responses triggered by inhaled NPs [2].

The toxicological behavior of NPs is profoundly influenced by their physicochemical characteristics, including particle size,

morphology, surface charge, solubility, and surface functionalization. Upon inhalation, NPs may (1) penetrate the alveolar–capillary barrier and enter systemic circulation; (2) be phagocytosed by alveolar macrophages (AMs) or interact with alveolar epithelial cells (AECs); (3) generate reactive oxygen species (ROS) via surface catalytic reactions or mitochondrial dysfunction; and (4) activate key inflammatory signaling cascades such as NF-κB, MAPK, and the NLRP3 inflammasome [3]. Distinct classes of nanomaterials elicit characteristic pulmonary responses. Carbon-based nanomaterials (e.g., multi-walled carbon nanotubes and graphene) are potent inducers of chronic inflammation and fibrotic remodeling, whereas metal and metal oxide NPs (e.g., Ni, Ag, TiO_2, ZnO) primarily induce oxidative stress and immune sensitization, thereby promoting asthma-like phenotypes [4]. The pulmonary fate and biological activity of inhaled NPs are thus governed by their size, geometry, surface chemistry, solubility, and tendency to agglomerate. Carbon-based NPs such as MWCNTs possess needle-like morphologies that cause persistent epithelial injury and sustained inflammatory responses. In contrast, metal and metal oxide NPs often act as catalytic sources of ROS and can function as immunological adjuvants, enhancing allergic sensitization. Following deposition, NPs may be engulfed by AMs or traverse epithelial barriers, leading to intracellular accumulation and organelle-targeted toxicity, with mitochondria emerging as key subcellular targets in NP-induced pulmonary pathogenesis.

Mechanisms of Inhaled Nanoparticles in Pulmonary Fibrosis and Asthma

Mitochondria serve as both critical targets and amplifiers of nanoparticle (NP)-induced toxicity. Upon inhalation, NPs can accumulate within mitochondria, leading to excessive reactive oxygen species (ROS) generation, disruption of mitochondrial membrane potential, depletion of ATP, and activation of intrinsic apoptotic cascades [5]. This oxidative imbalance triggers downstream signaling pathways, including NF-κB, MAPK, and TGF-β1/Smad, thereby promoting inflammatory and fibrogenic responses. In asthma, mitochondrial dysfunction in airway epithelial and immune cells enhances ROS-dependent release of damage-associated molecular patterns (DAMPs), facilitating Th2/Th17 polarization and airway hyperresponsiveness. Carbon nanotubes (CNTs), encompassing single-walled (SWCNTs) and multi-walled (MWCNTs) forms, have been extensively investigated as prototypical fibrous nanomaterials. Their high aspect ratio, rigidity, and limited biodegradability confer substantial pulmonary toxicity. Exposure to MWCNTs induces alveolar structural disorganization, macrophage infiltration, and interstitial fibrosis [6-7]. Although SWCNTs are widely utilized in biomedical applications such as drug delivery and imaging, they can provoke mitochondrial injury and apoptosis through ROS overproduction, collapse of mitochondrial membrane potential, and activation of caspase-9 and caspase-3 signaling [8]. Animal studies have demonstrated that SWCNTs can accumulate in multiple organs, including the lungs and liver, resulting in chronic inflammation, autophagy impairment, and ultrastructural damage [9]. Due to their structural stability and resistance to degradation, MWCNTs exhibit stronger chronic toxicity by inhibiting mitochondrial electron transport chain complexes I and III, diminishing ATP synthesis, and activating TLR4/NF-κB and NLRP3 inflammasome pathways, thereby sustaining inflammation and fibrosis (Adedara et al., 2018). Comparative analyses by Xu et al. (2024) revealed that SWCNTs, MWCNTs, and graphene oxide (GO) can traverse the air–blood and blood–brain barriers, induce ROS accumulation, and impair antioxidant defenses—iron impurities acting as major sources of redox-active radicals.

Long-term exposure (12–18 months) to MWCNTs significantly decreased hepatic and renal glutathione (GSH), altered glutathione S-transferase (GST) activity, and elevated nitric oxide (NO) levels, suggesting that oxidative stress biomarkers may serve as sensitive indicators of chronic exposure [10]. Subchronic inhalation studies (30–90 days) revealed immunosuppressive outcomes—such as reduced T-cell responsiveness and natural killer (NK) cell activity—even in the absence of overt pneumonia, particularly at doses exceeding the NIOSH-recommended exposure limit [11]. Beyond fibrotic injury, CNTs exhibit potent pro-inflammatory and tumor-promoting properties. A single exposure to MWCNTs markedly enhanced metastatic progression of breast cancer to pulmonary and extrapulmonary sites, attributed to CNT-induced angiogenesis and systemic inflammation [12]. Similarly, SWCNTs promote epithelial–mesenchymal transition (EMT) and fibroblast-to-myofibroblast transition (FMT) by desensitizing neutrophil G-protein-coupled receptors (GPCRs), further exacerbating fibrosis [14]. Pharmacological interventions, such as the glycyrrhetinic acid derivative GAMG, have been shown to attenuate SWCNT-induced pulmonary inflammation and fibrosis via modulation of the PI3K/AKT/NF-κB axis [13]. Importantly, alveolar macrophage polarization represents a critical determinant in CNT-induced pulmonary fibrosis. CNTs initially provoke a pro-inflammatory M1 phenotype and subsequently promote M2 polarization, which facilitates EMT and FMT processes. Among CNTs, SWCNTs demonstrate the strongest capacity to drive M2 polarization and fibrotic remodeling [15]. Although mitochondrial dysfunction is increasingly recognized as a key regulator of macrophage polarization and downstream fibrogenic signaling, the precise molecular mechanisms underlying these interactions remain to be fully elucidated.

Disease-specific pathways: fibrosis and asthma

In pulmonary fibrosis, persistent mitochondrial injury disrupts cellular energy metabolism, enhances ROS signaling, and impairs mitophagy, resulting in apoptosis-resistant myofibroblasts and excessive ECM deposition [16]. In asthma, mitochondrial ROS and DAMPs from epithelial cells amplify allergic inflammation by activating dendritic cells and enhancing Th2 cytokine production (Cattani-Cavalieri et al., 2024). Both diseases share the common theme of redox imbalance, mitochondrial stress, and chronic immune activation, suggesting that mitochondria-targeted therapeutic strategies could mitigate NP-induced respiratory damage.

Conclusions and perspectives

Mitochondrial dysfunction is a central, targetable mechanism by which inhaled nanoparticles promote both fibrotic remodeling and allergic airway disease. Future priorities include: (1) establishing chronic, low-dose inhalation models that capture realistic mitochondrial responses; (2) deploying single-cell and spatial omics to map cell-type specific mitochondrial signatures; (3) validating mitochondria-focused interventions (mitochondrial antioxidants, mitophagy modulators, mitochondrial transplantation) in translational models; and (4) leveraging safe-by-design approaches to reduce mitochondrial reactivity of engineered NPs. Integrating mitochondrial endpoints into regulatory testing frameworks will strengthen nanoparticle safety assessment and guide development of safer nanomaterials.

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