Mitochondrial Membrane Oxidative Perforation (Mitoxyperiosis): A Unique Mechanism of Cell Death Driven by Plasma Membrane Lipid Peroxidation

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Abstract. Plasma membrane lipid peroxidation represents a critical mechanism of oxidative stress-induced cellular damage, contributing to the pathogenesis of inflammation, and cancer. While several regulated cell death pathways such as ferroptosis, necroptosis, and pyroptosis have been characterized, the full spectrum of oxidative cell death mechanisms remains incompletely understood. Recent studies have identified a novel mitochondrial-dependent lytic cell death pathway termed mitoxyperiosis, which is triggered by the synergistic activation of innate immunity and metabolic disruption (IIAMD). However, the biochemical basis and molecular mechanisms underlying this unique form of cell death require systematic elucidation. This review outlines the biochemical foundations of plasma membrane lipid peroxidation and compared mitoxyperiosis with established oxidative cell death modalities, with particular attention to its exclusive mitochondrial ROS production under IIAMD, the unique spatial specificity of peroxidation at mitochondria–plasma membrane contact sites, and the molecular machinery involving mTORC2-dependent mitochondrial trafficking and BAX/BAK1-mediated damage. Its pathophysiological implications for inflammatory diseases and cancer, together with potential therapeutic applications, are also discussed. These findings provide new insights into the diversity of regulated cell death mechanisms and highlight mitoxyperiosis as a promising therapeutic target. Future research should focus on identifying the specific molecular tethers that mediate stable mitochondria-plasma membrane contact and validating the clinical relevance of mitoxyperiosis in human diseases to facilitate precision-targeted therapeutic interventions.

Keywords: Mitoxopercussion, Lipid Peroxidation, Mitochondria, Plasma Membrane Damage, Cell Death.

1. Introduction

Regulated cell death is an essential component of tissue homeostasis and immune defense, while oxidative stress and lipid peroxidation are common downstream drivers of lytic cell death. Lipid peroxidation targets polyunsaturated fatty acids (PUFAs) in the plasma membrane, disrupting cellular barrier integrity and generating cytotoxic byproducts that lead to various pathological conditions. Known forms of oxidative cell death include ferroptosis, necroptosis, and pyroptosis. However, an article published in 2025 introduced a novel mitochondrial-dependent form of lytic cell death—mitoxyperiosis—triggered by the combined activation of innate immunity and carbon starvation (termed IIAMD). Unlike established pathways, mitoxyperiosis relies on contacting between mitochondria and the plasma membrane to locally generate ROS, initiate site-specific lipid peroxidation, and ultimately lead to membrane rupture. This article discusses the molecular mechanisms underlying mitoxyperiosis and explores its role in inflammation and cancer, offering new perspectives for therapeutic intervention[1,2].

ROS and lipid peroxidation serve as fundamental mediators of regulated cell death, propagating oxidative damage to biomembranes when antioxidant capacity is exhausted. Recent investigations in 2025 have advanced understanding of ferroptosis by delineating its metabolic determinants, including iron, selenium, amino acid, and lipid metabolic pathways, as well as surveillance systems such as the cyst(e)ine/GSH/GPX4 axis and the NAD(P)H/FSP1/CoQ pathway. Additionally, endoplasmic reticulum–mitochondria contact sites have been recognized as critical hubs for phospholipid peroxide

accumulation, modulating cellular sensitivity to ferroptotic demise. Beyond established modalities, a newly characterized lytic cell death pathway termed mitoxyperiosis has emerged, wherein innate immune activation synergizes with metabolic stress to drive mTORC2-dependent mitochondrial redistribution toward the plasma membrane[3]. Localized mitochondrial ROS generation at membrane contact sites elicits site-specific lipid peroxidation and membrane lysis. This process promotes NLRP3 inflammasome activation and pro-inflammatory cytokine release, establishing mechanistic links between oxidative cell death and inflammation. Furthermore, therapeutic induction of mitoxyperiosis through combined innate immune stimulation and metabolic stress has demonstrated efficacy in eliciting tumor regression, suggesting translational potential for cancer immunotherapy[2].

This review examines the biochemical mechanisms of mitoxyperiosis, compares it with established oxidative cell death pathways, and explores therapeutic implications for inflammatory diseases and cancer.

2. Biochemistry of Plasma Membrane Lipid Peroxidation

The cell membrane is a dynamic phospholipid bilayer, which is composed of glycerophospholipids, sphingolipids, cholesterol, and proteins. Glycerophospholipids include several parts. For example phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol that containing fatty acyl chains of varying lengths and degrees of saturation[4].

PUFAs contain two or more carbon-carbon double bonds. Their allylic hydrogen atoms have lower dissociation energies, leading them more easily to be oxidized through the free radical reaction. Lipid peroxidation proceeds via a spontaneous chain reaction that include three steps: initiation, propagation, and termination[5].

2.1. Initiation

The initiation of lipid peroxidation requires an initial oxidative stress, typically caused by highly reactive oxygen radicals such as the hydroxyl radical (·OH), peroxynitrite ($ONOO^-$), or singlet oxygen ($^1O_2$)[5]. These oxidants can capture a allylic hydrogen atom from a PUFA chain to form a carbon centered lipid radical (L·). This step is exothermic and irreversible, indicating the start of oxidative chain damage. In mitoxyperiosis, the primary initiator is mitochondria derived •OH, which is generated in the intermembrane space and released directly at the mitochondria–plasma membrane contact sites[1].

2.2. Propagation

The L· is highly unstable and rapidly reacts with molecular O_2 to form a LOO·. This radical retains the high reactivity and capture a hydrogen atom from an nearby PUFA molecule to form a new L· and a LOOH. This process is continued to create a chain reaction which deliver the oxidative damage across the phospholipid bilayer[6]. LOOHs are more stable than that, but have further decomposition in the presence of transition metals to form additional free radicals and cytotoxic aldehydes[6]. In mitoxyperiosis, propagation is limited by the mitochondria–membrane contact interface, resulting in gathering of LOOHs and 4-HNE[1].

2.3. Termination

Lipid peroxidation is normally restrained by cellular antioxidant systems, which eliminate free radicals and neutralize LOOHs. Small molecule antioxidants include glutathione, vitamin , and ascorbic acid. The glutathione acts as a major cellular reductant, detoxifying ROS and reducing LOOHs to non-toxic alcohols through glutathione peroxidase. Enzymatic antioxidants such as GPX4 are essencial for preventing lipid peroxidation; GPX4 specifically reduces phospholipid hydroperoxides, thus blocking chain propagation[7]. Under the environment of serious oxidative stress, however, antioxidant defenses become termination fails, resulting in uncontrolled lipid

peroxidation and membrane destruction[7]. In mitoxyperiosis, GSH is depleted by carbon starvation, while massive ROS production is driven by mitochondrial dysfunction, collectively disabling antioxidant defenses at the contact site[1].

2.4. Biological Consequences of Lipid Peroxidation

Membrane function is damaged by uncontrolled lipid peroxidation severely. Oxidative modification of PUFA chains reduces membrane mobility, improves the activity of integral membrane protein, and disrupts the asymmetric distribution of phospholipids between the bilayer[6]. Cytotoxic aldehydes covalently modify proteins and DNA, inducing protein misfolding, endoplasmic reticulum stress, and DNA damage[6]. In conclusion, these effects disrupt ion balance and lead to cell death. While lipid peroxidation is a common process of many cell death pathways, its space limitation and local intensity are special to mitoxyperiosis[1].

3. Comparison of Oxidative Cell Death Modalities

Oxidative stress induced cell death is various, with different pathways defined by triggers, signaling intermediates, and patterns of membrane damage. The mitoxyperiosis with three major oxidative cell death modalities are compared below.

3.1. Ferroptosis

Ferroptosis is an iron dependent cell death pathway that characterized by widespread, diffuse lipid peroxidation through the whole plasma membrane[6]. It is triggered by iron overload, inactivation of GPX4 or inhibition of the cysteine-glutamate transporter. ·OH is produced in the ferrous ion mediated Fenton reaction, which oxidizes PUFAs containing phospholipids. Ferroptosis leads to increased overall membrane permeability, swelling of organelles, and cell rupture. Ferroptosis is non-targeted and has no relation to mitochondrial-plasma membrane contact, which distinguishes it from mitoxyperiosis[1].

3.2. Necroptosis

The other regulated form of necrosis mediated by the RIPK3–MLKL signaling axis is Necroptosis[5]. Under conditions of caspase inhibition, necroptosis is triggered by TNFα, TLR ligands, or viral infection. RIPK3 could phosphorylates MLKL, which oligomerizes and trans to the plasma membrane to forming pores which would disrupt membrane integrity[5]. While ROS contribute to necroptosis by increasing MLKL activation and enhancing lipid peroxidation, the oxidative damage is diffuse and secondary to MLKL pore formation[5]. Necroptosis does not require mitochondria–membrane contact, while independent of PUFA specific peroxidation.

3.3. Pyroptosis

Pyroptosis is an inflammatory lytic cell death driven by gasdermin family proteins[4]. Pyroptosis is triggered by pathogen associated molecular patterns or damage associated molecular pattern, which activate inflammasome. Caspase 1 mediated cleavage of GSDMD promoted by inflammasomes, could release a nitrogen terminal fragment that oligomerizes in the plasma membrane to form large pores[5]. These pores allow the release of pro-inflammatory cytokines and DAMPs. However, pyroptosis is not driven by lipid peroxidation and does not require mitochondrial ROS production[1].

3.4. Mitoxyperiosis

Mitoxyperiosis differs fundamentally from ferroptosis, necroptosis, and pyroptosis in four key mechanistic dimensions. Regarding initiating triggers, it is triggered by the synergy of innate immune activation and carbon starvation (IIAMD), not iron overload, caspase inhibition, or inflammasome activation[1]. In terms of ROS source, oxidative mediators are exclusively derived from mitochondria, produced via respiratory chain dysfunction and reverse electron transport. For oxidative pattern, it is

marked by focal, site-specific lipid peroxidation restricted to mitochondria–plasma membrane contact sites, not diffuse pan-membrane oxidation[1]. In regulatory mechanisms, this pathway is kept independent of GPX4, RIPK3/MLKL, and gasdermins, and is instead controlled by mTORC2-dependent mitochondrial trafficking and BAX/BAK1-mediated mitochondrial damage[1]. These unique features are seen as proof that mitoxyperiosis is a novel, previously unrecognized cell death pathway.

4. Mechanisms of Mitoxyperiosis

The coordinated sequence of mitoxyperiosis was delineated as follows: IIAMD was induced, followed by mitochondrial dysfunction and ROS burst; subsequently, mTORC2-mediated mitochondria–plasma membrane contact was established, focal lipid peroxidation was initiated, nanopores were formed, and ultimately membrane rupture (mitoxyperilysis) was achieved. Each step was tightly regulated and was demonstrated to be essential for cell death.

4.1. Exclusive Mitochondrial ROS Production under IIAMD Conditions

Mitoxyperiosis is driven by mitochondria-specific ROS production, enabled by three synergistic effects of IIAMD[1]. Carbon starvation depletes cellular GSH, disabling antioxidant defenses firstly. Glucose deprivation inhibits the pentose phosphate pathway and de novo GSH synthesis, reducing intracellular GSH levels by >70%[1]. This severe GSH depletion eliminates the primary buffer against oxidative stress, allowing unimpeded accumulation of mitochondrial ROS.

Then, the BAX/BAK1-dependent mitochondrial damage is triggered by innate immune signaling. TLR4 activation by LPS induces the expression and activation of the BH3 only protein BID. This protein would transfer to mitochondria and activate the pro-apoptotic proteins BAX and BAK1[8]. The activated BAX/BAK1 oligomerize in the outer mitochondrial membrane, causing membrane permeabilization and respiratory chain complex I dysfunction[8]. This damaged complex I activity promotes reverse electron transport, a major source of superoxide anion in the mitochondrial intermembrane space[8]. Superoxide anion is further converted to hydroxyl radical via the Fenton reaction, generating highly toxic oxidants. Genetic ablation of BAX/BAK1 or BID blocks ROS production and mitoxyperiosis completely, to confirm their essential role[1].

Continuous mitochondria–plasma membrane contact is driven by mTORC2 activation. Under IIAMD, mTORC2 is activated selectively, independent of mTORC1[8]. mTORC2 phosphorylates and inhibits the small GTPase RhoA, reducing RhoA dependent actin polymerization and cytoskeletal contractility[8]. This strengthening of the actin cytoskeleton allows mitochondria to leave the cytoplasmic microtubule network and transfer to and locate at the plasma membrane[1]. The contact continues more than 20 minutes, far longer than the transient (<4 min) physiological contacts that is observed in healthy cells[9,10]. The long-time contact creates a closed microenvironment where mitochondrial ROS accumulate to 20–50 μM, concentrations that beyond local antioxidant capacity limitation form an oxidative hotspot[1]. Inhibition of mTORC2 with Torin 1 or genetic knockout restores actin cytoskeleton integrity, prevents mitochondrial translocation, and fully restrain mitoxyperiosis[1].

4.2. Unique Biochemical and Spatial Specificity of Lipid Peroxidation in Mitoxyperiosis

Lipid peroxidation during mitoxyperiosis exhibits four particular features that can distinguish it from ferroptosis and other cell death pathways[1].

ROS and lipid peroxidation are strictly confined to mitochondria–plasma membrane contact spaces[1]. Confocal immunofluorescence microscopy proved that 4-HNE, a marker of lipid peroxidation, co-localizes merely with mitochondria which attached to the plasma membrane, while non contact regions show minimal 4-HNE staining[1]. Transmission electron microscopy revealed that membrane rupture sites are directly neighboring swollen mitochondria with disrupted cristae,

confirming a spatial relationship between mitochondrial contact, oxidative damage, and membrane breakdown[1].

Lipidomic analysis based on mass spectrometry shown that mitoxyperiosis preferentially oxidizes PUFA containing phospholipids in the inner leaflet of the plasma membrane, particularly PC and inner-leaflet PS[7]. In contrast, ferroptosis primarily targeted outer leaflet PE and PS[7]. This asymmetric oxidation disrupted the transverse asymmetry of the bilayer, released membrane curvature, and promoted nanopore formation[1].

Mitoxyperiosis does not require lipoxygenases or cyclooxygenases for lipid peroxidation[1]. Hydroxyl radical derived by mitochondria abstracted bis allylic hydrogens from PUFA chains directly, initiating non-enzymatic chain peroxidation[1]. LOX inhibitors failed to block 4-HNE production or cell death, while the antioxidants N-acetylcysteine (NAC) and vitamin E dose-dependently inhibit lipid peroxidation and mitoxyperilysis, confirming the non-enzymatic nature of the reaction[1].

At contact sites, ROS concentrations reached 20–50 μM, far over the eliminating capacity of residual GSH (<5 μM) and GPX4[1]. The lipid peroxidation chain reaction became self-sustaining and irreversible[1]. Even if IIAMD is reversed after contact establishment, lipid peroxidation continued to process, leading to progressive membrane damage and cell death[1].

4.3. Membrane Perforation, Ion Dyshomeostasis, and Inflammatory Consequences

Local lipid peroxidation directly disrupted the hydrophobic core of the plasma membrane bilayer, leading to the formation of nanopores (10–50 nm in diameter). These pores initiate a series of destructive events[1].

Nanopores allow the passive leakage of ions and small molecules. Potassium ions efflux and calcium ions influx would disrupt cellular ion homeostasis, triggering cytoskeletal remodeling and cellular shrinkage. ATP leakage and mitochondrial dysfunction reduced intracellular ATP levels, impairing energy dependent repair mechanisms and exacerbating injury[1].

Continuous lipid peroxidation enlarged nanopores to 100–500 nanometer, enabling the release of large intracellular molecules[10]. The release of these DAMPs is a mark of lytic cell death and triggers pro-inflammatory signaling in neighboring cells[11].

Extracellular ATP released during mitoxyperiosis could activate the P2X7 purinergic receptor on macrophages and other immune cells[11]. P2X7 activation triggered NLRP3 inflammasome assembly, caspase-1 activation, and maturation/secretion of the pro-inflammatory cytokines IL-1β and IL-18[11]. These cytokines recruited and activated neutrophils, monocytes, and T cells, amplifying local inflammation and promoting tissue damage[11]. In preclinical sepsis models, mitoxyperiosis drove excessive inflammation and organ injury, showing its pathological relevance[1].

Progressive lipid peroxidation and pore expansion reached to complete plasma membrane disintegration, releasing cellular contents into the extracellular space[1]. This terminal event, mitoxyperilysis, is irreversible and defines the end stage of mitoxyperiosis[1]. Genetic or pharmacological inhibition of any upstream step prevented membrane rupture and cell death[1].

5. Pathophysiological Implications and Therapeutic Perspectives

The discovery of mitoxyperiosis provided new insights into the pathogenesis of inflammatory diseases and cancer, and identified new therapeutic targets.

5.1. Diseases

Inflammatory disorders such as sepsis, acute lung injury, and rheumatoid arthritis are characterized by concurrent innate immune activation and metabolic stress[1]. In sepsis, LPS induced TLR4 activation and tissue hypoxia/nutrient deprivation created IIAMD conditions, triggering mitoxyperiosis in macrophages and endothelial cells[1]. The resulting lytic cell death and DAMP release drove excessive inflammation, cytokine storm, and organ dysfunction[1]. Inhibition of mitoxyperiosis with mTOR inhibitors or antioxidants reduced inflammation and improved survival

in preclinical sepsis models[1]. A novel strategy for treating severe inflammatory disorders may represented by targeting mitoxyperiosis.

5.2. Cancer

Cancer cells exhibit dysregulated metabolism and chronic innate immune signaling frequently, creating a permissive environment for mitoxyperiosis[1]. While mitoxyperiosis promoted inflammation driven tumor progression in some cases, it can also be exploited for cancer therapy[1]. Combined immune activatio and metabolic stress could selectively induce mitoxyperiosis in cancer cells, which are more likely to oxidative stress than normal cells[1]. Induction of mitoxyperilysis eliminated tumor cells and released DAMPs, which promote antitumor immunity[1]. Targeted activation of mitoxyperiosis may offer a new approach for overcoming therapy resistance in cancer.

5.3. Future Directions and Unresolved Questions

Despite significant advances, several key questions of mitoxyperiosis need to be completely addressed. First, the specific molecular bridged that mediate stable mitochondria plasma membrane contact are poorly defined, as the exact protein or lipid tethers anchoring mitochondria to the plasma membrane during mitoxyperiosis are still need to be identified[9]. The characterization of these tethering factors may reveal newl and specific therapeutic targets for regulating this cell death pathway[10]. Second, the functional contributions of lipid peroxidation byproducts such as 4-HNE and MDA to plasma membrane structural damage and subsequent inflammatory cascades remain not clear, requiring further mechanistic investigation[6]. Third, the clinical relevance of mitoxyperiosis didn't be proved, with its prevalence and functional role in human inflammatory disorders and malignant tumors wait for verification by using primary clinical samples[1]. Finally, a major translational bottleneck of therapeutic specificity, as developing selective interventions that modulate mitoxyperiosis activity without disruption with other regulated cell death pathways represents a critical on-going challenge. In conclusion, addressing these unresolved questions will deepen our mechanistic understanding of mitoxyperiosis and promote the development of precision targeted therapeutic interventions for mitoxyperiosis associated diseases.

6. Conclusion

This review argued mitoxyperiosis as a distinct, mitochondria-dependent lytic cell death pathway , which is triggered by the synergistic activation of IIAMD. It outlined the biochemical basis of plasma membrane lipid peroxidation, including the initiation, propagation, and termination phases, and highlighted how mitoxyperiosis different from ferroptosis, necroptosis, and pyroptosis in terms of triggering stimuli, ROS sources, spatial patterns of oxidative damage, and regulatory mechanisms. Additionally, this review discussed the continuous molecular mechanisms underlying this pathway, from IIAMD-induced mitochondrial dysfunction and BAX/BAK1-mediated respiratory chain damage to mTORC2-dependent mitochondria-plasma membrane contact, focal lipid peroxidation, nanopore formation, and ultimate membrane rupture. Mitoxyperiosis requires none of the canonical death regulators—GPX4, RIPK3/MLKL, and the gasdermins are all dispensable. This independence is one of the strongest argument for treating it as a separate entity, and it explains how innate immune signals and metabolic stress can converge to produce highly localized membrane damage.

However, what physically tethers mitochondria to the plasma membrane was not clear, and whether mitoxyperiosis even occurs in patients remains untested. All the evidence so far came from experimental models, not from primary clinical material. There is some work that should come next: identifying the contact-site tethering proteins and the specific lipids that become oxidized, and developing pharmacological modulators selective enough to inhibit or induce mitoxyperiosis without interfering with other regulated cell death pathways. These would do more than clarify mechanism—they would make it realistic to ask whether targeting this pathway helps in sepsis, inflammatory disease, or cancer.

References

[1] Wang Y, Lu J, Carisey AF, et al. Innate immune and metabolic signals induce mitochondria dependent membrane lysis via mitoxyperiosis. Cell. 2025;188(24):5012 5027.e15.

[2] Randhawa J, O'Neill LAJ. Mitochondria target the plasma membrane to cause mitoxyperiosis. Cell Research. 2026;36:1 2.

[3] Zheng, J., et al. (2025). Metabolic determinants of ferroptosis. Trends in Endocrinology and Metabolism.

[4] Voeltz GK, Sawyer EM, Hajnoczky G, et al. Making the connection: How membrane contact sites have changed our view of organelle biology. Cell. 2024;187(2):257 270.

[5] Chen P, Lu Y, He B, et al. Rab32 promotes glioblastoma migration and invasion via regulation of ERK/Drp1 mediated mitochondrial fission. Cell Death & Disease. 2023;14(3):198.

[6] Nakajima K, Nakano T, Tanaka A. Cytotoxic phospholipid oxidation products. Cell death from mitochondrial damage and the intrinsic caspase cascade. Clinical Chemistry. 2006;52(7):1358 1365.

[7] Feng F, Zhang Y, Liu Y, et al. Mitochondria mediated ferroptosis in diseases therapy: From molecular mechanisms to implications. Aging and Disease. 2024;15(2):714 732.

[8] Yamazaki T, Galluzzi L. BAX and BAK dynamics control mitochondrial DNA release during apoptosis. Cell Death & Differentiation. 2022;29:1296-1298.

[9] Jacinto E, Loewith R, Schmidt A, et al. Mammalian TOR complex 2 controls the actin cytoskeleton and is rapamycin insensitive. Nature Cell Biology. 2004;6(10):1122-1128.

[10] Montes de Oca Balderas P. Mitochondria–plasma membrane interactions and communication. Journal of Biological Chemistry. 2021;297(4):101164.

[11] Karmakar M, Katsnelson MA, Dubyak GR, et al. Neutrophil $P2X_7$ receptors mediate NLRP3 inflammasome-dependent IL-1β secretion in response to ATP. Nature Communications. 2016;7:10555.