

Review

The Mitochondrial Battleground: A Review of Microplastic-Induced Oxidative Stress and Inflammatory Pathways in Human Health

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Abstract: This review synthesizes research on mechanisms of microplastic-induced mitochondrial damage, focusing on oxidative stress and inflammation to address the mechanistic pathways linking microplastic exposure to mitochondrial dysfunction and cellular toxicity. Analysis of diverse in vitro and in vivo studies across aquatic, terrestrial, and mammalian systems was conducted, emphasizing molecular, cellular, and functional mitochondrial parameters. Findings reveal consistent microplastic-induced reactive oxygen species generation, disrupting mitochondrial membrane potential and bioenergetics, with smaller and aged particles exerting greater toxicity. Inflammatory signalling via NF- κ B, the NLRP3 inflammasome, and immune cell necroptosis is closely associated with oxidative stress, forming a feedback loop that exacerbates mitochondrial impairment. Molecular mechanisms implicate endocytic uptake pathways, mitochondrial calcium dysregulation, and apoptosis-related cascades, though causal validation remains limited. The interplay between oxidative stress and inflammation emerges as a central driver of mitochondrial damage across models. These integrated insights highlight the critical influence of microplastic physicochemical properties and biological context on mitochondrial and inflammatory responses. The findings inform future mechanistic research and underscore the need for standardized models to assess microplastic toxicity, advancing understanding of environmental and human health risks associated with microplastic pollution.

Keywords: microplastic; nanoplastics; mitochondrial dysfunctions; ROS; oxidative stress

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1. Introduction

Research on mechanisms of microplastic-induced mitochondrial damage, focusing on oxidative stress and inflammation, has emerged as a critical area of inquiry due to the pervasive presence of microplastics (MPs) and nanoplastics (NPs) in the environment and their potential health impacts [1,2]. Since the early identification of MPs as plastic debris less than 5 mm in diameter [3], research has evolved to reveal their widespread distribution in aquatic and terrestrial ecosystems, as well as their bioaccumulation in human

tissues including liver, lungs, and reproductive organs [4,5]. The increasing environmental concentrations of MPs/NPs and their ability to cross biological barriers underscore their significance as emerging pollutants with implications for cellular and systemic health [6,7]. Notably, oxidative stress and inflammation are key mechanisms underlying microplastic-induced toxicity and are mechanistically linked to pathways involved in cardiovascular and neurodegenerative disease development, although direct causal relationships remain to be established (Tables S2, S3 and S7 in Supplementary Materials) [8–11].

The specific problem addressed in this review is the elucidation of the molecular and cellular mechanisms by which MPs and NPs induce mitochondrial damage through oxidative stress and inflammatory responses [12,13]. Despite growing evidence of MPs/NPs triggering reactive oxygen species (ROS) production and mitochondrial dysfunction in various models [14–17], critical knowledge gaps remain regarding the precise signalling pathways, and the interplay between oxidative stress and inflammation [18–20]. Controversies exist concerning the relative contributions of direct particle effects versus secondary inflammatory cascades, as well as the protective roles of cellular antioxidant systems such as Nrf2 (Table S6 in Supplementary Materials) [7,14]. These gaps hinder comprehensive risk assessment and the development of mitigation strategies [21].

This review adopts a conceptual framework integrating oxidative stress, mitochondrial dysfunction, and inflammation as interconnected processes driving MP/NP-induced cytotoxicity [7,13]. Oxidative stress arises from excessive ROS generation, primarily within mitochondria, leading to mitochondrial membrane potential disruption and activation of apoptotic and inflammatory signalling pathways [1,15]. Inflammation is mediated through NF- κ B and inflammasome activation, further exacerbating mitochondrial damage and cellular injury (Table S3 in Supplementary Materials) [6,22]. This framework guides the examination of mechanistic studies to clarify causal relationships and identify therapeutic targets.

The expanding literature on microplastic and nanoplastic toxicity has consistently identified oxidative stress and inflammatory responses as recurring biological outcomes; however, substantial heterogeneity in particle size, polymer composition, surface chemistry, and exposure paradigms has limited mechanistic integration across studies [23,24]. In particular, the causal links between particle internalization, mitochondrial dysfunction, redox imbalance, and downstream inflammatory signalling remain incompletely defined, complicating interpretation and risk-relevant extrapolation [4,5].

In this context, the present review provides a structured narrative synthesis of mechanistic evidence describing how microplastics and nanoplastics interact with cellular systems, with a specific focus on mitochondrial perturbation, reactive oxygen species generation, and inflammatory pathway activation. Priority is given to studies reporting molecular and cellular endpoints, including alterations in mitochondrial membrane potential, electron transport chain activity, calcium homeostasis, inflammasome signalling, and regulated cell death pathways [6–8]. By integrating findings from *in vitro*, *in vivo*, and emerging human-relevant models, this review aims to identify convergent mechanisms while acknowledging model-specific limitations [16,22,25,26].

Rather than offering a quantitative assessment, this review emphasizes mechanistic coherence and biological plausibility, applying transparent study selection principles to synthesize evidence in a reproducible manner. Through this approach, the review seeks to clarify mechanistic trajectories linking microplastic exposure to mitochondrial stress and immune activation, and to highlight critical knowledge gaps relevant to hazard characterization, experimental standardization, and future regulatory assessment.

2. Materials and Methods

2.1. Literature Search Strategy and Study Selection

This review was conducted as a structured narrative synthesis aimed at consolidating mechanistic evidence linking microplastic and nanoplastic exposure to mitochondrial dysfunction, oxidative stress, and inflammatory signalling. A comprehensive literature search was performed using the electronic databases PubMed, Scopus, and Web of Science, covering peer-reviewed publications available up to 2025. Search strings were constructed using combinations of keywords including microplastics, nanoplastics, mitochondrial dysfunction, oxidative stress, reactive oxygen species, inflammation, NF- κ B, NLRP3 inflammasome, and cell death. To ensure completeness, reference lists of relevant articles and recent reviews were manually screened to identify additional eligible studies [18,22,27].

2.2. Eligibility Criteria

Study selection followed predefined inclusion and exclusion criteria to ensure relevance to the mechanistic scope of the review. Inclusion criteria comprised: (i) peer-reviewed original research articles and high-quality review papers published in English; (ii) studies investigating microplastics or nanoplastics in relation to mitochondrial function, oxidative stress, and/or inflammatory pathways; (iii) experimental investigations conducted using *in vitro*, *in vivo*, or advanced human-relevant models, including organoids; and (iv) studies reporting molecular, cellular, or biochemical endpoints such as reactive oxygen species generation, mitochondrial membrane potential disruption, electron transport chain impairment, inflammasome activation, or regulated cell death pathways.

Exclusion criteria included: (i) studies focused solely on environmental occurrence, polymer characterization, or exposure assessment without biological or mechanistic endpoints; (ii) articles lacking primary experimental data or mechanistic interpretation, such as editorials, commentaries, or opinion pieces; (iii) investigations addressing ecological or population-level outcomes without cellular or mitochondrial relevance; and (iv) non-English publications or conference abstracts without full peer-reviewed manuscripts.

2.3. Data Extraction and Narrative Synthesis

Relevant information was extracted systematically and organized into thematic categories, including particle physicochemical properties, cellular uptake and intracellular localization, mitochondrial bioenergetics and dynamics, oxidative stress responses, inflammatory signalling pathways, and cell death mechanisms. Evidence was synthesized narratively to integrate findings across diverse experimental systems and exposure paradigms, enabling identification of recurring mechanistic patterns, areas of convergence, and inconsistencies within the literature.

To enhance transparency and clarity, synthesized findings are summarized in a series of Supplementary Tables. Supplementary Table S1 is a Chronological Review of Literature on Microplastic-Induced Oxidative Stress, Inflammation, and Mitochondrial Dysfunction. Table S2 summarizes experimental models used in microplastic research, highlighting their respective strengths and limitations. Supplementary Table S3 presents a thematic overview of mitochondrial damage, oxidative stress, and inflammatory mechanisms. Supplementary Table S4 compares key findings across studies focusing on oxidative stress and inflammatory outcomes. Supplementary Table S5 outlines methodological and interpretative limitations identified in the literature, while Supplementary Table S6 synthesizes identified knowledge gaps and proposed future research directions and Table S7 Classification of correlative and causal mechanistic validation approaches used in microplastic toxicology studies.

The figures included in this manuscript were created in bioRender software (version 04). bioRender was used to design illustrations that visually represent key concepts of the study. Afterwards, the authors thoroughly reviewed and edited the generated outputs using Microsoft PowerPoint 2021 to ensure accuracy, clarity, and alignment with the study's objectives. For language clarity, the authors employed ChatGPT (OpenAI, GPT-5) to assist in refining the manuscript text. Additionally, Mendeley Reference Manager (v 1.19.8, 2021) was used to organize citations and generate the bibliography. The authors carefully reviewed and edited the language and references, taking full responsibility for the content of this publication.

3. Microplastics Versus Nanoplastics: Size-Dependent Cellular Uptake and Toxicity

Particle size is a critical determinant of the biological behaviour and toxicological impact of plastic debris. Microplastics (MPs) are commonly defined as plastic particles smaller than 5 mm, whereas nanoplastics (NPs) are typically classified as particles below 100 nm in size [23]. This distinction has important implications for cellular uptake, intracellular distribution, and downstream toxicological outcomes. Micro- and nanoplastics originate from both primary and secondary sources. Primary micro- and nanoplastics are intentionally manufactured for use in applications such as cosmetic exfoliants, pharmaceutical delivery systems, and industrial processes, whereas secondary particles are generated through the environmental fragmentation of larger plastic debris in terrestrial and aquatic environments [24]. Environmental degradation of macroplastics produces large quantities of secondary microplastics (<5 mm) and nanoplastics (<0.1 μm). Notably, a single microplastic particle can fragment into billions of nanoplastics, greatly increasing their environmental prevalence and potential biological relevance [23].

Although microplastic pollution has been widely documented, the occurrence, toxicity, and human health implications of nanoplastics remain comparatively poorly understood [24]. Emerging *in vitro* studies indicate that nanoplastic toxicity is strongly influenced by polymer type, particle size, surface chemistry, and surface charge [23]. For instance, amine-modified and cationic polystyrene nanoparticles (~50–70 nm) consistently induce mitochondrial ROS production, oxidative stress, and apoptosis, underscoring the importance of surface charge in mediating cellular interactions [28,29]. Unmodified or functionalized polystyrene nanoparticles in the 20–100 nm size range exhibit clear size-dependent cytotoxic responses, while nanoplastics composed of polymers such as polyvinyl chloride (PVC) and poly(methyl methacrylate) (PMMA) have been shown to disrupt cellular redox balance and mitochondrial integrity in a polymer-specific manner [30].

Experimental evidence consistently demonstrates size-dependent toxicity, with smaller plastic particles inducing more pronounced mitochondrial dysfunction and oxidative damage [23]. In addition, environmental aging processes, such as ultraviolet radiation, oxidation, and mechanical abrasion, modify particle surface properties and further enhance toxicity. Aged micro- and nanoplastics exhibit increased surface roughness and altered surface chemistry, which promote cellular uptake and exacerbate ROS generation and mitochondrial impairment (Figure 1) [31]. This enhanced uptake is strongly associated with increased mitochondrial exposure, leading to elevated mitochondrial reactive oxygen species (ROS) production, disruption of mitochondrial membrane potential, and impairment of oxidative phosphorylation [22,27]. As a result, nanoplastics frequently induce stronger oxidative stress and inflammatory responses at lower concentrations compared to microplastics.

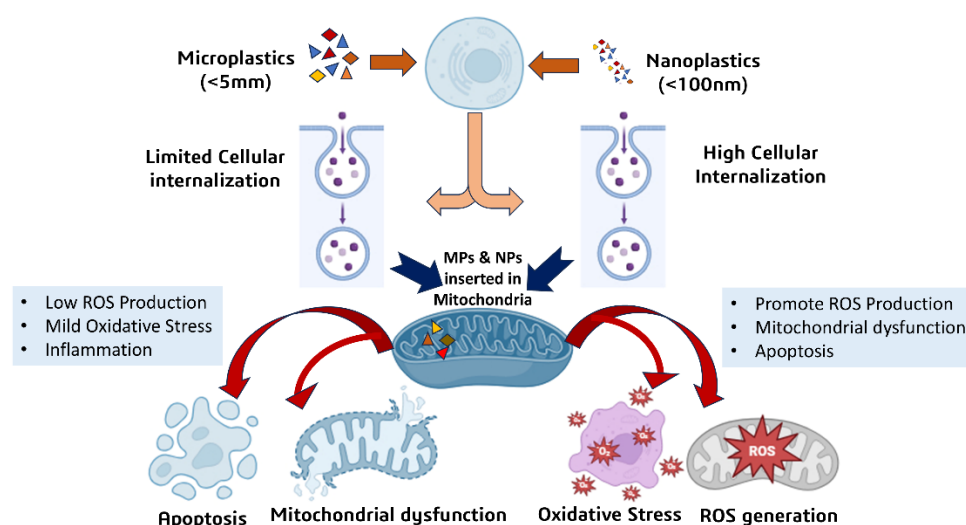


Figure 1. Size-dependent cellular uptake and mitochondrial toxicity of microplastics and nanoplastics. Microplastics (<5 mm) show limited cellular internalization and induce mild oxidative and inflammatory responses. In contrast, nanoplastics (<100 nm) are readily internalized, directly interact with mitochondria, and promote reactive oxygen species (ROS) production, mitochondrial dysfunction, and apoptosis. (Partially Created in BioRender. Saha, R. (2026) <https://BioRender.com/eo6nb6c> and further edited in Microsoft PowerPoint, 2021).

4. Mechanistic Pathways of Microplastic-Induced Mitochondrial Damage

This section deconstructs the molecular and cellular mechanisms by which MPs and NPs compromise mitochondrial integrity and function, emphasizing the critical roles of particle internalization, organelle interactions, calcium dysregulation, electron transport chain (ETC) collapse, reactive oxygen species (ROS) generation, and the subsequent activation of inflammatory and cell death pathways [27].

4.1. Integrin $\alpha 5 \beta 1$ -Mediated Internalization

4.1.1. Endocytic Drivers

Cellular uptake of microplastics and nanoplastics is a complex process driven by various endocytic pathways. These pathways facilitate the entry of particles into the cytoplasm, where they can then interact with cellular organelles, including mitochondria (Figure 2) [25,32]. The efficiency and specific route of internalization are influenced by factors such as particle size, shape, and surface chemistry. For instance, nanoplastics, due to their smaller dimensions, are more readily internalized via endocytic mechanisms compared to larger microplastics [32]. Integrin $\alpha 5 \beta 1$ -mediated endocytosis facilitating nanoplastic internalization has been highlighted. This suggests a receptor-mediated endocytosis pathway for certain nanoplastics (Figure 2) [32].

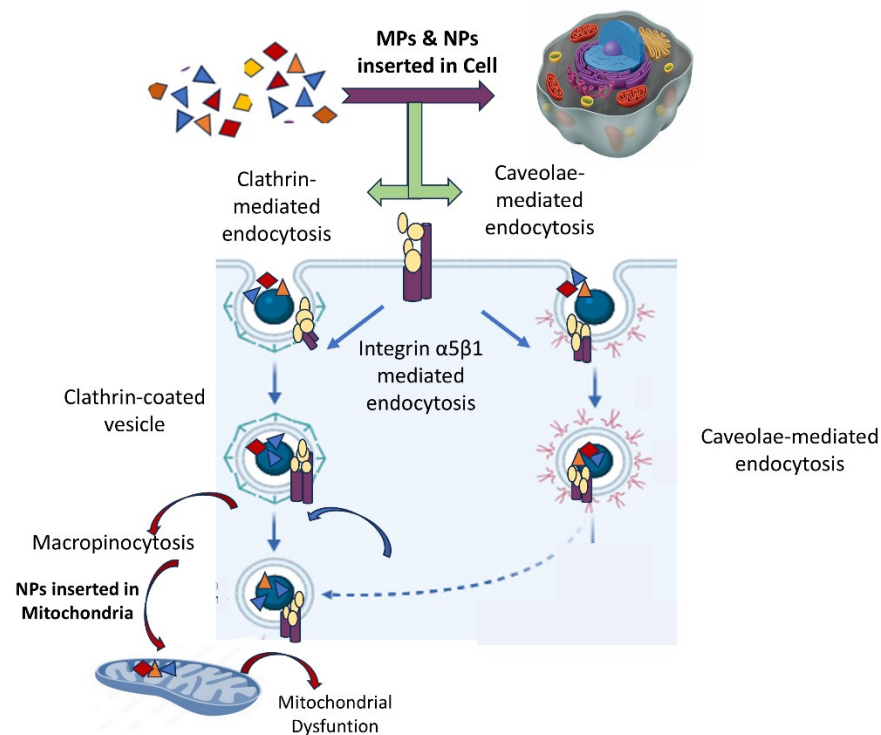


Figure 2. Multiple endocytic mechanisms contribute to the cellular uptake of microplastics and nanoplastics. Depending on their physicochemical characteristics, particles may enter cells through clathrin-dependent pathways, caveolae-mediated endocytosis, or macropinocytosis. Emerging evidence further identifies integrin $\alpha5\beta1$ as a receptor involved in nanoplastic internalization, suggesting a ligand-dependent mode of uptake for specific particle types. These distinct uptake routes influence the efficiency of entry, intracellular trafficking behavior, and the subsequent likelihood of interactions with subcellular organelles, including mitochondria. (Partially Created in BioRender. Saha, R. (2026) <https://BioRender.com/ms6r83i> and further edited in Microsoft PowerPoint, 2021).

4.1.2. Endosome Escape Mechanisms

Following internalization, microplastics and nanoplastics reside within endosomes. For these particles to exert their effects on cytoplasmic organelles like mitochondria, they must escape the endosomal compartment [33]. The mechanisms of endosome escape are not fully elucidated but are crucial for the particles to reach their intracellular targets [34]. Lysosomal rupture, often triggered by the physical properties of the particles or their interaction with lysosomal membranes, is a proposed mechanism that allows particles to enter the cytosol [32]. Once in the cytosol, they can directly interact with mitochondria or trigger downstream signaling cascades (Figure 3).

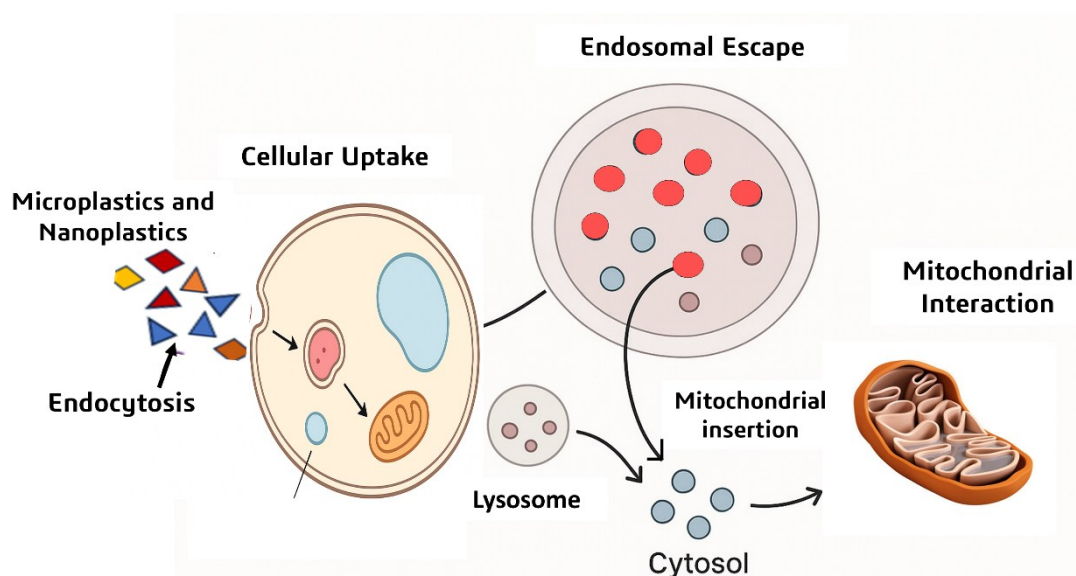


Figure 3. Microplastics and nanoplastics undergo a stepwise intracellular journey before engaging mitochondria. After binding to the cell membrane, particles are internalized through endocytic pathways and compartmentalized within endosomes. Subsequent escape from endosomal and lysosomal vesicles—likely driven by membrane destabilization or rupture—permits their release into the cytosol. Cytosolic particles are then positioned to physically associate with mitochondria or stimulate signaling events that impair mitochondrial function. The requirement for endosomal/lysosomal escape highlights the importance of intracellular trafficking in determining whether plastics reach mitochondria and initiate downstream stress responses. (Partially Created in BioRender. Saha, R. (2026) <https://BioRender.com/a568q8m> and further edited in Microsoft PowerPoint, 2021).

4.2. Cytosolic Trafficking & Organelle Contact Sites

Once internalized and potentially escaped from endosomes, microplastics and nanoplastics navigate the crowded cytosolic environment via passive (diffusion) or active (via motor proteins, though less studied for MPs/NPs) [9]. Their movement and ultimate cellular targets are influenced by their size, surface properties, and interactions with cellular components [35]. Proximity to mitochondria allows for direct physical interaction or the release of soluble mediators that affect mitochondrial function [36,37]. These interactions can occur at organelle contact sites, specialized regions where membranes of different organelles come into close contact, facilitating lipid and ion exchange [9]. While direct evidence of MPs/NPs at these specific contact sites is not extensively detailed in the provided context, their presence in the cytosol allows for such interactions [35].

4.3. Ca^{2+} Dysregulation & Permeability Transition

Mitochondrial calcium (Ca^{2+}) homeostasis is a critical regulator of cellular metabolism, signaling, and cell fate. Microplastic exposure can profoundly disrupt this delicate balance, leading to an overload of Ca^{2+} within the mitochondrial matrix possibly through direct interaction or by inducing ROS [38]. This dysregulation is a significant event in the cascade of mitochondrial damage. Excessive mitochondrial Ca^{2+} accumulation can trigger the opening of the mitochondrial permeability transition pore (mPTP), a non-specific channel in the inner mitochondrial membrane [32]. The sustained opening of the mPTP leads to a loss of mitochondrial membrane potential ($\Delta\Psi\text{m}$), swelling of the mitochondrial matrix, and rupture of the outer mitochondrial membrane, ultimately contributing to cell death [39–41] (Figure 4).

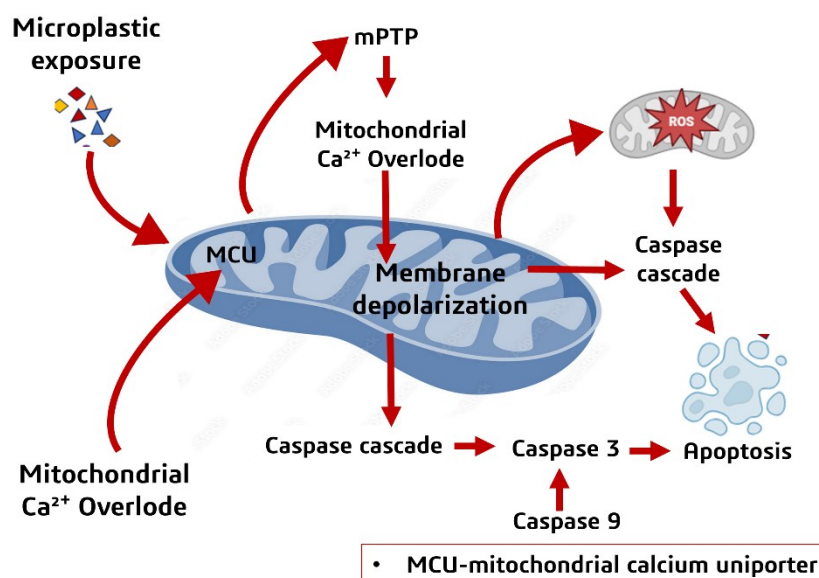


Figure 4. Schematic representation of the mechanistic pathway through which microplastic exposure induces mitochondrial dysfunction and apoptosis. Microplastic particles entering the cell trigger excessive mitochondrial Ca^{2+} influx through the MCU complex, resulting in mitochondrial Ca^{2+} overload. Elevated matrix Ca^{2+} promotes the opening of the mitochondrial permeability transition pore (mPTP), leading to loss of mitochondrial membrane potential ($\Delta\Psi_m$ depolarization) and structural destabilization of the organelle. Membrane depolarization and Ca^{2+} overload drive the release of cytochrome-c into the cytosol and initiate the caspase cascade, with activation of caspase-9 followed by caspase-3, ultimately culminating in apoptotic cell death. Excessive production of reactive oxygen species (ROS) amplifies mitochondrial injury and caspase signaling, creating a feed-forward loop that further exacerbates cellular dysfunction. (Partially Created in BioRender. Saha, R. (2026) <https://BioRender.com/34l01wj> and further edited in Microsoft PowerPoint, 2021).

4.4. ETC Collapse & ATP Failure

The electron transport chain (ETC), located in the inner mitochondrial membrane, is the primary site of ATP production through oxidative phosphorylation. Microplastic exposure can severely impair the function of the ETC, leading to a collapse of its activity and a subsequent failure in ATP synthesis [18]. This bioenergetic disruption is a critical aspect of mitochondrial damage, as cells rely heavily on ATP for various metabolic processes and maintaining homeostasis [42]. Impairment of the ETC can also contribute to increased ROS generation, creating a vicious cycle of damage [43].

Microplastics, through direct interaction with ETC complexes, oxidative damage to ETC components, or Ca^{2+} dysregulation, can inhibit the flow of electrons along the chain [44]. This inhibition reduces the proton gradient across the inner mitochondrial membrane, which is essential for ATP synthase activity [16]. Mitochondrial dysfunction and bioenergetic disruption are observed with polystyrene nanoplastics [18]. The consequence is a significant reduction in ATP production, leading to cellular energy crisis and dysfunction (Figure 5).

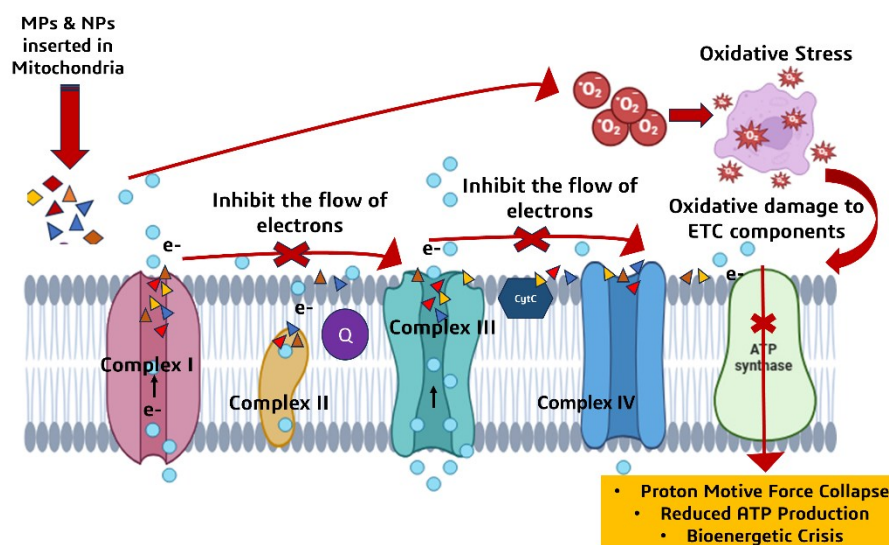


Figure 5. Microplastic exposure induces mitochondrial bioenergetic collapse through direct disruption of the electron transport chain (ETC). Microplastic particles accumulate on the inner mitochondrial membrane and physically obstruct proton translocation, thereby preventing the maintenance of the proton-motive force required for ATP synthase activity. The inhibition of Complexes I–III–IV decreases electron flow and suppresses oxidative phosphorylation, leading to a marked reduction in ATP generation. In parallel, ETC impairment enhances reactive oxygen species (ROS) formation, which further damages ETC complexes and intensifies H^+ gradient dissipation, forming a self-reinforcing feedback loop of mitochondrial dysfunction. Together, these events drive progressive mitochondrial failure and cellular energy imbalance. (Partially Created in BioRender. Saha, R. (2026) <https://BioRender.com/fo4paan> and further edited in Microsoft PowerPoint, 2021).

4.5. mtROS & Antioxidant System Exhaustion

Mitochondria are a major source of reactive oxygen species (ROS) within the cell, particularly when their function is compromised. Microplastic exposure consistently leads to elevated ROS generation, primarily within mitochondria [18]. This excessive ROS production, coupled with the disruption and exhaustion of cellular antioxidant defence systems, creates a state of oxidative stress that is central to microplastic-induced mitochondrial damage and cellular dysfunction, as shown in Figure 6 [14,45].

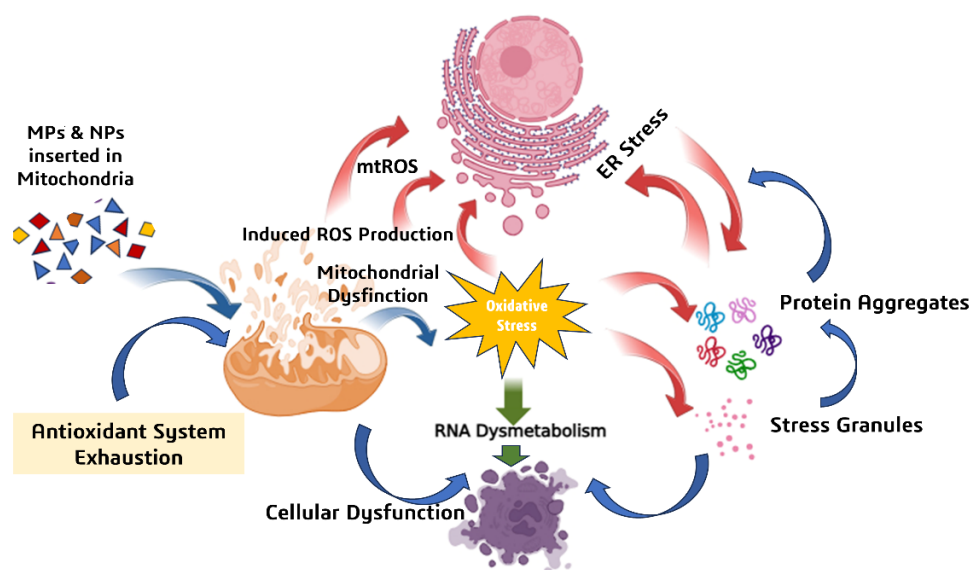


Figure 6. Diagram illustrating the cascade of cellular events triggered by microplastic exposure. The figure highlights the central role of oxidative stress in mitochondrial dysfunction, antioxidant system exhaustion, and cellular damage. Red arrows represent the pathway of oxidative stress and its impact on ER stress and protein aggregation. Blue arrows show the flow from microplastic exposure to increased ROS production in mitochondria. Green arrows indicate the progression towards RNA dysmetabolism. The central yellow starburst represents Oxidative Stress, which is the key event in the disruption of cellular homeostasis, ultimately leading to cellular dysfunction. (Partially Created in BioRender. Saha, R. (2026) <https://BioRender.com/izpkwpp> and further edited in Microsoft PowerPoint, 2021).

4.5.1. Complex I/III Superoxide Leakage

Under normal physiological conditions, a small percentage of electrons leak from the ETC, primarily at Complex I and Complex III, reacting with oxygen to form superoxide radicals. However, when the ETC is impaired, as seen with microplastic exposure, this leakage significantly increases [46]. The impairing electron transport and electron transport chain downregulation caused by microplastics can lead to a backlog of electrons, increasing the probability of their premature transfer to oxygen, thereby generating excessive superoxide. This superoxide is a primary mtROS that initiates a cascade of oxidative damage [14,45]. This increased superoxide production overwhelms the mitochondrial antioxidant defenses, leading to oxidative stress [47] (Figure 7). Reports of elevated reactive oxygen species, ROS-driven disruptions of mitochondrial membrane potential and bioenergetics, PS-nanoplastic-induced ROS production, NADPH oxidase-derived ROS, and increased mitochondrial ROS collectively indicate a robust oxidative stress response to microplastic exposure [18]. Although the specific ETC sites responsible for electron leakage are not explicitly identified, the repeated emphasis on mitochondrial ROS strongly implicates canonical leakage points—particularly Complexes I and III—given their established roles as primary generators of superoxide under conditions of electron transport dysfunction [22].

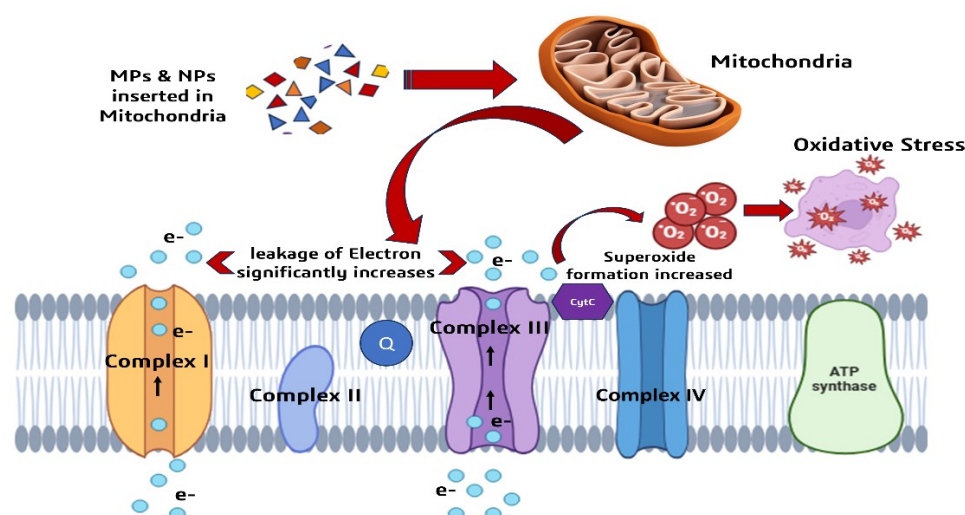


Figure 7. Mechanism of mitochondrial oxidative stress induced by microplastic (MPs) and nanoplastic (NPs) exposure. The figure illustrates how MPs and NPs, when inserted into mitochondria, increase the leakage of electrons from the electron transport chain (ETC), particularly at Complexes I and III. This increased leakage leads to a higher formation of superoxide radicals, a primary mitochondrial reactive oxygen species (mtROS). The excessive superoxide generation overwhelms mitochondrial antioxidant defenses, resulting in oxidative stress. The diagram highlights the key components involved, including Complexes I, II, III, IV, and ATP synthase, with the pathway linking electron leakage to superoxide formation and oxidative damage. (Partially Created in BioRender. Saha, R. (2026) <https://BioRender.com/4cq47ii> and further edited in Microsoft PowerPoint, 2021).

4.5.2. SOD2–SIRT3 Axis Disruption

Mitochondria possess their own antioxidant defense systems to counteract mtROS. Superoxide dismutase 2 (SOD2), a manganese-dependent enzyme, converts superoxide into hydrogen peroxide, which is then detoxified by other enzymes. The activity of SOD2 is regulated by sirtuin 3 (SIRT3), a mitochondrial deacetylase. Disruption of this SOD2–SIRT3 axis can impair the mitochondrial capacity to neutralize ROS, leading to an accumulation of oxidative damage. Microplastic exposure can exhaust or inhibit these protective systems, exacerbating oxidative stress [48].

Microplastic-induced oxidative stress can overwhelm or directly inhibit mitochondrial antioxidant enzymes like SOD2 [45]. Furthermore, the regulatory axis involving SIRT3, which maintains SOD2 activity, might be compromised. This disruption leads to an unchecked accumulation of superoxide and other ROS [49], causing damage to mitochondrial components (Figure 8).

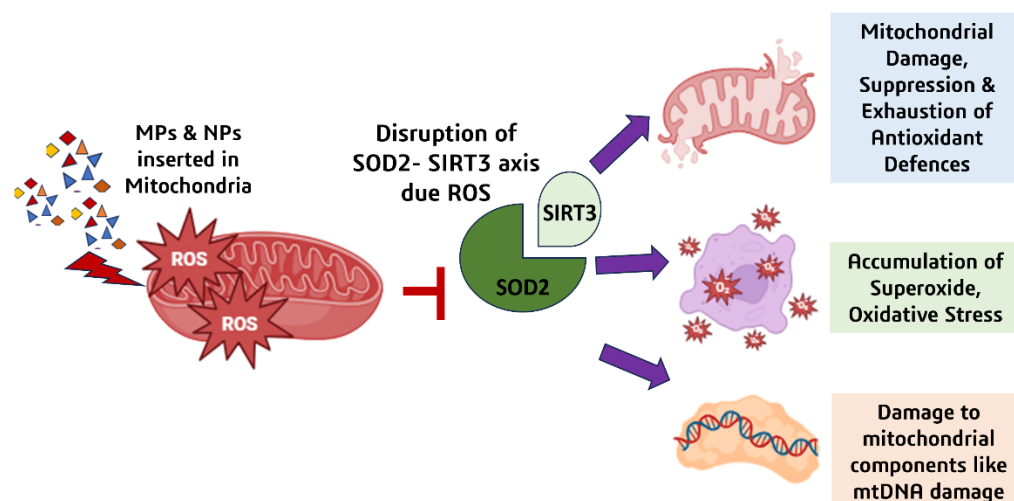


Figure 8. Impact of microplastic exposure on the SOD2-SIRT3 axis in mitochondria. The figure demonstrates how microplastics (MPs) and nanoplastics (NPs) inserted into mitochondria lead to increased reactive oxygen species (ROS) production. This results in the disruption of the SOD2-SIRT3 axis, where SOD2, an enzyme responsible for converting superoxide into hydrogen peroxide, is regulated by the mitochondrial deacetylase SIRT3. Microplastic-induced oxidative stress impairs the antioxidant defense system, causing an accumulation of superoxide and other ROS, ultimately leading to mitochondrial damage, oxidative stress, and mtDNA damage. (Partially Created in Bio-Render. Saha, R. (2026) <https://BioRender.com/pgumziw> and further edited in Microsoft PowerPoint, 2021).

4.5.3. mtDNA Oxidation Effects

Mitochondrial DNA (mtDNA) is particularly vulnerable to oxidative damage due to its proximity to the primary site of ROS generation (the ETC), lack of protective histones, and less efficient repair mechanisms compared to nuclear DNA. Excessive mtROS generated by microplastic exposure can lead to oxidative modifications of mtDNA [45]. Damage to mtDNA can impair the synthesis of essential ETC components encoded by mtDNA, further exacerbating ETC dysfunction, increasing ROS production, and perpetuating a cycle of mitochondrial damage [22].

Reports of elevated ROS and DNA damage alongside increased DNA damage markers indicate activation of oxidative stress-driven genotoxic signaling pathways [37]. Polyethylene- and PET-derived microplastics have been shown to reduce mitochondrial membrane potential and compromise mtDNA integrity, highlighting a coordinated disruption of redox balance, mitochondrial genome stability, and downstream DNA damage-response signaling (Figure 9) [50].

Elevated ROS and DNA damage are observed with aged MPs. Size-dependent ROS increase; DNA damage markers elevated are seen with polystyrene microplastics [22]. Decreased mitochondrial membrane potential and mtDNA integrity are linked to polyethylene and PET microplastics [9].

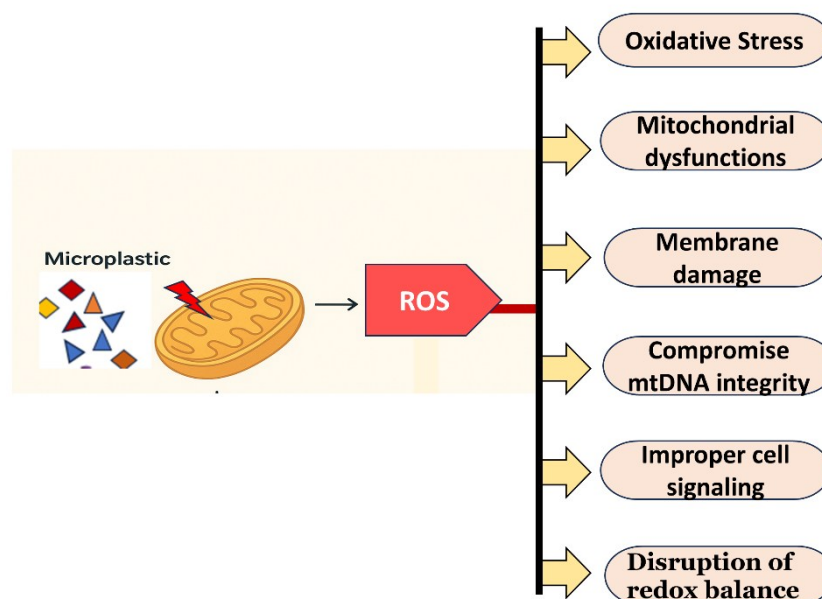


Figure 9. Microplastic-induced oxidative stress and downstream cellular dysfunction. (Created using the Microsoft PowerPoint, 2021).

4.6. *NF-κB* Stress Signalling

Beyond direct mitochondrial damage, microplastic exposure triggers broader cellular stress responses, notably the activation of inflammatory pathways. The nuclear factor-kappa B (NF-κB) signaling pathway is a central mediator of inflammation and immune responses. Microplastic-induced oxidative stress and mitochondrial dysfunction are potent activators of NF-κB, leading to the transcription of pro-inflammatory genes [51]. This activation represents a critical link between mitochondrial damage and systemic inflammatory responses (Figure 10).

Microplastic-induced ROS and mitochondrial damage act as upstream signals that activate the NF-κB pathway. This typically involves the phosphorylation and degradation of IκB, allowing NF-κB to translocate to the nucleus [9]. Once in the nucleus, NF-κB binds to specific DNA sequences, initiating the transcription of genes encoding pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β), chemokines, and adhesion molecules [52]. This perpetuates and amplifies the inflammatory response [6].

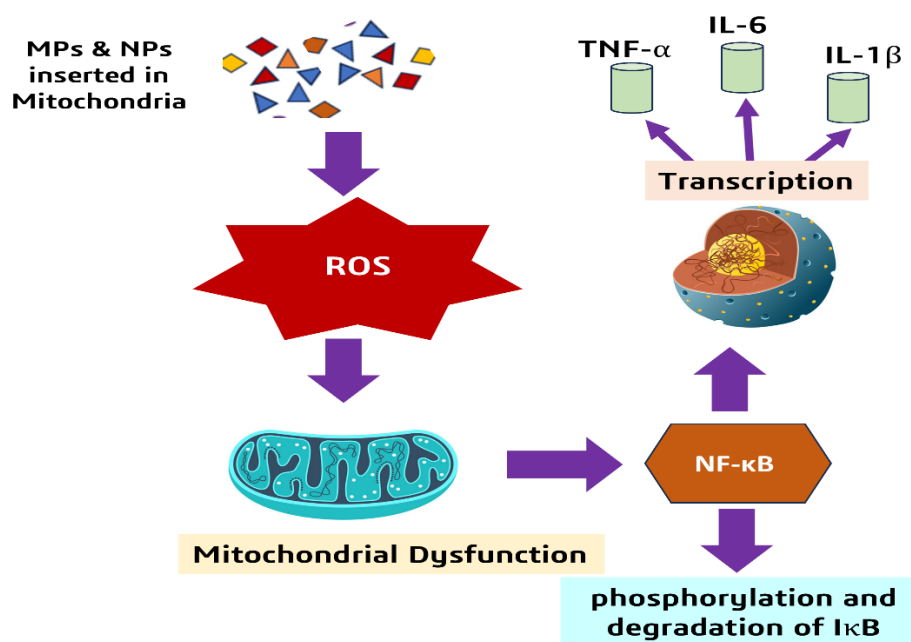


Figure 10. Microplastic-induced activation of the NF- κ B signaling pathway. The figure shows how microplastic (MP) and nanoplastic (NP) exposure leads to mitochondrial dysfunction and oxidative stress (ROS), which then activates the NF- κ B pathway. This activation results in the phosphorylation and degradation of I κ B, allowing NF- κ B to translocate to the nucleus. In the nucleus, NF- κ B initiates the transcription of pro-inflammatory cytokines such as TNF- α , IL-6, and IL-1 β , contributing to the inflammatory response. (Created using the Microsoft PowerPoint, 2021).

4.7. NLRP3 Inflammasome Priming & Activation

The NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome is a multi-protein complex that plays a crucial role in innate immunity by sensing pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). Microplastic exposure, particularly through the generation of mtROS and lysosomal damage, can prime and activate the NLRP3 inflammasome [22]. This activation leads to the proteolytic cleavage of pro-caspase-1 into active caspase-1, which then processes pro-IL-1 β and pro-IL-18 into their mature, secreted forms, driving potent inflammatory responses [51].

Evidence from multiple studies indicates that microplastic exposure activates innate immune signaling through the NLRP3 inflammasome [53–55]. Describing NLRP3 inflammasome activation, ROS/NLRP3/caspase-1 pathway engagement, and subsequent cytokine release collectively highlight a central role for this inflammatory platform in microplastic-induced immunotoxicity [37]. Activation of the NLRP3 complex promotes caspase-1-dependent processing and secretion of pro-inflammatory mediators and is consistently associated with elevated levels of TNF- α , IL-6, and IL-1 β [56]. These findings underscore the contribution of ROS-driven NLRP3 signaling to the amplification of inflammatory responses under microplastic exposure (Figure 11).

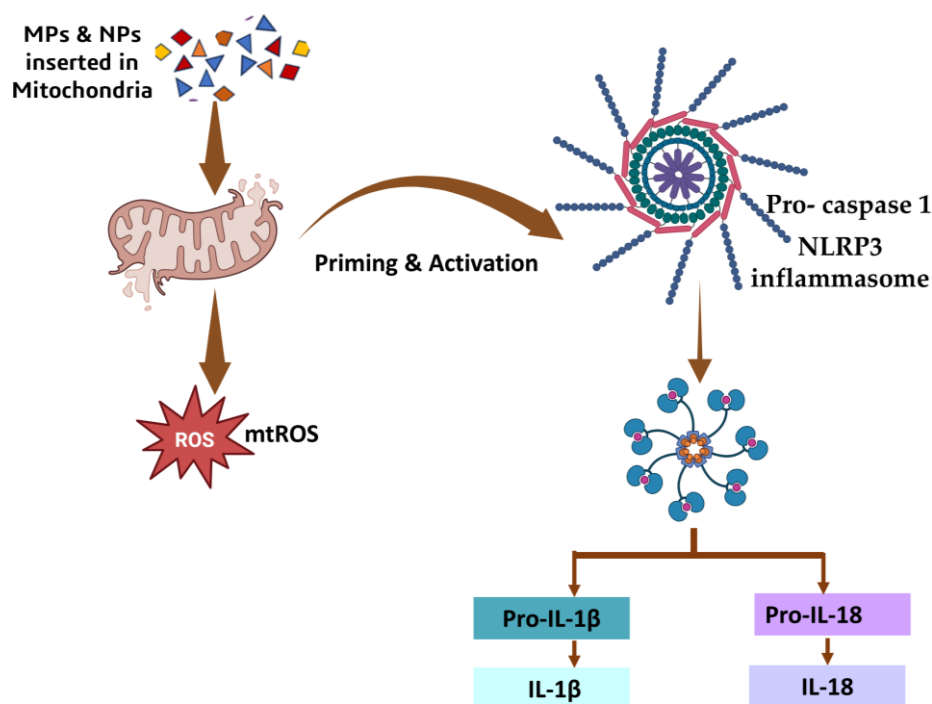


Figure 11. The NLRP3 inflammasome activation pathway induced by microplastic exposure. Exposure to microplastics and nanoplastics results in lysosomal damage and mtROS production, which prime and activate the NLRP3 inflammasome. This triggers caspase-1 activation, leading to the cleavage of pro-IL-1 β and pro-IL-18 into their active forms, resulting in the release of inflammatory cytokines that drive the immune response. (Partially Created in BioRender. Saha, R. (2026) <https://BioRender.com/fbthu8c> and further edited in Microsoft PowerPoint, 2021).

4.8. Cell Death Execution (Apoptosis & Pyroptosis)

The culmination of severe mitochondrial damage, oxidative stress, and sustained inflammation often leads to programmed cell death. Microplastic exposure can trigger various forms of cell death, primarily apoptosis and pyroptosis, both of which contribute to tissue damage and disease pathogenesis.

4.8.1. Cytochrome-c/Caspase-3/9 Cascade

Mitochondrial dysfunction plays a central role in initiating the intrinsic apoptotic pathway. When mitochondrial integrity is compromised, particularly through the loss of mitochondrial membrane potential and outer membrane permeabilization, pro-apoptotic factors like cytochrome c are released from the intermembrane space into the cytosol. Cytosolic cytochrome c then binds to Apaf-1, forming the apoptosome, which recruits and activates pro-caspase-9 [43]. Active caspase-9 subsequently cleaves and activates effector caspases, such as caspase-3, leading to the systematic dismantling of the cell [12].

Microplastic-induced mitochondrial damage (e.g., ROS, Ca²⁺ dysregulation, mPTP opening) leads to the permeabilization of the outer mitochondrial membrane [7]. This allows cytochrome c to leak into the cytosol. Cytochrome c then initiates the caspase cascade, leading to the activation of caspase-9 and subsequently caspase-3, which executes the apoptotic program (Figure 12) [43].

Multiple studies indicate that microplastic exposure activates intrinsic cell death programs, particularly those governed by mitochondrial integrity. Reports describing apoptosis-related cascades, upregulation of apoptosis-associated genes, and activation of caspase-3 and caspase-9 consistently demonstrate engagement of the mitochondrial apoptotic pathway [43]. In addition, evidence of microplastic-induced mitochondrial damage,

cytochrome c release, and initiation of pyroptotic and necroptotic signaling further highlights the involvement of multiple programmed cell death modalities [57]. Collectively, these findings suggest that microplastics trigger a coordinated disruption of mitochondrial homeostasis that propagates apoptosis, pyroptosis, and necroptosis, contributing to broader cytotoxic and inflammatory outcomes [27].

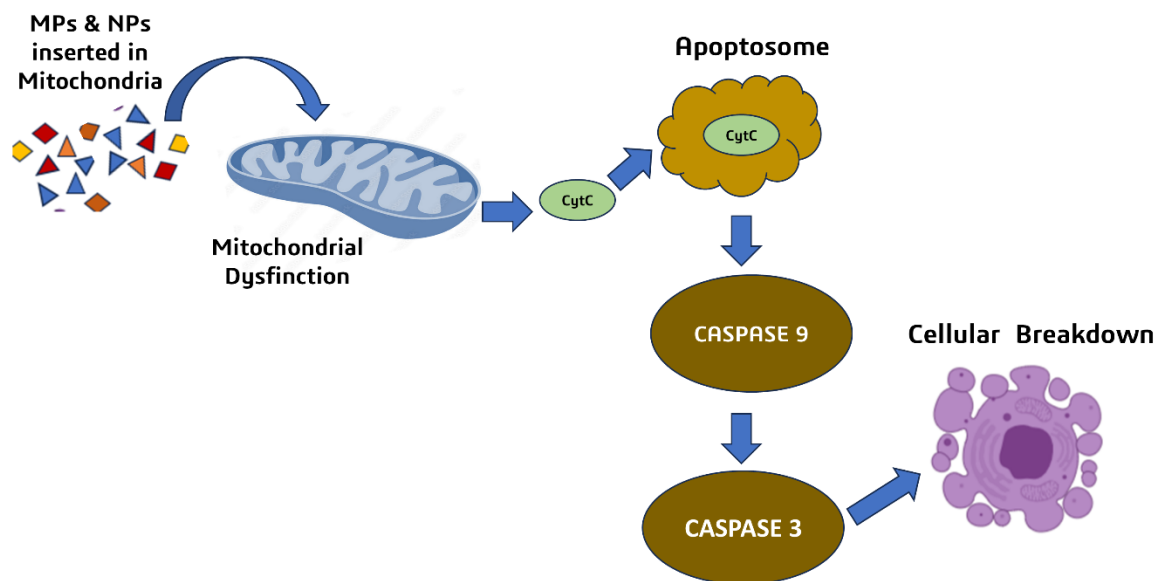


Figure 12. Activation of the apoptotic pathway by microplastics through the cytochrome c/caspase cascade. The figure demonstrates how microplastic-induced mitochondrial damage leads to cytochrome c release, activating the apoptosome. This cascade activates caspase-9, which cleaves caspase-3, ultimately causing cellular breakdown via apoptosis. (Created using the Microsoft Power Point, 2021).

4.8.2. Gasdermin-D Pore Formation

Pyroptosis is a highly inflammatory form of programmed cell death, distinct from apoptosis, characterized by cell swelling, plasma membrane rupture, and the release of pro-inflammatory intracellular contents. It is typically mediated by activated caspases (e.g., caspase-1, caspase-4/5/11) that cleave gasdermin D (GSDMD) [19]. The N-terminal fragment of cleaved GSDMD then oligomerizes and inserts into the cell membrane, forming pores that lead to cell lysis and the release of mature IL-1 β and IL-18, further amplifying inflammation [6].

Microplastic exposure activates the NLRP3 inflammasome, leading to the activation of caspase-1. Active caspase-1 then cleaves GSDMD. The N-terminal fragment of GSDMD forms pores in the plasma membrane, causing cell swelling, membrane rupture, and the release of inflammatory mediators, thus driving pyroptosis [43] (Figure 13).

Several studies highlight the involvement of pyroptosis as a key cell death pathway activated by microplastic exposure [6]. Reports describing engagement of mitochondrial apoptosis and pyroptosis, together with evidence that microplastic-induced mitochondrial damage triggers inflammasome-associated cell death, indicate a strong linkage between mitochondrial dysfunction and inflammatory cytotoxicity [22].

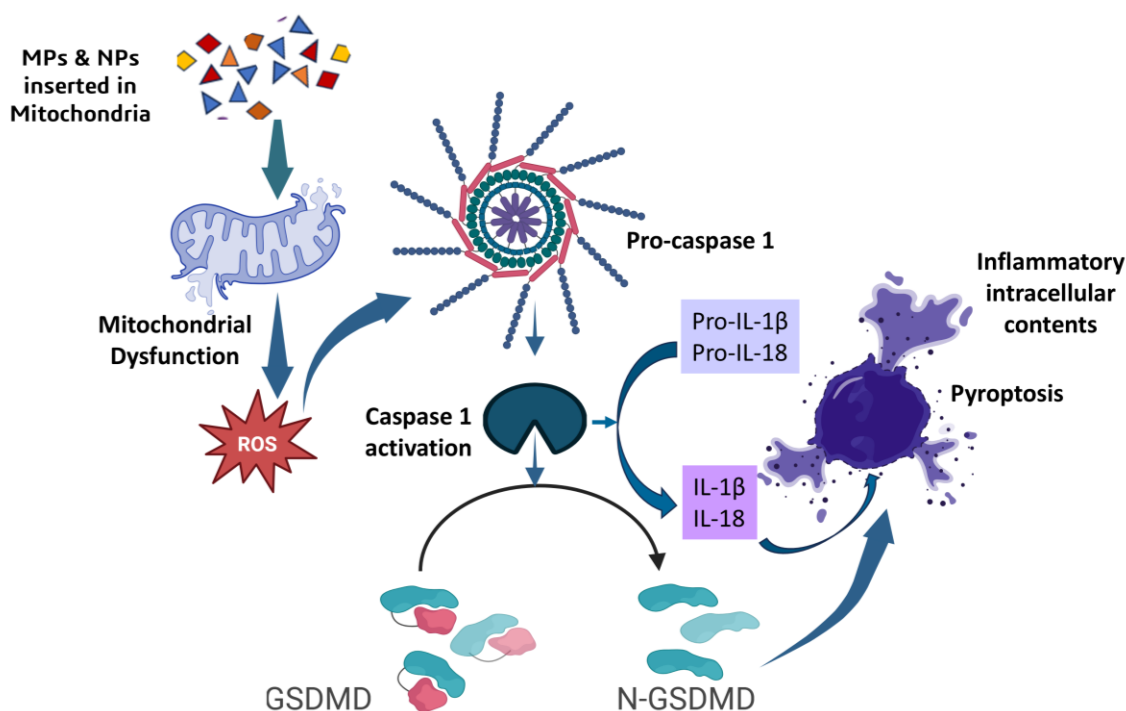


Figure 13. Gasdermin-D (GSDMD)-mediated pyroptosis induced by microplastic exposure. This figure illustrates the activation of the NLRP3 inflammasome by microplastics, followed by caspase-1 activation and GSDMD cleavage. The GSDMD N-terminal fragment forms pores in the plasma membrane, resulting in cell rupture, the release of inflammatory cytokines (IL-1 β , IL-18), and the induction of pyroptosis. (Partially Created in BioRender. Saha, R. (2026) <https://BioRender.com/6f5ml9y> and further edited in Microsoft PowerPoint, 2021).

4.9. Mitochondria-Associated ROS-Independent and Partially Independent Inflammatory Pathways Induced by Microplastics

Although mitochondrial reactive oxygen species (mtROS) generation is widely recognized as a central mechanism linking microplastic and nanoplastic exposure to cellular stress and inflammation, increasing evidence indicates that mitochondrial involvement is not exclusively ROS dependent. Several experimental studies demonstrate that inflammatory and cytotoxic responses can arise through ROS-independent or partially mtROS-independent pathways (Figure 14), particularly depending on particle size, surface chemistry, polymer composition, and cellular context [58,59]. One well-characterized mechanism involves lysosomal membrane destabilization following particle internalization. Micro- and nanoplastics can accumulate within endo-lysosomal compartments, leading to membrane rupture and cytosolic release of cathepsins. This process has been shown to activate the NLRP3 inflammasome, promoting the maturation and secretion of pro-inflammatory cytokines such as interleukin-1 β (IL-1 β) and interleukin-18 (IL-18), even in models where mitochondrial oxidative stress is minimal or occurs downstream of inflammasome activation [60,61]. In such cases, mitochondrial dysfunction appears to function primarily as an amplifying rather than initiating signal.

In addition, pattern recognition receptor (PRR) signaling, particularly via Toll-like receptor 4 (TLR4), has been implicated in microplastic-induced inflammatory responses. Surface charge and functionalization of plastic particles can facilitate receptor engagement at the plasma membrane, triggering NF- κ B-dependent transcription of pro-inflammatory cytokines independently of direct mtROS generation [1,62]. These findings indicate that

microplastics may initiate inflammation through membrane-proximal signalling prior to detectable mitochondrial perturbation.

Disruption of intracellular calcium homeostasis represents another partially ROS-independent pathway linking microplastic exposure to mitochondrial dysfunction. Particle-induced membrane perturbation and endoplasmic reticulum stress can elevate cytosolic Ca^{2+} levels, leading to mitochondrial calcium overload. This process impairs mitochondrial bioenergetics, promotes mitochondrial permeability transition pore opening, and sensitizes cells to apoptosis, even in the absence of substantial mtROS accumulation [63–65].

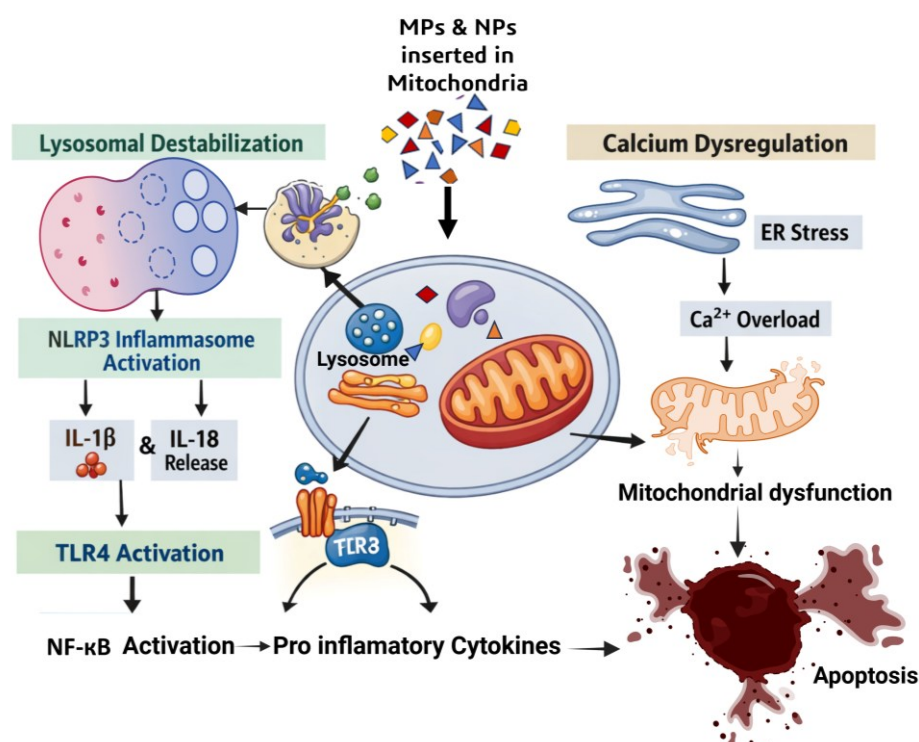


Figure 14. ROS-independent and partially ROS-independent inflammatory pathways induced by microplastics. The figure demonstrates how microplastic (MP) and nanoplastic (NP) exposure triggers lysosomal destabilization, leading to cathepsin release and NLRP3 inflammasome activation. This process promotes the secretion of pro-inflammatory cytokines, such as $\text{IL-1}\beta$ and IL-18 , through Toll-like receptor 4 (TLR4) and NF- κ B signaling pathways. Additionally, particle-induced calcium dysregulation further contributes to mitochondrial dysfunction and inflammation, independent of mitochondrial reactive oxygen species (mtROS) generation. (Partially Created in BioRender. Saha, R. (2026) <https://BioRender.com/dya3uir> and further edited in Microsoft PowerPoint, 2021).

5. Overview of Evidence on Microplastic-Induced Oxidative Stress and Mitochondrial Dysfunction

Microplastic and nanoplastic exposure has been consistently associated with oxidative stress, mitochondrial perturbation, and inflammatory responses across a wide range of experimental systems. However, variability in particle characteristics, exposure conditions, and biological models has contributed to heterogeneity in reported outcomes and mechanistic interpretation. To provide a concise overview of the available evidence, Table 1 summarizes representative studies reporting key mechanistic endpoints related to oxidative stress, mitochondrial dysfunction, and inflammation.

Table 1. Summary of representative studies reporting microplastic- and nanoplastic-induced oxidative stress, inflammatory responses, and mitochondrial dysfunction across experimental models.

Oxidative Stress Markers	Inflammatory Mediator Expression	Mitochondrial Functional Parameters	Microplastic Physicochemical Characteristics	Biological Model Systems	References
Elevated ROS and DNA damage; oxidative damage higher with aged MPs	Upregulation of apoptosis-related genes; caspase-3/9 activation	Decreased mitochondrial membrane potential; cytochrome c release	Aged polystyrene MPs with increased crystallinity and oxygen content	Zebrafish larvae and embryonic fibroblast cells	(Ding et al., 2024) [1]
ROS production induced by PS nanoparticles	Activation of inflammatory pathways linked to integrin $\alpha 5 \beta 1$ -mediated uptake	Mitochondrial Ca^{2+} dysfunction and depolarization	Polystyrene nanoparticles with surface-mediated endocytosis	Human lung epithelial cells (in vitro)	(Han et al., 2024) [32]
ROS generation activating Nrf2 pathway; NAC inhibits damage	Inflammatory response is partially independent of p62	Mitochondrial damage reversed by Nrf2 activation	Polystyrene Nanoplastics, size ~50 nm	HepG2 and L02 liver cell lines	(Guo et al., 2024) [14]
Excessive ROS via NADPH oxidases; antioxidant system disruption	NF- κ B pathway activation; pro-inflammatory cytokines increased	Mitochondrial depolarization; electron transport chain downregulation	Polystyrene Nanoplastics, environmental relevant doses	Zebrafish larvae and ZF4 cells	(Jiang et al., 2023) [15]
Mitochondrial ROS increase in macrophages	Necroptosis signalling in macrophages; inflammation via cross-talk	Mitochondrial integrity disruption; mtROS elevation	20 nm polystyrene nanoparticles	Mouse macrophages and hepatocytes in vivo	(Fan et al., 2024) [27]
ROS induction and oxidative stress	Multiple cell death pathways including pyroptosis and necroptosis	Mitochondrial dysfunction and bioenergetic disruption	Polystyrene nanoparticles with size and surface modifications	Various cellular models reviewed	(Bu et al., 2024) [13]
Increased ROS across models; oxidative damage to macromolecules	Pro-inflammatory cytokine production; NF- κ B activation	Mitochondrial dysfunction linked to senescence	Micro- and nanoparticles of diverse types	Cell lines, organoids, animal systems	(Mahmud et al., 2024) [7]

Mitochondrial ROS accumulation due to iron overload	Elevated inflammatory cytokines; suppressed mitophagy	Mitochondrial autophagy inhibition exacerbates damage	Polystyrene nanoparticles	Human esophageal cell lines	(Lu & Wei, 2024) [25]
ROS-mediated oxidative stress; antioxidant enzyme suppression	Activation of P62/Keap1/Nrf2 pathway; apoptosis induction	Decreased mitochondrial membrane potential and ATP	Polystyrene micro- and nanoplastics, size-dependent	Mouse gastric tissue and cells	(Sun et al., 2024) [18]
Size-dependent ROS increase; DNA damage markers elevated	Redox-dependent β -catenin/YAP pathway activation	Mitochondrial damage and barrier injury	Polystyrene microplastics of varying sizes	Rat gastric epithelium in vivo and in vitro	(Ding et al., 2024) [43]
Mitochondrial ROS and Ca^{2+} overload	cGAS-STING pathway activation; inflammatory signaling	Decreased mitochondrial membrane potential	100 nm polystyrene nanoplastics	Human lung and macrophage cell lines	(Xuan et al., 2023) [26]
Mitochondrial ROS overproduction; respiration suppression	Metabolic pathway disruption linked to mitochondrial damage	Altered mitochondrial membrane potential and respiration	80 nm nanoplastics	Human liver and lung cells	(Lin et al., 2022) [16]
Increased ROS and oxidative stress markers	Autophagy activation with LC3 and p62 upregulation	Decreased mitochondrial membrane potential and mtDNA integrity	Polyethylene and PET microplastics	HepG2 human liver cells	(Najahi et al., 2025) [37]
Oxidative stress and mitochondrial dysfunction	NF- κ B, MAPK, and NLRP3 inflammasome activation	Mitochondrial apoptosis and pyroptosis pathways	Micro- and nanoplastics	Immune cells and animal models reviewed	(Fan & Ha, 2025) [6]
Oxidative stress and mitochondrial dysfunction	Pro-inflammatory cytokine activation; epigenetic changes	Mitochondrial impairment in epithelial and immune cells	Polyethylene microplastics	In vitro human cell models	(Valdivia et al., 2025) [4]
ROS increase as molecular initiating event	Testicular inflammation and cytokine upregulation	Mitochondrial dysfunction and apoptosis in testicular cells	Micro- and nanoplastics	Mammalian reproductive toxicity models	(Hu et al., 2024) [66]
Mitochondrial ROS overproduction in testes	Testicular inflammation and BTB disruption	Mitochondrial structural damage in sperm	Polylactic acid micro/nanoplastics	Mouse reproductive system in vivo	(Zhao et al., 2025) [67]
ROS-induced mitochondrial damage; reversible after recovery	Apoptosis and inflammatory gene expression changes	Mitochondrial membrane potential and dynamics restored post-exposure	Polystyrene microplastics, 5 μm size	Male mice reproductive tissues	(Liu et al., 2022) [68]
Oxidative stress and mitochondrial dysfunction in vascular cells	NF- κ B and NLRP3 inflammasome activation	Endothelial mitochondrial impairment	Polystyrene and polyethylene microplastics	Vascular tissue and animal models	(Sivakumar et al., 2025) [8]
ROS and mitochondrial dysfunction in neural cells	Neuroinflammation and cytokine elevation	Mitochondrial impairment in neurons and glia	Micro- and nanoplastics	In vitro and in vivo neural models	(Araújo et al., 2025) [9]

Oxidative stress and apoptosis in organoids	Inflammatory signaling and mitochondrial dysfunction	Impaired tissue morphogenesis	Micro- and nano-plastics	Human organoid platforms	(Cho & Kim, 2025) [46]
Elevated ROS and oxidative stress in respiratory cells	Inflammatory cytokines and apoptosis	Mitochondrial dysfunction in lung epithelial cells	Airborne micro-plastics	In vitro and in vivo respiratory models	(Vattanasit et al., 2023) [49]
Oxidative stress and mitochondrial dysfunction	Proinflammatory environment and apoptosis	Energy imbalance via mitochondrial impairment	Polystyrene micro- and nanoplastics	A549 lung epithelial cells	(Shahzadi et al., 2023) [5]
ROS increase and antioxidant enzyme activity changes	Apoptosis and ferroptosis pathway activation	Mitochondrial damage and increased mitochondrial count	Polyester micro-plastic fibers	Daphnia carinata aquatic model	(Jiang et al., 2023) [15]
Size-dependent oxidative stress; SIRT3 and SOD2 downregulation	Liver inflammation and apoptosis markers elevated	Mitochondrial vacuolation and membrane potential decrease	Polystyrene micro-plastics, 0.5 and 5 µm	Mouse liver in vivo	(Zou et al., 2025) [45]
Mitochondrial dysfunction and oxidative stress in brain	Chronic neuroinflammation and cytokine elevation	Mitochondrial impairment in neural tissue	Nano- and micro-plastics	Neural tissue and animal models	(Baroni et al., 2025) [69]
ROS generation and lipid peroxidation	Inflammatory signaling and apoptosis	Mitochondrial dysfunction and lysosomal defects	Microplastics of various sizes	Review of cellular and organismal studies	(Kadac-Czapska et al., 2024) [70]
Size- and shape-dependent ROS and redox gene changes	No direct inflammatory mediator measurement	Mitochondrial DNA content and morphology altered	Polystyrene micro-plastics, spheres and fibers	Caco-2 intestinal epithelial cells	(Saenen et al., 2023) [19]
Oxidative stress markers unchanged; antioxidant system affected	No significant inflammation detected	Mitochondrial function decreased with LDPE exposure	PVC and LDPE microplastics	Earthworm soil ecosystem model	(Lee et al., 2024) [50]
miRNA-mediated oxidative stress regulation	miRNA-linked inflammatory gene modulation	Mitochondrial dysfunction via miRNA pathways	Micro- and nano-plastics	Molecular and cellular models	(Chen et al., 2024) [39]
ROS production and mitochondrial membrane potential changes	NF-κB and apoptotic signaling activation	Altered mitochondrial dynamics and mitophagy	Micro- and nano-plastics	Review of cellular studies	(Dal Yöntem, 2024) [2]
ROS/NLRP3 inflammasome activation	IL-6, TNFα cytokine elevation	Mitochondrial ROS triggers inflammasome	Irregular micro-plastics from infant bottles	Human intestinal cells	(Xu et al., 2023) [22]
Oxidative stress and ER stress markers elevated	NF-κB, TNF-α, IL-6 upregulated; apoptosis genes increased	Mitochondrial dysfunction linked to nephrotoxicity	Polystyrene micro-plastics, 1 µm size	Juvenile rat kidney model	(Wang et al., 2023) [51]

6. Discussion and Future Directions

The current literature employs a wide range of experimental models—including zebrafish larvae, human lung and liver cell lines, and mammalian *in vivo* systems—allowing comprehensive assessment of microplastic toxicity across taxa and organ systems [1,14,27,32,37]. This diversity provides multifaceted insights into molecular pathways, enhancing both ecological and biomedical relevance and allowing for cross-validation of findings. Studies have successfully identified key molecular pathways involved in microplastic internalization and subsequent mitochondrial dysfunction, including calcium dysregulation, caspase activation, and necroptosis. Microplastic physicochemical characteristics—including size, shape, aging status, and polymer type—significantly modulate cellular uptake, ROS generation, and mitochondrial injury, with smaller and aged particles generally exerting greater toxicity [1,19,43,45]. The literature consistently supports a bidirectional interaction between oxidative stress and inflammation, wherein each process amplifies the other to exacerbate mitochondrial damage [6,15,22]. Interventions such as N-acetylcysteine mitigate both oxidative and inflammatory endpoints, reinforcing this mechanistic link [14,51]. Application of advanced methodologies—including transmission electron microscopy, flow cytometry, transcriptomics, metabolomics, and targeted inhibition or siRNA knockdown—has strengthened mechanistic interpretations and enhanced the overall rigor of microplastic toxicity research [1,14,16,19,27].

Despite these advancements, several limitations persist within the current research landscape. A notable challenge is the variability in experimental designs, particle characteristics, and exposure conditions, which complicates direct comparisons and generalizations across studies. Many mechanistic links between microplastic exposure and inflammation or apoptosis are currently based on correlative data, lacking definitive causal validation through direct manipulation of candidate pathways. The influence of microplastic physicochemical properties on toxicity remains incompletely characterized, and the complexity of mitochondrial quality control processes in response to microplastics is still under-investigated [42,53,71]. Furthermore, the integration of multi-omics data, while promising, remains preliminary.

A significant constraint on the translational relevance to human health is the predominance of *in vitro* cellular models, which cannot fully replicate complex *in vivo* physiological interactions and systemic responses [4,16,32,42,46,49]. There is a scarcity of longitudinal studies and human epidemiological data, hindering our understanding of chronic exposure effects and real-world human health impacts [72]. Secondary microplastics—tiny fragments under 5 mm that form from the breakdown of larger plastic items such as bottles, bags, and tires—are more environmentally abundant than primary microplastics and remain underrepresented in research, leaving their distinct toxicological profiles poorly understood [3]. Crucially, few studies address the reversibility of mitochondrial and cellular damage post-exposure, limiting insights into long-term health implications and recovery potential. Most research also tends to focus on single organs or cell types, neglecting systemic interactions and multi-organ effects, thereby restricting a comprehensive understanding of integrated physiological responses and cumulative toxicity [1,19,46,73,74].

Available *in vivo* studies do not identify a discrete exposure threshold at which microplastic or nanoplastic exposure results in abrupt mitochondrial collapse. Rather, mitochondrial outcomes typically follow a graded, dose-dependent pattern, with functional impairments emerging at exposure concentrations that are generally higher than those currently estimated for routine human environmental exposure [4]. These findings highlight the need for standardized exposure metrics and long-term low-dose studies to better define biologically relevant thresholds and improve human health risk assessment.

Interpretation of mechanistic pathways is further influenced by the level of experimental validation applied. Although many studies report consistent associations between

microplastic exposure, oxidative stress, mitochondrial dysfunction, and inflammatory signaling, much of this evidence remains correlative. As summarized in Supplementary Table S7, only a limited number of studies employ functional perturbation strategies, such as pharmacological inhibition or genetic knockdown, to support causal inference. Strengthening mechanistic conclusions through systematic application of these approaches is critical to reducing uncertainty regarding direct causal pathways of microplastic-induced cellular toxicity. Although direct evidence of microplastic-induced mitochondrial dysfunction in humans is currently limited, experimental models consistently identify mitochondria as key targets of oxidative and inflammatory stress. Notably, many mechanistic studies employ exposure concentrations that exceed environmentally realistic human levels. To enhance the relevance of these findings, future research should focus on human-relevant experimental systems, incorporate environmentally realistic dosing, and employ rigorous particle characterization. Such approaches will improve the assessment of mitochondrial vulnerability and facilitate the translation of mechanistic insights to human health risk evaluation.

Looking forward, future research should prioritize longitudinal *in vivo* studies and physiologically relevant exposure scenarios to better understand chronic effects and real-world implications (Tables S4 and S5 of Supplementary Materials). There is a critical need for multi-omics integration and standardized characterization of microplastic properties to elucidate precise molecular mechanisms and dose–response relationships under environmentally relevant conditions. Investigating the reversibility of mitochondrial damage and exploring mitigation strategies targeting mitochondrial protection and inflammation control are essential next steps. Furthermore, efforts should focus on establishing causal relationships for identified signaling pathways and expanding research into the systemic effects of microplastics on mitochondrial function and their role in chronic diseases [16,38]. Addressing these gaps will be crucial for advancing comprehensive risk assessment and developing effective intervention strategies to mitigate the significant environmental and human health risks posed by microplastic pollution [4,46].

7. Conclusions

This review summarizes that microplastics (MPs) and nanoplastics (NPs) induce mitochondrial damage mainly through oxidative stress and inflammation. Particle internalization triggers excessive ROS generation, disrupting mitochondrial membrane potential, electron transport, and dynamics (fission, fusion, mitophagy), leading to impaired bioenergetics despite activation of antioxidant pathways such as Nrf2. Oxidative stress and inflammation form a self-amplifying loop via activation of NF- κ B, NLRP3, MAPK, and cGAS-STING pathways, elevating pro-inflammatory cytokines and promoting programmed cell death. Toxicity depends on particle size, aging, surface chemistry, and contaminants, with smaller and aged particles exerting stronger effects. However, current research limitations include inconsistent particle characterization and limited causal validation, highlighting the need for standardized, longitudinal, and mechanistically integrated studies. By standardizing research methodologies, employing advanced models, and expanding into epidemiological studies, the field will be better positioned to develop effective mitigation strategies and inform public health policy.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/microplastics5010036/s1>, Table S1: Chronological Review of Literature on Microplastic-Induced Oxidative Stress, Inflammation, and Mitochondrial Dysfunction; Table S2: Experimental Models in Microplastic Research: Strengths and Weaknesses; Table S3: Thematic Overview of Literature on Microplastic-Induced Mitochondrial Damage, Oxidative Stress, and Inflammation; Table S4: Comparison of Key Findings Across Studies on Microplastic-Induced Oxidative Stress and Inflammation; Table S5: Limitations Identified in Microplastic Toxicity Studies; Table S6: Identified Gaps in Microplastic Research and Future Directions; Table S7: Classification of correlative and causal mechanistic validation approaches used in microplastic toxicology studies.

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Abbreviations

MPs	Microplastics
NPs	Nanoplastics
ROS	Reactive Oxygen Species
ETC	Electron Transport Chain
mPTP	Mitochondrial Permeability Transition Pore
$\Delta\Psi_m$	Mitochondrial Membrane Potential
MCU	Mitochondrial Calcium Uniporter
ATP	Adenosine Triphosphate
MtROS	Mitochondrial Reactive Oxygen Species
SOD2	Superoxide Dismutase 2
SIRT3	Sirtuin 3
Nrf2	Nuclear Factor Erythroid 2-Related Factor 2
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
mtDNA	Mitochondrial DNA
PET	Polyethylene Terephthalate
NF- κ B	Nuclear Factor Kappa B
I κ B	Inhibitor of Kappa B
TNF- α	Tumour Necrosis Factor Alpha
IL-6	Interleukin 6
IL-1 β	Interleukin 1 Beta
NLRP3	NOD-Like Receptor Family Pyrin Domain-Containing 3
PAMPs	Pathogen-Associated Molecular Patterns
cGAS-STING	Cyclic GMP-AMP Synthase-Stimulator of Interferon Genes
MAPK	Mitogen-Activated Protein Kinases
GSDMD	Gasdermin D

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