Proceedings of ICBioMed 2026 Symposium: Biomedical Engineering and Public Health: Real-Time Wearables for Disease Detection
DOI: 10.54254/2753-8818/2026.ES38694

Molecular Mechanisms by Which Mitochondrial Homeostasis Imbalance Regulates Ferroptosis and Inflammatory Responses

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Abstract. Mitochondria coordinate energy conversion, redox buffering, iron utilization, lipid metabolism, organelle dynamics, and innate immune sensing. Disruption of these processes alters the threshold for ferroptosis, an iron-dependent form of regulated cell death driven by phospholipid peroxidation, and also supplies inflammatory signals that reshape tissue microenvironments. Work published during the past five years has moved the field beyond a simple view in which mitochondria act only as sources of reactive oxygen species. Mitochondrial iron handling, tricarboxylic acid cycle activity, electron transport, ubiquinone metabolism, mitochondrial glutathione, dihydroorotate dehydrogenase, outer-membrane permeabilization, mitophagy, and organelle contact sites each contribute to ferroptotic susceptibility in a context-dependent manner. Mitochondrial damage further releases mitochondrial DNA, cardiolipin-related danger signals, oxidized lipids, and metabolic intermediates that engage cGAS-STING, inflammasome, NF-kappaB, and macrophage polarization pathways. This review summarizes recent progress in mitochondrial homeostasis, ferroptosis regulation, and inflammatory signaling, with emphasis on molecular coupling among mitochondrial iron imbalance, lipid peroxidation, redox stress, quality control failure, and inflammation-driven feedback. A more integrated interpretation of these pathways may support biomarker development and therapeutic strategies for cancer, ischemic injury, neurodegeneration, infection-related organ damage, and chronic inflammatory diseases.

Keywords: Mitochondrial homeostasis, Ferroptosis, Inflammation, Iron metabolism, Lipid peroxidation

1. Introduction

Mitochondria maintain cellular homeostasis through coordinated control of oxidative phosphorylation, metabolite exchange, calcium handling, reactive oxygen species generation, iron-sulfur cluster biogenesis, lipid remodeling, and regulated cell death. These processes are not independent modules. A change in electron transport can modify mitochondrial redox tone, redox imbalance can alter iron handling, iron excess can accelerate phospholipid peroxidation, and impaired organelle turnover can convert reversible stress into persistent tissue injury. Ferroptosis has

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DOI: 10.54254/2753-8818/2026.ES38694

become a central framework for analyzing this transition because its execution depends on iron availability, lipid peroxide accumulation, and failure of antioxidant systems, all of which intersect with mitochondrial metabolism [1-3].

The relationship between mitochondria and ferroptosis has been defined with increasing precision during the past five years. Early studies established that ferroptosis is biochemically distinct from apoptosis and necroptosis, whereas recent work has shown that mitochondrial functions can either drive or restrain ferroptotic death depending on cell type, metabolic state, and the initiating stimulus [1, 2, 4, 5]. In cells exposed to cystine deprivation or system xc minus inhibition, tricarboxylic acid cycle activity, glutaminolysis, mitochondrial membrane potential, and electron transport often amplify lipid peroxidation. In contrast, mitochondrial antioxidant systems, including dihydroorotate dehydrogenase and mitochondrial glutathione metabolism, can limit lipid peroxide propagation under specific conditions [6, 7]. These apparently divergent functions indicate that mitochondrial homeostasis determines the distance between adaptive stress responses and ferroptotic commitment.

Inflammation adds another layer of regulation. Ferroptotic cells release oxidized phospholipids, damage-associated molecular patterns, and immunomodulatory metabolites that influence macrophages, neutrophils, dendritic cells, and tissue-resident immune cells [7-9]. Mitochondrial damage can initiate inflammatory signaling through mitochondrial DNA leakage, cGAS-STING activation, NLRP3 inflammasome assembly, NF-kappaB-dependent cytokine production, and defective clearance of damaged organelles [10-13]. Conversely, inflammatory cytokines and immune-derived reactive oxygen or nitrogen species impair mitochondrial respiration, remodel iron transport, induce ferritinophagy, and lower the threshold for lipid peroxidation. The resulting reciprocal circuit is relevant to sterile inflammation, infection-associated organ injury, cancer therapy response, kidney disease, cardiovascular pathology, neurodegeneration, and tissue fibrosis [14-17].

This review focuses on recent advances in the molecular mechanisms by which mitochondrial homeostasis imbalance regulates ferroptosis and inflammatory responses. The discussion is organized around mitochondrial dynamics and quality control, energy and redox metabolism, mitochondrial iron handling, lipid peroxidation, damage-associated inflammatory signaling, ferroptosis-driven inflammatory microenvironment remodeling, and feedback regulation by inflammatory mediators.

2. Molecular basis and disruption of mitochondrial homeostasis

Mitochondrial homeostasis is maintained by coordinated regulation of organelle shape, respiratory function, redox buffering, iron utilization, lipid exchange, and stress-responsive degradation. These processes define mitochondrial fitness at both single-organelle and network levels. A functional mitochondrial network preserves membrane potential, supports ATP generation, limits uncontrolled reactive oxygen species production, and supplies metabolites needed for biosynthesis and immune adaptation. When one component becomes unstable, compensatory pathways are recruited to restore balance. Persistent stress, however, can exhaust these compensatory responses and generate a mitochondrial state that favors lipid oxidation, iron mishandling, inflammatory signaling, and regulated cell death [4, 10, 11].

2.1. Regulation of mitochondrial dynamics and quality control

Mitochondrial homeostasis requires balanced fission, fusion, biogenesis, proteostasis, and selective removal of damaged organelles. Dynamin-related protein 1, mitofusins, and optic atrophy 1 regulate

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organelle morphology, whereas PINK1-Parkin signaling, receptor-mediated mitophagy, mitochondrial unfolded protein responses, and lysosome-dependent degradation determine whether damaged mitochondria are repaired or eliminated. Excessive fission can fragment the network and reduce respiratory efficiency, while impaired fusion restricts matrix content exchange and weakens compensation for local damage. Current experimental models connect these structural changes with ferroptosis through alterations in mitochondrial reactive oxygen species, lipid oxidation, membrane potential, and stress signaling [5, 18, 19].

Quality control failure converts transient mitochondrial stress into a persistent source of oxidants and inflammatory stimuli. In models of cardiovascular injury, lung disease, glioblastoma, and septic cardiomyopathy, impaired mitophagy is associated with mitochondrial reactive oxygen species accumulation, ferroptosis-related changes in ACSL4, GPX4, SLC7A11, and ferritinophagy markers, and increased inflammatory cytokine production [19-22]. The direction of this relationship is context-dependent. Enhanced mitophagy can remove oxidant-producing mitochondria and attenuate ferroptosis, but excessive mitophagic flux may deplete bioenergetic capacity and sensitize cells to metabolic collapse. The functional outcome depends on the timing of mitochondrial damage, the intensity of lysosomal clearance, and the availability of compensatory biogenesis.

2.2. Regulation of mitochondrial energy metabolism and redox homeostasis

Mitochondrial energy metabolism shapes ferroptosis through carbon flux, reducing equivalent production, respiratory chain activity, and antioxidant regeneration. The tricarboxylic acid cycle supplies NADH and FADH2 to electron transport, while also producing intermediates that connect amino acid, lipid, and nucleotide metabolism. Under ferroptotic stress induced by cystine limitation, active glutaminolysis and mitochondrial respiration support reactive oxygen species generation and lipid peroxidation. Cells with high dependence on oxidative phosphorylation may display increased ferroptosis sensitivity when antioxidant capacity is limited, whereas cells relying on glycolytic compensation can show a different death threshold [4, 5, 23].

Redox homeostasis is maintained by glutathione, thioredoxin systems, NADPH-generating enzymes, coenzyme Q pools, and compartment-specific lipid peroxide detoxification. GPX4 remains a central suppressor of phospholipid hydroperoxide accumulation, but recent work has expanded the antioxidant network to include FSP1 at the plasma membrane and dihydroorotate dehydrogenase at the inner mitochondrial membrane [1, 6, 24]. Dihydroorotate dehydrogenase reduces ubiquinone during pyrimidine biosynthesis and counteracts mitochondrial lipid peroxidation, making mitochondrial metabolism both a source of pro-ferroptotic stress and a site of ferroptosis defense. Mitochondrial glutathione transport and regeneration add another control layer because local depletion may allow inner membrane lipids and cardiolipin-associated structures to undergo oxidative modification before global cellular antioxidant failure becomes apparent [25].

2.3. Regulation of mitochondrial iron homeostasis and damage responses

Mitochondria are essential sites for iron-sulfur cluster assembly and heme synthesis.Their iron economy depends on cytosolic iron import, mitochondrial transport, storage, utilization, and export. Cellular iron availability is regulated by transferrin receptor-mediated uptake, ferritin storage, ferroportin-dependent export, iron regulatory proteins, and ferritinophagy. Mitochondrial iron accumulation becomes pathogenic when import exceeds biosynthetic demand or when iron-sulfur cluster assembly is impaired. Labile iron can promote Fenton chemistry and damage mitochondrial

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proteins and lipids.It also increase the susceptibility of polyunsaturated phospholipids to peroxidation [11, 26].

The systemic and cellular iron-regulatory framework is summarized in Figure 1.This diagram links iron uptake, storage, utilization, and efflux with pathways relevant to mitochondrial iron stress.

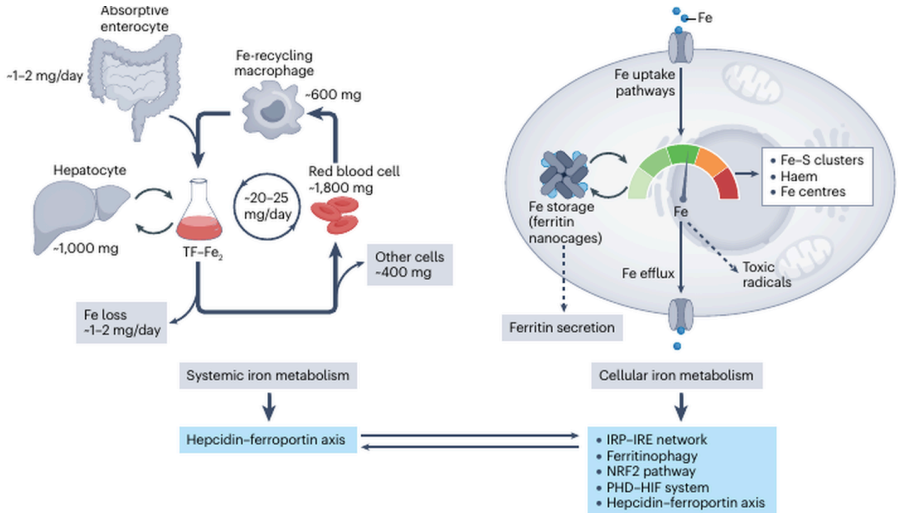


Figure 1. Systemic and cellular iron metabolism supporting mitochondrial iron homeostasis [11]

Damage responses induced by mitochondrial iron imbalance overlap with innate immune signaling. Respiratory complexes can be impaired by defective iron-sulfur cluster maintenance.Electron leakage is favored , and mitochondrial nucleic acid stress is promoted . In cancer and tissue injury models, altered iron-sulfur protein handling and mitochondrial nucleic acid release have been linked to innate immune activation and ferroptosis-associated inflammatory signaling [27, 28]. This evidence supports a model in which mitochondrial iron dysregulation is not restricted to metabolic injury. Mitochondrial iron dysregulation can act as an upstream trigger for organelle-derived danger signaling, especially when mitophagy and antioxidant buffering fail to contain damaged mitochondrial components.

3. Mechanisms by which mitochondrial homeostasis imbalance mediates ferroptosis

Mitochondrial regulation of ferroptosis is best understood as a threshold-setting process. Ferroptosis requires the convergence of oxidizable phospholipid substrates, redox-active iron, and insufficient lipid peroxide detoxification. Mitochondria influence each component through metabolism rather than through a single linear pathway. They supply electron leakage and metabolic intermediates that affect oxidative tone, determine local ubiquinone and glutathione-dependent antioxidant capacity, regulate iron-sulfur cluster assembly and labile iron buffering, and shape interorganelle lipid transfer. The consequence is a ferroptotic program whose dependence on mitochondria varies by stimulus. Cystine deprivation and metabolic stress often require mitochondrial activity, whereas direct GPX4 inhibition can proceed with a stronger contribution from extramitochondrial lipid peroxidation systems [4, 7].

3.1. Mitochondrial iron metabolic imbalance and lipid peroxidation

Ferroptosis is executed by the accumulation of lipid peroxides in cellular membranes, particularly phospholipids containing polyunsaturated fatty acyl chains. Mitochondrial iron imbalance

DOI: 10.54254/2753-8818/2026.ES38694

accelerates this process through redox-active iron pools, impaired iron-sulfur cluster biogenesis, and respiratory dysfunction. Although plasma membrane and endoplasmic reticulum membranes are major sites of phospholipid peroxidation. Mitochondria influence the initiation and spread of oxidative lipid damage .They control reactive oxygen species production, cardiolipin oxidation, and organelle contact-dependent lipid exchange [2, 5, 29].

The central biochemical sequence of ferroptosis is shown in Figure 2. It highlights the convergence of iron, reactive oxygen species, phospholipid peroxidation, and antioxidant defense failure.

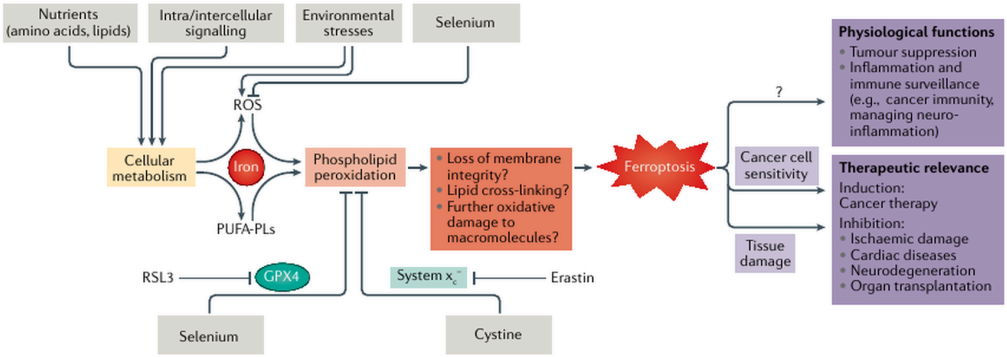


Figure 2. Overview of ferroptosis driven by iron-dependent phospholipid peroxidation [1]

Organelle contact sites now occupy a defined position in ferroptotic lipid chemistry. Endoplasmic reticulum-mitochondria contacts provide spatially organized regions for phospholipid remodeling, calcium exchange, and redox communication. Experimental work has confirmed these contact sites.They can become hotspots for phospholipid peroxidation during ferroptosis. This sites link mitochondrial function and endoplasmic reticulum lipid metabolism. This view avoids treating each organelle as an isolated compartment [29]. This organization helps explain why mitochondrial stress can influence ferroptosis even when the terminal membrane rupture is detected at the plasma membrane. Iron-dependent lipid peroxide propagation is shaped by interorganelle architecture, not only by total cellular iron or total reactive oxygen species.

3.2. Mitochondrial energy metabolic remodeling and redox imbalance

Energy metabolic remodeling determines whether mitochondrial activity supports survival or ferroptotic execution. Cystine deprivation limits glutathione synthesis and increases reliance on metabolic pathways that sustain electron transport and reactive oxygen species production. Under these conditions, glutamine-fueled anaplerosis, TCA cycle activation, and mitochondrial hyperpolarization can intensify lipid peroxidation. Such change are observed when oxidative phosphorylation is pharmacologically or genetically suppressed, and cystine starvation-included ferroptosis can be attenuated in some cellular models, which indicates that active mitochondria are required for full execution of specific ferroptotic programs [4, 5].

The mitochondrial redox network also contains ferroptosis-suppressive elements. Dihydroorotate dehydrogenase-mediated ubiquinone reduction shields the inner mitochondrial membrane from lipid peroxidation, and this pathway gains special importance when GPX4 activity is compromised [6]. OPA1, a core regulator of inner membrane fusion and cristae organization, was recently shown to promote ferroptosis by increasing mitochondrial reactive oxygen species and limiting integrated stress response signaling in certain contexts. The concept of mitochondrial involvement is refined by

DOI: 10.54254/2753-8818/2026.ES38694

this evidence . The organelle does not simply increase or decrease ferroptosis. Instead, distinct mitochondrial subprograms determine whether respiration, cristae organization, ubiquinone metabolism, and stress adaptation converge toward lipid peroxide accumulation or resistance.

3.3. Disturbed mitochondrial dynamics and impaired quality control

Mitochondrial dynamics influence ferroptosis through changes in membrane morphology, cristae integrity, metabolic compartmentalization, and susceptibility to mitophagy. Reactive oxygen species can be amplified and pro-inflammatory components can be released fragmented mitochondria with disrupted membrane potential. Conversely, excessive fusion or insufficient fission may prevent segregation of damaged mitochondrial regions and impede selective clearance. The crosstalk between ferroptosis and mitochondrial dynamic regulatory networks has been described across cancer, neurodegeneration, ischemic injury, and inflammatory disease models, with recurrent involvement of DRP1, OPA1, PINK1-Parkin, FUNDC1, BNIP3, and ferritinophagy-related pathways [18, 19, 30].

Impaired quality control can also modify iron handling. Ferritinophagy mediated by NCOA4 increases labile iron availability and can promote ferroptosis when antioxidant systems are insufficient [11, 28]. Mitophagy dysfunction, by contrast, allows iron-loaded and oxidant-producing mitochondria to persist. In septic cardiomyopathy, loss of the mitophagy receptor FUNDC1 worsens mitochondrial integrity and enhances ACSL4-dependent ferroptotic injury [19]. In glioblastoma, targeting SIRT3 has been reported to sensitize tumor cells to ferroptosis through promotion of mitophagy and suppression of SLC7A11 [21]. The same quality control system may protect normal tissues while remaining exploitable in tumors, where mitochondrial adaptation supports stress resistance.

4. Interactions among mitochondrial homeostasis imbalance, ferroptosis, and inflammatory responses

The coupling of mitochondrial injury, ferroptosis, and inflammation reflects the immunological consequences of damaged metabolism. Ferroptosis does not merely remove injured cells. It changes the biochemical composition of the surrounding environment through lipid oxidation products, organelle-derived molecules, and immune-active stress signals. Mitochondrial dysfunction increases the probability that ferroptosis will occur in a context rich in danger-associated molecular patterns, while inflammatory mediators generated by immune cells can further perturb mitochondrial respiration and iron handling. This reciprocal regulation creates self-reinforcing tissue injury circuits in sterile inflammation and infection, but it may also contribute to antitumor immunity when ferroptosis is selectively induced in malignant cells [7-9, 15].

4.1. Mitochondrial damage-associated molecular signals and inflammatory pathway activation

Mitochondrial injury activates inflammation through signals that are interpreted by the innate immune system as evidence of cellular danger. Mitochondrial DNA released into the cytosol or extracellular space can engage cGAS-STING signaling and induce type I interferon-related and NF-kappaB-dependent transcriptional programs. Oxidized mitochondrial lipids, cardiolipin exposure, ATP release, succinate accumulation, and altered mitochondrial reactive oxygen species can support inflammasome activation and cytokine production. These responses become more sustained when

DOI: 10.54254/2753-8818/2026.ES38694

mitophagy is insufficient to remove damaged mitochondria before danger signals accumulate [10, 12, 13].

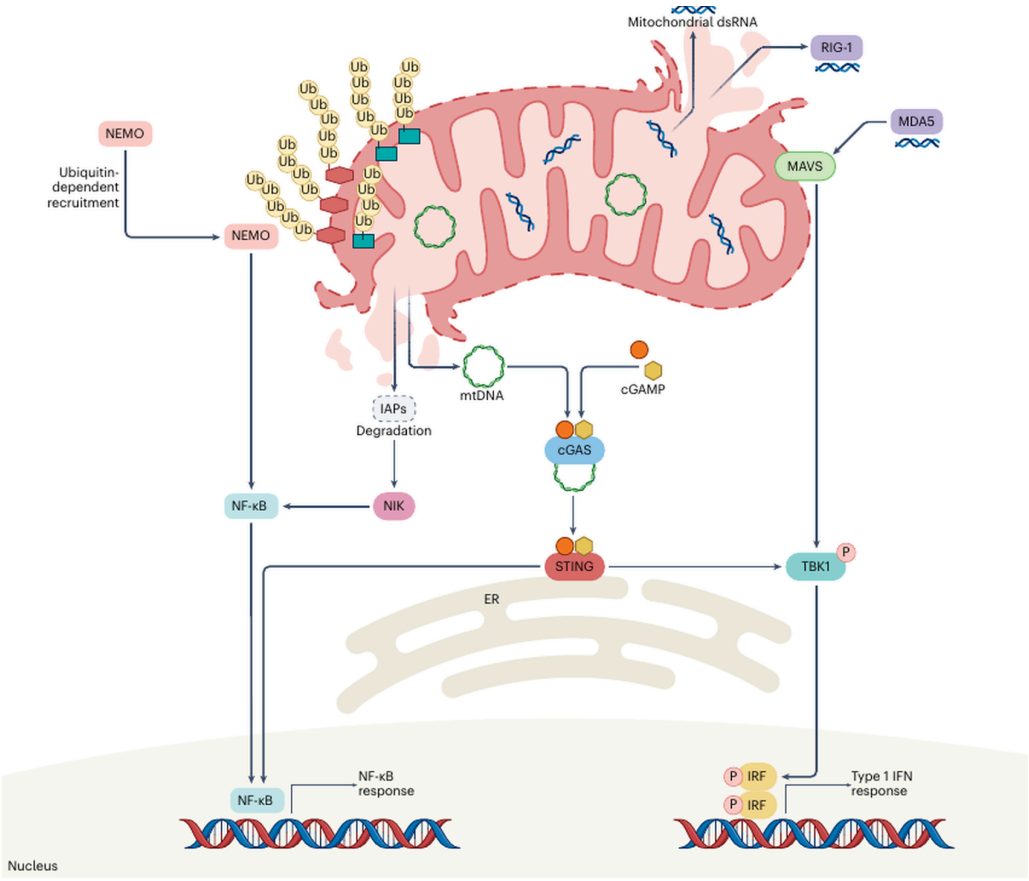


Figure 3. Mitochondrial permeabilization and inflammatory signaling activation [10]

The inflammatory consequences of mitochondrial permeabilization are illustrated in Figure 3, emphasizing mtDNA-, dsRNA-, cGAS-STING-, MAVS-, and NF-kappaB-related signaling routes.

Ferroptosis and mitochondrial danger signaling are increasingly connected through VDAC1 oligomerization, mitochondrial membrane damage, and cGAS-STING activation. Evidence from radiation dermatitis, doxorubicin cardiotoxicity, post-myocardial infarction inflammation, and epithelial injury shows that mitochondrial membrane disruption can couple ferroptosis with cytosolic nucleic acid sensing [13, 25, 26, 29]. This relationship does not imply that all ferroptosis requires cGAS-STING signaling. It indicates that mitochondrial damage can convert ferroptotic lipid peroxidation into a broader inflammatory program, particularly in tissues exposed to radiation, toxins, ischemia, or persistent oxidative injury.

4.2. Mechanisms of ferroptosis-driven remodeling of the inflammatory microenvironment

Ferroptotic cells reshape inflammatory microenvironments through the release of oxidized phospholipids, lipid-derived electrophiles, HMGB1, mitochondrial components, and other damage-associated mediators. These molecules can recruit and activate innate immune cells, modify antigen presentation, alter macrophage polarization, and influence adaptive immune responses [7-9, 15]. In tumors, ferroptosis may promote immunogenic cell death and improve cytotoxic lymphocyte activity under some conditions, whereas excessive lipid peroxidation and ferroptotic debris can also

DOI: 10.54254/2753-8818/2026.ES38694

create immunosuppressive or tissue-damaging environments. The inflammatory outcome depends on the cell undergoing ferroptosis, the clearance capacity of phagocytes, the lipid mediator profile, and the cytokine context.

Macrophages occupy a central position in this network. They can undergo ferroptosis, clear ferroptotic debris, or produce inflammatory mediators that sensitize surrounding cells to iron-dependent lipid peroxidation [9, 15]. Iron recycling by macrophages influences tissue iron availability, while cytokines such as IL-1 beta, TNF, and interferon gamma can modulate SLC7A11, ferritin, nitric oxide metabolism, and mitochondrial function. In inflammatory organs, these processes may establish spatially heterogeneous regions where damaged parenchymal cells, activated macrophages, endothelial cells, and fibroblasts exchange iron, oxidized lipids, and inflammatory mediators. Ferroptosis-driven microenvironment remodeling accordingly operates as a tissue-level process rather than a purely cell-autonomous death pathway.

4.3. Feedback regulation of mitochondrial homeostasis and ferroptosis by inflammatory responses

Inflammatory responses feed back onto mitochondrial homeostasis through cytokine signaling, immune-derived oxidants, metabolic reprogramming, and altered nutrient availability. TNF, IL-1 beta, interferons, and pathogen-associated signals can impair electron transport, increase nitric oxide or superoxide production, alter mitochondrial biogenesis, and induce mitochondrial permeability transition. Persistent inflammatory signaling also affects iron metabolism through hepcidin, transferrin receptor expression, ferritin turnover, and macrophage iron sequestration. Iron availability for pathogens and tumors can be restricted by these changes . Labile iron can also be accumulated in vulnerable cells, thereby modifying ferroptotic susceptibility [11, 15, 16].

The feedback relationship is evident in disease models where inhibition of ferroptosis improves inflammatory pathology. Ferroptosis is suppressed. Tissue injury is attenuated in models of acute lung injury, retinal ganglion cell damage, fibrotic kidney disease, and sepsis-induced myocardial injury. Decreased inflammatory cytokines, oxidative stress, or immune cell activation are observed along with this effect [19, 29-31]. At the same time, tumor therapy may require the opposite strategy, since inducing ferroptosis can enhance antitumor immunity when immunosuppressive constraints are controlled [9, 27]. Therapeutic interpretation depends on whether ferroptosis is primarily pathogenic in normal tissue or therapeutically useful in diseased cells. Mitochondrial state, immune context, and disease stage should be considered together when targeting this axis.

5. Conclusions and outlook

Ferroptosis and inflammation are regulated by Mitochondrial homeostasis imbalance. A series of interconnected mechanisms are involved in this progress. This mechanisms include iron handling, electron transport, redox buffering, lipid peroxidation, organelle dynamics, mitophagy, and innate immune signaling. Recent findings indicate that mitochondria can function as ferroptosis amplifiers. This occurs when phospholipid peroxidation is promoted by respiration, iron overload, and reactive oxygen species generation . The same organelle can also restrain ferroptosis through dihydroorotate dehydrogenase, ubiquinone metabolism, mitochondrial glutathione, and timely removal of damaged organelles. This dual function explains why mitochondrial interventions produce variable outcomes across cell types and disease models.

A mechanistic view of this field should integrate compartment-specific lipid oxidation, mitochondrial iron pools, contact-site biology, and inflammatory signal release. Multiple questions

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are still unresolved in this field. Signals exchanged between mitochondrial and non-mitochondrial lipid peroxide pools have not been fully clarified. The sensing of iron-sulfur cluster disruption by innate immunity also need further exploration. Ferroptosis sensitivity can be determined by the mitophagy timing. In addition, the behavior of macrophage and lymphocyte in vivoand is shaped by ferroptotic debris. Progress will depend on spatial lipidomics, genetically encoded redox and iron sensors, organelle-resolved proteomics, single-cell inflammatory profiling, and disease models that preserve tissue immune architecture.

Therapeutically, the mitochondrial homeostasis-ferroptosis-inflammation axis offers opportunities for both cytoprotection and disease-cell elimination. In ischemic, degenerative, septic, and inflammatory diseases, strategies that stabilize mitochondrial redox balance, limit iron-driven lipid peroxidation, enhance appropriate mitophagy, or suppress excessive cGAS-STING and inflammasome signaling may reduce tissue injury. In cancer treatment, immune-mediated tumor control can be improved by the induction of mitochondrial ferroptosis. This therapeutic effect is achieved when combined with approaches that prevent systemic toxicity and counteract immunosuppressive lipid signaling. Future translational work should define biomarkers that identify mitochondrial ferroptosis states in patient tissues, clarify dosing windows for ferroptosis modulation, and evaluate whether combined targeting of mitochondrial damage and inflammatory feedback yields more durable therapeutic effects than single-pathway intervention. Methodological integration is also required. Many current studies infer mitochondrial participation from changes in membrane potential, mitochondrial reactive oxygen species, or morphology, yet these markers do not establish causality by themselves. Stronger evidence can be obtained by combining organelle-targeted genetic perturbation, rescue experiments, lipid peroxide imaging, labile iron measurement, and mitochondrial functional assays in the same model. Inflammatory outcomes should be measured alongside ferroptotic endpoints because suppression of cell death may not fully normalize cytokine production or immune cell recruitment. This combined strategy would reduce ambiguity in assigning mitochondrial ferroptosis as a driver rather than a correlate of tissue inflammation. Disease specificity should remain a central consideration in future work. Neurons, cardiomyocytes, hepatocytes, renal tubular cells, endothelial cells, macrophages, and malignant cells differ in mitochondrial density, iron turnover, lipid composition, antioxidant reserve, and immune communication. A pathway that protects one tissue may weaken desired tumor cell killing or disrupt host defense in another setting. Therapeutic development requires cell-type-resolved mapping of mitochondrial ferroptosis states and inflammatory outputs before broad pathway inhibition or activation can be translated into durable clinical benefit for patient treatment in early prospective clinical studies.

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