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The importance of mitochondria and mitochondrial calcium signaling in health and disease: an updated outlook on inflammation

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Abstract

Background: Mitochondria are central regulators of cellular bioenergetics, calcium homeostasis and apoptosis. Beyond these classical roles, emerging evidence highlights their pivotal involvement in inflammation and related disease progression. Under physiological conditions, mitochondria sustain metabolism and signaling; however, when dysfunctional, they can release mitochondrial damage-associated molecular patterns, such as mitochondrial DNA, reactive oxygen species, cardiolipin and ATP, into the intra- or extracellular environment.

Main body: The release of these mitochondrial components activates innate immune receptors and inflammasomes, thereby initiating or sustaining inflammatory cascades implicated in aging and a broad range of diseases, including cancer and neurodegenerative, cardiovascular, gastrointestinal and respiratory disorders. Mitochondrial calcium signaling plays a crucial role in energy production and metabolic adaptation; yet when dysregulated, it promotes ROS generation, membrane permeabilization and cell death, all of which further amplify inflammation. Structural and functional mitochondrial messengers, including mtDNA fragments and mitochondria-derived vesicles, also contribute to intercellular communication, enhancing immune activation or driving chronic

inflammation depending on their context. Therapeutically, mitochondria are emerging as promising targets to counteract inflammation. Investigational strategies include mitochondrial transplantation, engineered mitovesicles, pharmacological modulators of Ca^{2+} flux, antioxidants, and agents that restore mitochondrial biogenesis and metabolism. By reestablishing mitochondrial integrity, these interventions aim to reduce inflammatory signaling, restore cellular homeostasis, and slow disease progression.

Conclusions: This review underscores mitochondria as both initiators and regulators of inflammatory processes across multiple diseases, highlighting their dual role as drivers of pathology and as promising therapeutic targets. A deeper understanding of mitochondrial signaling, mitochondrial messengers, and inter-organelle communication will be essential for developing effective mitochondria-based therapies to mitigate inflammation and improve patient outcomes.

Keywords: mitochondria, inflammation, ROS, mitochondria targeted-therapy, mtDNA, cancer, cardiovascular diseases, aging, respiratory diseases, neurodegenerative diseases, IBD

Background

Inflammation is a fundamental and protective biological process that defends the body against external and/or internal harmful stimuli, supporting tissue repair mechanisms to maintain homeostasis [1]. However, when the inflammatory response becomes excessive or prolonged, it can lead to tissue damage and contribute to the progression and exacerbation of disease. Inflammation is initiated through the activation of Pattern Recognition Receptors (PRRs), such as plasma membrane-expressing Toll-like Receptors (TLRs) and cytosolic-expressing NOD-like Receptors (NLRs), in response to the detection of exogenous Pathogen-Associated Molecular Patterns (PAMPs). The latter includes molecules conserved in microbes or endogenous Damage-Associated Molecular Patterns (DAMPs), such as adenosine triphosphate (ATP), nucleic acids and proteins [2]. However, under normal physiological conditions, DAMPs are typically restricted from accessing the cellular compartments where PRRs reside [3]. Cellular stress or cell death can disrupt this compartmentalization releasing subcellular contents (including DAMPs) into the cytosol, thereby stimulating PRRs towards the activation of pro-inflammatory pathways and the production and release of pro-inflammatory mediators [4].

Increasing evidence shows that mitochondria appear to play a pivotal role in regulating inflammation through two key mechanisms: (i) as checkpoints in intracellular signaling pathways downstream of PRRs and (ii) as source of freely or encapsulated mitochondrial DAMPs (mtDAMPs), including mitochondrial DNA (mtDNA), mitochondrial reactive oxygen species (mtROS), Ca^{2+} , cardiolipin, and ATP, which are released into the intracellular and extracellular environment to regulate biological responses associated to inflammation [5]. Mitochondrial Ca^{2+} signal contribute in an essential activity for the proper functioning of cellular processes, such as cell metabolism and cell death. In fact, mitochondrial Ca^{2+} plays a central role in maintaining mitochondrial function; its dysregulation impairs mitochondrial respiration, favoring the generation of ROS, promotes the membrane permeabilization triggering cell death and inflammation [6–8].

Because of their central role in both cellular homeostasis and inflammation, novel therapeutic strategies are being explored for inflammatory-related diseases in which mitochondrial dysfunction plays a central role in driving disease progression and exacerbation. Mitochondrial transplantation, mitochondria-derived vesicles (MDVs) and engineered artificial mitovesicles administration are examples of alternative mitochondria-based approaches that aims to preserve cellular bioenergetics and counteract mitochondrial impairment in order to slow or reverse pathological processes, restoring mitochondrial activity mediating the transfer of functional mitochondria or of mitochondrial components [9,10].

This review aims to emphasize the significance and role of mitochondria in inflammation-related diseases, discussing also of recent discoveries that support the development of mitochondria-based therapeutic strategies in aging and in pathological conditions such as cancer, lung, neurodegenerative, gastrointestinal and cardiovascular diseases.

Mitochondrial workload and calcium signaling

Central to their functionality, Ca^{2+} plays a crucial role in regulating mitochondrial workload and overall cellular homeostasis [8,11]. Structurally, mitochondria are defined by two distinct phospholipid membranes: the outer mitochondrial membrane (OMM) and the inner mitochondrial membrane (IMM), which delineate in turn two distinct compartments: intermembrane space and mitochondrial matrix.

OMM permits the movement of water, ions and small molecules via various channels, including the Voltage-Dependent Anion Channel (VDAC) family [12]. In contrast, IMM is selectively permeable, allowing only specific molecules such as water, metabolites, oxygen and carbon dioxide to pass through [13–16]. This selective permeability is critical for generating the electrochemical gradient through mitochondrial electron transport chain (mETC), necessary for ATP production and in maintaining ion homeostasis, including Ca^{2+} ions. Among the four major complexes that make up the mETC, complex I (NADH-CoQ reductase) and complex III (cytochrome c reductase) are the primary sources of mtROS. The IMS is essential for various processes, including mitochondrial respiration, protein import, lipid regulation and metal ion exchange. By contrary, the matrix is house of mtDNA, ribosomes and a wide range of metabolic pathways, such as tricarboxylic acid (TCA) cycle, β -oxidation and heme biosynthesis.

Mitochondria participate in controlling intracellular Ca^{2+} homeostasis, transiently sequestering Ca^{2+} released from endoplasmic reticulum (ER) and transfer through ER-mitochondria contact sites, dynamic regions that bridge two organelles to regulate size, organelle-spacing and frequency interactions in response to cellular demands [17] (Figure 1). Mitochondrial Ca^{2+} uptake primarily occurs through a low-affinity, high-selectivity channel the mitochondrial Ca^{2+} uniporter (MCU)

complex located on the IMM [18]. The MCU complex enables the rapid influx of Ca^{2+} into the mitochondrial matrix in response to cellular signals. This channel is tightly controlled by several associated proteins, including the mitochondrial Ca^{2+} uptake proteins (MICUs) and the essential MCU regulator (EMRE). MICU1, MICU2 and MICU3 serve as gatekeepers for pore-forming protein MCU, regulating the channel's opening in response to cytosolic Ca^{2+} levels, ensuring that Ca^{2+} uptake occurs only when necessary to prevent mitochondrial Ca^{2+} overload [18] (Figure 1). Once in the matrix, Ca^{2+} activates Ca^{2+} -dependent dehydrogenases within TCA cycle, thereby enhancing the production of reducing equivalents such as NADH and FADH_2 , which are crucial for ATP synthesis via oxidative phosphorylation [19,20]. This process highlights the essential role of Ca^{2+} in linking cellular energy demand with mitochondrial ATP production.

Figure 1. Core components of mitochondrial Ca^{2+} handling under physiological conditions. The diagram provides an overview of the molecular machinery that regulates mitochondrial Ca^{2+} uptake and efflux in healthy cells.

The efflux of Ca^{2+} from mitochondria is equally critical in maintaining cellular homeostasis. The Ca^{2+} efflux is primarily mediated by Na^+ -dependent exchangers, $\text{Na}^+/\text{Ca}^{2+}/\text{Li}^+$ exchanger (NCLX) located in the IMM and $\text{Na}^+/\text{Ca}^{2+}$ exchanger (NCX) expressed at the OMM, respectively [21,22]. NCX can operate in forward mode (exporting one Ca^{2+} in exchange for three Na^+) or reverse mode (Ca^{2+} influx and Na^+ efflux). In contrast, NCLX is localized to the IMM and mediates Ca^{2+} extrusion from the matrix in exchange for either Na^+ or Li^+ at similar rates. The Na^+ -dependent exchangers extrude Ca^{2+} in both excitable and non-excitabile cells while in non-excitabile cells the mitochondrial Ca^{2+} may be also extruded via $\text{H}^+/\text{Ca}^{2+}$ exchanger [23], anyway all contribute to the regulation of mitochondrial Ca^{2+} homeostasis preventing Ca^{2+} overload, and the maintenance of the mitochondrial membrane potential.

The role of mitochondrial Ca^{2+} dysregulation in determining cell fate is well established. Increasing evidence suggests that this alteration is also involved in additional cellular processes underlying various pathologies. In particular, mitochondrion and mitochondrial Ca^{2+} signaling are emerging as crucial modulators of inflammation, a common feature among these diseases. Abnormal Ca^{2+} handling led to mitochondrial membrane permeabilization with consequent release of either mtDAMPs and MDVs to promote and sustain the inflammation or cytochrome c and pro-apoptotic factors to active caspases and trigger apoptosis, exacerbating the disease progression [24–26]. Mitochondrial metabolism also plays a critical role in shaping the inflammatory response of immune cells, where changes in mitochondrial function and metabolic reprogramming are pivotal to coordinate the nature and extension of the inflammatory responses [5,27]. There is also evidence that Transient Receptor Potential Vanilloid 4 (TRPV4), a mechanosensitive ion channel permeable to Ca^{2+} , influences macrophage function under inflammatory conditions. The activation of TRPV4 in macrophages exposed to inflammatory stimuli increases intracellular Ca^{2+} influx, which then triggers phosphorylation/activation of the transcription factor CREB. Activated CREB binds to regulatory elements in the IL-10 gene promoter, thereby up-regulating IL-10 production. Elevated IL-10 in turn reprograms the macrophages toward a less pro-inflammatory, more anti-inflammatory phenotype [28].

The interplay between mitochondrial Ca^{2+} handling and inflammatory signaling pathways is an emergent area of study, understanding this intricate relationship will be essential for developing mitochondria-based therapeutic approaches to contrast the inflammatory-related diseases [24].

“Mitochondrial messengers” in inflammation

The dynamic plasticity of mitochondria is essential for their ability to communicate with other organelles and even with cells, thereby facilitating the exchange of metabolites and signaling molecules. To ensure effective functionality and interconnected signaling, several molecular mechanisms have evolved to generate and release mitochondrial messengers under physiological as well as pathological conditions.

Despite classical origin of DAMPs includes plasma membrane, nuclear and intracellular proteins; it has been identified that mitochondrial constituent play a crucial role to stimulate inflammation, acting as mtDAMPs (Figure 2) [8,29,30]. These mitochondrial messengers may act both intracellularly and extracellularly, either in free form as a consequence of indirect release during mitochondrial stress or packaged within whole mitochondria or vesicles through specific biogenetic and release mechanisms (Table 1). This allows a “protected transfer” of mitochondrial messengers to other intracellular compartments or to recipient cells [31].

Table 1. A summary on the roles of mitochondria and mitochondrial calcium-induced inflammation in specific diseases.

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Mitochondrial Component	Disease	Inflammation	Resulting function	References
Circulating mtDNA	Progressively rise in Aging	Activates innate immune receptors on the plasma membrane of immune cells, such as monocytes, triggering the release of pro-inflammatory mediators.	Increases levels of pro-inflammatory cytokines (IL-6, TNF- α , IL-1 receptor antagonist) in the plasma.	[1,2]
	Increases in plasma and bronchial alveolar lavage in Idiopathic pulmonary fibrosis (IPF) patients	Regulates alveolar epithelial cell programmed cell death and promotes fibroblast activation contributing to fibrosis	Reflects the disease severity and represents a potential biomarker of mitochondrial stress and fibrosis.	[3,4]
	Is increased in plasma and in excrement of patients with inflammatory bowel disease (IBD)	It may activate innate immune receptors, such as TLR9, leading inflammatory responses	It may serve as a non-invasive biomarker to monitor subclinical disease activity.	[5]
Extracellular mtDNA	Parkinson's disease (PD)	Degenerated dopaminergic neurons contribute to mtDNA release	Contributes to neuroinflammation activating microglia, and reflects the status of neurodegeneration in PD and MS.	[6]
	Multiple Sclerosis (MS)	Elevated level in the cerebrospinal fluid of MS patients, correlating with disease severity.		[7]
	Idiopathic pulmonary fibrosis (IPF)	The accumulation reflects mitochondrial distress, acting as mtDAMPs	Induces metabolic remodeling, and fibroblast activation.	[3,4]
	Myocarditis	mtDNA release from endothelial cells contributed to impaired cardiac contractility	Contribute to the inflammatory response, triggering cardiomyocyte death.	[8]
mtDNA encapsulated in Extracellular vesicles (EVs)	Prostate Cancer	Evs, released from senescent tumor cells, are taken up by neutrophils and polymorphonuclear myeloid-derived	Functionally reprograms PMN-MDSCs to acquire a more immunosuppressive phenotype,	[9]

		suppressor cells (PMN-MDSC), activating the cGAS-STING-NF- κ B-PERK axis	thereby promoting tumor progression.	
	Pneumococcal Pneumonia	EVs, released from lung epithelial cells, are taken up by neutrophils suppressing their ability to produce ROS	Compromises a critical host-defense mechanisms	[10,11]
Mitochondria encapsulated in EVs	Acute respiratory distress syndrome (ARDS)	Mesenchymal stem cell-derived EVs promote an anti-inflammatory and highly phagocytic macrophage phenotype through EV-mediated mitochondrial transfer	Mesenchymal stem cell-based mitochondria changed the macrophage phenotype ameliorating the lung injury in vivo.	[12] [13]
Mitochondria transplantation	Aging	Attenuates systemic inflammation and tissue dysfunction, ameliorating the bioenergetics and the intercellular communication	The transferring restored mitochondrial function, bioenergetics, ameliorating the inflammatory response, and preserving the tissue integrity.	[14,15] [16,17]
	Chronic obstructive pulmonary disease (COPD)	Mesenchymal stem cell-based mitochondria attenuated cigarette smoke-induced mitochondrial ROS production and apoptosis in airway cells		[18]
	Parkinson's Disease	Mesenchymal stem cell-based mitochondria protected dopaminergic neurons, decreasing microglial activation		[15]
		mitochondrial replacement prevented experimental PD progress through increasing the activity of electron transport chain, decreasing ROS, and preventing cell death		[19]

	Ischemia/Reperfusion injury	Mitochondrial injection restored mitochondrial respiration and ATP production in cardiomyocytes, improving contractile recovery		[20,21]
Intracellular{Citiation} mtDNA	Aging	Recognized by intracellular innate immune sensors, such as cGAS–STING and NLRP3 inflammasome, promote the release of pro-inflammatory mediators.	Persistent inflammasome activation has been implicated in several age-related conditions, including neurodegeneration and metabolic disorders	[22–25]
	Lung carcinoma		increased dendritic cell activation and antitumor immunity.	[26]
	Atherosclerosis		Exacerbate the inflammation favoring the formation of atherosclerotic lesion	[27]
	Ischemia-Reperfusion injury		Sustain the inflammation-induced damage, which worsen post-I/R injury.	[28]
	Alzheimer's Disease (AD)		Promote the secretion of pro-inflammatory mediators, contributing to synaptic dysfunction and neuronal loss.	[29]
	Parkinson's disease (PD)			[6,30]
	Cystic fibrosis		Promote epithelial and endothelial barrier disruption, alveolar edema, and impaired gas exchange.	[31,32]
	Acute respiratory distress syndrome (ARDS)			[33]
Mitochondrial respiratory chain	Cancer	Mutations promote mitochondrial ROS-induced damaged, favoring the activation of inflammasomes	Establish a chronic inflammatory microenvironment that fuels cancer cell proliferation, angiogenesis and immune evasion.	[34]
	Alzheimer's disease (AD)	Alteration of mitochondrial respiration activity impairs the bioenergetics	Promoting cellular damage and the progression of neurodegeneration.	[29]

		promoting the oxidative stress		
	Parkinson's disease (PD)	The deficiency of mitochondrial complex I leads to the accumulation of depolarized mitochondria with consequent production of mtROS		[30]
	Multiple Sclerosis (MS)	Contributes to a metabolic reprogramming that stalls oligodendrocytes in an undifferentiated state.	Hinder remyelination in MS through mitochondrial and metabolic dysregulation.	[35]
	Cystic Fibrosis (CF)	Deficiency in mitochondrial complex I enhances NADPH oxidase activity and oxidative stress.	Leads to glutathione depletion and impaired energy homeostasis.	[36,37]
Mitochondrial Reactive Oxygen Species (ROS)	Aging	Senescent cells produce more mtROS enhancing inflammation.	NF- κ B activation and hyperproduction of pro-inflammatory cytokines	[38]
	Breast Cancer	Accumulation of damaged mitochondria, which generate ROS that activate the inflammasome.	Promoting the secretion of pro-inflammatory mediators that fostering bone metastasis.	[39]
	Parkinson's disease (PD) Multiple Sclerosis (MS)	Contribute to microglial activation, favoring the inflammasome assembly and activation.	The resulting secretion of pro-inflammatory cytokines sustain the neuroinflammation, exacerbating the synaptic dysfunction.	[40,41]
	Alzheimer's disease	Amyloid- β accumulation induces ROS production, which promote the pathological aggregation of tau protein.	Contribute to disrupt the mitochondrial trafficking to and from synaptic terminals, promoting synaptic impairment and neurodegeneration	[42]
	Asthma	Promote cytokine production in airway smooth muscle cells.	Contribute to airway remodeling and hyperresponsiveness.	[43,44]

	Inflammatory Bowel Diseases (IBD)	Low levels of ROS maintain intestinal stem cell function and antimicrobial responses	The persistent presence of ROS has deleterious effects on intestinal integrity, which sustain the intestinal inflammation, also through the recruitment of NLRP3 inflammasome; but in specific contexts this may contribute to epithelial regeneration, indicating a dual and potentially opposing roles within the gastrointestinal system.	[45–47] 29/01/2022 09:28:00
		Excessive ROS disrupt barrier function, inducing apoptosis of intestinal epithelial cells, and perpetuating mucosal inflammation		
	Atherosclerosis	Mitochondrial ROS accumulation promote inflammasome activation and macrophage pyroptosis	Promote the decline of vascular health, amplifying inflammation mediating the release of pro-inflammatory mediators and the death of phagocytes.	[45]
Mitochondrial Ca²⁺ Uniporter (MCU) complex	Aging	Mitochondria control the cytosolic Ca ²⁺ levels but this ability declines with age, resulting in cytosolic Ca ²⁺ -overload, which activates Ca ²⁺ -dependent degradative enzymes	Onset of damage to cellular structures and DNA, which exacerbates injury and amplifies inflammatory signaling	[46–48]
	Cancer	Lower MCU expression in aged macrophages disrupts metabolism and promotes inflammation in tumor environment	Increases production of cytokines, such as IL-6 and TNF- α , impairs oxidative phosphorylation and increases dependence on glycolysis.	[49,50]
	Cystic Fibrosis (CF)	Increased mitochondrial Ca ²⁺ uptake, during pathogen infection, promote mitochondrial permeabilization and	Controls the secretion of pro-inflammatory mediators from bronchial epithelia cells, sustaining the inflammation and	[32,51]

		inflammasomes activation	favoring tissue damages	
	Cerebral amyloid angiopathy (CAA)	MICU3 interacting with PINK1, in neurons and glia, preserves mitochondrial homeostasis during amyloid- β accumulation	Controls amyloid β -driven neurovascular and neuroinflammatory damage.	[52]
	Vascular Inflammation and Atherosclerosis, Cardiomyopathy and heart failure	Loss of MICU1/2 expression contribute to mitochondrial ROS generation, reducing the function of scavenger enzymes	Amplification of inflammatory signals, which worsen cardiovascular damage.	[53–55]
	Ischemic Heart Disease	MICU3 interacting with VDAC1 increases the ER-mitochondria Ca^{2+} transfer during ischemia-reperfusion in peripheral blood neutrophils		
Voltage dependent anionic channel (VDAC)	Cancer	Changes in VDAC2 expression in cancer cells disrupt mitochondrial integrity and bioenergetics, favoring the release of mtDAMPs	Reducing VDAC2 expression in cancer cells activates anti-tumor immune response.	[56,57]
	Inflammatory bowel disease (IBD)	VDAC-interacting drugs prevent VDAC-oligomerization and subsequent mtDNA release	VDAC controls the mitochondrial membrane permeabilization, attenuating experimental colitis and preserving intestinal epithelial integrity	[58,59]
	Atherosclerosis	Dissociation of hexokinase 2 from VDAC induces mitochondrial Ca^{2+} overload with consequent VDAC oligomerization, which mediates the release of mtDNA fragments in macrophages	This contributes to NLRP3 activation, which exacerbates the atherosclerotic lesions	[27,60]

Figure 2: Several mitochondrial-derived molecules contribute to inflammation.

Schematic representation of the mitochondrial pathways involved in the regulation of innate immune responses. Mitochondrial outer membrane permeabilization through B-cell lymphoma 2 (BCL2)-associated protein X/BCL2 homologous antagonist killer (BAX/BAK) or voltage-dependent anionic channel/ mitochondrial permeabilization transition pore (VDAC/mPTP) leads to the release of mitochondrial DNA (mtDNA), cardiolipin, adenosine triphosphate (ATP), and N-formylated peptides into the cytosol or extracellular space. mtDNA activates cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) signaling, leading to interferon regulatory factor (IRF3/7) activation and interferon (IFN) gene transcription. mtDNA fragments also trigger NOD-like Receptor (NLR) pyrin domain-containing protein 3 (NLRP3) and NLR family CARD domain containing 4 (NLRC4) inflammasomes, promoting caspase-1 activation and interleukin (IL)-1 β /IL-18 maturation. Circulating CpG-rich mtDNA is sensed by Toll-like receptor 9 (TLR9), initiating the Myeloid differentiation primary response 88 (MyD88)-dependent pathway that induces IL-6 and Tumor Necrosis Factor alpha (TNF- α) production. Mitochondrial reactive oxygen species (mtROS), cardiolipin exposure, ATP levels, and mitochondrial Ca²⁺ fluxes further modulate inflammasomes activation and redox-sensitive transcription factors, like nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), inducing pro-inflammatory cytokines. Mitochondrial damage also generates mitovesicles and mitochondrial-derived vesicles (MDVs), which participate in intercellular communication and immune modulation. Together, these mitochondrial signals orchestrate the interplay among the cells, including immune cells, during inflammation.

mtDNA is a pivotal immunostimulator when exhibits persistent, stereotypical oxidative damage modifications or mutagenic signatures. This double-stranded circular DNA encodes 37 genes, which 13 are essential components of mETC and ATP synthase [32]. Several mtDNA copies are present in each cell, and its copy number is regulated basally by cell-specific mechanisms and in response to various intrinsic and environmental stresses. The low methylation levels of mtDNA, respect to nuclear DNA, the lack of histone protection, and the proximity to ROS made by mETC system results in a major exposure to oxidation, leading to mtDNA more prone to damage [33–35]. The release into the cytoplasm of either whole or fragmented mtDNA, but also in the extracellular space and in the circulatory stream, may engage multiple receptors based on cell-type and context-dependent manner, triggering cell death, immune cells activation and antimicrobial responses [36–40].

Studies have highlighted the role of VDAC1 and mitochondrial permeability transition pore (mPTP) in mtDNA release (Figure 2). VDAC1 can oligomerize in response to mtDNA fragments, facilitating their escape into the cytosol [41]. Although VDAC1 was once thought to be a key component of the mPTP, experiments in VDAC1-deficient mice showed no significant impact on mPTP formation, suggesting that VDAC1 is either not essential for mPTP or its role is compensated by other VDAC isoforms [42]. The potential synergistic relationship between mPTP opening and VDAC1 oligomerization in mediating mtDNA release remains unclear. While during apoptosis BAX/BAK macropores can permeabilize the OMM, allowing mtDNA extrusion [43], under certain stress conditions mtDNA might cross both the IMM and OMM, ultimately entering the cytosol. However, the precise mechanisms governing the formation and regulation of these pores require further investigation.

After cellular injury, mtDNA may be sensed by PPRs in the cytosol and in the extracellular space [44]: i) cytosolic mtDNA could be recognized by the cyclic GMP-AMP synthase (cGAS), which after activation triggers conformational alterations of the ER-resident protein stimulator of interferon genes

(STING). Consequently, the binding with TANK-binding kinase 1 activates interferon regulatory factor 3 (IRF3) or IRF7 to prompt transcription of type I interferons (IFNs) genes; ii) circulating mtDNA may activate human polymorphonuclear neutrophils via TLR9, resulting in the pro-inflammatory mediator production and release. TLR9 is a type I transmembrane receptor with a horseshoe-shaped extracellular domain that is crucial for ligand-induced dimerization. It detects unmethylated CpG-DNA [45,46] which triggers the MyD88-dependent signaling cascade, leading to the production of pro-inflammatory cytokines, such as Tumor Necrosis Factor (TNF α) and IL-6, through the activation of MAPKs and NF- κ B [47]; iii) fragments of mtDNA of several hundred base pairs in length, in the cytosol, may activate NLRs, including NLRP3 and NLRC4 inflammasomes (Figure 2).

These intracellular receptors require a double activation steps: firstly the priming step, where the expression and post-translational modifications of inflammasome components are induced in reply to pro-inflammatory stimuli and subsequent NF- κ B activation [48]; secondly the activation step, which is controlled by an amplitude of signals and it needs the physical interaction with mitochondria, mediating mitochondrial antiviral-signaling (MAVS) protein, for the assembly of inflammasome and the consequent auto-cleavage of pro caspase-1, responsible for the production of mature cytokines IL-1 β and IL-18 [49]. MAVS is a key protein involved in both inflammation and viral infection. It acts as a signaling adaptor on OMM. RIG-I-like receptors (RLRs) include RIG-I and MDA5; they are cytoplasmic sensors that detect viral double-stranded RNA. Upon RNA binding, these receptors initiate a signaling cascade by interacting with MAVS on the OMM. This interaction induces MAVS oligomerization, which in turn activates transcription factors, such as IRF3, IRF7 and NF- κ B, ultimately promoting the expression of IFNs and other antiviral genes to fight off viruses [50]. However, dysregulation of MAVS can also contribute to excessive inflammation in various diseases [51].

Additional key players in driving inflammation are mtROS, produced during oxidative phosphorylation (OXPHOS) and consisting of the anion superoxide which is then converted to hydrogen peroxide by mitochondrial superoxide dismutase (SOD) enzyme [52,53]. Generally, mtROS levels increase during mitochondrial dysfunction; for instance, in the presence of unfolded proteins or excessive Ca²⁺ accumulation, that impair OXPHOS. At low and moderate concentrations mtROS have a role as signaling molecule and of pro-inflammatory activator, acting on redox-sensitive transcription factors, such as NF- κ B, with consequent production of inflammatory mediators; while they are the principal cause of cellular injuries at higher concentrations (Figure 2). The excessive mtROS levels lead to a vicious cycle of oxidative stress, promoting further damage to mETC with consequent more electron leakage and mtROS production [5]. mtROS can directly contribute to NLRP3 activation, driving the translocation of NLRP3 and its adaptor ASC to mitochondria [54]. Other mtDAMPs promote the IRF1-dependent transcription of Cytidine/Uridine monophosphate kinase 2, a mitochondrial key enzyme in mtDNA synthesis, via TRL signaling, generating the oxidized mtDNA fragments necessary to complete the inflammasome activation [55]. To avoid mitochondrial or cellular damage, mtROS levels are strictly controlled by mitochondrial antioxidants systems and mitochondrial stress responses, which intervene to restore the mitochondrial homeostasis. Furthermore, an important driver in mtROS stimulation is Ca²⁺, which can directly stimulate mtROS production by activating mitochondrial resident ROS-generating enzymes, or indirectly, by the Ca²⁺-dependent activation of nitric oxide synthase [56–58].

Mitochondria are widely recognized as the primary site of ATP production, a process essential for maintaining cellular health and function. Under stress conditions, when energy demands increase,

elevated intracellular ATP levels can lead to its release into the extracellular space. In this context, extracellular ATP acts as a signaling molecule, activating purinergic receptors that promote inflammatory responses [32,59]. Specifically, ATP binds to the P2X7 receptor, a member of the P2X family of plasma membrane non-selective cation channels that are activated by ATP [60,61]. Activation of P2X7 triggers potassium efflux, a critical event that leads to the further activation of NLRP3 inflammasome (Figure 2). Beyond inflammasome activation, ATP also plays a key role in the immune system by mediating chemotaxis and neutrophil adhesion. It enhances neutrophil degranulation and the production of ROS, thereby facilitating the destruction of invading pathogens [62,63].

The binding of cardiolipin (CL) is also necessary to NLRP3 inflammasome activation. A phospholipid that constitutes up to 20% of the total lipid content of IMM, which is essential for the proper function of mETC [32,64,65]. However, during mitochondrial dysfunction, CL translocates from IMM to OMM, and once externalized, it directly binds NLRP3 at Leucine-Rich Repeat domain, promoting caspase-1 activation and subsequent cytokine release [48].

As remnants of their bacterial ancestry, also the N-formylated peptides contained into mitochondria, once released into the extracellular environment, increase the production of pro-inflammatory mediators and ROS. They do it through the formyl peptide receptors (FPRs) binding on neutrophils and macrophages, thereby inducing receptor-mediated activation and directed chemotaxis (Figure 2) [66,67].

In recent years, extracellular vesicles (EVs) have gained much attention for their crucial role in translating inflammatory signals into recipient cells. Specifically, EVs cargo includes plasma membrane and endosomal proteins, but also contain material from other cellular compartments, including mitochondria. Specifically, studies have shown that subpopulation of EVs may transport whole mitochondria, mitochondrial materials and/or mtDAMPs to modulate the metabolic and inflammatory responses of recipient cells. Among the various subtypes of EVs, MDVs represent a distinct subset of mitochondrial origin. These vesicles, typically ranging from 60 to 150 nm in diameter, are formed through two mechanistic models: i) budding of the mitochondrial membrane and subsequently released by clathrin-mediated exocytosis [68]; or ii) long membrane protrusion are pulled out of mitochondria and released by scission event [69]. Initially, MDVs were identified as a potential mechanism for removing damaged mitochondrial components [70]. Their formation may be regulated by pathways involving the Parkinson's disease-associated proteins PINK1 and Parkin (linked to mitophagy, the selective autophagic removal of dysfunctional mitochondria mediated by the Parkin/PINK1 pathway through lysosomes), or through a dynamin-related protein 1 (DRP1)-dependent mechanism, both of which have been comprehensively reviewed [71,72]. A failure in PINK1 import into mitochondria leads to the recruitment of Parkin, which triggers mitophagy and may promote MDV formation.

To date, two different types of MDVs have been identified, called single-membraned MDVs, exclusively formed by OMM and double-membraned MDVs containing both outer and IMM contents [73]. Studies demonstrated that MDVs are released under both basal and upon various forms of mitochondrial stress, and that their biogenesis and cargo are strictly dependent to the nature of stress. Their functional and biological role in immunity and inflammatory signaling is under investigations, it is clear that MDV cargoes, expelled from mitochondria to organelles or cells, can serve as signals to trigger inter-organelle and inter-cellular responses (Figure 2) [74,75].

More recently, a novel subtype of MDVs, termed "mitovesicles," has been identified in brain tissue using an optimized isolation method [76,77]. Intriguingly, mitovesicles appear to possess properties

that are entirely distinct from conventional EVs. When isolated via high-resolution density gradients, these vesicles were enriched in mitochondrial proteins such as VDAC, COX-IV and PDH-E1 α , while lacking typical markers of microvesicles, exosomes and EVs of endocytic origin. Indeed, their lack of several mitochondrial proteins that are abundant in MDVs, such as TOMM20, mitofusin-2 (MFN2), suggesting that mitovesicles may arise through unique biogenetic and biophysical mechanisms, separate from those of traditional EV subtypes, like MDVs, microvesicles and exosomes (Figure 2) [76,77]. However, the exact mechanisms underlying mitovesicles biogenesis remain to be elucidated. In summary, current evidence supports the notion that MDVs may follow distinct biogenetic pathways and exhibit unique biological characteristics based on their cargo.

Inflammation and mitochondria in aging

Aging is a complex biological process characterized by the gradual decline in physiological functions, leading to increased vulnerability to diseases and mortality. It begins with accumulative damage and destabilization of the genome: over time cells and tissues accrue mutations, chromosomal rearrangements and impaired DNA repair. This hallmark of genomic instability erodes the foundations of cellular integrity and promotes cellular dysfunction. Closely linked is telomere attrition, the progressive shortening of chromosome ends as cells divide, which eventually triggers replicative arrest or genome instability when telomeric protection fails. Ageing cell also suffers epigenetic alterations: modifications of DNA methylation, histone marks, chromatin architecture and non-coding RNAs that disturb the correct regulation of genes, thereby impairing cell function. Equally important is the breakdown of protein quality control or the loss of proteostasis by which damaged or mis-folded proteins accumulate, chaperone and clearance systems falter and the cellular protein landscape becomes dysfunctional. Complementing that is the deficiency in cellular “house-keeping” clearance: the hallmark disabled macroautophagy reduces the ability of cells to recycle damaged components and maintain homeostasis [78]. Cells progressively enter a state of non-division and altered function: cellular senescence describes accumulation of cells that have irreversibly exited the cell cycle but remain metabolically active and often secrete pro-inflammatory mediators, thereby contributing to ageing and tissue deterioration. Moreover, with ageing inter-cellular communications change with hormonal changes, immune-system drift and the senescence-associated secretory phenotype (SASP) affecting distant cells. Persistent low-grade immune activation (inflammaging) becomes a chronic reality [79] [80]. Chronic inflammation emerges when the immune system remains in a state of heightened activation, driving decline and age-related pathologies. Finally, also dysbiosis, an imbalanced microbiome and altered microbial-host interactions reflects how microbial ecology influences the host’s ageing process via immune, metabolic and barrier-integrity effects [78,81].

One of the most important traffic light intersection of pathways in aging is that one involving autophagy, endolysosomal system (ELS) and mitophagy. Autophagy is essential for degrading and recycling damaged proteins and organelles. As organisms age, a gradual decline in autophagic efficiency emerges; this is not merely a matter of waste accumulation, it has far-reaching consequences for inflammatory homeostasis [82]. Autophagy normally acts as a brake on innate immune activation, removing sources of intracellular danger signals such as oxidized proteins, dysfunctional mitochondria (through mitophagy) and protein aggregates that would otherwise stimulate PPRs. In this way, basal autophagy serves as a key anti-inflammatory mechanism that prevents chronic activation of pathways like NF- κ B, NLRP3 inflammasome and the cGAS–STING axis. With advancing age, autophagic flux becomes impaired at multiple levels: autophagosome formation, lysosomal fusion and lysosomal degradation. The resulting buildup of damaged organelles

and undegraded material increases intracellular stress, generating ROS and releasing DAMPs. Closely tied to this process is the ELS, a complex network of endosomes and lysosomes responsible for degradation, trafficking and secretion. The ELS has recently been recognized as a key regulator of aging and inflammation [83]. Lysosomes are not simply degradative compartments but also signalling hubs that coordinate nutrient sensing and immune responses. During aging, lysosomal integrity and enzyme activity decline, leading to inefficient degradation and partial leakage of lysosomal contents into the cytosol. Such lysosomal membrane permeabilization (LMP) releases cathepsins and other hydrolases, which in turn activate the inflammasomes. Interestingly, when lysosomal degradation is compromised, cells often reroute cargo through secretory autophagy or EV pathways. While this may temporarily alleviate intracellular stress, it also results in the release of undegraded materials, including mitochondrial fragments and oxidized lipids, into the extracellular space. With age, also impaired mitophagy occurs with persisting damaged mitochondria, generating oxidative stress and releasing mtDNA into the cytoplasm.

This creates a feed-forward cycle: impaired autophagy and ELS function lead to defective mitophagy, which allows the persistence of damaged mitochondria that, in turn, generate inflammatory DAMPs. These DAMPs activate innate immune sensors, which then exacerbate cellular stress and lysosomal dysfunction, further suppressing autophagic clearance. At the molecular level, this network is tightly linked to nutrient-sensing pathways, particularly mTORC1 and its downstream target S6 kinase (S6K). Persistent mTOR activation with age inhibits both autophagy and lysosomal biogenesis, while S6K signalling influences ELS trafficking and immune activation [83].

After the age of 50, levels of circulating mtDNA progressively rise and are associated with increased levels of pro-inflammatory cytokines, such as IL-6, TNF- α and IL-1 receptor antagonist [84]. Remarkably, exposing monocytes to mtDNA, at concentrations like those found *in vivo*, has been shown to increase TNF- α production, indicating that circulating mtDNA play a direct role in inflammaging [85]. Moreover, one of the key features of aging mitochondria is the accumulation of mutations in mtDNA. These mutations can impair mitochondrial function, further exacerbating oxidative stress and contributing to the decline in cellular and tissue function observed in aging [86]. Oxidized mtDNA released into the cytosol is an inflammasome activator, promoting IL-1 β and IL-18 secretion and amplifying systemic inflammation [54,87]. Persistent inflammasome activation has been implicated in several age-related conditions, including neurodegeneration and metabolic disorders [88].

Mitochondria play a significant role in buffering cytosolic Ca²⁺ levels, and their ability to do so declines with age [25]. An altered mitochondrial Ca²⁺ buffering may lead to prolonged elevation of intracellular Ca²⁺ levels, activating various enzymes that can damage cellular structures and contribute to the inflammatory response. This dysregulation primarily occurs at the ER-mitochondria contact sites; with aging mitochondrial Ca²⁺-uptake capacity declines alongside alterations in MCU-complex components and regulatory gatekeepers, impairing buffering and promoting cytosolic Ca²⁺-overload [89–91]. The sustained rise in Ca²⁺ activates Ca²⁺-dependent enzymes, including calpains, phospholipase A and Ca²⁺/Mg²⁺-dependent endonucleases, degrading cytoskeletal proteins, lipidic membranes, and DNA, thereby exacerbating injury and amplifying inflammatory signaling [92,93]. Mitochondria in senescent cells exhibit a fragmented morphology and impaired function, leading to increased mtROS production and mtDAMPs release, which further amplifies inflammatory signaling [94]. The decline in mitochondrial biogenesis also contributes to the aging process and the associated inflammation [95,96]. Mitochondrial biogenesis is regulated by various signaling pathways, including those involving peroxisome proliferator-activated receptor-gamma coactivator 1-alpha

(PGC-1 α) and nuclear respiratory factors (NRFs) [97]. With age, the expression and activity of these regulators decline, leading to a reduction in mitochondrial number and function. Pharmacological activation of PGC-1 α has been shown to improve mitochondrial function and reduce inflammation in aging models [98]. This activation counteracts cellular aging by stimulating mitochondrial biogenesis and enhancing the efficiency of the respiratory chain, thereby increasing ATP production. Moreover, PGC-1 α reduces the generation of ROS and modulates anti-inflammatory pathways, particularly by suppressing aberrant activation of the transcription factor NF- κ B, a key driver of chronic inflammation. Through these mechanisms, PGC-1 α activation alleviates oxidative stress and inflammation associated with aging [99].

A growing body of literature suggests that targeting mitochondrial health may represent a promising avenue to counteract inflammaging and age-related functional decline. Beyond the well-established role of mitochondria as central regulators of bioenergetics, Ca²⁺ homeostasis, and ROS signaling, recent studies have explored their potential as rejuvenation tools. For instance, mitochondrial transplantation has emerged as a novel therapeutic strategy capable of restoring cellular function in aged tissues. Transplantation of mitochondria isolated from young, healthy donors into aged animal models has been shown to alleviate anxiety-like behaviors, improve synaptic plasticity, and restore bioenergetic capacity in the brain [100,101]. Importantly, mitochondrial transplantation not only reversed age-associated cognitive impairment but also enhanced ATP production, mitochondrial complex activity, and Wnt signaling, thereby supporting neurogenesis and synaptic repair [102]. From a molecular standpoint, mitochondrial transplantation has been linked to increased succinate dehydrogenase activity in the hippocampus of aged mice, a key component of complex II that regulates both ATP production and ROS control [103].

These findings align with the broader hypothesis that mitochondrial decline is a driver of aging and that its reversal could attenuate systemic inflammation and tissue dysfunction. Indeed, mitochondria have been increasingly recognized as mediators of cellular communication, not only through mtDNA and mtROS release but also via EVs that can carry mitochondrial components to modulate immune responses [104]. This interplay suggests that mitochondrial-targeted interventions, ranging from pharmacological modulators to direct organelle transfer, may hold translational potential in mitigating age-related diseases. Phua et al. proposed that mitochondria could be harnessed as powerful rejuvenation tools, representing a paradigm shift in strategies aimed at extending health span and combating the pathophysiological consequences of aging [105].

Noteworthy, a recent study uncovers a direct mechanistic link between mtDNA instability and inflammation, offering new insight into how mitochondria can trigger immune activation during ageing and stress [106]. The researchers show that when the balance between deoxyribonucleotides (dNTPs) and ribonucleotides (rNTPs) becomes disrupted, such as through decreased dNTP availability or increased rNTP levels, mtDNA replication becomes error-prone, leading to the incorporation of ribonucleotides into mtDNA. Because mitochondria lack efficient repair mechanisms for removing ribonucleotides, this incorporation destabilizes the mitochondrial genome, causing strand breaks and the accumulation of fragmented mtDNA. These damaged fragments are then released into the cytosol, where they are recognized by innate immune sensors, particularly the cGAS–STING pathway, which detects cytosolic DNA. Activation of this pathway triggers a type I interferon response and expression of inflammatory genes, linking mitochondrial genome damage directly to innate immune activation. In models where ribonucleotide incorporation was experimentally increased, such as mice lacking the mitochondrial exonuclease MGME1 or the protease YME1L, researchers observed strong inflammatory signatures, tissue damage and activation

of interferon-stimulated genes. Similar effects occurred in senescent human cells, where cell-cycle arrest limits dNTP synthesis, making mtDNA especially prone to rNTP incorporation [106]. This mechanism provides a biological explanation for the chronic, low-grade inflammation that accompanies cellular senescence and inflammaging. In aged mouse tissues, increased ribonucleotide incorporation into mtDNA correlated with signs of mitochondrial stress and immune activation, suggesting that nucleotide imbalance in mitochondria becomes more pronounced with age. Importantly, when the researchers restored the dNTP pool by supplementing cells and animals with deoxyribonucleosides, the extent of rNTP incorporation was reduced, mtDNA integrity was preserved and the inflammatory response was markedly diminished.

Inflammation and mitochondria in cancer

The relationship between mitochondria, inflammation and cancer has emerged as a dynamic and reciprocal axis that plays a pivotal role in tumor development and resistance to therapy [107]. In cancer, mitochondrial dysfunction profoundly alters cellular signaling pathways, particularly those involved in inflammatory responses. The most known contributors are mtROS; under stress conditions, such as oncogene activation [108], hypoxia or exposure to chemotherapy [109], mtROS levels can surge, leading to oxidative damage, mutations and structural changes to mitochondrial genome and the concomitant release of mtDAMPs into the cytosol [110]. The importance of mitochondria in full NLRP3 activation has been described recently in a seminal paper by Billingham LK and colleagues who reported the influence of mitochondrial integrity and electron transport chain activity on NLRP3-mediated inflammation [111]. These cytokines, in turn, can establish a chronic inflammatory microenvironment that fuels cancer cell proliferation, angiogenesis and immune evasion (Figure 3).

Figure 3. Deregulation of mitochondrial Ca^{2+} signaling across major disease contexts.

The figure shows how altered Ca^{2+} transfer to mitochondria causes increased ROS production, mitochondrial permeabilization, release of mtDAMPs and activation of inflammatory pathways.

Disease panels display typical outcomes of this imbalance: neuroinflammation in Alzheimer's disease, heightened epithelial inflammatory responses in cystic fibrosis, mitochondrial stress responses and survival strategies in cancer, and Ca^{2+} -related mitochondrial failure leading to cardiomyocyte death in cardiovascular diseases. Overall, the schematic emphasizes mitochondrial Ca^{2+} imbalance as a common mechanism that drives inflammation and tissue dysfunction.

ROS-induced oxidative damage exacerbates mitochondrial dysfunction, creating a harmful feedback loop. Beyond causing injury, mtROS act as signaling molecules regulating cell migration, invasiveness, proliferation, and gene transcription [54].

Examples of association between oncogenes activation and mtROS in the signaling cascade outlined above are given by H-RAS and K-RAS [112,113]; an increase in mitochondrial activity driven by significant alterations in mitochondrial membrane potential and Ca^{2+} has been described during oncogenic transformation, with the concomitant increase in ROS production. This enhanced mitochondrial function cannot be maintained throughout all stages of tumor development [113]. Excessive mtROS can harm the organelle itself, amplifying mitochondrial-related oncogenic stress. To cope with this, cancer cells initiate mitochondrial stress response mechanisms like mitophagy and the mitochondrial unfolded protein response (mtUPR), which help restore mitochondrial function and

enhance cell survival and resistance to environmental stressors. mtROS generated by cancer cells act as signaling molecules within the tumor microenvironment, influencing nearby cancer-associated cells (i.e., fibroblasts) and infiltrating immune cells [114,115].

In the tumor microenvironment, hypoxia plays a central role in driving cancer progression and chronic inflammation. Both chronic and intermittent (cycling) hypoxia led to the stabilization of hypoxia-inducible factor 1- α (HIF-1 α), a key transcription factor that orchestrates the cellular response to low oxygen levels. In colorectal cancer cells this happens through the activation of the OMA1-OPA1 signaling axis, which boosts mtROS production [116]. This stabilization promotes the transcription of genes that support tumor survival, such as those involved in glycolysis and angiogenesis, creating an acidic and nutrient-deprived environment that paradoxically favors cancer cell adaptation and proliferation. One of the major molecular consequences of hypoxia is its interplay with intracellular Ca^{2+} signaling. Under hypoxic stress, intracellular Ca^{2+} levels rise, often due to altered activity of Ca^{2+} channels and transporters [117–119]. This activates Ca^{2+} /calmodulin-dependent protein kinase II (CaMK2) [120], which in turn stimulates the IKK complex, leading to the activation of the transcription factor NF- κ B. Notably, this pathway can be triggered independently of the classical I κ B degradation route, underscoring Ca^{2+} a direct role in modulating inflammatory responses in hypoxic cancer cells. The activation of NF- κ B under these conditions leads to the production of a range of pro-inflammatory cytokines, such as TNF- α and IL-1 β , and enzymes, including COX-2 [121]. Furthermore, HIF-1 α can enhance the expression of Ca^{2+} -effectors, such as TRPC1 and STIM1, reinforcing Ca^{2+} entry into the cell and thus further stabilizing HIF-1 α in a self-perpetuating loop [117]. This mutual reinforcement between Ca^{2+} signaling and HIF-1 α enhances the transcription of pro-inflammatory genes, thereby contributing to a sustained inflammatory state in the tumor environment. So far, we have seen how intracellular (and mitochondrial) Ca^{2+} increase is predominantly associated to inflammation; by contrast, aged macrophages usually encounter a shift toward the pro-inflammatory phenotype due to a reduced expression of MCU, increasing production of cytokines like IL-6 and TNF- α . This age-related decline in mitochondrial Ca^{2+} impairs oxidative phosphorylation and increases reliance on glycolysis, a metabolic switch associated with inflammation [122]. Thus, for some reasons, Ca^{2+} signaling can be exploited in different ways to achieve a mitochondrial-dependent inflammatory phenotype.

Moreover, cancer cells frequently co-opt mitochondrial quality control mechanisms to survive stress and maintain chronic inflammation [123]. For example, in certain tumors, mitophagy is elicited to allow tumor progression and chemoresistance [124,125]. A mitochondrial protease, LonP1, which is involved in mitophagy, is often upregulated in cancer cells. LonP1, beyond its proteolytic role, contributes to resistance against chemotherapeutic agents like cisplatin by modulating mitochondrial Ca^{2+} handling and promoting retrograde pro-inflammatory signaling. Specifically, LonP1 can activate the mitochondrial NCLX, leading to the release of Ca^{2+} into the cytoplasm. Elevated cytosolic Ca^{2+} level activates kinases, like PYK2 and SRC, which culminate in the nuclear translocation of STAT3, a transcription factor well-known for its dual role in promoting survival and driving inflammation in the tumor microenvironment. This signaling not only upregulates anti-apoptotic proteins such as Bcl-2 but also stimulates the secretion of IL-6, reinforcing an autocrine and paracrine loop that sustains inflammation and tumor growth [126].

In breast cancer, the loss of ULK1, a key mitophagy regulator, leads to impaired clearance of dysfunctional mitochondria and increased mtROS, which activates NLRP3 inflammasome, promoting secretion of IL-1 β and IL-6 and fostering bone metastasis [127]. Along similar lines, promyelocytic leukemia protein (PML) may localize at ER-mitochondria contact sites, where it forms

a trimeric complex with NLRP3 and the P2X7 receptor, thereby further modulating inflammasome activation and shaping the tumor microenvironment [128]. Pharmacological targeting of mtROS (e.g. using silibinin) reduces ROS generation and NLRP3 activation, thereby suppressing inflammatory signaling and breast cancer cell migration [129,130].

The mitochondria-inflammatory signaling loop extends to the tumor microenvironment. Tumor-derived mtDAMPs can activate surrounding immune cells, particularly macrophages, and skew them toward an M2-like phenotype, commonly referred to as tumor-associated macrophages (TAMs). These macrophages, in response to signals like succinate or IL-6, suppress cytotoxic T cell responses and secrete additional pro-tumoral factors, effectively transforming inflammation into a tool for immune escape and metastasis [131]. This especially happens in those cells with suppressed succinate dehydrogenase (SDH) activity translating in elevated levels of succinate in the serum of lung cancer patients and associated with increased expression of the succinate receptor SUCNR1 on TAMs [131]. Upon binding to SUCNR1, succinate triggers intracellular Ca^{2+} signaling through G-protein-coupled mechanisms. Although the study does not measure intracellular Ca^{2+} levels directly, the known signaling mechanisms of SUCNR1 strongly imply a role for Ca^{2+} in regulating downstream responses. This metabolite-induced inflammatory signaling has been shown to enhance endothelial cell activation and contribute to a feed-forward loop of vascular remodeling and metastatic dissemination [131].

Mitochondrial stress (e.g., after TFAM knockdown) leads to mtDNA leakage and cGAS-STING activation, triggering phosphorylation of TBK1, IRF3, and STING, with increased dendritic cell activation and antitumor immunity in lung carcinoma models [132]. STING antagonists can reverse these effects and promote metastasis [133,134]. Similarly, Raddeanin A enhances mtDNA release and activates cGAS-STING and NF- κ B pathways, increasing cytokine secretion and tumor immunogenicity. Conversely, in regulatory T cells, inhibition of FABP5 causes mitochondrial dysfunction and mtDNA release, which activates cGAS-STING and type I IFNs, paradoxically supporting immune suppression [135].

Interestingly, the E3 ligase TRIM21 limits mtDNA release by promoting VDAC2 degradation; its loss enhances cGAS-STING activation and improves CD8⁺ T cell responses after radiotherapy [136]. On the other hand, senescent tumor cells release mtDNA via extracellular vesicles (EVs) that are taken up by neutrophils and polymorphonuclear myeloid-derived suppressor cells, activating the cGAS-STING-NF- κ B-PERK axis and enhancing their immunosuppressive function [137]. This duality exemplifies the context-dependent outcomes of cGAS-STING signaling in tumors.

Given this intricate crosstalk, therapeutic strategies that target mitochondrial function (including Ca^{2+} signaling) and inflammation are being actively explored. Recent research shows how the loss of isoform VDAC2, a key OMM protein involved in metabolite transport and apoptosis regulation, can trigger profound mitochondrial dysfunction and mito-inflammation that selectively destroys tumor cells [138]. The study demonstrates that knocking down VDAC2 in cancer cells disrupts mitochondrial integrity and bioenergetics, leading to the release of mtDAMPs, which activate innate immune pathways and inflammasomes within the tumor microenvironment. This mitochondrial stress-induced inflammation recruits and activates immune effector cells, promoting an anti-tumor immune response that not only causes direct cancer cell death but also reprograms the tumor microenvironment to support sustained tumor clearance. Importantly, VDAC2 loss was shown to synergize with immunotherapies, enhancing their efficacy by overcoming immune suppression commonly observed in tumors [138].

Inflammation and mitochondria in respiratory diseases

Respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), acute respiratory distress syndrome (ARDS), idiopathic pulmonary fibrosis (IPF) and pneumonia, despite their heterogeneous clinical presentations, share two fundamental pathogenic mechanisms: chronic inflammation and mitochondrial dysfunction. These two processes are closely interrelated and mutually reinforcing, establishing a vicious cycle that drives persistent tissue injury and disease progression [30,139–142]. Mitochondrial dysfunction in epithelial, immune and structural lung cells triggers the release of mtDAMPs, which activate PRRs and inflammasomes, amplifying pro-inflammatory signaling cascades. The resulting inflammatory mediator secretion shapes disease-specific immune signatures, as seen in asthma, where Th2-driven inflammation promotes mucus hypersecretion and airway remodeling [143,144], or in COPD, where neutrophilic and macrophage-mediated inflammation leads to alveolar destruction [145,146].

In COPD, mitochondrial dysfunction is characterized by reduced mitochondrial density and mtDNA content in both airway epithelial cells and skeletal muscle, contributing to impaired bioenergetics and diminished functional capacity [147,148]. Environmental factors such as cigarette smoke (CS) and fine particulate matter (PM_{2.5}) exacerbate mitochondrial injury by increasing oxidative stress and impairing mitophagy [149–152]. The pathological relevance of defective mitophagy is illustrated by evidence that Pink1-deficient mice are protected from CS-induced emphysema [152], and that decreased Parkin levels in skeletal muscle contribute to muscle wasting in COPD patients [153]. Mitochondrial quality control disruption, similar to that observed in CF, IPF and ARDS, links mitophagy failure with persistent inflammation and tissue damage [8,154–156]. In COPD, CS-induced bronchial epithelial cell-derived EVs carry microRNAs such as miR-210 and miR-21 that suppress autophagy and promote fibrosis through pVHL/HIF-1-dependent mechanisms [157–160]. CS-conditioned lung epithelial cell-derived EVs also modulate macrophage activation and polarization [161,162], and CS-conditioned macrophages release EVs with gelatinolytic and collagenolytic activities enriched in matrix metalloproteinase (MMP)-14, contributing to extracellular matrix degradation and emphysema development [163,164]. Notably, the abundance and content of EVs correlate with disease severity in COPD [165]. Circulating mitochondrial components, particularly mtDNA, reflect disease severity and represent potential biomarkers of mitochondrial stress [166–169]. Therapeutically, mitochondria-targeted antioxidants such as MitoQ, MitoE and Mito-TEMPO effectively reduce mtROS and restore mitochondrial integrity in experimental models [170–173]. Clinical studies indicate that MitoQ may improve vascular function in COPD patients [171] (clinical trials NCT05605548; NCT02966665).

In IPF, a disease closely associated with aging, mitochondria exhibit increased size, cristae disruption and mtDNA mutations, all hallmarks of senescence-associated mitochondrial dysfunction in alveolar epithelial cells, fibroblasts and macrophages [174–176]. This phenotype is accompanied by elevated expression of the cyclin-dependent kinase inhibitor CDKN2A, which correlates with disease severity [177] and by downregulation of PINK1 and Parkin, leading to defective mitophagy [154,155,178]. Mitochondrial dysfunction in IPF enhances TGF- β signaling, promoting fibroblast-to-myofibroblast transition and extracellular matrix deposition [179]. This process can be modulated by pirfenidone, which improves mitochondrial quality through PDGFR–PI3K–AKT activation and Parkin stabilization [180]. Circulating mtDNA in IPF not only reflects mitochondrial distress but also serves as a biomarker of fibrotic burden [169,181].

Asthma is also characterized by alterations in mitochondrial dynamics. Drp1 upregulation, induced by CS, drives mitochondrial fragmentation in airway cells [161]. Elevated mtROS in airway smooth

muscle cells lead to increased cytokine production, contributing to airway hyperreactivity and remodeling, while allergen exposure induces mitochondrial biogenesis and structural disorganization in airway epithelial cells [182–184]. Extracellular mitochondrial ATP activates dendritic cells and promotes Th2-type immune responses, an effect reversible with apyrase or P2 receptor antagonists [185]. Therapeutic interventions such as mesenchymal stem cell (MSC)-based mitochondrial transfer have shown efficacy in restoring mitochondrial function and reducing airway hyperresponsiveness in experimental models [186].

In CF, mitochondrial defects extend beyond CFTR dysfunction. Deficiency in mitochondrial complex I enhances NADPH oxidase activity and oxidative stress, leading to glutathione depletion and impaired energy homeostasis [187–189]. Mitochondrial impairment also interferes with the mtUPR and mitophagy, sustaining chronic inflammation. Disturbed Ca^{2+} signaling between the endoplasmic reticulum and mitochondria further enhances mitochondrial Ca^{2+} uptake via the mitochondrial calcium uniporter (MCU), activating the NLRP3 inflammasome and promoting IL-1 β and IL-18 secretion [190–193]. Pharmacologic MCU inhibition restores autophagy and immune function in CF models, highlighting MCU as a promising target to modulate inflammation [194]. Moreover, in CF as well as in COPD, macrophages exhibit impaired polarization and autophagy, reducing their capacity to clear pathogens and thereby sustaining inflammation [195–198] (Figure 3).

In ARDS, mitochondrial dysfunction is primarily linked to oxidative stress and activation of the NLRP3 inflammasome and NF- κ B signaling pathways, which together compromise mitochondrial ATP production. This leads to epithelial and endothelial barrier disruption, alveolar edema, and impaired gas exchange. Similar to other respiratory diseases, defective mitophagy contributes to ongoing inflammation and lung injury [8,154–156]. Application of MSC-based therapies in ARDS improves mitochondrial bioenergetics, reduces inflammation and enhances epithelial barrier integrity [99,199,200].

In pneumonia, particularly in pneumococcal pneumonia, the bacterial toxin pneumolysin induces mitochondrial Ca^{2+} overload, opening of the mitochondrial permeability transition pore (mPTP), and ATP depletion, thereby promoting the release of mtDNA-enriched EVs that amplify the inflammatory response [201,202]. When internalized by neutrophils, these EVs impair ROS production and antimicrobial functions [203]. Conversely, MSC-derived EVs can restore macrophage mitochondrial metabolism and reduce lung inflammation, although those derived from emphysematous donors are less effective [204]. The accumulation of extracellular mtDNA not only reflects mitochondrial distress but also acts as an mtDAMP, promoting inflammation and serving as a biomarker of fibrotic burden [169,181]. Excessive alcohol exposure further impairs mitochondrial homeostasis by promoting the release of mtDNA-rich EVs, which compromise alveolar epithelial integrity and macrophage responses, thereby increasing susceptibility to respiratory infections [205].

Across these respiratory diseases, mitochondrial signaling emerges as a central regulator of immune function and inflammation. Damaged airway epithelial cells release mtDNA and N-formyl peptides that activate STING and NF- κ B pathways in immune cells, amplifying inflammation [141]. The failure of conventional antioxidant therapies in clinical trials [206,207] has spurred growing interest in mitochondria-based therapeutic approaches aimed at restoring cellular bioenergetics and resolving chronic inflammation [208–210]. MSC-derived CD44⁺ EVs containing functional mitochondria enhance macrophage phagocytosis and promote anti-inflammatory M2 polarization [199,200], while mitochondria-targeted small molecules such as MitoQ, MitoE and Mito-TEMPO effectively reduce mtROS and restore mitochondrial integrity [170–173]. Collectively, these findings reinforce that mitochondrial dysfunction is not merely a secondary consequence of chronic inflammation but a

fundamental driver of respiratory disease pathogenesis, offering a promising strategic target for therapeutic intervention.

Inflammation and mitochondria in neurodegenerative diseases

Neurodegenerative diseases, which include Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS), are characterized by progressive neuronal loss and are increasingly recognized as disorders of chronic inflammation and mitochondrial dysfunction. In recent years, a growing body of evidence has linked mitochondrial damage to aberrant activation of innate immune responses, underscoring the crucial interplay between metabolic impairment and inflammation in neurodegeneration. Mitochondrial dysfunction and impaired mitophagy act both as a trigger and amplifier of neuroinflammation [211,212].

In AD, mitochondrial impairment is an early and prominent feature, with reduced respiratory chain activity, abnormal mitochondrial dynamics and Ca^{2+} -overload observed in affected neurons [213]. Damaged mitochondria release mtDNA and mtROS, which contribute to microglial activation and NLRP3 inflammasome assembly [214,215]. The resulting secretion of pro-inflammatory cytokines, such as IL-1 β and IL-18, exacerbates synaptic dysfunction and neuronal loss. Moreover, defective mitophagy further amplifies neuroinflammation by allowing the accumulation of dysfunctional organelles [216] (Figure 3). Furthermore, complementary evidence from human studies has shown that mitophagy biomarkers are reduced in the serum of patients with AD and mild cognitive impairment [217]. This systemic reduction in mitochondrial quality control markers may reflect an impaired ability to clear damaged mitochondria, contributing to neurodegenerative cascades. Such findings support the hypothesis that compromised mitophagy is not only a hallmark of AD but may be part of a shared mitochondrial vulnerability across several neurodegenerative diseases. Intriguingly, experiments in AD mouse models have shown that systemic administration of freshly isolated human mitochondria enhances cognitive performance within just two weeks, while reducing neuronal degeneration and gliosis in the hippocampus. These beneficial effects were associated with the restoration of mitochondrial respiratory function, as indicated by normalized activity of citrate synthase and cytochrome c oxidase [218] (Figure 3).

Notably, amyloid- β (A β) and tau proteins are the primary contributors to cell damage and death in AD. At the same time, they represent a main cause of mitochondrial impairment. A β accumulation induces oxidative stress and enhances mitochondrial production of ROS, which in turn exacerbates mitochondrial damage. Elevated ROS levels further promote the pathological aggregation of tau [219]. Moreover, both A β and tau disrupt mitochondrial trafficking to and from synaptic terminals and promote excessive mitochondrial fission, ultimately contributing to synaptic impairment and neurodegeneration [220]. One study addresses how MICU3, a regulatory subunit of the mitochondrial calcium uniporter complex influences pathology in a mouse model of cerebral amyloid. In the transgenic Tg-SwDI mouse line MICU3 expression was found to decline in cortex and hippocampus with age. Over-expression of MICU3 via AAV9 (AAV-MICU3) led to improved cerebral blood flow, behavioral performance and reduced vessel- and parenchymal A β burden. Importantly, neuronal death in cortex/hippocampus was markedly reduced and activation of glial cells (microglia, astrocytes) and neuroinflammatory markers were attenuated. Mechanistically, MICU3 over-expression rescued mitochondrial dysfunction: it reduced oxidative stress, restored mitochondrial membrane potential, elevated ATP production and mitochondrial DNA copy number and improved overall mitochondrial morphology. In vitro experiments further revealed that the protective effects of MICU3 (on neurons, glia, oxidative stress) required PINK1, as knockdown of PINK1 abolished

MICU3's benefits; co-immunoprecipitation confirmed a MICU3-PINK1 interaction. Thus, the MICU3-PINK1 axis appears central to preserving mitochondrial homeostasis, limiting A β -driven neurovascular and neuroinflammatory damage [221].

In PD, mitochondrial complex I deficiency and mutations in genes regulating mitochondrial quality control, including *PINK1* and *Parkin*, lead to accumulation of depolarized mitochondria and elevated mtROS production. This triggers microglial activation and chronic inflammation within substantia nigra. Furthermore, *Parkin* has been also found to regulate the activation of the inflammasome NLRP3 [222]. Consistently, *Parkin* loss determines microglial NLRP3 accumulation and neuronal damage and loss. In line with this evidence, a recent study demonstrated that the cytosolic DNA sensor cGAS, through activation of the cGAS–STING pathway in microglia, amplifies neuroinflammation and dopaminergic neurodegeneration in neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced models of PD, highlighting this axis as a potential therapeutic target [223]. For what concern PINK1-dependent mitophagy in astrocytes, HK2 is a critical regulator [224]. Astrocytes exhibit more rapid and broadly-distributed mitophagy upon mitochondrial damage compared to neurons, as indicated by faster *Parkin* translocation and phosphorylated ubiquitin formation. HK2 is highly expressed in astrocytes and following mitochondrial stress a glucose-dependent complex forms between HK2 and PINK1. Knockdown of HK2 or disruption of its mitochondrial localization strongly impairs PINK1 stabilization, ubiquitin phosphorylation and subsequent mitolysosome formation. Importantly, when astrocytes are exposed to inflammatory stimuli (e.g., TNF- α /IL-1 α /C1q), the HK2–PINK1 axis becomes up-regulated, enhancing mitophagy and reducing neurotoxic outcomes in neuron–astrocyte co-culture models and in vivo. Loss of HK2 or PINK1 markedly increases neuronal death in the inflammatory context [224].

Given that mitochondria are source of mtDAMPs, it is plausible that mtDNA released from stressed or degenerating dopaminergic neurons contributes to the activation of the cGAS–STING pathway in microglia, thereby linking mitochondrial dysfunction with innate immune activation and neurodegeneration in PD. Both genetic ablation and pharmacological inhibition of cGAS conferred neuroprotection by suppressing antiviral inflammatory signaling, highlighting cGAS as a potential therapeutic target in PD [223]. Similarly, pharmacological inhibition of the STING pathway or restoration of mitophagy has been shown to ameliorate neuroinflammation and neuronal death in preclinical models of PD [225], highlighting the therapeutic potential of targeting mitochondria-mediated inflammation.

Direct mitochondrial delivery in mice was able to attenuate PD progression, with biodistribution analyses revealing that transplanted organelles can reach not only the brain but also peripheral tissues including liver, kidney, muscle and heart [226]. Beyond direct injection, intercellular transfer of mitochondria has emerged as an additional mechanism of protection. Scheiblich and colleagues demonstrated that microglia are capable of exchanging mitochondria through tunneling nanotubes, a process that concurrently reduces intracellular α -synuclein aggregates and dampens inflammatory responses [214]. Eo et al. reported that intravenous administration of mitochondria derived from MSCs protected dopaminergic neurons in a PD mouse model, while also decreasing microglial activation and pro-inflammatory cytokine release in the striatum, ultimately translating into improved behavioral outcomes [227]. Similarly, Jain et al. explored the use of exercise-induced liver mitochondria, highlighting that these organelles display enhanced respiratory activity compared to sedentary counterparts [228]. When transplanted into PD mice, exercise-primed mitochondria provided superior protection against dopaminergic neurodegeneration, with F-actin-dependent uptake mechanisms identified as critical for their incorporation into recipient cells [228]. Together, these

findings suggest that mitochondrial transplantation and transfer strategies represent a rapidly evolving frontier in the search for disease-modifying therapies in AD, PD and related neurodegenerative conditions.

ALS is another neurodegenerative disorder characterized by prominent mitochondrial abnormalities and neuroinflammation. In motor neurons from ALS patients and mouse models, mitochondrial fragmentation, reduced ATP production, and increased oxidative stress are common features. Mislocalized TDP-43 and mutant SOD1, hallmarks of ALS pathology [229], have been shown to accumulate at mitochondria, interfering with their function [230] and promoting NLRP3 inflammasome activation in glial cells [231]. This interplay leads to the release of IL-1 β and IL-6, reinforcing a feedforward loop of neuroinflammation and neurodegeneration.

Given the central role of mitochondrial dysfunction in ALS, recent evidence indicates that impaired mitophagy may contribute significantly to disease progression by allowing the accumulation of damaged mitochondria, thereby enhancing oxidative stress, energy failure, and inflammation [232]. Emerging evidence further implicates impaired autophagy in ALS pathogenesis. Autophagosome accumulation and inefficient cargo degradation are consistently detected in patient tissues, suggesting defective autophagic flux [233,234]. Familial ALS models expressing mutant SOD1 exhibit autophagy impairment due to aberrant interaction with BECN1, a key regulator of autophagosome formation [235]. Moreover, mutations in *SQSTM1/p62*, a selective autophagy receptor, have been identified in ALS patients and may contribute to disease susceptibility and onset [236]. Functional studies confirm that disruption of autophagy-related genes exacerbates motor neuron degeneration: the conditional deletion of *Atg5* or *Atg7* in motor neurons results in pathological protein aggregation and progressive motor dysfunction [237,238].

In MS, a demyelinating disorder with both autoimmune and neurodegenerative components, mitochondrial dysfunction contributes significantly to neuroaxonal injury. Oxidative stress generated by dysfunctional mitochondria exacerbates demyelination and impairs axonal transport. Recent findings reveal that inflammatory conditions impair oligodendrocyte differentiation by disrupting mitochondrial function, including altered mitochondrial Ca²⁺-uptake, reduced membrane potential, decreased complex I activity and elevated ROS levels. This mitochondrial dysfunction, along with AMPK activation, contributes to a metabolic reprogramming that stalls oligodendrocytes in an undifferentiated state, suggesting that inflammatory cytokines may hinder remyelination in MS through mitochondrial and metabolic dysregulation [239]. Moreover, mtDNA levels are elevated in the cerebrospinal fluid of MS patients and correlate with disease severity [240], further supporting a role for mitochondria-induced inflammation. Elevated levels of markers related to mitochondrial functioning (mainly mitophagy process) in the cerebrospinal fluid and serum of MS patients have been observed, suggesting a persistent activation of these degradative pathways in response to mitochondrial stress [241,242]. This altered autophagic response may initially act as a compensatory mechanism; however, its chronic dysregulation ultimately impairs mitochondrial clearance and exacerbates neuroinflammation. Supporting this view, recent *in vitro* studies and animal models of MS have demonstrated that enhanced mitophagy is associated with demyelination and inflammatory processes [216]. Interestingly, the same study revealed that antipsychotic drugs, frequently prescribed off-label to MS patients for symptom management, may inhibit autophagy and mitophagy both *in vitro* and *in vivo*, exacerbating mitochondrial dysfunction and inflammation [241]. Other evidence confirms that impaired mitophagy plays a central role in MS. One of the key regulators of this process is CLEC16A, a gene previously linked to autoimmune susceptibility. In-depth genetic and neuropathological studies have revealed that specific CLEC16A polymorphisms are significantly

associated with increased MS risk [243,244] and with the presence of chronic active lesions in the central nervous system, pointing to its involvement in sustaining inflammatory activity and lesion progression. A recent work further investigates the specific role of CLEC16A. Astrocyte-specific loss of CLEC16A exacerbates neuroinflammation and demyelination in an MS mouse model and corresponds with mitophagic deficits in human MS plaques, highlighting CLEC16A as a novel therapeutic target [245].

Inflammation and mitochondria in gastric-colon diseases

Disruption of intestinal epithelial cell (IEC) homeostasis is a hallmark of inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD) and colorectal cancer (CRC) [246]. IBD pathogenesis is multifactorial, involving genetic predisposition, immune dysregulation, environmental influences, and alterations in the gut microbiome [247]. These interplaying factors contribute to chronic immune activation, predominantly involving CD4⁺ T cells, macrophages and neutrophils, which perpetuates tissue damage and barrier dysfunction [248]. A growing body of literature has positioned mitochondrial dysfunction as a central contributor to both IBD pathogenesis and the development of colitis-associated CRC. Mitochondria are essential for maintaining intestinal barrier integrity, regulating immune responses, and fueling the high metabolic demands of epithelial renewal. Their impairment initiates a cascade of events, ranging from bioenergetic failure and ROS overproduction to the release of pro-inflammatory mtDAMPs, that drive mucosal inflammation and epithelial damage [249] (Figure 3).

Metabolomic analyses of inflamed IBD tissues reveal disturbances in core mitochondrial pathways, including fatty acid β -oxidation, TCA cycle activity and amino acid metabolism [250]. Transcriptomic profiling in pediatric UC shows significant downregulation of genes encoding mitochondrial components, including all 13 mtDNA-encoded subunits of the OXPHOS system [251,252]. Notably, CD patients with milder disease and protective genotypes display enhanced mitochondrial gene expression signatures [253], suggesting that mitochondrial competence may modulate disease severity. Proteomic studies corroborate these findings, reporting decreased levels of proteins involved in mitochondrial energetics, ETC function, redox balance and stress response pathways in IBD mucosa [254,255] (Figure 3). Ultrastructural analyses consistently demonstrate mitochondrial abnormalities, including swollen organelles, disrupted cristae and altered fission-fusion dynamics in IECs of IBD patients [256–258]. Pharmacologic inhibition of mitochondrial fission, using P110, reduces inflammation and preserves epithelial structure in murine colitis [259]. Genetic studies further support the role of mitochondria in IBD. Approximately 5% of genes proximal to IBD-associated loci are linked to mitochondrial processes, such as iron metabolism, ROS regulation, protein ubiquitination and mtUPR [260,261]. Variants in mitophagy-related genes, like ATG16L1, IRGM and LRRK2, impair mitochondrial quality control, resulting in accumulation of dysfunctional mitochondria and excessive mtROS production [262–264]. The mtROS regulation is particularly relevant in IBD. While low levels of ROS maintain intestinal stem cell (ISC) function and antimicrobial responses [265,266], excessive ROS disrupt barrier function, induce IEC apoptosis, and perpetuate mucosal inflammation [267,268].

Direct evidence for mitochondrial dysfunction as a driver rather than consequence of intestinal inflammation comes from mouse models with IEC-specific deletions of key mitochondrial genes. Loss of Prohibitin-1 (Phb1), a mitochondrial membrane protein, induces crypt apoptosis, Paneth cell loss and spontaneous ileitis, which may be reversed by ROS scavenging [269]. Reduced STARD7 expression, a phosphatidylcholine transfer protein, in ulcerative colitis impairs mitochondrial

function, decreased tight junction protein levels compromising barrier integrity. This could be restored by AMPK activation [270]. Similar phenotypes are observed with deletion of autophagy genes *Atg16l1*, *Atg5* or *Atg7*, which impair mitophagy and lead to accumulation of damaged mitochondria, impaired energy metabolism, crypt cell loss and heightened sensitivity to colitis [271]. Defective autophagy in intestinal antigen-presenting cells and epithelial cells resulted in mtROS production and inflammasome activation, enhancing intestinal inflammation, T helper 17 cell responses and susceptibility to DSS-induced colitis [272] [273]. Although the release of some cytokines, NLRP3 may also participate in epithelial regeneration in specific contexts, suggesting that the inflammasome, in gastro-intestinal apparatus, may have dual and controversial roles [274].

Pro-inflammatory cytokine TNF α and IL-1 β , upregulated in IBD, target mitochondria to inhibit ETC complex I and increase mtROS production in intestinal cell culture models [275,276]. Anti-TNF α therapy, a breakthrough in IBD, has demonstrated protective effects against mitochondrial dysfunction in various tissues, including the intestine [277,278], suggesting that its benefits extend beyond immunomodulation to preservation of mitochondrial health [277].

Alternative mitochondrial-based therapies are emerging, such as MitoQ and MitoTEMPO, mitochondrially-antioxidants that attenuate experimental colitis and preserving epithelial integrity by scavenging mtROS, while VBIT-12, interacting with VDAC, prevents VDAC-oligomerization and subsequent mtDAMPs release [260,279,280]. Some agents have progressed to clinical trials for UC (NCT04276740, NCT05539625), highlighting the translational relevance of modulating mitochondrial redox balance to prevent the mitochondrial membrane permeabilization. Koumine, a natural anti-inflammatory alkaloid, acts in the context of intestinal inflammation induced by Citrinin (CTN), a mycotoxin. CTN exposure in mice and intestinal epithelial cells triggers activation of the IP3R1–GRP75–VDAC1 ER-mitochondria tethering complex, leading to mitochondrial Ca²⁺ overload, increased mtROS and subsequent pyroptosis (inflammatory programmed cell-death) of intestinal epithelial cells. Treatment with Koumine significantly attenuated CTN-induced intestinal damage. Mechanistically, it down-regulated the expression or activation of the IP3R1–GRP75–VDAC1 complex, thereby decreasing mitochondrial Ca²⁺ uptake [281].

The transcriptional coactivator PGC-1 α plays a pivotal role in regulating mitochondrial biogenesis and antioxidant defenses. Its expression is markedly reduced in both IBD patients and mouse models, correlating with reduced mitochondrial mass, elevated mtROS and impaired energy production [282,283]. Therapeutic strategies to enhance PGC-1 α activity, such as the use of rosiglitazone, improve mitochondrial function and suppress colitis [284]. Conventional IBD therapies, such as mesalamine, may also exert mitochondrial effects, including ROS scavenging and PGC1 α activation [285]. Phytochemicals, like oleuropein, activate the NRF2/HO-1 pathway, reducing inflammation and oxidative stress in experimental colitis [286], and NRF2-deficient mice exhibit severe disease, further supporting NRF2 as a mitochondrial stress-responsive pathway with therapeutic value [287]. Perturbations in NAD⁺ metabolism further link mitochondrial health to IBD pathogenesis. NAD⁺ depletion in IBD impairs mitochondrial biogenesis through downregulation of the SIRT1-PGC1 α axis, exacerbating epithelial dysfunction [252,288]. Supplementation with NAD⁺ precursors, such as nicotinamide riboside, restored mitochondrial function and ameliorated colitis in preclinical models [252]. However, the effects of NAD⁺ are cell-type dependent: while epithelial cells benefit from NAD⁺ restoration, reduced NAD⁺ levels in immune cells may dampen inflammation by altering T cell polarization [289]. These observations emphasize the need for targeted approaches that consider the cellular context of NAD⁺ modulation.

Paneth cells and goblet cells, specialized IECs with high metabolic demands, are particularly vulnerable to mitochondrial damage. This leads to defective antimicrobial peptide secretion, which compromises the mucosal protection and predispose to microbial translocation, sustaining the inflammation [290]. In CD, Paneth cell mitochondrial abnormalities, including swelling and cristae disruption, correlate with disease severity and recurrence risk [291,292].

Mitochondrial dysfunction also reshapes cellular metabolism in the inflamed gut. IECs undergoing inflammation switch from oxidative phosphorylation to glycolysis, increasing oxygen levels in the lumen and favoring the expansion of facultative anaerobes, such as *Enterobacteriaceae*, which are implicated in dysbiosis [293,294]. In parallel, microbial products (e.g., hydrogen sulfide and nitric oxide) inhibit mitochondrial respiration; while the decline in butyrate-producing bacteria, and thus in short-chain fatty acid availability, deprives colonocytes of their primary energy source, further destabilizing mitochondrial metabolism [295,296].

Beyond inflammation, mitochondrial impairment contributes to the oncogenic transformation of the intestinal epithelium. CRC commonly develops through genetic mutations along two principal pathways: the APC-KRAS-p53 pathway or the BRAF-MLH1 hypermethylation and microsatellite instability pathway. IBD is a known risk factor for CRC, with disease duration, severity, and extent contributing to cancer development [297,298]. In CRC tissues, mitophagy regulators are downregulated resulting dysfunctional mitochondria accumulation, excessive ROS, cytokine release and tumor-promoting inflammation [299,300]. TRAP1, a mitochondrial chaperone, is upregulated during UC-associated CRC progression, driving tumorigenesis via mitochondrial fragmentation and enhanced glycolysis [301,302] (Figure 3). Additionally, elevated levels of circulating and fecal mtDNA have been found in active UC and CD patients, suggesting that mitochondrial stress markers could be a potential biomarkers for disease monitoring and CRC risk stratification [303].

Mitochondrial dysfunction is not limited to IBD but also contributes to gastrointestinal motility disorders. In mitochondrial neurogastrointestinal encephalomyopathy, systemic mitochondrial defects result in chronic intestinal pseudo-obstruction through smooth muscle atrophy, cytochrome c oxidase deficiency, and mtDNA depletion [304–306]. Interstitial cells of Cajal, essential for gut motility, are likewise affected due to their high mitochondrial requirements [307]. Interestingly, mtDNA polymorphisms have been associated with functional disorders such as irritable bowel syndrome (IBS), suggesting that mitochondrial vulnerability spans rare monogenic syndromes and common multifactorial conditions [308].

Collectively, this extensive body of evidence highlights mitochondrial dysfunction as both a key pathogenic mechanism and a promising therapeutic target in IBD and CRC. From genetic susceptibility and epithelial damage to dysbiosis and cancer evolution, mitochondria emerge as central regulators of intestinal health. Future research should aim to delineate cell-specific mitochondrial roles, develop reliable biomarkers of mitochondrial stress, and optimize mitochondria-targeted interventions for clinical application (Figure 4) (MARVEL trials: NCT04276740, NCT05539625) [252,284]. Tailoring these approaches to individual patient profiles, potentially through biomarker-guided trials like MUSIC (NCT04760964), could revolutionize treatment paradigms in gastrointestinal inflammatory and neoplastic diseases.

Inflammation and mitochondria in cardiovascular diseases

Etiologically, the cardiovascular diseases (CVDs) for which the role of inflammation is predominant are myocarditis, pericarditis and endocarditis. There, inflammation of the heart muscle, of the sac surrounding the heart or of the heart valves respectively, may lead to damage and weaken the heart's

ability to pump blood effectively [309]. However, inflammation can be a direct driver of several other diseases by accomplishing the progression of atherosclerosis, a process (and a pathology) which entails plaque buildup, largely composed of lipids that trigger a chronic inflammatory response [310]. The significant contribution of inflammation it has also been reported in some types of cardiomyopathies and to peripheral artery diseases [311]. One important point of contact between inflammation and cardiovascular pathology is the mitochondrion; on one hand, its activity contributes to cardiac contraction, on the other hand, an organelle whose activity can produce and release several biomolecules which activate mitochondria-mediated inflammatory pathways [312]. Also here, Ca^{2+} covers an important role, its alteration in the mitochondrial matrix triggers the release mtDAMPs into the cytosol or in the extracellular milieu amplifying inflammation [313].

Chronic inflammation of the heart muscle is mainly due to infectious and immune-mediated causes. Prevalence and incidence vary widely depending on population and diagnostic criteria with an estimated incidence of 10-20 cases per 100.000 people [314]. Myocarditis has become a widely discussed topic in the literature since the onset of the SARS-CoV-2 pandemic in 2020, due to its suspected association with the virus [315]. One of the most recent studies investigated the effects of viral infection on mitochondria and inflammation using a 3D organ-on-a-chip model [316]. This platform allowed researchers to simultaneously examine the interactions between cardiomyocytes, endothelial cells, and peripheral blood mononuclear cells (PBMCs). Following viral exposure in the presence of PBMCs, the authors observed a marked increase in inflammation, which led to cardiac dysfunction. Mitochondria appeared reduced in number, showed increased vacuolization and were associated with elevated levels of circulating cell-free mtDNA, presumably released by endothelial cells. This was accompanied by diminished intracellular Ca^{2+} transients, potentially contributing to impaired cardiac contractility [316]. The study also demonstrated that EVs derived from quiescent human endothelial cells, when administered along with PBMCs in the same model, reduced cytokine release and restored Ca^{2+} transients to normal levels. A concurrent reduction in mtDNA trafficking was also observed. Although the authors did not establish a direct link between mtDNA release, EV cargo and function, they attributed mitochondrial dysfunction to inflammation, in which cytokines triggered ROS production, increased mtDNA release, and cell death [316].

Similar disruptions in Ca^{2+} transients were observed in an *in vivo* model of viral myocarditis using a transgenic mouse strain containing the coxsackievirus B3 genome [317], as well as in a model of endotoxemia-mediated myocarditis [318], both showing delayed kinetics and impaired sarcomere relaxation.

Atherosclerosis is recognized as a chronic inflammatory condition characterized by the accumulation of lipids and is widely regarded as the leading cause of CVDs. The onset of atherosclerosis is associated with abnormal lipid levels in the blood, particularly elevated cholesterol [319]. However, its precise triggering mechanisms are complex and likely involve multiple, not yet fully understood, factors. Inflammation also plays a critical role in the progression of atherosclerosis [311], and this is at least partly linked to mitochondrial Ca^{2+} dysregulation and activation of the inflammasome.

Recently, the Journal of Clinical Investigation reported a gene expression study conducted in human endothelial cells with depleted MICU1 levels. The study revealed a significant upregulation of genes involved in inflammation-related pathways, including $\text{TNF}\alpha$, TLR, NOD-like receptor and JAK-STAT signaling. Additionally, cytokines and chemokines were found at increased levels following MICU1 suppression. These *in silico* findings were validated in both *in vitro* and *in vivo* models, where MICU1-silenced tissues showed increased expression of VCAM1, IL-6, and $\text{TNF}\alpha$ after LPS treatment compared to controls with normal MICU1 expression [320].

MICU1 functions as a gatekeeper of mitochondrial Ca^{2+} levels and influences ROS production through the downregulation of SIRT3 [320]. This, in turn, affects the acetylation status of SOD2, which increases, leading to a reduced function of this key scavenger enzyme. Overall, the data suggest that MICU1 plays a protective role in endothelial cells by preventing mitochondrial Ca^{2+} overload and suppressing basal inflammatory signaling. Its proper function contributes to the mitigation of atherosclerosis progression [320].

The inhibition of NLRP3 inflammasome has also shown protective effects against atherosclerosis. For instance, treatment with MCC950 significantly reduces atherosclerotic lesions in preclinical models [321]. An upstream event in inflammasome activation is mediated by mitochondrial Ca^{2+} , which is released from ER following the dissociation of hexokinase 2 (HK2) from VDAC. This Ca^{2+} overload promotes VDAC oligomerization, enabling the release of small mtDNA fragments that activate NLRP3, driving inflammation [322]. However, the specific stimuli that cause HK2 to dissociate from OMM remain to be clarified.

The ER-mitochondria interface, typically characterized by the interaction between IP3Rs and VDAC proteins to favor the inter-organelle Ca^{2+} exchange, has also been studied in the context of hyperhomocysteinemia, a known cardiovascular risk factor [323]. Hyperhomocysteinemia promotes pyroptosis and contributes to plaque formation during atherosclerosis. Elevated levels of circulating homocysteine induce ER stress and enhance ER-mitochondria contact sites, facilitating rapid Ca^{2+} transfer to mitochondria in macrophages. As a result, mitochondrial ROS production and mtDNA release are increased, ultimately leading to macrophage pyroptosis and amplified inflammation [323] (Figure 3). Furthermore, modulation of macrophage Ca^{2+} dynamics has been observed with a ketone body-enriched diet, which improves vascular health by maintaining mitochondrial integrity and controlling inflammation. Activation of the GPR109A receptor significantly increases intracellular Ca^{2+} and stabilizes ER-mitochondria Ca^{2+} flux, preventing mitochondrial Ca^{2+} overload. This, in turn, limits NLRP3 inflammasome activation, reduces pro-inflammatory M1 macrophage polarization, enhances cholesterol efflux, and ultimately diminishes lesion formation in ApoE^{-/-} mice [324].

While increased mitochondrial Ca^{2+} uptake is typically associated with the initiation of NLRP3-mediated inflammation, a study by Coon B. and colleagues highlighted a protective role for this process [325]. Specifically, they demonstrated that enhanced mitochondrial Ca^{2+} -uptake, induced by high laminar shear stress and ROS generation, triggers mitophagy which activates the MEKK-MEK5-ERK5 signaling pathway and promotes KLF2 expression. KLF2 is known for its anti-inflammatory properties and vascular protective effects. Conversely, inhibition of mitochondrial Ca^{2+} uptake, via MCU, impaired KLF2 expression and contributed to disease progression [325].

Extracellular ATP is also recognized as a trigger of inflammation and atherosclerosis [326]. In THP-1-derived macrophages, researchers investigated the role of ATP in activating inflammatory responses via the Transient Receptor Potential Ankyrin 1 (TRPA1) channel. Their findings showed that ATP stimulation significantly increased TRPA1 expression and activity, leading to elevated intracellular Ca^{2+} influx. This Ca^{2+} signaling cascade activated oxidative stress pathways and upregulated the expression of key pro-inflammatory cytokines, including IL-1 β and TNF- α , thereby exacerbating vascular inflammation and promoting plaque instability [327].

Ischemia-reperfusion (I/R) injury occurs when blood supply returns to the heart after a period of ischemia, paradoxically causing additional tissue damage. A central mechanism of this injury involves Ca^{2+} dysregulation. During ischemia, intracellular Ca^{2+} accumulates due to impaired ATP-dependent pumps and altered ion exchange. Upon reperfusion, the sudden influx of oxygen and restoration of pH exacerbate Ca^{2+} overload, especially within mitochondria [328,329]. This excessive

mitochondrial Ca^{2+} -uptake can trigger mPTP opening, leading to mitochondrial depolarization, ATP depletion, swelling and release of pro-apoptotic factors culminating in cell death [330,331] (Figure 3). This also has implications for inflammation. One of the mechanistic insights has been proposed few months ago in a rat model of I/R injury, where RNA-seq analysis on tissues revealed the overexpression of MICU3. It was found to interact with VDAC1, enhancing ER-mitochondria Ca^{2+} flux, as a result of transcriptional changes induced by circulating lactate during I/R and in charge of neutrophils population, promoting mitochondrial Ca^{2+} overload and inflammation [332]. Similar findings about mitochondrial Ca^{2+} contribution in inflammation were observed following the overexpression of Piezo1 in I/R. Increased Piezo1 expression led to enhanced extracellular Ca^{2+} influx in cardiomyocytes, triggering calpain activation and mitochondrial damage. This cascade resulted in elevated ROS production and inflammation [333].

The maintenance of proper cristae architecture is essential for mitochondrial function, including its role in mitochondria-mediated inflammatory pathways. Mitofilin, a key component of IMM, has been identified as critical in preserving cristae structure [334]; in fact, complete knockout of Mitofilin *in vivo* is lethal. Its depletion has been studied in an *in vivo* model of I/R, where it was found to cause mitochondrial fragmentation and increased sensitivity to mPTP opening, following mitochondrial Ca^{2+} overload. This led to excessive ROS production and mtDNA release into the cytosol during reperfusion, responsible for exacerbating the inflammatory response [335].

Cardiomyopathies (CM) are a group of diseases leading to impaired cardiac function and potentially life-threatening complications. They are classified into several main types characterized by different macroscopic maladaptive remodeling of the heart. Causes can be genetic or acquired, including viral infections, metabolic disorders, alcohol abuse and chronic diseases. Three major studies suggested a role for mitochondrial Ca^{2+} in inflammation-mediated disease progression with direct and indirect evidence.

Direct evidence comes from a pair of studies highlighting the loss of expression and function of MICU1 and MICU2 in experimental cardiomyopathy's models. Both proteins are key regulators of mitochondrial Ca^{2+} -uptake, playing crucial roles in both physiological and pathological contexts. In the first model represented by diabetic cardiomyocytes, MICU1 expression is downregulated, leading to mitochondrial Ca^{2+} imbalance. This dysregulation contributes to cardiomyocyte apoptosis and the progression of diabetic cardiomyopathy. In the same model, MICU1 deficiency has also been observed in endothelial cells, where it results in unregulated Ca^{2+} influx into mitochondria, triggering mitochondrial dysfunction, increased nitrosative stress and nitrosation-induced inflammation [336]. MICU2, in cooperation with MICU1, helps prevent mitochondrial Ca^{2+} overload under resting conditions while enabling appropriate Ca^{2+} -uptake during cellular stimulation. The second study demonstrated also MICU2 deficiency, resulting in excessive mitochondrial Ca^{2+} accumulation. This leads to a harmful cascade including elevated ROS production and mPTP opening. Crucially, MICU2 loss was linked to the activation of inflammatory pathways. The elevated mitochondrial Ca^{2+} triggered the release of mtDNA and ROS, both potent activators of NLRP3 inflammasome. Functionally, MICU2-deficient models displayed impaired cardiovascular homeostasis, characterized by compromised cardiac contractility and structural abnormalities. These findings emphasize the critical role of MICU2 in regulating mitochondrial Ca^{2+} flux and in protecting the heart from inflammation-induced damage [337].

Indirect evidence comes from an *in vivo* model studying a C452F missense mutation in Drp1 protein which is strongly linked to a form of monogenic dilated cardiomyopathy. This mutation enhances Drp1's GTPase activity but impairs its ability to disassemble oligomers, leaving them permanently

assembled. Consequently, mitophagy is impaired, leading to the accumulation of dysfunctional mitochondria [338]. These damaged mitochondria become depolarized and lose their ability to effectively buffer Ca^{2+} in the cytosol. Experimental data show reduced mitochondrial Ca^{2+} -uptake, which in turn diminishes the activation of oxidative phosphorylation and compromises ATP production. The buildup of defective mitochondria initiates a sterile inflammatory response in the heart. Activation of innate immune pathways including inflammasomes, TLR9, STING, and MAVS leads to sustained pro-inflammatory signaling. Over time, the failure of mitophagy and persistent inflammation result in dilated CM, as observed in the Python mouse model. Inflammation further disrupts Ca^{2+} handling and contributes to energy failure [338].

Cardiometabolic diseases like obesity and type 2 diabetes mellitus (T2DM) are increasingly recognized not only as metabolic disorders but also as chronic inflammatory conditions. The term metaflammation has been coined to describe the persistent, low-grade inflammation that accompanies metabolic overload and insulin resistance. This inflammatory state is distinct from acute immune activation seen in infection; rather, it is subtle, chronic, and sterile in nature, sustained by endogenous danger signals derived from metabolic stress. Mitochondria lie at the heart of this process, acting as both metabolic regulators and key orchestrators of innate immune responses. In conditions of nutrient excess, as seen in obesity and insulin resistance, mitochondria become overloaded with substrates such as glucose and free fatty acids. This excess drives an increase in mitochondrial membrane potential and electron leak, resulting in enhanced ROS generation. Sustained oxidative stress damages mitochondrial proteins, lipids and DNA, impairing their function and creating a self-perpetuating cycle of dysfunction. The accumulation of damaged mitochondria acts as danger patterns capable of activating innate immune sensors such as the cGAS–STING pathway, TLR9 and the NLRP3 inflammasome [339–342]. Tissues suffering from that are the adipose one, the liver, the endothelium and the heart of course. Thus, mitochondrial dysfunction becomes a molecular bridge linking nutrient excess to inflammation and metabolic dysregulation.

Considering the importance of these findings, researches started to explore promising therapeutic approaches to mitigate vascular inflammation associated with CVDs, as mitochondrial transplantation (MTx) [343,344]. These studies which we briefly report below, maybe can overcome past failures in targeting mitochondria [345] and collectively are demonstrating that MTx offers significant cardioprotection when applied in models of I/R injury. Injection of isolated mitochondria during early reperfusion was shown to reduce infarct size (IS) by approximately 35-40%, to restore mitochondrial respiration and ATP production by 20-25%, and decrease ROS by roughly 30%. This reduction in oxidative stress was accompanied by improved contractile recovery, with left ventricular ejection fraction (LVEF) increasing by 15-20% compared to untreated controls [346–348].

Importantly, transplantation of autologously derived mitochondria has been tested to be a safe and effective approach to rescue ischemic myocardium. This treatment decreased cardiomyocyte apoptosis by up to 40%, reduced IS by 30-35% and enhanced myocardial contractility, reflected in an 18% increase in fractional shortening. Improvements in mitochondrial membrane potential and Ca^{2+} handling were also observed, indicating an impact on cellular metabolism in damaged cardiomyocytes [347]. Different ways for MTx are available, such as the intracoronary delivery of mitochondria, that provide a minimally invasive method [349]. This approach facilitated mitochondrial uptake by cardiomyocytes, resulting in a 30% decrease in IS and about a 25% increase in myocardial ATP content. Cardiac output and stroke volume improvements were confirmed by echocardiographic measurements, showing enhanced systolic function following treatment [350]. In a larger animal model, specifically in pigs, has been obtained similar findings: autologous

mitochondrial transplantation during reperfusion reduced IS by 30-40% and increased myocardial ATP levels by approximately 20%. Additionally, this intervention attenuated inflammatory cytokines such as TNF- α and IL-6 by around 35%, suggesting a strong anti-inflammatory effect. Functional improvements in cardiac performance, including LVEF increases of 15-18%, were sustained for several weeks post-treatment [348].

The timing of mitochondrial delivery was also explored in the reported publications, with delayed transplantation several hours after reperfusion still providing cardioprotective benefits. Although the reductions in IS were somewhat smaller (20-25%), improvements in mitochondrial respiration, ATP production, oxidative stress reduction and microvascular perfusion were still significant, facilitating myocardial recovery [351]. Furthermore, preischemic intracoronary injection of autologous mitochondria served as a form of preconditioning, reducing IS and preserving cardiac contractile function as measured by stroke volume and cardiac output. This preconditioning was associated with increased mitochondrial biogenesis and antioxidant defense mechanisms, demonstrated by elevated expression of PGC-1 α and superoxide dismutase enzymes in myocardial tissue [352].

MTx also protected against sepsis-induced myocardial dysfunction through multiple mechanisms: enhancing mitochondrial biogenesis, as evidenced by increased expression of PGC-1 α and NRF1, regulating mitochondrial fission/fusion balance through Drp1 and MFN1/2 and dampening the inflammatory response in terms of TNF- α and IL-6 [353].

Conclusions

Mitochondria and their components can exist in multiple forms, inside or outside the cell, membrane-bound or free, often with complex and still unclear implications for human health. This review underscored the expanding recognition of mitochondria as central players in numerous diseases, where they act as key amplifiers of inflammation. Their multifaceted role in inflammation is driving the development of mitochondria-targeted interventions (Figure 4) [32,354]. These approaches aim to preserve mitochondrial bioenergetics and structural integrity in compromised cells, thereby mitigating inflammation and slowing disease progression. Among these, MitoQ is the most advanced compound, having entered clinical trials and raising hopes that its preclinical success will soon translate into clinical benefit. Recent studies have further revealed that mitochondria form dynamic micron-sized compartments capable of selective cargo incorporation and vesicle formation. Determining how and where these molecules are released, whether as whole mitochondria, fragmented components, or vesicle-packaged cargo, will be essential for understanding their physiological functions and clinical significance as biomarkers or therapeutic targets. Parallel progress is now unfolding in mitochondrial and MDV transplantation. Notably, mitochondrial transplantation is not constrained by phylogenetic barriers, suggesting broad therapeutic versatility and even potential applications in bioenhancement [355]. Although many questions remain regarding mitochondrial biology, mitochondria are increasingly recognized as central therapeutic targets. Once viewed merely as remnants of bacterial ancestry, they now stand at the forefront of biomedical research, representing a precise and promising avenue for intervention across a wide spectrum of human diseases.

Figure 4. Mitochondria-targeted strategies for restoring cellular homeostasis and preventing inflammation. Overview of therapeutic approaches aimed at preserving or restoring mitochondrial integrity to counteract the release of mitochondrial damage-associated molecular patterns (mtDAMPs) and subsequent inflammatory responses. Mitochondrial transplantation and the use of

mitovesicles or mitochondrial-derived vesicles (MDVs) support mitochondrial physiology and inter-organelle communication. Mitochondrial antioxidants, such as MitoQ and MitoTEMPO, prevent ROS-dependent damage and inflammasome activation. Modulators of mitochondrial calcium (Ca^{2+}) homeostasis protect against Ca^{2+} overload and dysfunction. Regulators of mitochondrial dynamics and biogenesis maintain structural and energetic balance, while mitophagy and the mitochondrial unfolded protein response ensure mitochondrial quality control. Finally, metabolic regulators such as NAD^+ precursors enhance bioenergetics, reducing mitochondrial stress. Together, these strategies highlight potential therapeutic avenues for modulating mitochondrial function and inflammation.

Future directions

Future research should aim to define the precise mechanisms linking mitochondrial dysfunction and immune activation, particularly the spatiotemporal dynamics of mitochondrial Ca^{2+} flux, ROS production and mtDNA release. The heterogeneity of mitochondrial messengers requires standardized methods for their isolation, quantification and characterization to clarify their distinct roles in physiological and pathological contexts. Integrative multi-omics and advanced imaging technologies will be instrumental in mapping mitochondrial interactions with other organelles, immune receptors and metabolic networks.

Many open questions remain to be elucidated: i) how do specific mitochondrial Ca^{2+} handling proteins interact with immune signaling pathways under physiological and pathological conditions? ii) Can precise modulation of mitochondrial Ca^{2+} flux restore immune balance without impairing essential metabolic functions? iii) What are the distinct biological effects of free versus vesicle-associated mtDNA and other mitochondrial DAMPs? iv) How do MDVs and mitovesicles mediate intercellular signaling in inflammation or tissue repair? v) How do variables such as age, sex and metabolic status affect mitochondrial biomarker profiles? vi) What patient-specific mitochondrial signatures could guide tailored therapeutic interventions?

Abbreviations

A β	amyloid- β
AD	Alzheimer's disease
ALS	amyotrophic lateral sclerosis
ARDS	acute respiratory distress syndrome
ATP	adenosine triphosphate
CaMK2	Ca^{2+} /calmodulin-dependent protein kinase II
CDKN2	Acyclin-dependent kinase inhibitor 2A
CD	Crohn's disease
CF	cystic fibrosis
cGAS	cyclic GMP-AMP synthase
COPD	chronic obstructive pulmonary disease
CRC	colorectal cancer
CS	cigarette smoke
CVDs	cardiovascular diseases

DAMPs Damage-Associated Molecular Patterns
 DRP1 dynamin-related protein 1
 EMRE essential MCU regulator
 ER endoplasmic reticulum
 EVs extracellular vesicles
 HK2 hexokinase 2
 IBD inflammatory bowel diseases
 IEC intestinal epithelial cell
 IFNs interferons
 IMM inner mitochondrial membrane
 IPF idiopathic pulmonary fibrosis
 IS infarct size
 IRF3 interferon regulatory factor 3
 LVEF left ventricular ejection fraction
 MAVS Mitochondrial antiviral-signaling protein
 MCU mitochondrial Ca^{2+} uniporter
 MDVs mitochondria-derived vesicles
 MICUs mitochondrial Ca^{2+} uptake proteins
 mtDNA mitochondrial DNA
 MFN2 mitofusin-2
 mPTP mitochondrial permeability transition pore
 MPTP neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
 mETC mitochondrial electron transport chain
 mtROS mitochondrial reactive oxygen species
 mtUPR mitochondrial unfolded protein response
 MTx mitochondrial transplantation
 MS multiple sclerosis
 MSCs mesenchymal stem cells
 NCLX $\text{Na}^+/\text{Ca}^{2+}/\text{Li}^+$ exchanger
 NCX $\text{Na}^+/\text{Ca}^{2+}$ exchanger
 NLRs NOD-like Receptors
 NRFs nuclear respiratory factors
 OMM outer mitochondrial membrane
 OXPHOS oxidative phosphorylations
 PAMPs Pathogen-Associated Molecular Patterns
 PBMCs peripheral blood mononuclear cells
 PD Parkinson's disease
 PGC-1 α proliferator-activated receptor-gamma coactivator 1-alpha
 Phb1 Prohibitin-1
 PRRs Pattern Recognition Receptors
 RLRs RIG-I-like receptors
 SASP senescence-associated secretory phenotype
 SDH succinate dehydrogenase
 SOD superoxide dismutase
 STING stimulator of interferon genes

TAMs tumor-associated macrophages
TCA tricarboxylic acid
TLRs Toll-like Receptors
TNF α Tumor Necrosis Factor
TRPA1 Transient Receptor Potential Ankyrin 1
UC ulcerative colitis
VDAC Voltage-Dependent Anion Channel

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Authors' contribution

GM, EDA, SP, GP, CP and AR wrote the manuscript; EDA and GP made figures; GM and AR supervised the manuscript; D.F., L.R. and K.K. improved the text during revision; PP, GM and AR revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests

References

1. Medzhitov R. Origin and physiological roles of inflammation. *Nature*. 2008;454:428–35. <https://doi.org/10.1038/nature07201>
2. Barton GM. A calculated response: control of inflammation by the innate immune system. *J Clin Invest*. 2008;118:413–20. <https://doi.org/10.1172/JCI34431>
3. Vanpouille-Box C, Hoffmann JA, Galluzzi L. Pharmacological modulation of nucleic acid sensors - therapeutic potential and persisting obstacles. *Nat Rev Drug Discov*. 2019;18:845–67. <https://doi.org/10.1038/s41573-019-0043-2>
4. Kroemer G, Galassi C, Zitvogel L, Galluzzi L. Immunogenic cell stress and death. *Nat Immunol*. 2022;23:487–500. <https://doi.org/10.1038/s41590-022-01132-2>
5. Patergnani S, Bouhamida E, Leo S, Pinton P, Rimessi A. Mitochondrial Oxidative Stress and “Mito-Inflammation”: Actors in the Diseases. *Biomedicines*. 2021;9:216. <https://doi.org/10.3390/biomedicines9020216>
6. Kolmychkova KI, Zhelankin AV, Karagodin VP, Orekhov AN. Mitochondria and inflammation. *Patol Fiziol Eksp Ter*. 2016;60:114–21.
7. Marchi S, Patergnani S, Missiroli S, Morciano G, Rimessi A, Wieckowski MR, et al. Mitochondrial and endoplasmic reticulum calcium homeostasis and cell death. *Cell Calcium*. 2018;69:62–72. <https://doi.org/10.1016/j.ceca.2017.05.003>
8. Patergnani S, Vitto VAM, Pinton P, Rimessi A. Mitochondrial Stress Responses and “Mito-Inflammation” in Cystic Fibrosis. *Front Pharmacol*. 2020;11:581114. <https://doi.org/10.3389/fphar.2020.581114>
9. Kubat GB, Picone P, Tuncay E, Aryan L, Girgenti A, Palumbo L, et al. Biotechnological approaches and therapeutic potential of mitochondria transfer and transplantation. *Nat Commun*. 2025;16:5709. <https://doi.org/10.1038/s41467-025-61239-6>
10. Lou P, Zhou X, Zhang Y, Xie Y, Wang Y, Wang C, et al. Harnessing tissue-derived mitochondria-rich extracellular vesicles (Ti-mitoEVs) to boost mitochondrial biogenesis for regenerative medicine. *Sci Adv*. 2025;11:eadt1318. <https://doi.org/10.1126/sciadv.adt1318>
11. Rimessi A, Giorgi C, Pinton P, Rizzuto R. The versatility of mitochondrial calcium signals: from stimulation of cell metabolism to induction of cell death. *Biochim Biophys Acta*. 2008;1777:808–16. <https://doi.org/10.1016/j.bbabi.2008.05.449>
12. Colombini M. Voltage gating in the mitochondrial channel, VDAC. *J Membr Biol*. 1989;111:103–11. <https://doi.org/10.1007/BF01871775>
13. Madesh M, Hajnóczky G. VDAC-dependent permeabilization of the outer mitochondrial membrane by superoxide induces rapid and massive cytochrome c release. *J Cell Biol*. 2001;155:1003–15. <https://doi.org/10.1083/jcb.200105057>
14. Kühlbrandt W. Structure and function of mitochondrial membrane protein complexes. *BMC Biol*. 2015;13:89. <https://doi.org/10.1186/s12915-015-0201-x>
15. Palmieri F, Bisaccia F, Capobianco L, Dolce V, Fiermonte G, Iacobazzi V, et al. Mitochondrial metabolite transporters. *Biochim Biophys Acta*. 1996;1275:127–32. [https://doi.org/10.1016/0005-2728\(96\)00062-x](https://doi.org/10.1016/0005-2728(96)00062-x)
16. Palmieri L, Pardo B, Lasorsa FM, del Arco A, Kobayashi K, Iijima M, et al. Citrin and aralar1 are Ca(2+)-stimulated aspartate/glutamate transporters in mitochondria. *EMBO J*. 2001;20:5060–9. <https://doi.org/10.1093/emboj/20.18.5060>
17. Simmen T, Herrera-Cruz MS. Plastic mitochondria-endoplasmic reticulum (ER) contacts use chaperones and tethers to mould their structure and signaling. *Curr Opin Cell Biol*. 2018;53:61–9. <https://doi.org/10.1016/j.ceb.2018.04.014>
18. Marchi S, Pinton P. The mitochondrial calcium uniporter complex: molecular components,

- structure and physiopathological implications. *J Physiol*. 2014;592:829–39. <https://doi.org/10.1113/jphysiol.2013.268235>
19. Bonora M, Patergnani S, Rimessi A, De Marchi E, Suski JM, Bononi A, et al. ATP synthesis and storage. *Purinergic Signal*. 2012;8:343–57. <https://doi.org/10.1007/s11302-012-9305-8>
 20. Morciano G, Imamura H, Patergnani S, Pedriali G, Giorgi C, Pinton P. Measurement of ATP concentrations in mitochondria of living cells using luminescence and fluorescence approaches. *Methods Cell Biol*. 2020;155:199–219. <https://doi.org/10.1016/bs.mcb.2019.10.007>
 21. Marinelli F, Almagor L, Hiller R, Giladi M, Khananshvil D, Faraldo-Gómez JD. Sodium recognition by the Na⁺/Ca²⁺ exchanger in the outward-facing conformation. *Proc Natl Acad Sci U S A*. 2014;111:E5354–5362. <https://doi.org/10.1073/pnas.1415751111>
 22. Palty R, Silverman WF, Hershfinkel M, Caporale T, Sensi SL, Parnis J, et al. NCLX is an essential component of mitochondrial Na⁺/Ca²⁺ exchange. *Proc Natl Acad Sci U S A*. 2010;107:436–41. <https://doi.org/10.1073/pnas.0908099107>
 23. Nishizawa T, Kita S, Maturana AD, Furuya N, Hirata K, Kasuya G, et al. Structural basis for the counter-transport mechanism of a H⁺/Ca²⁺ exchanger. *Science*. 2013;341:168–72. <https://doi.org/10.1126/science.1239002>
 24. Di Mambro T, Pelliello G, Agyapong ED, Carinci M, Chianese D, Giorgi C, et al. The Tricky Connection between Extracellular Vesicles and Mitochondria in Inflammatory-Related Diseases. *Int J Mol Sci*. 2023;24:8181. <https://doi.org/10.3390/ijms24098181>
 25. Matuz-Mares D, González-Andrade M, Araiza-Villanueva MG, Vilchis-Landeros MM, Vázquez-Meza H. Mitochondrial Calcium: Effects of Its Imbalance in Disease. *Antioxidants (Basel)*. 2022;11:801. <https://doi.org/10.3390/antiox11050801>
 26. Morciano G, Naumova N, Koprowski P, Valente S, Sardão VA, Potes Y, et al. The mitochondrial permeability transition pore: an evolving concept critical for cell life and death. *Biol Rev Camb Philos Soc*. 2021;96:2489–521. <https://doi.org/10.1111/brv.12764>
 27. Marques E, Kramer R, Ryan DG. Multifaceted mitochondria in innate immunity. *NPJ Metab Health Dis*. 2024;2:6. <https://doi.org/10.1038/s44324-024-00008-3>
 28. Arfath Y, Kotra T, Faizan MI, Akhtar A, Abdullah ST, Ahmad T, et al. TRPV4 facilitates the reprogramming of inflamed macrophages by regulating IL-10 production via CREB. *Inflamm Res*. 2024;73:1687–97. <https://doi.org/10.1007/s00011-024-01923-3>
 29. Garg AD, Nowis D, Golab J, Vandenabeele P, Krysko DV, Agostinis P. Immunogenic cell death, DAMPs and anticancer therapeutics: an emerging amalgamation. *Biochim Biophys Acta*. 2010;1805:53–71. <https://doi.org/10.1016/j.bbcan.2009.08.003>
 30. Dela Cruz CS, Kang M-J. Mitochondrial dysfunction and damage associated molecular patterns (DAMPs) in chronic inflammatory diseases. *Mitochondrion*. 2018;41:37–44. <https://doi.org/10.1016/j.mito.2017.12.001>
 31. König T, McBride HM. Mitochondrial-derived vesicles in metabolism, disease, and aging. *Cell Metab*. 2024;36:21–35. <https://doi.org/10.1016/j.cmet.2023.11.014>
 32. Garg M, Johri S, Chakraborty K. Immunomodulatory role of mitochondrial DAMPs: a missing link in pathology? *FEBS J*. 2023;290:4395–418. <https://doi.org/10.1111/febs.16563>
 33. Zhong F, Liang S, Zhong Z. Emerging Role of Mitochondrial DNA as a Major Driver of Inflammation and Disease Progression. *Trends Immunol*. 2019;40:1120–33. <https://doi.org/10.1016/j.it.2019.10.008>
 34. Ding Z, Liu S, Wang X, Dai Y, Khaidakov M, Deng X, et al. LOX-1, mtDNA damage, and NLRP3 inflammasome activation in macrophages: implications in atherogenesis. *Cardiovasc Res*. 2014;103:619–28. <https://doi.org/10.1093/cvr/cvu114>
 35. Riley JS, Tait SW. Mitochondrial DNA in inflammation and immunity. *EMBO Rep*. 2020;21:e49799. <https://doi.org/10.15252/embr.201949799>
 36. Zhang B, Asadi S, Weng Z, Sismanopoulos N, Theoharides TC. Stimulated human mast

- cells secrete mitochondrial components that have autocrine and paracrine inflammatory actions. *PLoS One*. 2012;7:e49767. <https://doi.org/10.1371/journal.pone.0049767>
37. Schwarzenbach H, Hoon DSB, Pantel K. Cell-free nucleic acids as biomarkers in cancer patients. *Nat Rev Cancer*. 2011;11:426–37. <https://doi.org/10.1038/nrc3066>
 38. Yousefi S, Gold JA, Andina N, Lee JJ, Kelly AM, Kozlowski E, et al. Catapult-like release of mitochondrial DNA by eosinophils contributes to antibacterial defense. *Nat Med*. 2008;14:949–53. <https://doi.org/10.1038/nm.1855>
 39. Yousefi S, Mihalache C, Kozlowski E, Schmid I, Simon HU. Viable neutrophils release mitochondrial DNA to form neutrophil extracellular traps. *Cell Death Differ*. 2009;16:1438–44. <https://doi.org/10.1038/cdd.2009.96>
 40. Boudreau LH, Duchez A-C, Cloutier N, Soulet D, Martin N, Bollinger J, et al. Platelets release mitochondria serving as substrate for bactericidal group IIA-secreted phospholipase A2 to promote inflammation. *Blood*. 2014;124:2173–83. <https://doi.org/10.1182/blood-2014-05-573543>
 41. Kim J, Gupta R, Blanco LP, Yang S, Shteinifer-Kuzmine A, Wang K, et al. VDAC oligomers form mitochondrial pores to release mtDNA fragments and promote lupus-like disease. *Science*. 2019;366:1531–6. <https://doi.org/10.1126/science.aav4011>
 42. Krauskopf A, Eriksson O, Craigen WJ, Forte MA, Bernardi P. Properties of the permeability transition in VDAC1(-/-) mitochondria. *Biochim Biophys Acta*. 2006;1757:590–5. <https://doi.org/10.1016/j.bbabi.2006.02.007>
 43. McArthur K, Whitehead LW, Heddleston JM, Li L, Padman BS, Oorschot V, et al. BAK/BAX macropores facilitate mitochondrial herniation and mtDNA efflux during apoptosis. *Science*. 2018;359:eaao6047. <https://doi.org/10.1126/science.aao6047>
 44. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. *Cell*. 2010;140:805–20. <https://doi.org/10.1016/j.cell.2010.01.022>
 45. Bell JK, Botos I, Hall PR, Askins J, Shiloach J, Segal DM, et al. The molecular structure of the Toll-like receptor 3 ligand-binding domain. *Proc Natl Acad Sci U S A*. 2005;102:10976–80. <https://doi.org/10.1073/pnas.0505077102>
 46. Botos I, Segal DM, Davies DR. The structural biology of Toll-like receptors. *Structure*. 2011;19:447–59. <https://doi.org/10.1016/j.str.2011.02.004>
 47. West AP, Shadel GS. Mitochondrial DNA in innate immune responses and inflammatory pathology. *Nat Rev Immunol*. 2017;17:363–75. <https://doi.org/10.1038/nri.2017.21>
 48. Liu Q, Zhang D, Hu D, Zhou X, Zhou Y. The role of mitochondria in NLRP3 inflammasome activation. *Mol Immunol*. 2018;103:115–24. <https://doi.org/10.1016/j.molimm.2018.09.010>
 49. Próchnicki T, Latz E. Inflammasomes on the Crossroads of Innate Immune Recognition and Metabolic Control. *Cell Metab*. 2017;26:71–93. <https://doi.org/10.1016/j.cmet.2017.06.018>
 50. Hou F, Sun L, Zheng H, Skaug B, Jiang Q-X, Chen ZJ. MAVS forms functional prion-like aggregates to activate and propagate antiviral innate immune response. *Cell*. 2011;146:448–61. <https://doi.org/10.1016/j.cell.2011.06.041>
 51. Wang X, Wang Q, Zheng C, Wang L. MAVS: The next STING in cancers and other diseases. *Crit Rev Oncol Hematol*. 2025;207:104610. <https://doi.org/10.1016/j.critrevonc.2024.104610>
 52. Nohl H, Gille L, Staniek K. Intracellular generation of reactive oxygen species by mitochondria. *Biochem Pharmacol*. 2005;69:719–23. <https://doi.org/10.1016/j.bcp.2004.12.002>
 53. Rimessi A, Previati M, Nigro F, Wieckowski MR, Pinton P. Mitochondrial reactive oxygen species and inflammation: Molecular mechanisms, diseases and promising therapies. *Int J Biochem Cell Biol*. 2016;81:281–93. <https://doi.org/10.1016/j.biocel.2016.06.015>
 54. Zhou R, Yazdi AS, Menu P, Tschopp J. A role for mitochondria in NLRP3 inflammasome activation. *Nature*. 2011;469:221–5. <https://doi.org/10.1038/nature09663>

55. Zhong Z, Liang S, Sanchez-Lopez E, He F, Shalapour S, Lin X-J, et al. New mitochondrial DNA synthesis enables NLRP3 inflammasome activation. *Nature*. 2018;560:198–203. <https://doi.org/10.1038/s41586-018-0372-z>
56. Ichimura H, Parthasarathi K, Quadri S, Issekutz AC, Bhattacharya J. Mechano-oxidative coupling by mitochondria induces proinflammatory responses in lung venular capillaries. *J Clin Invest*. 2003;111:691–9. <https://doi.org/10.1172/JCI17271>
57. Traaseth N, Elfering S, Solien J, Haynes V, Giulivi C. Role of calcium signaling in the activation of mitochondrial nitric oxide synthase and citric acid cycle. *Biochim Biophys Acta*. 2004;1658:64–71. <https://doi.org/10.1016/j.bbabbio.2004.04.015>
58. Görlach A, Bertram K, Hudecova S, Krizanov O. Calcium and ROS: A mutual interplay. *Redox Biol*. 2015;6:260–71. <https://doi.org/10.1016/j.redox.2015.08.010>
59. Sivaramakrishnan V, Fountain SJ. Evidence for Extracellular ATP as a Stress Signal in a Single-Celled Organism. *Eukaryot Cell*. 2015;14:775–82. <https://doi.org/10.1128/EC.00066-15>
60. Ferrari D, Chiozzi P, Falzoni S, Dal Susino M, Melchiorri L, Baricordi OR, et al. Extracellular ATP triggers IL-1 beta release by activating the purinergic P2Z receptor of human macrophages. *J Immunol*. 1997;159:1451–8.
61. Falzoni S, Vultaggio-Poma V, Chiozzi P, Tarantini M, Adinolfi E, Boldrini P, et al. The P2X7 Receptor is a Master Regulator of Microparticle and Mitochondria Exchange in Mouse Microglia. *Function (Oxf)*. 2024;5:zqae019. <https://doi.org/10.1093/function/zqae019>
62. Chen Y, Corriden R, Inoue Y, Yip L, Hashiguchi N, Zinkernagel A, et al. ATP release guides neutrophil chemotaxis via P2Y2 and A3 receptors. *Science*. 2006;314:1792–5. <https://doi.org/10.1126/science.1132559>
63. Desai BN, Leitinger N. Purinergic and calcium signaling in macrophage function and plasticity. *Front Immunol*. 2014;5:580. <https://doi.org/10.3389/fimmu.2014.00580>
64. Gebert N, Joshi AS, Kutik S, Becker T, McKenzie M, Guan XL, et al. Mitochondrial cardiolipin involved in outer-membrane protein biogenesis: implications for Barth syndrome. *Curr Biol*. 2009;19:2133–9. <https://doi.org/10.1016/j.cub.2009.10.074>
65. Schlame M, Greenberg ML. Biosynthesis, remodeling and turnover of mitochondrial cardiolipin. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2017;1862:3–7. <https://doi.org/10.1016/j.bbalip.2016.08.010>
66. Dahlgren C, Gabl M, Holdfeldt A, Winther M, Forsman H. Basic characteristics of the neutrophil receptors that recognize formylated peptides, a danger-associated molecular pattern generated by bacteria and mitochondria. *Biochem Pharmacol*. 2016;114:22–39. <https://doi.org/10.1016/j.bcp.2016.04.014>
67. Ott M, Amunts A, Brown A. Organization and Regulation of Mitochondrial Protein Synthesis. *Annu Rev Biochem*. 2016;85:77–101. <https://doi.org/10.1146/annurev-biochem-060815-014334>
68. Neuspiel M, Schauss AC, Braschi E, Zunino R, Rippstein P, Rachubinski RA, et al. Cargo-selected transport from the mitochondria to peroxisomes is mediated by vesicular carriers. *Curr Biol*. 2008;18:102–8. <https://doi.org/10.1016/j.cub.2007.12.038>
69. König T, Nolte H, Aaltonen MJ, Tatsuta T, Krols M, Stroh T, et al. MIROs and DRP1 drive mitochondrial-derived vesicle biogenesis and promote quality control. *Nat Cell Biol*. 2021;23:1271–86. <https://doi.org/10.1038/s41556-021-00798-4>
70. Peng T, Xie Y, Sheng H, Wang C, Lian Y, Xie N. Mitochondrial-derived vesicles: Gatekeepers of mitochondrial response to oxidative stress. *Free Radic Biol Med*. 2022;188:185–93. <https://doi.org/10.1016/j.freeradbiomed.2022.06.233>
71. Heyn J, Heuschkel MA, Goettsch C. Mitochondrial-Derived Vesicles-Link to Extracellular Vesicles and Implications in Cardiovascular Disease. *Int J Mol Sci*. 2023;24:2637. <https://doi.org/10.3390/ijms24032637>

72. Popov L-D. Mitochondrial-derived vesicles: Recent insights. *J Cell Mol Med*. 2022;26:3323–8. <https://doi.org/10.1111/jcmm.17391>
73. Soubannier V, Rippstein P, Kaufman BA, Shoubridge EA, McBride HM. Reconstitution of mitochondria derived vesicle formation demonstrates selective enrichment of oxidized cargo. *PLoS One*. 2012;7:e52830. <https://doi.org/10.1371/journal.pone.0052830>
74. Todkar K, Chikhi L, Desjardins V, El-Mortada F, Pépin G, Germain M. Selective packaging of mitochondrial proteins into extracellular vesicles prevents the release of mitochondrial DAMPs. *Nat Commun*. 2021;12:1971. <https://doi.org/10.1038/s41467-021-21984-w>
75. Crewe C, Funcke J-B, Li S, Joffin N, Gliniak CM, Ghaben AL, et al. Extracellular vesicle-based interorgan transport of mitochondria from energetically stressed adipocytes. *Cell Metab*. 2021;33:1853-1868.e11. <https://doi.org/10.1016/j.cmet.2021.08.002>
76. D’Acunzo P, Pérez-González R, Kim Y, Hargash T, Miller C, Alldred MJ, et al. Mitovesicles are a novel population of extracellular vesicles of mitochondrial origin altered in Down syndrome. *Sci Adv*. 2021;7:eabe5085. <https://doi.org/10.1126/sciadv.abe5085>
77. D’Acunzo P, Kim Y, Ungania JM, Pérez-González R, Goulbourne CN, Levy E. Isolation of mitochondria-derived mitovesicles and subpopulations of microvesicles and exosomes from brain tissues. *Nat Protoc*. 2022;17:2517–49. <https://doi.org/10.1038/s41596-022-00719-1>
78. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. *Cell*. 2023;186:243–78. <https://doi.org/10.1016/j.cell.2022.11.001>
79. Di Micco R, Krizhanovsky V, Baker D, d’Adda di Fagagna F. Cellular senescence in ageing: from mechanisms to therapeutic opportunities. *Nat Rev Mol Cell Biol*. 2021;22:75–95. <https://doi.org/10.1038/s41580-020-00314-w>
80. Coppé J-P, Desprez P-Y, Krtolica A, Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. *Annu Rev Pathol*. 2010;5:99–118. <https://doi.org/10.1146/annurev-pathol-121808-102144>
81. Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann N Y Acad Sci*. 2000;908:244–54. <https://doi.org/10.1111/j.1749-6632.2000.tb06651.x>
82. Green DR, Galluzzi L, Kroemer G. Mitochondria and the autophagy-inflammation-cell death axis in organismal aging. *Science*. 2011;333:1109–12. <https://doi.org/10.1126/science.1201940>
83. Zhang P, Catterson JH, Grönke S, Partridge L. Inhibition of S6K lowers age-related inflammation and increases lifespan through the endolysosomal system. *Nat Aging*. 2024;4:491–509. <https://doi.org/10.1038/s43587-024-00578-3>
84. Picca A, Lezza AMS, Leeuwenburgh C, Pesce V, Calvani R, Bossola M, et al. Circulating Mitochondrial DNA at the Crossroads of Mitochondrial Dysfunction and Inflammation During Aging and Muscle Wasting Disorders. *Rejuvenation Res*. 2018;21:350–9. <https://doi.org/10.1089/rej.2017.1989>
85. Pinti M, Cevenini E, Nasi M, De Biasi S, Salvioli S, Monti D, et al. Circulating mitochondrial DNA increases with age and is a familiar trait: Implications for “inflamm-aging.” *Eur J Immunol*. 2014;44:1552–62. <https://doi.org/10.1002/eji.201343921>
86. Lawless C, Greaves L, Reeve AK, Turnbull DM, Vincent AE. The rise and rise of mitochondrial DNA mutations. *Open Biol*. 2020;10:200061. <https://doi.org/10.1098/rsob.200061>
87. Shimada K, Crother TR, Karlin J, Dagvadorj J, Chiba N, Chen S, et al. Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. *Immunity*. 2012;36:401–14. <https://doi.org/10.1016/j.immuni.2012.01.009>
88. Youm Y-H, Grant RW, McCabe LR, Albarado DC, Nguyen KY, Ravussin A, et al. Canonical Nlrp3 inflammasome links systemic low-grade inflammation to functional decline in aging. *Cell Metab*. 2013;18:519–32. <https://doi.org/10.1016/j.cmet.2013.09.010>
89. Gherardi G, Weiser A, Bermont F, Migliavacca E, Brinon B, Jacot GE, et al. Mitochondrial

- calcium uptake declines during aging and is directly activated by oleuropein to boost energy metabolism and skeletal muscle performance. *Cell Metab.* 2025;37:477-495.e11. <https://doi.org/10.1016/j.cmet.2024.10.021>
90. Mallilankaraman K, Doonan P, Cárdenas C, Chandramoorthy HC, Müller M, Miller R, et al. MICU1 is an essential gatekeeper for MCU-mediated mitochondrial Ca^{2+} uptake that regulates cell survival. *Cell.* 2012;151:630–44. <https://doi.org/10.1016/j.cell.2012.10.011>
 91. Kamer KJ, Mootha VK. MICU1 and MICU2 play nonredundant roles in the regulation of the mitochondrial calcium uniporter. *EMBO Rep.* 2014;15:299–307. <https://doi.org/10.1002/embr.201337946>
 92. Ji J, Su L, Liu Z. Critical role of calpain in inflammation. *Biomed Rep.* 2016;5:647–52. <https://doi.org/10.3892/br.2016.785>
 93. Yakovlev AG, Wang G, Stoica BA, Boulares HA, Spoonde AY, Yoshihara K, et al. A role of the $\text{Ca}^{2+}/\text{Mg}^{2+}$ -dependent endonuclease in apoptosis and its inhibition by Poly(ADP-ribose) polymerase. *J Biol Chem.* 2000;275:21302–8. <https://doi.org/10.1074/jbc.M001087200>
 94. Miwa S, Kashyap S, Chini E, von Zglinicki T. Mitochondrial dysfunction in cell senescence and aging. *J Clin Invest.* 2022;132:e158447. <https://doi.org/10.1172/JCI158447>
 95. Chistiakov DA, Sobenin IA, Revin VV, Orekhov AN, Bobryshev YV. Mitochondrial aging and age-related dysfunction of mitochondria. *Biomed Res Int.* 2014;2014:238463. <https://doi.org/10.1155/2014/238463>
 96. Mone P, Agyapong ED, Morciano G, Jankauskas SS, De Luca A, Varzideh F, et al. Dysfunctional mitochondria elicit bioenergetic decline in the aged heart. *J Cardiovasc Aging.* 2024;4:13. <https://doi.org/10.20517/jca.2023.50>
 97. Popov L-D. Mitochondrial biogenesis: An update. *J Cell Mol Med.* 2020;24:4892–9. <https://doi.org/10.1111/jcmm.15194>
 98. Anderson R, Prolla T. PGC-1 α in aging and anti-aging interventions. *Biochim Biophys Acta.* 2009;1790:1059–66. <https://doi.org/10.1016/j.bbagen.2009.04.005>
 99. Eisele PS, Salatino S, Sobek J, Hottiger MO, Handschin C. The peroxisome proliferator-activated receptor γ coactivator 1 α/β (PGC-1) coactivators repress the transcriptional activity of NF- κ B in skeletal muscle cells. *J Biol Chem.* 2013;288:2246–60. <https://doi.org/10.1074/jbc.M112.375253>
 100. Zhao Z, Yu Z, Hou Y, Zhang L, Fu A. Improvement of cognitive and motor performance with mitotherapy in aged mice. *Int J Biol Sci.* 2020;16:849–58. <https://doi.org/10.7150/ijbs.40886>
 101. Javani G, Babri S, Farajdokht F, Ghaffari-Nasab A, Mohaddes G. Mitochondrial transplantation improves anxiety- and depression-like behaviors in aged stress-exposed rats. *Mech Ageing Dev.* 2022;202:111632. <https://doi.org/10.1016/j.mad.2022.111632>
 102. Zhang Z, Wei D, Li Z, Guo H, Wu Y, Feng J. Hippocampal Mitochondrial Transplantation Alleviates Age-Associated Cognitive Decline via Enhancing Wnt Signaling and Neurogenesis. *Comput Intell Neurosci.* 2022;2022:9325302. <https://doi.org/10.1155/2022/9325302>
 103. Adlimoghaddam A, Benson T, Albensi BC. Mitochondrial Transfusion Improves Mitochondrial Function Through Up-regulation of Mitochondrial Complex II Protein Subunit SDHB in the Hippocampus of Aged Mice. *Mol Neurobiol.* 2022;59:6009–17. <https://doi.org/10.1007/s12035-022-02937-w>
 104. Kim Y, Pérez-González R, Miller C, Kurz M, D’Acunzo P, Goulbourne CN, et al. Sex Differentially Alters Secretion of Brain Extracellular Vesicles During Aging: A Potential Mechanism for Maintaining Brain Homeostasis. *Neurochem Res.* 2022;47:3428–39. <https://doi.org/10.1007/s11064-022-03701-1>
 105. Phua QH, Ng SY, Soh B-S. Mitochondria: A Potential Rejuvenation Tool against Aging. *Aging Dis.* 2024;15:503–16. <https://doi.org/10.14336/AD.2023.0712>

106. Bahat A, Milenkovic D, Cors E, Barnett M, Niftullayev S, Katsalifis A, et al. Ribonucleotide incorporation into mitochondrial DNA drives inflammation. *Nature*. 2025; <https://doi.org/10.1038/s41586-025-09541-7>
107. Pandey S, Anang V, Schumacher MM. Mitochondria driven innate immune signaling and inflammation in cancer growth, immune evasion, and therapeutic resistance. *Int Rev Cell Mol Biol*. 2024;386:223–47. <https://doi.org/10.1016/bs.ircmb.2024.01.006>
108. Doppler W, Jansen-Dürr P. Regulation of mitochondrial ROS production by HIC-5: a common feature of oncogene-induced senescence and tumor invasiveness? *FEBS J*. 2019;286:456–8. <https://doi.org/10.1111/febs.14746>
109. Salaroglio IC, Belisario DC, Akman M, La Vecchia S, Godel M, Anobile DP, et al. Mitochondrial ROS drive resistance to chemotherapy and immune-killing in hypoxic non-small cell lung cancer. *J Exp Clin Cancer Res*. 2022;41:243. <https://doi.org/10.1186/s13046-022-02447-6>
110. Porporato PE, Payen VL, Pérez-Escuredo J, De Saedeleer CJ, Danhier P, Copetti T, et al. A mitochondrial switch promotes tumor metastasis. *Cell Rep*. 2014;8:754–66. <https://doi.org/10.1016/j.celrep.2014.06.043>
111. Billingham LK, Stoolman JS, Vasani K, Rodriguez AE, Poor TA, Szibor M, et al. Mitochondrial electron transport chain is necessary for NLRP3 inflammasome activation. *Nat Immunol*. 2022;23:692–704. <https://doi.org/10.1038/s41590-022-01185-3>
112. Hu Y, Lu W, Chen G, Wang P, Chen Z, Zhou Y, et al. K-ras(G12V) transformation leads to mitochondrial dysfunction and a metabolic switch from oxidative phosphorylation to glycolysis. *Cell Res*. 2012;22:399–412. <https://doi.org/10.1038/cr.2011.145>
113. Rimessi A, Marchi S, Patergnani S, Pinton P. H-Ras-driven tumoral maintenance is sustained through caveolin-1-dependent alterations in calcium signaling. *Oncogene*. 2014;33:2329–40. <https://doi.org/10.1038/onc.2013.192>
114. Sena LA, Li S, Jairaman A, Prakriya M, Ezponda T, Hildeman DA, et al. Mitochondria are required for antigen-specific T cell activation through reactive oxygen species signaling. *Immunity*. 2013;38:225–36. <https://doi.org/10.1016/j.immuni.2012.10.020>
115. Liu D, Fang L. Oxidative stress-related genes score predicts prognosis and immune cell infiltration landscape characterization in breast cancer. *Heliyon*. 2024;10:e34046. <https://doi.org/10.1016/j.heliyon.2024.e34046>
116. Wu Z, Zuo M, Zeng L, Cui K, Liu B, Yan C, et al. OMA1 reprograms metabolism under hypoxia to promote colorectal cancer development. *EMBO Rep*. 2021;22:e50827. <https://doi.org/10.15252/embr.202050827>
117. Nielsen N, Kondratska K, Ruck T, Hild B, Kovalenko I, Schimmelpfennig S, et al. TRPC6 channels modulate the response of pancreatic stellate cells to hypoxia. *Pflugers Arch*. 2017;469:1567–77. <https://doi.org/10.1007/s00424-017-2057-0>
118. Li Y, Guo B, Xie Q, Ye D, Zhang D, Zhu Y, et al. STIM1 Mediates Hypoxia-Driven Hepatocarcinogenesis via Interaction with HIF-1. *Cell Rep*. 2015;12:388–95. <https://doi.org/10.1016/j.celrep.2015.06.033>
119. Vig M, Peinelt C, Beck A, Koomoa DL, Rabah D, Koblan-Huberson M, et al. CRACM1 is a plasma membrane protein essential for store-operated Ca²⁺ entry. *Science*. 2006;312:1220–3. <https://doi.org/10.1126/science.1127883>
120. Salnikow K, Kluz T, Costa M, Piquemal D, Demidenko ZN, Xie K, et al. The regulation of hypoxic genes by calcium involves c-Jun/AP-1, which cooperates with hypoxia-inducible factor 1 in response to hypoxia. *Mol Cell Biol*. 2002;22:1734–41. <https://doi.org/10.1128/MCB.22.6.1734-1741.2002>
121. Rius J, Guma M, Schachtrup C, Akassoglou K, Zinkernagel AS, Nizet V, et al. NF- κ B links innate immunity to the hypoxic response through transcriptional regulation of HIF-1 α . *Nature*. 2008;453:807–11. <https://doi.org/10.1038/nature06905>

122. Seegren PV, Harper LR, Downs TK, Zhao X-Y, Viswanathan SB, Stremeska ME, et al. Reduced mitochondrial calcium uptake in macrophages is a major driver of inflammaging. *Nat Aging*. 2023;3:796–812. <https://doi.org/10.1038/s43587-023-00436-8>
123. Jin P, Jiang J, Zhou L, Huang Z, Nice EC, Huang C, et al. Mitochondrial adaptation in cancer drug resistance: prevalence, mechanisms, and management. *J Hematol Oncol*. 2022;15:97. <https://doi.org/10.1186/s13045-022-01313-4>
124. Yao J, Wang J, Xu Y, Guo Q, Sun Y, Liu J, et al. CDK9 inhibition blocks the initiation of PINK1-PRKN-mediated mitophagy by regulating the SIRT1-FOXO3-BNIP3 axis and enhances the therapeutic effects involving mitochondrial dysfunction in hepatocellular carcinoma. *Autophagy*. 2022;18:1879–97. <https://doi.org/10.1080/15548627.2021.2007027>
125. Hou H, Er P, Cheng J, Chen X, Ding X, Wang Y, et al. High expression of FUNDC1 predicts poor prognostic outcomes and is a promising target to improve chemoradiotherapy effects in patients with cervical cancer. *Cancer Med*. 2017;6:1871–81. <https://doi.org/10.1002/cam4.1112>
126. Tangeda V, Lo YK, Babuhasankar AP, Chou H-Y, Kuo C-L, Kao Y-H, et al. Lon upregulation contributes to cisplatin resistance by triggering NCLX-mediated mitochondrial Ca²⁺ release in cancer cells. *Cell Death Dis*. 2022;13:241. <https://doi.org/10.1038/s41419-022-04668-1>
127. Deng R, Zhang H-L, Huang J-H, Cai R-Z, Wang Y, Chen Y-H, et al. MAPK1/3 kinase-dependent ULK1 degradation attenuates mitophagy and promotes breast cancer bone metastasis. *Autophagy*. 2021;17:3011–29. <https://doi.org/10.1080/15548627.2020.1850609>
128. Missiroli S, Perrone M, Gafà R, Nicoli F, Bonora M, Morciano G, et al. PML at mitochondria-associated membranes governs a trimeric complex with NLRP3 and P2X7R that modulates the tumor immune microenvironment. *Cell Death Differ*. 2023;30:429–41. <https://doi.org/10.1038/s41418-022-01095-9>
129. Mai M, Wang Y, Luo M, Li Z, Wang D, Ruan Y, et al. Silibinin ameliorates deoxycholic acid-induced pyroptosis in steatotic HepG2 cells by inhibiting NLRP3 inflammasome activation. *Biochem Biophys Rep*. 2023;35:101545. <https://doi.org/10.1016/j.bbrep.2023.101545>
130. Khodzhaeva V, Schreiber Y, Geisslinger G, Brandes RP, Brüne B, Namgaladze D. Mitofusin 2 Deficiency Causes Pro-Inflammatory Effects in Human Primary Macrophages. *Front Immunol*. 2021;12:723683. <https://doi.org/10.3389/fimmu.2021.723683>
131. Wu J-Y, Huang T-W, Hsieh Y-T, Wang Y-F, Yen C-C, Lee G-L, et al. Cancer-Derived Succinate Promotes Macrophage Polarization and Cancer Metastasis via Succinate Receptor. *Mol Cell*. 2020;77:213–227.e5. <https://doi.org/10.1016/j.molcel.2019.10.023>
132. Li Q, Wu P, Du Q, Hanif U, Hu H, Li K. cGAS-STING, an important signaling pathway in diseases and their therapy. *MedComm (2020)*. 2024;5:e511. <https://doi.org/10.1002/mco2.511>
133. Liu Y, Sun Q, Zhang C, Ding M, Wang C, Zheng Q, et al. STING-IRG1 inhibits liver metastasis of colorectal cancer by regulating the polarization of tumor-associated macrophages. *iScience*. 2023;26:107376. <https://doi.org/10.1016/j.isci.2023.107376>
134. Zhang W, Huang X. Targeting cGAS-STING pathway for reprogramming tumor-associated macrophages to enhance anti-tumor immunotherapy. *Biomark Res*. 2025;13:43. <https://doi.org/10.1186/s40364-025-00750-w>
135. Field CS, Baixauli F, Kyle RL, Puleston DJ, Cameron AM, Sanin DE, et al. Mitochondrial Integrity Regulated by Lipid Metabolism Is a Cell-Intrinsic Checkpoint for Treg Suppressive Function. *Cell Metab*. 2020;31:422–437.e5. <https://doi.org/10.1016/j.cmet.2019.11.021>
136. Li J-Y, Zhao Y, Gong S, Wang M-M, Liu X, He Q-M, et al. TRIM21 inhibits irradiation-induced mitochondrial DNA release and impairs antitumour immunity in

- nasopharyngeal carcinoma tumour models. *Nat Commun.* 2023;14:865.
<https://doi.org/10.1038/s41467-023-36523-y>
137. Lai P, Liu L, Bancaro N, Troiani M, Calì B, Li Y, et al. Mitochondrial DNA released by senescent tumor cells enhances PMN-MDSC-driven immunosuppression through the cGAS-STING pathway. *Immunity.* 2025;58:811-825.e7.
<https://doi.org/10.1016/j.immuni.2025.03.005>
 138. Yuan S, Sun R, Shi H, Chapman NM, Hu H, Guy C, et al. VDAC2 loss elicits tumour destruction and inflammation for cancer therapy. *Nature.* 2025;640:1062–71.
<https://doi.org/10.1038/s41586-025-08732-6>
 139. Nakahira K, Hisata S, Choi AMK. The Roles of Mitochondrial Damage-Associated Molecular Patterns in Diseases. *Antioxid Redox Signal.* 2015;23:1329–50.
<https://doi.org/10.1089/ars.2015.6407>
 140. Zong Y, Li H, Liao P, Chen L, Pan Y, Zheng Y, et al. Mitochondrial dysfunction: mechanisms and advances in therapy. *Signal Transduct Target Ther.* 2024;9:124.
<https://doi.org/10.1038/s41392-024-01839-8>
 141. Zhan X, Cui R, Geng X, Li J, Zhou Y, He L, et al. LPS-induced mitochondrial DNA synthesis and release facilitate RAD50-dependent acute lung injury. *Signal Transduct Target Ther.* 2021;6:103. <https://doi.org/10.1038/s41392-021-00494-7>
 142. Dorward DA, Lucas CD, Doherty MK, Chapman GB, Scholefield EJ, Conway Morris A, et al. Novel role for endogenous mitochondrial formylated peptide-driven formyl peptide receptor 1 signalling in acute respiratory distress syndrome. *Thorax.* 2017;72:928–36. <https://doi.org/10.1136/thoraxjnl-2017-210030>
 143. Foster PS, Maltby S, Rosenberg HF, Tay HL, Hogan SP, Collison AM, et al. Modeling TH 2 responses and airway inflammation to understand fundamental mechanisms regulating the pathogenesis of asthma. *Immunol Rev.* 2017;278:20–40.
<https://doi.org/10.1111/imr.12549>
 144. Hammad H, Lambrecht BN. The basic immunology of asthma. *Cell.* 2021;184:1469–85. <https://doi.org/10.1016/j.cell.2021.02.016>
 145. Kim G-D, Lim EY, Shin HS. Macrophage Polarization and Functions in Pathogenesis of Chronic Obstructive Pulmonary Disease. *Int J Mol Sci.* 2024;25:5631.
<https://doi.org/10.3390/ijms25115631>
 146. Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. *J Allergy Clin Immunol.* 2016;138:16–27.
<https://doi.org/10.1016/j.jaci.2016.05.011>
 147. Puente-Maestu L, Pérez-Parra J, Godoy R, Moreno N, Tejedor A, González-Aragoneses F, et al. Abnormal mitochondrial function in locomotor and respiratory muscles of COPD patients. *Eur Respir J.* 2009;33:1045–52.
<https://doi.org/10.1183/09031936.00112408>
 148. Rabinovich RA, Bastos R, Ardite E, Llinàs L, Orozco-Levi M, Gea J, et al. Mitochondrial dysfunction in COPD patients with low body mass index. *Eur Respir J.* 2007;29:643–50. <https://doi.org/10.1183/09031936.00086306>
 149. Antunes MA, Lopes-Pacheco M, Rocco PRM. Oxidative Stress-Derived Mitochondrial Dysfunction in Chronic Obstructive Pulmonary Disease: A Concise Review. *Oxid Med Cell Longev.* 2021;2021:6644002. <https://doi.org/10.1155/2021/6644002>
 150. Li R, Kou X, Geng H, Xie J, Yang Z, Zhang Y, et al. Effect of ambient PM(2.5) on lung mitochondrial damage and fusion/fission gene expression in rats. *Chem Res Toxicol.* 2015;28:408–18. <https://doi.org/10.1021/tx5003723>
 151. Ito S, Araya J, Kurita Y, Kobayashi K, Takasaka N, Yoshida M, et al. PARK2-mediated mitophagy is involved in regulation of HBEC senescence in COPD pathogenesis. *Autophagy.* 2015;11:547–59. <https://doi.org/10.1080/15548627.2015.1017190>
 152. Mizumura K, Cloonan SM, Nakahira K, Bhashyam AR, Cervo M, Kitada T, et al.

- Mitophagy-dependent necroptosis contributes to the pathogenesis of COPD. *J Clin Invest.* 2014;124:3987–4003. <https://doi.org/10.1172/JCI74985>
153. Ito A, Hashimoto M, Tanihata J, Matsubayashi S, Sasaki R, Fujimoto S, et al. Involvement of Parkin-mediated mitophagy in the pathogenesis of chronic obstructive pulmonary disease-related sarcopenia. *J Cachexia Sarcopenia Muscle.* 2022;13:1864–82. <https://doi.org/10.1002/jcsm.12988>
 154. Bueno M, Lai Y-C, Romero Y, Brands J, St Croix CM, Kanga C, et al. PINK1 deficiency impairs mitochondrial homeostasis and promotes lung fibrosis. *J Clin Invest.* 2015;125:521–38. <https://doi.org/10.1172/JCI74942>
 155. Bueno M, Calyeca J, Rojas M, Mora AL. Mitochondria dysfunction and metabolic reprogramming as drivers of idiopathic pulmonary fibrosis. *Redox Biol.* 2020;33:101509. <https://doi.org/10.1016/j.redox.2020.101509>
 156. Abo-Alhassan F, Rat P, Facy O. Laparoscopic Postlethwait procedure. *J Visc Surg.* 2021;158:182–4. <https://doi.org/10.1016/j.jvisurg.2020.12.005>
 157. Kadota T, Fujita Y, Yoshioka Y, Araya J, Kuwano K, Ochiya T. Extracellular Vesicles in Chronic Obstructive Pulmonary Disease. *Int J Mol Sci.* 2016;17:1801. <https://doi.org/10.3390/ijms17111801>
 158. Kadota T, Fujita Y, Araya J, Watanabe N, Fujimoto S, Kawamoto H, et al. Human bronchial epithelial cell-derived extracellular vesicle therapy for pulmonary fibrosis via inhibition of TGF- β -WNT crosstalk. *J Extracell Vesicles.* 2021;10:e12124. <https://doi.org/10.1002/jev2.12124>
 159. Fujita Y, Araya J, Ito S, Kobayashi K, Kosaka N, Yoshioka Y, et al. Suppression of autophagy by extracellular vesicles promotes myofibroblast differentiation in COPD pathogenesis. *J Extracell Vesicles.* 2015;4:28388. <https://doi.org/10.3402/jev.v4.28388>
 160. Xu H, Ling M, Xue J, Dai X, Sun Q, Chen C, et al. Exosomal microRNA-21 derived from bronchial epithelial cells is involved in aberrant epithelium-fibroblast cross-talk in COPD induced by cigarette smoking. *Theranostics.* 2018;8:5419–33. <https://doi.org/10.7150/thno.27876>
 161. Aravamudan B, Kiel A, Freeman M, Delmotte P, Thompson M, Vassallo R, et al. Cigarette smoke-induced mitochondrial fragmentation and dysfunction in human airway smooth muscle. *Am J Physiol Lung Cell Mol Physiol.* 2014;306:L840-854. <https://doi.org/10.1152/ajplung.00155.2013>
 162. Khodayari N, Oshins R, Mehrad B, Lascano JE, Qiang X, West JR, et al. Cigarette smoke exposed airway epithelial cell-derived EVs promote pro-inflammatory macrophage activation in alpha-1 antitrypsin deficiency. *Respir Res.* 2022;23:232. <https://doi.org/10.1186/s12931-022-02161-z>
 163. Li C-J, Liu Y, Chen Y, Yu D, Williams KJ, Liu M-L. Novel proteolytic microvesicles released from human macrophages after exposure to tobacco smoke. *Am J Pathol.* 2013;182:1552–62. <https://doi.org/10.1016/j.ajpath.2013.01.035>
 164. Tetley TD. Macrophages and the pathogenesis of COPD. *Chest.* 2002;121:156S-159S. https://doi.org/10.1378/chest.121.5_suppl.156s
 165. Nieri D, Daniele M, Lombardi S, Bazzan E, Santerini S, De Cusatis G, et al. Circulating Extracellular Vesicles Are Associated with Disease Severity and Interleukin-6 Levels in COPD: A Pilot Study. *J Clin Med.* 2021;10:5014. <https://doi.org/10.3390/jcm10215014>
 166. Cloonan SM, Choi AMK. Mitochondria in lung disease. *J Clin Invest.* 2016;126:809–20. <https://doi.org/10.1172/JCI81113>
 167. Ware SA, Kliment CR, Giordano L, Redding KM, Rumsey WL, Bates S, et al. Cell-free DNA levels associate with COPD exacerbations and mortality. *Respir Res.* 2024;25:42. <https://doi.org/10.1186/s12931-023-02658-1>
 168. Giordano L, Gregory AD, Pérez Verdaguer M, Ware SA, Harvey H, DeVallance E,

- et al. Extracellular Release of Mitochondrial DNA: Triggered by Cigarette Smoke and Detected in COPD. *Cells*. 2022;11:369. <https://doi.org/10.3390/cells11030369>
169. Ryu C, Sun H, Gulati M, Herazo-Maya JD, Chen Y, Osafo-Addo A, et al. Extracellular Mitochondrial DNA Is Generated by Fibroblasts and Predicts Death in Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med*. 2017;196:1571–81. <https://doi.org/10.1164/rccm.201612-2480OC>
 170. Chen S, Wang Y, Zhang H, Chen R, Lv F, Li Z, et al. The Antioxidant MitoQ Protects Against CSE-Induced Endothelial Barrier Injury and Inflammation by Inhibiting ROS and Autophagy in Human Umbilical Vein Endothelial Cells. *Int J Biol Sci*. 2019;15:1440–51. <https://doi.org/10.7150/ijbs.30193>
 171. Fairley LH, Das S, Dharwal V, Amorim N, Hegarty KJ, Wadhwa R, et al. Mitochondria-Targeted Antioxidants as a Therapeutic Strategy for Chronic Obstructive Pulmonary Disease. *Antioxidants (Basel)*. 2023;12:973. <https://doi.org/10.3390/antiox12040973>
 172. Li Y, Du Z, Li T, Ren X, Yu Y, Duan J, et al. MitoQ ameliorates PM2.5-induced pulmonary fibrosis through regulating the mitochondria DNA homeostasis. *Chemosphere*. 2023;330:138745. <https://doi.org/10.1016/j.chemosphere.2023.138745>
 173. Han Y, Chen L, Liu H, Jin Z, Wu Y, Wu Y, et al. Airway Epithelial cGAS Is Critical for Induction of Experimental Allergic Airway Inflammation. *J Immunol*. 2020;204:1437–47. <https://doi.org/10.4049/jimmunol.1900869>
 174. van Deursen JM. The role of senescent cells in ageing. *Nature*. 2014;509:439–46. <https://doi.org/10.1038/nature13193>
 175. Mora AL, Bueno M, Rojas M. Mitochondria in the spotlight of aging and idiopathic pulmonary fibrosis. *J Clin Invest*. 2017;127:405–14. <https://doi.org/10.1172/JCI87440>
 176. Mora AL, Rojas M, Pardo A, Selman M. Emerging therapies for idiopathic pulmonary fibrosis, a progressive age-related disease. *Nat Rev Drug Discov*. 2017;16:755–72. <https://doi.org/10.1038/nrd.2017.170>
 177. Schafer MJ, White TA, Iijima K, Haak AJ, Ligresti G, Atkinson EJ, et al. Cellular senescence mediates fibrotic pulmonary disease. *Nat Commun*. 2017;8:14532. <https://doi.org/10.1038/ncomms14532>
 178. Bueno M, Brands J, Voltz L, Fiedler K, Mays B, St Croix C, et al. ATF3 represses PINK1 gene transcription in lung epithelial cells to control mitochondrial homeostasis. *Aging Cell*. 2018;17:e12720. <https://doi.org/10.1111/ace1.12720>
 179. Caldeira D de AF, Weiss DJ, Rocco PRM, Silva PL, Cruz FF. Mitochondria in Focus: From Function to Therapeutic Strategies in Chronic Lung Diseases. *Front Immunol*. 2021;12:782074. <https://doi.org/10.3389/fimmu.2021.782074>
 180. Kurita Y, Araya J, Minagawa S, Hara H, Ichikawa A, Saito N, et al. Pirfenidone inhibits myofibroblast differentiation and lung fibrosis development during insufficient mitophagy. *Respir Res*. 2017;18:114. <https://doi.org/10.1186/s12931-017-0600-3>
 181. Kim S-J, Cheres P, Jablonski RP, Williams DB, Kamp DW. The Role of Mitochondrial DNA in Mediating Alveolar Epithelial Cell Apoptosis and Pulmonary Fibrosis. *Int J Mol Sci*. 2015;16:21486–519. <https://doi.org/10.3390/ijms160921486>
 182. Li M, Shang Y-X. Ultrastructural changes in rat airway epithelium in asthmatic airway remodeling. *Pathol Res Pract*. 2014;210:1038–42. <https://doi.org/10.1016/j.prp.2014.03.010>
 183. Mabalirajan U, Dinda AK, Kumar S, Roshan R, Gupta P, Sharma SK, et al. Mitochondrial structural changes and dysfunction are associated with experimental allergic asthma. *J Immunol*. 2008;181:3540–8. <https://doi.org/10.4049/jimmunol.181.5.3540>
 184. Song Y, Wang Z, Jiang J, Piao Y, Bai Q, Piao Q, et al. miR-181-5p attenuates neutrophilic inflammation in asthma by targeting DEK. *Int Immunopharmacol*. 2022;112:109243. <https://doi.org/10.1016/j.intimp.2022.109243>

185. Idzko M, Hammad H, van Nimwegen M, Kool M, Willart MAM, Muskens F, et al. Extracellular ATP triggers and maintains asthmatic airway inflammation by activating dendritic cells. *Nat Med.* 2007;13:913–9. <https://doi.org/10.1038/nm1617>
186. Li X, Michaeloudes C, Zhang Y, Wiegman CH, Adcock IM, Lian Q, et al. Mesenchymal stem cells alleviate oxidative stress-induced mitochondrial dysfunction in the airways. *J Allergy Clin Immunol.* 2018;141:1634-1645.e5. <https://doi.org/10.1016/j.jaci.2017.08.017>
187. Valdivieso AG, Santa-Coloma TA. CFTR activity and mitochondrial function. *Redox Biol.* 2013;1:190–202. <https://doi.org/10.1016/j.redox.2012.11.007>
188. Valdivieso AG, Marcucci F, Taminelli G, Guerrico AG, Alvarez S, Teiber ML, et al. The expression of the mitochondrial gene MT-ND4 is downregulated in cystic fibrosis. *Biochem Biophys Res Commun.* 2007;356:805–9. <https://doi.org/10.1016/j.bbrc.2007.03.057>
189. Valdivieso AG, Clauzure M, Marín MC, Taminelli GL, Massip Copiz MM, Sánchez F, et al. The mitochondrial complex I activity is reduced in cells with impaired cystic fibrosis transmembrane conductance regulator (CFTR) function. *PLoS One.* 2012;7:e48059. <https://doi.org/10.1371/journal.pone.0048059>
190. Rimessi A, Bezzerri V, Patergnani S, Marchi S, Cabrini G, Pinton P. Mitochondrial Ca²⁺-dependent NLRP3 activation exacerbates the *Pseudomonas aeruginosa*-driven inflammatory response in cystic fibrosis. *Nat Commun.* 2015;6:6201. <https://doi.org/10.1038/ncomms7201>
191. Rimessi A, Pozzato C, Carparelli L, Rossi A, Ranucci S, De Fino I, et al. Pharmacological modulation of mitochondrial calcium uniporter controls lung inflammation in cystic fibrosis. *Sci Adv.* 2020;6:eaax9093. <https://doi.org/10.1126/sciadv.aax9093>
192. Zhang Y-B, Meng Y-H, Chang S, Zhang R-Y, Shi C. High fructose causes cardiac hypertrophy via mitochondrial signaling pathway. *Am J Transl Res.* 2016;8:4869–80.
193. Kleme ML, Sané A, Garofalo C, Seidman E, Brochiero E, Berthiaume Y, et al. CFTR Deletion Confers Mitochondrial Dysfunction and Disrupts Lipid Homeostasis in Intestinal Epithelial Cells. *Nutrients.* 2018;10:836. <https://doi.org/10.3390/nu10070836>
194. Rimessi A, Vitto VAM, Patergnani S, Pinton P. Update on Calcium Signaling in Cystic Fibrosis Lung Disease. *Front Pharmacol.* 2021;12:581645. <https://doi.org/10.3389/fphar.2021.581645>
195. Banschbach MW, Karam AG, Love PK, Hilman BC. Cystic fibrosis serum promotes [45Ca] uptake by normal human leukocytes. *Biochem Biophys Res Commun.* 1978;84:922–7. [https://doi.org/10.1016/0006-291x\(78\)91671-6](https://doi.org/10.1016/0006-291x(78)91671-6)
196. Bewley MA, Preston JA, Mohasin M, Marriott HM, Budd RC, Swales J, et al. Impaired Mitochondrial Microbicidal Responses in Chronic Obstructive Pulmonary Disease Macrophages. *Am J Respir Crit Care Med.* 2017;196:845–55. <https://doi.org/10.1164/rccm.201608-1714OC>
197. Ferrari E, Monzani R, Vilella VR, Esposito S, Saluzzo F, Rossin F, et al. Cysteamine re-establishes the clearance of *Pseudomonas aeruginosa* by macrophages bearing the cystic fibrosis-relevant F508del-CFTR mutation. *Cell Death Dis.* 2017;8:e2544. <https://doi.org/10.1038/cddis.2016.476>
198. Lara-Reyna S, Scambler T, Holbrook J, Wong C, Jarosz-Griffiths HH, Martinon F, et al. Metabolic Reprograming of Cystic Fibrosis Macrophages via the IRE1 α Arm of the Unfolded Protein Response Results in Exacerbated Inflammation. *Front Immunol.* 2019;10:1789. <https://doi.org/10.3389/fimmu.2019.01789>
199. Morrison TJ, Jackson MV, Cunningham EK, Kissenpfennig A, McAuley DF, O’Kane CM, et al. Mesenchymal Stromal Cells Modulate Macrophages in Clinically Relevant Lung Injury Models by Extracellular Vesicle Mitochondrial Transfer. *Am J Respir Crit Care Med.* 2017;196:1275–86. <https://doi.org/10.1164/rccm.201701-0170OC>

200. Dutra Silva J, Su Y, Calfee CS, Delucchi KL, Weiss D, McAuley DF, et al. Mesenchymal stromal cell extracellular vesicles rescue mitochondrial dysfunction and improve barrier integrity in clinically relevant models of ARDS. *Eur Respir J*. 2021;58:2002978. <https://doi.org/10.1183/13993003.02978-2020>
201. Vögele M, Bhaskara RM, Mulvihill E, van Pee K, Yildiz Ö, Kühlbrandt W, et al. Membrane perforation by the pore-forming toxin pneumolysin. *Proc Natl Acad Sci U S A*. 2019;116:13352–7. <https://doi.org/10.1073/pnas.1904304116>
202. Nerlich A, Mieth M, Letsiou E, Fatykhova D, Zscheppang K, Imai-Matsushima A, et al. Pneumolysin induced mitochondrial dysfunction leads to release of mitochondrial DNA. *Sci Rep*. 2018;8:182. <https://doi.org/10.1038/s41598-017-18468-7>
203. Letsiou E, Teixeira Alves LG, Fatykhova D, Felten M, Mitchell TJ, Müller-Redetzky HC, et al. Microvesicles released from pneumolysin-stimulated lung epithelial cells carry mitochondrial cargo and suppress neutrophil oxidative burst. *Sci Rep*. 2021;11:9529. <https://doi.org/10.1038/s41598-021-88897-y>
204. Antunes MA, Braga CL, Oliveira TB, Kitoko JZ, Castro LL, Xisto DG, et al. Mesenchymal Stromal Cells From Emphysematous Donors and Their Extracellular Vesicles Are Unable to Reverse Cardiorespiratory Dysfunction in Experimental Severe Emphysema. *Front Cell Dev Biol*. 2021;9:661385. <https://doi.org/10.3389/fcell.2021.661385>
205. Sadikot RT, Bedi B, Li J, Yeligar SM. Alcohol-induced mitochondrial DNA damage promotes injurious crosstalk between alveolar epithelial cells and alveolar macrophages. *Alcohol*. 2019;80:65–72. <https://doi.org/10.1016/j.alcohol.2018.08.006>
206. Rice TW, Wheeler AP, Thompson BT, deBoisblanc BP, Steingrub J, Rock P, et al. Enteral omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation in acute lung injury. *JAMA*. 2011;306:1574–81. <https://doi.org/10.1001/jama.2011.1435>
207. Li C, Bo L, Liu W, Lu X, Jin F. Enteral Immunomodulatory Diet (Omega-3 Fatty Acid, γ -Linolenic Acid and Antioxidant Supplementation) for Acute Lung Injury and Acute Respiratory Distress Syndrome: An Updated Systematic Review and Meta-Analysis. *Nutrients*. 2015;7:5572–85. <https://doi.org/10.3390/nu7075239>
208. Moskowitsova K, Orfany A, Liu K, Ramirez-Barbieri G, Thedsanamoorthy JK, Yao R, et al. Mitochondrial transplantation enhances murine lung viability and recovery after ischemia-reperfusion injury. *Am J Physiol Lung Cell Mol Physiol*. 2020;318:L78–88. <https://doi.org/10.1152/ajplung.00221.2019>
209. Cloer CM, Givens CS, Buie LK, Rochelle LK, Lin Y-T, Popa S, et al. Mitochondrial transplant after ischemia reperfusion promotes cellular salvage and improves lung function during ex-vivo lung perfusion. *J Heart Lung Transplant*. 2023;42:575–84. <https://doi.org/10.1016/j.healun.2023.01.002>
210. Maremanda KP, Sundar IK, Rahman I. Protective role of mesenchymal stem cells and mesenchymal stem cell-derived exosomes in cigarette smoke-induced mitochondrial dysfunction in mice. *Toxicol Appl Pharmacol*. 2019;385:114788. <https://doi.org/10.1016/j.taap.2019.114788>
211. Weinberg SE, Sena LA, Chandel NS. Mitochondria in the regulation of innate and adaptive immunity. *Immunity*. 2015;42:406–17. <https://doi.org/10.1016/j.immuni.2015.02.002>
212. Patergnani S, Morciano G, Carinci M, Leo S, Pinton P, Rimessi A. The “mitochondrial stress responses”: the “Dr. Jekyll and Mr. Hyde” of neuronal disorders. *Neural Regen Res*. 2022;17:2563–75. <https://doi.org/10.4103/1673-5374.339473>
213. D’Alessandro MCB, Kanaan S, Geller M, Praticò D, Daher JPL. Mitochondrial dysfunction in Alzheimer’s disease. *Ageing Res Rev*. 2025;107:102713. <https://doi.org/10.1016/j.arr.2025.102713>
214. Scheiblich H, Dansokho C, Mercan D, Schmidt SV, Bousset L, Wischhof L, et al. Microglia jointly degrade fibrillar alpha-synuclein cargo by distribution through tunneling

- nanotubes. *Cell*. 2021;184:5089-5106.e21. <https://doi.org/10.1016/j.cell.2021.09.007>
215. Patergnani S, Bataillard MS, Danese A, Alves S, Cazevieille C, Valéro R, et al. The Wolfram-like variant WFS1E864K destabilizes MAM and compromises autophagy and mitophagy in human and mice. *Autophagy*. 2024;20:2055–66. <https://doi.org/10.1080/15548627.2024.2341588>
 216. Patergnani S, Bonora M, Ingusci S, Prevati M, Marchi S, Zucchini S, et al. Antipsychotic drugs counteract autophagy and mitophagy in multiple sclerosis. *Proc Natl Acad Sci U S A*. 2021;118:e2020078118. <https://doi.org/10.1073/pnas.2020078118>
 217. Castellazzi M, Patergnani S, Donadio M, Giorgi C, Bonora M, Bosi C, et al. Autophagy and mitophagy biomarkers are reduced in sera of patients with Alzheimer's disease and mild cognitive impairment. *Sci Rep*. 2019;9:20009. <https://doi.org/10.1038/s41598-019-56614-5>
 218. Nitzan K, Benhamron S, Valitsky M, Kesner EE, Lichtenstein M, Ben-Zvi A, et al. Mitochondrial Transfer Ameliorates Cognitive Deficits, Neuronal Loss, and Gliosis in Alzheimer's Disease Mice. *J Alzheimers Dis*. 2019;72:587–604. <https://doi.org/10.3233/JAD-190853>
 219. Du F, Yu Q, Kanaan NM, Yan SS. Mitochondrial oxidative stress contributes to the pathological aggregation and accumulation of tau oligomers in Alzheimer's disease. *Hum Mol Genet*. 2022;31:2498–507. <https://doi.org/10.1093/hmg/ddab363>
 220. Averchuk AS, Ryazanova MV, Baranich TI, Stavrovskaya AV, Rozanova NA, Novikova SV, et al. The Neurotoxic Effect of β -Amyloid Is Accompanied by Changes in the Mitochondrial Dynamics and Autophagy in Neurons and Brain Endothelial Cells in the Experimental Model of Alzheimer's Disease. *Bull Exp Biol Med*. 2023;175:315–20. <https://doi.org/10.1007/s10517-023-05859-2>
 221. Zhou G, Ye Q, Xu Y, He B, Wu L, Zhu G, et al. Mitochondrial calcium uptake 3 mitigates cerebral amyloid angiopathy-related neuronal death and glial inflammation by reducing mitochondrial dysfunction. *Int Immunopharmacol*. 2023;117:109614. <https://doi.org/10.1016/j.intimp.2022.109614>
 222. Yan Y-Q, Zheng R, Liu Y, Ruan Y, Lin Z-H, Xue N-J, et al. Parkin regulates microglial NLRP3 and represses neurodegeneration in Parkinson's disease. *Aging Cell*. 2023;22:e13834. <https://doi.org/10.1111/accel.13834>
 223. Ma C, Liu Y, Li S, Ma C, Huang J, Wen S, et al. Microglial cGAS drives neuroinflammation in the MPTP mouse models of Parkinson's disease. *CNS Neurosci Ther*. 2023;29:2018–35. <https://doi.org/10.1111/cns.14157>
 224. Howden JH, Hakansson H, Nieto-Rostro M, McAdam R, Arber C, Brandon NJ, et al. Hexokinase 2 interacts with PINK1 to facilitate mitophagy in astrocytes and restrain inflammation-induced neurotoxicity. *Cell Rep*. 2025;44:115809. <https://doi.org/10.1016/j.celrep.2025.115809>
 225. Lu Y, Gao L, Yang Y, Shi D, Zhang Z, Wang X, et al. Protective role of mitophagy on microglia-mediated neuroinflammatory injury through mtDNA-STING signaling in manganese-induced parkinsonism. *J Neuroinflammation*. 2025;22:55. <https://doi.org/10.1186/s12974-025-03396-5>
 226. Shi X, Zhao M, Fu C, Fu A. Intravenous administration of mitochondria for treating experimental Parkinson's disease. *Mitochondrion*. 2017;34:91–100. <https://doi.org/10.1016/j.mito.2017.02.005>
 227. Eo H, Yu S-H, Choi Y, Kim Y, Kang YC, Lee H, et al. Mitochondrial transplantation exhibits neuroprotective effects and improves behavioral deficits in an animal model of Parkinson's disease. *Neurotherapeutics*. 2024;21:e00355. <https://doi.org/10.1016/j.neurot.2024.e00355>
 228. Jain R, Begum N, Rajan S, Tryphena KP, Khatri DK. Role of F-actin-mediated endocytosis and exercise in mitochondrial transplantation in an experimental Parkinson's

- disease mouse model. *Mitochondrion*. 2024;74:101824.
<https://doi.org/10.1016/j.mito.2023.11.007>
229. Huang C, Yan S, Zhang Z. Maintaining the balance of TDP-43, mitochondria, and autophagy: a promising therapeutic strategy for neurodegenerative diseases. *Transl Neurodegener*. 2020;9:40. <https://doi.org/10.1186/s40035-020-00219-w>
 230. Wang W, Li L, Lin W-L, Dickson DW, Petrucelli L, Zhang T, et al. The ALS disease-associated mutant TDP-43 impairs mitochondrial dynamics and function in motor neurons. *Hum Mol Genet*. 2013;22:4706–19. <https://doi.org/10.1093/hmg/ddt319>
 231. Deora V, Lee JD, Albornoz EA, McAlary L, Jagaraj CJ, Robertson AAB, et al. The microglial NLRP3 inflammasome is activated by amyotrophic lateral sclerosis proteins. *Glia*. 2020;68:407–21. <https://doi.org/10.1002/glia.23728>
 232. Zhao J, Wang X, Huo Z, Chen Y, Liu J, Zhao Z, et al. The Impact of Mitochondrial Dysfunction in Amyotrophic Lateral Sclerosis. *Cells*. 2022;11:2049.
<https://doi.org/10.3390/cells11132049>
 233. Soo KY, Sultana J, King AE, Atkinson R, Warraich ST, Sundaramoorthy V, et al. ALS-associated mutant FUS inhibits macroautophagy which is restored by overexpression of Rab1. *Cell Death Discov*. 2015;1:15030. <https://doi.org/10.1038/cddiscovery.2015.30>
 234. Sasaki S. Autophagy in spinal cord motor neurons in sporadic amyotrophic lateral sclerosis. *J Neuropathol Exp Neurol*. 2011;70:349–59.
<https://doi.org/10.1097/NEN.0b013e3182160690>
 235. Nassif M, Valenzuela V, Rojas-Rivera D, Vidal R, Matus S, Castillo K, et al. Pathogenic role of BECN1/Beclin 1 in the development of amyotrophic lateral sclerosis. *Autophagy*. 2014;10:1256–71. <https://doi.org/10.4161/auto.28784>
 236. Fecto F, Yan J, Vemula SP, Liu E, Yang Y, Chen W, et al. SQSTM1 mutations in familial and sporadic amyotrophic lateral sclerosis. *Arch Neurol*. 2011;68:1440–6.
<https://doi.org/10.1001/archneurol.2011.250>
 237. Rudnick ND, Griffey CJ, Guarnieri P, Gerbino V, Wang X, Piersaint JA, et al. Distinct roles for motor neuron autophagy early and late in the SOD1G93A mouse model of ALS. *Proc Natl Acad Sci U S A*. 2017;114:E8294–303.
<https://doi.org/10.1073/pnas.1704294114>
 238. Zhang R, Chen Y, Wang X, Tian H, Liu H, Xiang Z, et al. Spreading of pathological TDP-43 along corticospinal tract axons induces ALS-like phenotypes in Atg5^{+/-} mice. *Int J Biol Sci*. 2021;17:390–401. <https://doi.org/10.7150/ijbs.53872>
 239. Bonora M, De Marchi E, Patergnani S, Suski JM, Celsi F, Bononi A, et al. Tumor necrosis factor- α impairs oligodendroglial differentiation through a mitochondria-dependent process. *Cell Death Differ*. 2014;21:1198–208. <https://doi.org/10.1038/cdd.2014.35>
 240. Leurs CE, Podlesniy P, Trullas R, Balk L, Steenwijk MD, Malekzadeh A, et al. Cerebrospinal fluid mtDNA concentration is elevated in multiple sclerosis disease and responds to treatment. *Mult Scler*. 2018;24:472–80.
<https://doi.org/10.1177/1352458517699874>
 241. Patergnani S, Castellazzi M, Bonora M, Marchi S, Casetta I, Pugliatti M, et al. Autophagy and mitophagy elements are increased in body fluids of multiple sclerosis-affected individuals. *J Neurol Neurosurg Psychiatry*. 2018;89:439–41.
<https://doi.org/10.1136/jnnp-2017-316234>
 242. Patergnani S, Laudisi M, Bonora M, Righes G, Straudi S, Wieckowski MR, et al. Pathogenetic Involvement of Autophagy and Mitophagy in Primary Progressive Multiple Sclerosis. *J Cell Mol Med*. 2025;29:e70455. <https://doi.org/10.1111/jcmm.70455>
 243. Fransen NL, Crusius JBA, Smolders J, Mizze MR, van Eden CG, Luchetti S, et al. Post-mortem multiple sclerosis lesion pathology is influenced by single nucleotide polymorphisms. *Brain Pathol*. 2020;30:106–19. <https://doi.org/10.1111/bpa.12760>
 244. van Luijn MM, Kreft KL, Jongsma ML, Mes SW, Wierenga-Wolf AF, van Meurs

- M, et al. Multiple sclerosis-associated CLEC16A controls HLA class II expression via late endosome biogenesis. *Brain*. 2015;138:1531–47. <https://doi.org/10.1093/brain/awv080>
245. Kadowaki A, Wheeler MA, Li Z, Andersen BM, Lee H-G, Illouz T, et al. CLEC16A in astrocytes promotes mitophagy and limits pathology in a multiple sclerosis mouse model. *Nat Neurosci*. 2025;28:470–86. <https://doi.org/10.1038/s41593-025-01875-9>
 246. Alison MR. The cellular origins of cancer with particular reference to the gastrointestinal tract. *Int J Exp Pathol*. 2020;101:132–51. <https://doi.org/10.1111/iep.12364>
 247. Agrawal M, Allin KH, Petralia F, Colombel J-F, Jess T. Multiomics to elucidate inflammatory bowel disease risk factors and pathways. *Nat Rev Gastroenterol Hepatol*. 2022;19:399–409. <https://doi.org/10.1038/s41575-022-00593-y>
 248. Chang JT. Pathophysiology of Inflammatory Bowel Diseases. *N Engl J Med*. 2020;383:2652–64. <https://doi.org/10.1056/NEJMra2002697>
 249. Nanini HF, Bernardazzi C, Castro F, de Souza HSP. Damage-associated molecular patterns in inflammatory bowel disease: From biomarkers to therapeutic targets. *World J Gastroenterol*. 2018;24:4622–34. <https://doi.org/10.3748/wjg.v24.i41.4622>
 250. Aldars-García L, Gisbert JP, Chaparro M. Metabolomics Insights into Inflammatory Bowel Disease: A Comprehensive Review. *Pharmaceuticals (Basel)*. 2021;14:1190. <https://doi.org/10.3390/ph14111190>
 251. Haberman Y, Karns R, Dexheimer PJ, Schirmer M, Somekh J, Jurickova I, et al. Ulcerative colitis mucosal transcriptomes reveal mitochondriopathy and personalized mechanisms underlying disease severity and treatment response. *Nat Commun*. 2019;10:38. <https://doi.org/10.1038/s41467-018-07841-3>
 252. Novak EA, Crawford EC, Mentrup HL, Griffith BD, Fletcher DM, Flanagan MR, et al. Epithelial NAD⁺ depletion drives mitochondrial dysfunction and contributes to intestinal inflammation. *Front Immunol*. 2023;14:1231700. <https://doi.org/10.3389/fimmu.2023.1231700>
 253. Kugathasan S, Denson LA, Walters TD, Kim M-O, Marigorta UM, Schirmer M, et al. Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study. *Lancet*. 2017;389:1710–8. [https://doi.org/10.1016/S0140-6736\(17\)30317-3](https://doi.org/10.1016/S0140-6736(17)30317-3)
 254. Hsieh S-Y, Shih T-C, Yeh C-Y, Lin C-J, Chou Y-Y, Lee Y-S. Comparative proteomic studies on the pathogenesis of human ulcerative colitis. *Proteomics*. 2006;6:5322–31. <https://doi.org/10.1002/pmic.200500541>
 255. Mottawea W, Chiang C-K, Mühlbauer M, Starr AE, Butcher J, Abujamel T, et al. Altered intestinal microbiota-host mitochondria crosstalk in new onset Crohn's disease. *Nat Commun*. 2016;7:13419. <https://doi.org/10.1038/ncomms13419>
 256. Sifroni KG, Damiani CR, Stoffel C, Cardoso MR, Ferreira GK, Jeremias IC, et al. Mitochondrial respiratory chain in the colonic mucosal of patients with ulcerative colitis. *Mol Cell Biochem*. 2010;342:111–5. <https://doi.org/10.1007/s11010-010-0474-x>
 257. Santhanam S, Rajamanickam S, Motamarri A, Ramakrishna BS, Amirtharaj JG, Ramachandran A, et al. Mitochondrial electron transport chain complex dysfunction in the colonic mucosa in ulcerative colitis. *Inflamm Bowel Dis*. 2012;18:2158–68. <https://doi.org/10.1002/ibd.22926>
 258. Santhanam S, Venkatraman A, Ramakrishna BS. Impairment of mitochondrial acetoacetyl CoA thiolase activity in the colonic mucosa of patients with ulcerative colitis. *Gut*. 2007;56:1543–9. <https://doi.org/10.1136/gut.2006.108449>
 259. Kłos P, Dabrowski SA. The Role of Mitochondria Dysfunction in Inflammatory Bowel Diseases and Colorectal Cancer. *Int J Mol Sci*. 2021;22:11673. <https://doi.org/10.3390/ijms222111673>
 260. Ho G-T, Aird RE, Liu B, Boyapati RK, Kennedy NA, Dorward DA, et al. MDR1 deficiency impairs mitochondrial homeostasis and promotes intestinal inflammation.

- Mucosal Immunol. 2018;11:120–30. <https://doi.org/10.1038/mi.2017.31>
261. Özsoy M, Stummer N, Zimmermann FA, Feichtinger RG, Sperl W, Weghuber D, et al. Role of Energy Metabolism and Mitochondrial Function in Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2022;28:1443–50. <https://doi.org/10.1093/ibd/izac024>
 262. Liu B, Gulati AS, Cantillana V, Henry SC, Schmidt EA, Daniell X, et al. Irgm1-deficient mice exhibit Paneth cell abnormalities and increased susceptibility to acute intestinal inflammation. *Am J Physiol Gastrointest Liver Physiol*. 2013;305:G573–584. <https://doi.org/10.1152/ajpgi.00071.2013>
 263. Kabi A, Nickerson KP, Homer CR, McDonald C. Digesting the genetics of inflammatory bowel disease: insights from studies of autophagy risk genes. *Inflamm Bowel Dis*. 2012;18:782–92. <https://doi.org/10.1002/ibd.21868>
 264. Zhang H, Zheng L, McGovern DPB, Hamill AM, Ichikawa R, Kanazawa Y, et al. Myeloid ATG16L1 Facilitates Host-Bacteria Interactions in Maintaining Intestinal Homeostasis. *J Immunol*. 2017;198:2133–46. <https://doi.org/10.4049/jimmunol.1601293>
 265. Rodríguez-Colman MJ, Schewe M, Meerlo M, Stigter E, Gerrits J, Pras-Raves M, et al. Interplay between metabolic identities in the intestinal crypt supports stem cell function. *Nature*. 2017;543:424–7. <https://doi.org/10.1038/nature21673>
 266. Formentini L, Santacatterina F, Núñez de Arenas C, Stamatakis K, López-Martínez D, Logan A, et al. Mitochondrial ROS Production Protects the Intestine from Inflammation through Functional M2 Macrophage Polarization. *Cell Rep*. 2017;19:1202–13. <https://doi.org/10.1016/j.celrep.2017.04.036>
 267. Boyapati RK, Rossi AG, Satsangi J, Ho G-T. Gut mucosal DAMPs in IBD: from mechanisms to therapeutic implications. *Mucosal Immunol*. 2016;9:567–82. <https://doi.org/10.1038/mi.2016.14>
 268. Vrablicova Z, Tomova K, Tothova L, Babickova J, Gromova B, Konecna B, et al. Nuclear and Mitochondrial Circulating Cell-Free DNA Is Increased in Patients With Inflammatory Bowel Disease in Clinical Remission. *Front Med (Lausanne)*. 2020;7:593316. <https://doi.org/10.3389/fmed.2020.593316>
 269. Jackson DN, Panopoulos M, Neumann WL, Turner K, Cantarel BL, Thompson-Snipes L, et al. Mitochondrial dysfunction during loss of prohibitin 1 triggers Paneth cell defects and ileitis. *Gut*. 2020;69:1928–38. <https://doi.org/10.1136/gutjnl-2019-319523>
 270. Uddin J, Sharma A, Wu D, Tomar S, Ganesan V, Reichel PE, et al. STARD7 maintains intestinal epithelial mitochondria architecture, barrier integrity, and protection from colitis. *JCI Insight*. 2024;9:e172978. <https://doi.org/10.1172/jci.insight.172978>
 271. Foerster EG, Mukherjee T, Cabral-Fernandes L, Rocha JDB, Girardin SE, Philpott DJ. How autophagy controls the intestinal epithelial barrier. *Autophagy*. 2022;18:86–103. <https://doi.org/10.1080/15548627.2021.1909406>
 272. Ravindran R, Loebbermann J, Nakaya HI, Khan N, Ma H, Gama L, et al. The amino acid sensor GCN2 controls gut inflammation by inhibiting inflammasome activation. *Nature*. 2016;531:523–7. <https://doi.org/10.1038/nature17186>
 273. Bauer C, Duewell P, Mayer C, Lehr HA, Fitzgerald KA, Dauer M, et al. Colitis induced in mice with dextran sulfate sodium (DSS) is mediated by the NLRP3 inflammasome. *Gut*. 2010;59:1192–9. <https://doi.org/10.1136/gut.2009.197822>
 274. Allen IC, TeKippe EM, Woodford R-MT, Uronis JM, Holl EK, Rogers AB, et al. The NLRP3 inflammasome functions as a negative regulator of tumorigenesis during colitis-associated cancer. *J Exp Med*. 2010;207:1045–56. <https://doi.org/10.1084/jem.20100050>
 275. Han J, Yu C, Souza RF, Theiss AL. Prohibitin 1 modulates mitochondrial function of Stat3. *Cell Signal*. 2014;26:2086–95. <https://doi.org/10.1016/j.cellsig.2014.06.006>
 276. López-Armada MJ, Riveiro-Naveira RR, Vaamonde-García C, Valcárcel-Ares MN. Mitochondrial dysfunction and the inflammatory response. *Mitochondrion*. 2013;13:106–18. <https://doi.org/10.1016/j.mito.2013.01.003>

277. Billmeier U, Dieterich W, Neurath MF, Atreya R. Molecular mechanism of action of anti-tumor necrosis factor antibodies in inflammatory bowel diseases. *World J Gastroenterol.* 2016;22:9300–13. <https://doi.org/10.3748/wjg.v22.i42.9300>
278. Heller S, Penrose HM, Cable C, Biswas D, Nakhoul H, Baddoo M, et al. Reduced mitochondrial activity in colonocytes facilitates AMPK α 2-dependent inflammation. *FASEB J.* 2017;31:2013–25. <https://doi.org/10.1096/fj.201600976R>
279. Wang A, Keita ÁV, Phan V, McKay CM, Schoultz I, Lee J, et al. Targeting mitochondria-derived reactive oxygen species to reduce epithelial barrier dysfunction and colitis. *Am J Pathol.* 2014;184:2516–27. <https://doi.org/10.1016/j.ajpath.2014.05.019>
280. Verma A, Pittala S, Alhozeel B, Shteinfer-Kuzmine A, Ohana E, Gupta R, et al. The role of the mitochondrial protein VDAC1 in inflammatory bowel disease: a potential therapeutic target. *Mol Ther.* 2022;30:726–44. <https://doi.org/10.1016/j.ymthe.2021.06.024>
281. Li Y, Liu X, Zhang Q, Jiang Z, Zhang W, Yang C, et al. Koumine mediates the generation of mtROS through the IP3R1-GRP75-VDAC1 complex to improve Citrinin induced intestinal inflammation. *Phytomedicine.* 2025;142:156803. <https://doi.org/10.1016/j.phymed.2025.156803>
282. Cunningham KE, Vincent G, Sodhi CP, Novak EA, Ranganathan S, Egan CE, et al. Peroxisome Proliferator-activated Receptor- γ Coactivator 1- α (PGC1 α) Protects against Experimental Murine Colitis. *J Biol Chem.* 2016;291:10184–200. <https://doi.org/10.1074/jbc.M115.688812>
283. Vincent G, Novak EA, Siow VS, Cunningham KE, Griffith BD, Comerford TE, et al. Nix-Mediated Mitophagy Modulates Mitochondrial Damage During Intestinal Inflammation. *Antioxid Redox Signal.* 2020;33:1–19. <https://doi.org/10.1089/ars.2018.7702>
284. Lewis JD, Lichtenstein GR, Deren JJ, Sands BE, Hanauer SB, Katz JA, et al. Rosiglitazone for active ulcerative colitis: a randomized placebo-controlled trial. *Gastroenterology.* 2008;134:688–95. <https://doi.org/10.1053/j.gastro.2007.12.012>
285. Rousseaux C, Lefebvre B, Dubuquoy L, Lefebvre P, Romano O, Auwerx J, et al. Intestinal antiinflammatory effect of 5-aminosalicylic acid is dependent on peroxisome proliferator-activated receptor- γ . *J Exp Med.* 2005;201:1205–15. <https://doi.org/10.1084/jem.20041948>
286. Tian R, Liu X, Luo Y, Jiang S, Liu H, You F, et al. Apoptosis Exerts a Vital Role in the Treatment of Colitis-Associated Cancer by Herbal Medicine. *Front Pharmacol.* 2020;11:438. <https://doi.org/10.3389/fphar.2020.00438>
287. Randhawa PK, Singh K, Singh N, Jaggi AS. A review on chemical-induced inflammatory bowel disease models in rodents. *Korean J Physiol Pharmacol.* 2014;18:279–88. <https://doi.org/10.4196/kjpp.2014.18.4.279>
288. Kang YH, Tucker SA, Quevedo SF, Inal A, Korzenik JR, Haigis MC. Metabolic analyses reveal dysregulated NAD⁺ metabolism and altered mitochondrial state in ulcerative colitis. *PLoS One.* 2022;17:e0273080. <https://doi.org/10.1371/journal.pone.0273080>
289. Lv Q, Wang K, Qiao S, Yang L, Xin Y, Dai Y, et al. Norisoboldine, a natural AhR agonist, promotes Treg differentiation and attenuates colitis via targeting glycolysis and subsequent NAD⁺/SIRT1/SUV39H1/H3K9me3 signaling pathway. *Cell Death Dis.* 2018;9:258. <https://doi.org/10.1038/s41419-018-0297-3>
290. Novak EA, Mollen KP. Mitochondrial dysfunction in inflammatory bowel disease. *Front Cell Dev Biol.* 2015;3:62. <https://doi.org/10.3389/fcell.2015.00062>
291. Khaloian S, Rath E, Hammoudi N, Gleisinger E, Blutke A, Giesbertz P, et al. Mitochondrial impairment drives intestinal stem cell transition into dysfunctional Paneth cells predicting Crohn's disease recurrence. *Gut.* 2020;69:1939–51. <https://doi.org/10.1136/gutjnl-2019-319514>
292. Liu T-C, Gurram B, Baldridge MT, Head R, Lam V, Luo C, et al. Paneth cell defects

- in Crohn's disease patients promote dysbiosis. *JCI Insight*. 2016;1:e86907. <https://doi.org/10.1172/jci.insight.86907>
293. Byndloss MX, Olsan EE, Rivera-Chávez F, Tiffany CR, Cevallos SA, Lokken KL, et al. Microbiota-activated PPAR- γ signaling inhibits dysbiotic Enterobacteriaceae expansion. *Science*. 2017;357:570–5. <https://doi.org/10.1126/science.aam9949>
 294. Litvak Y, Byndloss MX, Bäumlér AJ. Colonocyte metabolism shapes the gut microbiota. *Science*. 2018;362:eaat9076. <https://doi.org/10.1126/science.aat9076>
 295. Kieffer DA, Martin RJ, Adams SH. Impact of Dietary Fibers on Nutrient Management and Detoxification Organs: Gut, Liver, and Kidneys. *Adv Nutr*. 2016;7:1111–21. <https://doi.org/10.3945/an.116.013219>
 296. Xi Y, Xu P. Global colorectal cancer burden in 2020 and projections to 2040. *Transl Oncol*. 2021;14:101174. <https://doi.org/10.1016/j.tranon.2021.101174>
 297. Yalchin M, Baker A-M, Graham TA, Hart A. Predicting Colorectal Cancer Occurrence in IBD. *Cancers (Basel)*. 2021;13:2908. <https://doi.org/10.3390/cancers13122908>
 298. Song M, Emilsson L, Roelstraete B, Ludvigsson JF. Risk of colorectal cancer in first degree relatives of patients with colorectal polyps: nationwide case-control study in Sweden. *BMJ*. 2021;373:n877. <https://doi.org/10.1136/bmj.n877>
 299. Yin K, Lee J, Liu Z, Kim H, Martin DR, Wu D, et al. Mitophagy protein PINK1 suppresses colon tumor growth by metabolic reprogramming via p53 activation and reducing acetyl-CoA production. *Cell Death Differ*. 2021;28:2421–35. <https://doi.org/10.1038/s41418-021-00760-9>
 300. da Silva-Camargo CCV, Svoboda Baldin RK, Costacurta Polli NL, Agostinho AP, Olandosk M, de Noronha L, et al. Parkin protein expression and its impact on survival of patients with advanced colorectal cancer. *Cancer Biol Med*. 2018;15:61–9. <https://doi.org/10.20892/j.issn.2095-3941.2017.0136>
 301. Chen R, Lai LA, Brentnall TA, Pan S. Biomarkers for colitis-associated colorectal cancer. *World J Gastroenterol*. 2016;22:7882–91. <https://doi.org/10.3748/wjg.v22.i35.7882>
 302. Xie S, Wang X, Gan S, Tang X, Kang X, Zhu S. The Mitochondrial Chaperone TRAP1 as a Candidate Target of Oncotherapy. *Front Oncol*. 2020;10:585047. <https://doi.org/10.3389/fonc.2020.585047>
 303. Boyapati RK, Dorward DA, Tamborska A, Kalla R, Ventham NT, Doherty MK, et al. Mitochondrial DNA Is a Pro-Inflammatory Damage-Associated Molecular Pattern Released During Active IBD. *Inflamm Bowel Dis*. 2018;24:2113–22. <https://doi.org/10.1093/ibd/izy095>
 304. Spinazzola A, Zeviani M. Disorders of nuclear-mitochondrial intergenomic signaling. *Gene*. 2005;354:162–8. <https://doi.org/10.1016/j.gene.2005.03.025>
 305. Chinnery PF, Turnbull DM. Mitochondrial medicine. *QJM*. 1997;90:657–67. <https://doi.org/10.1093/qjmed/90.11.657>
 306. Giordano C, Sebastiani M, Plazzi G, Travaglini C, Sale P, Pinti M, et al. Mitochondrial neurogastrointestinal encephalomyopathy: evidence of mitochondrial DNA depletion in the small intestine. *Gastroenterology*. 2006;130:893–901. <https://doi.org/10.1053/j.gastro.2006.01.004>
 307. Zimmer V, Feiden W, Becker G, Zimmer A, Reith W, Raedle J, et al. Absence of the interstitial cell of Cajal network in mitochondrial neurogastrointestinal encephalomyopathy. *Neurogastroenterol Motil*. 2009;21:627–31. <https://doi.org/10.1111/j.1365-2982.2009.01264.x>
 308. Camilleri M, Carlson P, Zinsmeister AR, McKinzie S, Busciglio I, Burton D, et al. Mitochondrial DNA and gastrointestinal motor and sensory functions in health and functional gastrointestinal disorders. *Am J Physiol Gastrointest Liver Physiol*. 2009;296:G510-516. <https://doi.org/10.1152/ajpgi.90650.2008>

309. Sagar S, Liu PP, Cooper LT. Myocarditis. *Lancet*. 2012;379:738–47.
[https://doi.org/10.1016/S0140-6736\(11\)60648-X](https://doi.org/10.1016/S0140-6736(11)60648-X)
310. Libby P. The changing landscape of atherosclerosis. *Nature*. 2021;592:524–33.
<https://doi.org/10.1038/s41586-021-03392-8>
311. Libby P. Inflammation during the life cycle of the atherosclerotic plaque. *Cardiovasc Res*. 2021;117:2525–36. <https://doi.org/10.1093/cvr/cvab303>
312. Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, et al. Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature*. 2010;464:104–7.
<https://doi.org/10.1038/nature08780>
313. Morciano G, Rimessi A, Patergnani S, Vitto VAM, Danese A, Kahsay A, et al. Calcium dysregulation in heart diseases: Targeting calcium channels to achieve a correct calcium homeostasis. *Pharmacol Res*. 2022;177:106119.
<https://doi.org/10.1016/j.phrs.2022.106119>
314. Ammirati E, Frigerio M, Adler ED, Basso C, Birnie DH, Brambatti M, et al. Management of Acute Myocarditis and Chronic Inflammatory Cardiomyopathy: An Expert Consensus Document. *Circ Heart Fail*. 2020;13:e007405.
<https://doi.org/10.1161/CIRCHEARTFAILURE.120.007405>
315. Fairweather D, Beetler DJ, Di Florio DN, Musick N, Heidecker B, Cooper LT. COVID-19, Myocarditis and Pericarditis. *Circ Res*. 2023;132:1302–19.
<https://doi.org/10.1161/CIRCRESAHA.123.321878>
316. Lu RXZ, Rafatian N, Zhao Y, Wagner KT, Beroncal EL, Li B, et al. Cardiac tissue model of immune-induced dysfunction reveals the role of free mitochondrial DNA and the therapeutic effects of exosomes. *Sci Adv*. 2024;10:eadi0164.
<https://doi.org/10.1126/sciadv.adk0164>
317. Rohrbeck M, Hoerr V, Piccini I, Greber E, Schulte JS, Hübner S-S, et al. Pathophysiological Mechanisms of Cardiac Dysfunction in Transgenic Mice with Viral Myocarditis. *Cells*. 2023;12:550. <https://doi.org/10.3390/cells12040550>
318. Preau S, Delguste F, Yu Y, Remy-Jouet I, Richard V, Saulnier F, et al. Endotoxemia Engages the RhoA Kinase Pathway to Impair Cardiac Function By Altering Cytoskeleton, Mitochondrial Fission, and Autophagy. *Antioxid Redox Signal*. 2016;24:529–42.
<https://doi.org/10.1089/ars.2015.6421>
319. Burnett JR, Hooper AJ, Hegele RA. Remnant Cholesterol and Atherosclerotic Cardiovascular Disease Risk. *J Am Coll Cardiol*. 2020;76:2736–9.
<https://doi.org/10.1016/j.jacc.2020.10.029>
320. Sun L, Leng R, Liu M, Su M, He Q, Zhang Z, et al. Endothelial MICU1 protects against vascular inflammation and atherosclerosis by inhibiting mitochondrial calcium uptake. *J Clin Invest*. 2025;135:e181928. <https://doi.org/10.1172/JCI181928>
321. van der Heijden T, Kritikou E, Venema W, van Duijn J, van Santbrink PJ, Slütter B, et al. NLRP3 Inflammasome Inhibition by MCC950 Reduces Atherosclerotic Lesion Development in Apolipoprotein E-Deficient Mice-Brief Report. *Arterioscler Thromb Vasc Biol*. 2017;37:1457–61. <https://doi.org/10.1161/ATVBAHA.117.309575>
322. Baik SH, Ramanujan VK, Becker C, Fett S, Underhill DM, Wolf AJ. Hexokinase dissociation from mitochondria promotes oligomerization of VDAC that facilitates NLRP3 inflammasome assembly and activation. *Sci Immunol*. 2023;8:eade7652.
<https://doi.org/10.1126/sciimmunol.ade7652>
323. Zhang S, Lv Y, Luo X, Weng X, Qi J, Bai X, et al. Homocysteine promotes atherosclerosis through macrophage pyroptosis via endoplasmic reticulum stress and calcium disorder. *Mol Med*. 2023;29:73. <https://doi.org/10.1186/s10020-023-00656-z>
324. Cotter DG, Schugar RC, Crawford PA. Ketone body metabolism and cardiovascular disease. *Am J Physiol Heart Circ Physiol*. 2013;304:H1060-1076.
<https://doi.org/10.1152/ajpheart.00646.2012>

325. Coon BG, Timalina S, Astone M, Zhuang ZW, Fang J, Han J, et al. A mitochondrial contribution to anti-inflammatory shear stress signaling in vascular endothelial cells. *J Cell Biol.* 2022;221:e202109144. <https://doi.org/10.1083/jcb.202109144>
326. Wei Z, Zhang Y, Chen J, Hu Y, Jia P, Wang X, et al. Pathogenic CARD11 mutations affect B cell development and differentiation through a noncanonical pathway. *Sci Immunol.* 2019;4:eaaw5618. <https://doi.org/10.1126/sciimmunol.aaw5618>
327. Tian C, Han X, He L, Tang F, Huang R, Lin Z, et al. Transient receptor potential ankyrin 1 contributes to the ATP-elicited oxidative stress and inflammation in THP-1-derived macrophage. *Mol Cell Biochem.* 2020;473:179–92. <https://doi.org/10.1007/s11010-020-03818-3>
328. Morciano G, Giorgi C, Bonora M, Punzetti S, Pavasini R, Wieckowski MR, et al. Molecular identity of the mitochondrial permeability transition pore and its role in ischemia-reperfusion injury. *J Mol Cell Cardiol.* 2015;78:142–53. <https://doi.org/10.1016/j.yjmcc.2014.08.015>
329. Campo G, Morciano G, Pavasini R, Bonora M, Sbrana L, Biscaglia S, et al. Fo ATP synthase C subunit serum levels in patients with ST-segment Elevation Myocardial Infarction: Preliminary findings. *International Journal of Cardiology.* 2016;221:993–7. <https://doi.org/10.1016/j.ijcard.2016.07.125>
330. Morciano G, Pinton P. Modulation of mitochondrial permeability transition pores in reperfusion injury: Mechanisms and therapeutic approaches. *Eur J Clin Invest.* 2025;55:e14331. <https://doi.org/10.1111/eci.14331>
331. Morciano G, Pedriali G, Bonora M, Pavasini R, Mikus E, Calvi S, et al. A naturally occurring mutation in ATP synthase subunit c is associated with increased damage following hypoxia/reoxygenation in STEMI patients. *Cell Rep.* 2021;35:108983. <https://doi.org/10.1016/j.celrep.2021.108983>
332. Zhang H, Liu L, Shen C, Jiang X, Liu J, Chen J, et al. Lactate-Induced Mitochondrial Calcium Uptake 3 Aggravates Myocardial Ischemia-Reperfusion Injury by Promoting Neutrophil Extracellular Trap Formation. *Research (Wash D C).* 2025;8:0705. <https://doi.org/10.34133/research.0705>
333. Xu H, Chen X, Luo S, Jiang J, Pan X, He Y, et al. Cardiomyocyte-specific Piezo1 deficiency mitigates ischemia-reperfusion injury by preserving mitochondrial homeostasis. *Redox Biol.* 2025;79:103471. <https://doi.org/10.1016/j.redox.2024.103471>
334. John GB, Shang Y, Li L, Renken C, Mannella CA, Selker JML, et al. The mitochondrial inner membrane protein mitofilin controls cristae morphology. *Mol Biol Cell.* 2005;16:1543–54. <https://doi.org/10.1091/mbc.e04-08-0697>
335. Feng Y, Imam Aliagan A, Tombo N, Bopassa JC. Mitofilin Heterozygote Mice Display an Increase in Myocardial Injury and Inflammation after Ischemia/Reperfusion. *Antioxidants (Basel).* 2023;12:921. <https://doi.org/10.3390/antiox12040921>
336. Shi X, Liu C, Chen J, Zhou S, Li Y, Zhao X, et al. Endothelial MICU1 alleviates diabetic cardiomyopathy by attenuating nitrate stress-mediated cardiac microvascular injury. *Cardiovasc Diabetol.* 2023;22:216. <https://doi.org/10.1186/s12933-023-01941-1>
337. Bick AG, Wakimoto H, Kamer KJ, Sancak Y, Goldberger O, Axelsson A, et al. Cardiovascular homeostasis dependence on MICU2, a regulatory subunit of the mitochondrial calcium uniporter. *Proc Natl Acad Sci U S A.* 2017;114:E9096–104. <https://doi.org/10.1073/pnas.1711303114>
338. Cahill TJ, Leo V, Kelly M, Stockenhuber A, Kennedy NW, Bao L, et al. Resistance of Dynamin-related Protein 1 Oligomers to Disassembly Impairs Mitophagy, Resulting in Myocardial Inflammation and Heart Failure. *J Biol Chem.* 2015;290:25907–19. <https://doi.org/10.1074/jbc.M115.665695>
339. Xu L, Yan X, Zhao Y, Wang J, Liu B, Yu S, et al. Macrophage Polarization Mediated by Mitochondrial Dysfunction Induces Adipose Tissue Inflammation in Obesity.

- Int J Mol Sci. 2022;23:9252. <https://doi.org/10.3390/ijms23169252>
340. Cheng W, Du Z, Lu B. Chronic low-grade inflammation associated with higher risk and earlier onset of cardiometabolic multimorbidity in middle-aged and older adults: a population-based cohort study. *Sci Rep.* 2024;14:22635. <https://doi.org/10.1038/s41598-024-72988-7>
 341. Mengozzi A, Armenia S, De Biase N, Punta LD, Cappelli F, Duranti E, et al. Circulating mitochondrial DNA signature in cardiometabolic patients. *Cardiovasc Diabetol.* 2025;24:106. <https://doi.org/10.1186/s12933-025-02656-1>
 342. DeConne TM, Muñoz ER, Sanjana F, Hobson JC, Martens CR. Cardiometabolic risk factors are associated with immune cell mitochondrial respiration in humans. *Am J Physiol Heart Circ Physiol.* 2020;319:H481–7. <https://doi.org/10.1152/ajpheart.00434.2020>
 343. Sun M, Jiang W, Mu N, Zhang Z, Yu L, Ma H. Mitochondrial transplantation as a novel therapeutic strategy for cardiovascular diseases. *J Transl Med.* 2023;21:347. <https://doi.org/10.1186/s12967-023-04203-6>
 344. Matiuto N, Applewhite B, Habash N, Martins A, Wang B, Jiang B. Harnessing Mitochondrial Transplantation to Target Vascular Inflammation in Cardiovascular Health. *JACC Basic Transl Sci.* 2025;10:101331. <https://doi.org/10.1016/j.jacbts.2025.101331>
 345. Campo G, Pavasini R, Morciano G, Lincoff AM, Gibson CM, Kitakaze M, et al. Clinical benefit of drugs targeting mitochondrial function as an adjunct to reperfusion in ST-segment elevation myocardial infarction: A meta-analysis of randomized clinical trials. *Int J Cardiol.* 2017;244:59–66. <https://doi.org/10.1016/j.ijcard.2017.06.040>
 346. McCully JD, Cowan DB, Pacak CA, Toumpoulis IK, Dayalan H, Levitsky S. Injection of isolated mitochondria during early reperfusion for cardioprotection. *Am J Physiol Heart Circ Physiol.* 2009;296:H94–105. <https://doi.org/10.1152/ajpheart.00567.2008>
 347. Masuzawa A, Black KM, Pacak CA, Ericsson M, Barnett RJ, Drumm C, et al. Transplantation of autologously derived mitochondria protects the heart from ischemia-reperfusion injury. *Am J Physiol Heart Circ Physiol.* 2013;304:H966–982. <https://doi.org/10.1152/ajpheart.00883.2012>
 348. Kaza AK, Wamala I, Friehs I, Kuebler JD, Rathod RH, Berra I, et al. Myocardial rescue with autologous mitochondrial transplantation in a porcine model of ischemia/reperfusion. *J Thorac Cardiovasc Surg.* 2017;153:934–43. <https://doi.org/10.1016/j.jtcvs.2016.10.077>
 349. Shin B, Saeed MY, Esch JJ, Guariento A, Blitzer D, Moskowitzova K, et al. A Novel Biological Strategy for Myocardial Protection by Intracoronary Delivery of Mitochondria: Safety and Efficacy. *JACC Basic Transl Sci.* 2019;4:871–88. <https://doi.org/10.1016/j.jacbts.2019.08.007>
 350. Cowan DB, Yao R, Akurathi V, Snay ER, Thedsanamoorthy JK, Zurakowski D, et al. Intracoronary Delivery of Mitochondria to the Ischemic Heart for Cardioprotection. *PLoS One.* 2016;11:e0160889. <https://doi.org/10.1371/journal.pone.0160889>
 351. Blitzer D, Guariento A, Doulamis IP, Shin B, Moskowitzova K, Barbieri GR, et al. Delayed Transplantation of Autologous Mitochondria for Cardioprotection in a Porcine Model. *Ann Thorac Surg.* 2020;109:711–9. <https://doi.org/10.1016/j.athoracsurg.2019.06.075>
 352. Guariento A, Blitzer D, Doulamis I, Shin B, Moskowitzova K, Orfany A, et al. Preischemic autologous mitochondrial transplantation by intracoronary injection for myocardial protection. *J Thorac Cardiovasc Surg.* 2020;160:e15–29. <https://doi.org/10.1016/j.jtcvs.2019.06.111>
 353. Mokhtari B, Hamidi M, Badalzadeh R, Mahmoodpoor A. Mitochondrial transplantation protects against sepsis-induced myocardial dysfunction by modulating mitochondrial biogenesis and fission/fusion and inflammatory response. *Mol Biol Rep.* 2023;50:2147–58. <https://doi.org/10.1007/s11033-022-08115-4>

354. Patergnani S, Bouhamida E, Leo S, Pinton P, Rimessi A. Mitochondrial Oxidative Stress and “Mito-Inflammation”: Actors in the Diseases. *Biomedicines*. 2021;9:216. <https://doi.org/10.3390/biomedicines9020216>
355. Lu X. Mitochondrial transplantation: adaptive bio-enhancement. *Cell Death Dis*. 2025;16:473. <https://doi.org/10.1038/s41419-025-07643-8>

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