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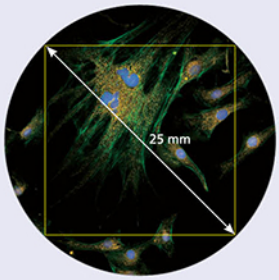

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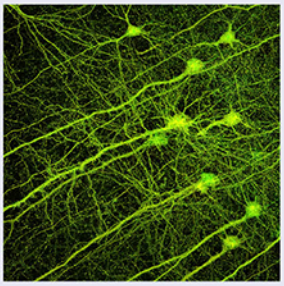

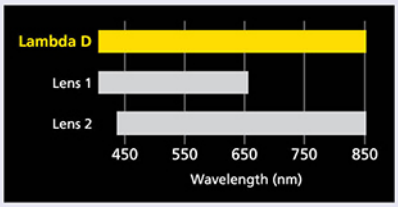

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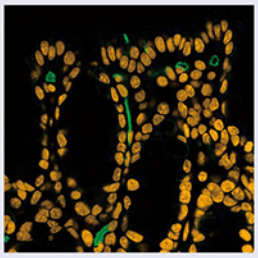

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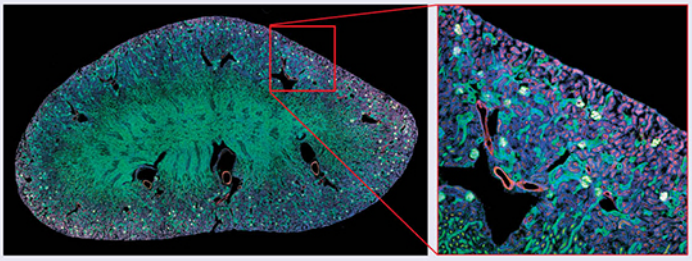

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REVIEW ARTICLE

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Extrusion of mitochondria: Garbage clearance or cell–cell communication signals?

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Abstract

Mitochondria are dynamic organelles that regulate various intracellular signaling pathways, including the mechanisms of programmed cell death, differentiation, inflammation, and so on. Mitochondria may be extruded as membrane enveloped or as free organelles during developmental processes, inflammatory activation, and in the process of "garbage clearance" of damaged mitochondria in postmitotic cells. Extracellular mitochondria can be engulfed by immune and nonimmune cells and trigger intracellular signaling leading to an inflammatory response. At the same time, it was reported that the release of extracellular vesicles containing mitochondria from mesenchymal stem cells contributes to their therapeutic anti-inflammatory effects. Numerous studies claim that engulfed mitochondria improve cellular bioenergetics, but this assumption requires further investigation. This review aims at a critical discussion of the mechanisms of mitochondrial extrusion in mammals, the reception of mitochondrial components, and the responses of recipient cells to extracellular mitochondria.

KEYWORDS

extracellular mitochondria, extracellular vesicles, mitochondria, mitophagy, quality control

1 | INTRODUCTION

Mitochondria are the subject of research interest in biomedical sciences since they regulate a plethora of processes in a cell. Besides their main function—ATP synthesis—mitochondria regulate metabolic reactions, calcium signaling, redox reactions, apoptosis, signaling pathways, and many more. Thus, mitochondrial dysfunction is central to the development of many diseases and pathophysiological conditions such as metabolic dysfunction, neurological diseases, skeletal and cardiac diseases, renal complications, inflammatory diseases, and cancer. Many efforts are being made to target mitochondrial dysfunction as a therapeutic approach (Murphy & Hartley, 2018; Zinovkin & Zamyatnin, 2019).

Mitochondria are highly dynamic organelles undergoing permanent fusion and fission processes. Mitochondrial dynamics facilitates organelle quality control, which includes intramitochondrial proteolysis and selective autophagy (mitophagy) (Pickles et al., 2018; Song et al., 2021).

Almost 20 years ago, we described massive extrusion of dysfunctional mitochondria induced by uncouplers of oxidative phosphorylation in highly glycolytic tumor cells (Lyamzaev et al., 2004, 2008, 2020). Later, however, a morphologically very similar extrusion of damaged mitochondria from neurons (Davis et al., 2014; Melentijevic et al., 2017) and cardiomyocytes (Nicolás-Ávila et al., 2020) was described in vivo, confirming the role of this process as a mechanism of "garbage clearance." In a parallel line of research, the pioneering work of C. Hauser (Q. Zhang et al., 2010) demonstrated the pro-inflammatory effect of extracellular mitochondria in vivo. At the same time, it was found that the release of extracellular vesicles (EVs) containing mitochondria from mesenchymal stem cells (MSCs) promotes their therapeutic anti-inflammatory effect (Morrison et al., 2017; Phinney et al., 2015). A similar anti-inflammatory effect has been described for mitochondria released from astrocytes (Joshi et al., 2019). Thus, dysregulation of mitochondrial extrusion and EVs production may have a great impact on the inflammatory status of the host.

The extrusion of mitochondria from living cells has been known for many decades since the pioneering work on the formation of mature erythrocytes from enucleated reticulocytes (Simpson & Kling, 1968). However, the detailed extrusion mechanism is not deciphered yet. The aim of this study is to review the possible mechanisms and biological significance of mitochondrial extrusion and EVs containing mitochondria.

1.1 | Developmental extrusion of mitochondria

The first example of mitochondrial extrusion from a living cell was described in erythropoiesis (Simpson & Kling, 1968). Electron microscopic studies have shown that enucleated reticulocytes extrude mitochondria, turning them into mature erythrocytes. Initially, membrane vesicles gather near mitochondria, fuse, and surround the mitochondria with a double membrane, a process characteristic of autophagosome formation. Mitochondria are released from the cell after the fusion of the surrounding membrane with the plasma membrane. This process resembles autophagy-based unconventional secretion, which is the main pathway for the secretion of proteins (including some cytokines) deficient in a signal peptide that directs them to the classic secretory mechanism through endoplasmic reticulum–Golgi (Claude-Taupin et al., 2017). It was later reported that autophagosomes containing mitochondria are packed into large vesicles derived from the plasma membrane before exocytosis (Griffiths et al., 2012). This mechanism resembles the release of mitochondria in blebs during apoptosis, as well as the release of damaged mitochondria in "exopheres" (see below). Alternatively, autophagosomes containing mitochondria can fuse with endosomes to form amphisomes, which are capable of releasing their contents after fusion with the plasma membrane (Betin et al., 2013; Ganesan & Cai, 2021).

The role of autophagy in the elimination of mitochondria during erythropoiesis has been clearly demonstrated in mice with knockout of the key autophagy genes ulk1 and atg7 (Kundu et al., 2008; Mortensen et al., 2010; J. Zhang et al., 2009) and the bnip3l/nix gene, which serves as an adapter for selective mitophagy (Sandoval et al., 2008; Schweers et al., 2007). The erythrocytes of all these mice have persistent mitochondria and live short lives, causing severe anemia. The immediate stimuli to mitophagy remain unknown. Probably, a decline of mitochondrial functions (e.g., a decrease in membrane potential) precedes mitophagy and mitochondrial extrusion.

During differentiation of reticulocytes, mitochondrial membranes are oxidized by 15-lipoxygenase, followed by ATP-dependent proteolysis of membrane proteins (Rapoport & Schewe, 1986). Interestingly, the genetic impairment of the corrector function in mitochondrial DNA (mtDNA) polymerase PolG prevents the elimination of mitochondria in reticulocytes (Ahlqvist et al., 2015), which indicates that mitochondria may play an active role in the process of erythropoiesis. The detailed mechanisms of mitochondrial extrusion during erythropoiesis remain unclear, but there is no doubt that they belong to a diversified endosomal-autophagosomal pathway (Figure 1).

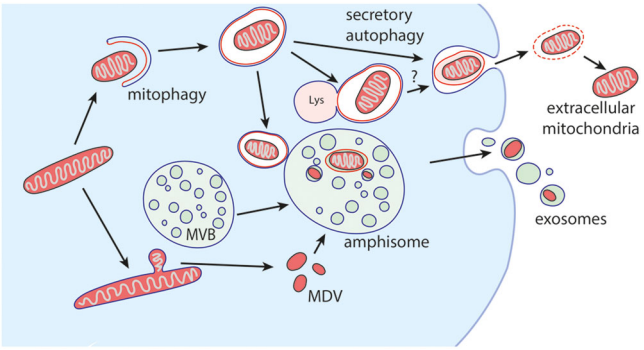

FIGURE 1 Mechanisms of mitochondrial extrusion via endosomal/autophagosomal pathways. Extrusion of mitochondria after mitophagy can be mediated by secretory autophagy either after fusion with lysosomes or without the fusion. In the latter case, the inner autophagosomal membrane covers secreted mitochondria. It is assumed that this membrane is unstable in the extracellular environment and free mitochondria are released. Alternatively, the mitophagosome can fuse with late endosomes (multivesicular bodies, MVB) to form an amphisome with subsequent exocytosis. Fragments of mitochondria may form mitochondrial-derived vesicles (MDV), which can also fuse with MVB for exocytosis

Another specific example of developmental mitochondrial extrusion has been described during sperm differentiation in *Drosophila* fruit flies (DeLuca & O'Farrell, 2012). The destruction of mtDNA and the elimination of mitochondrial nucleoids are coordinated with sperm elongation and depend on the mitochondrial endonuclease EndoG. However, in mutants with inactive EndoG, mtDNA is still removed along with mitochondria. During spermatogenesis, a syncytial bundle of 64 spermatids synchronously begins to develop tails. Each spermatid contains two mitochondria that elongate in association with an elongating microtubule axoneme. Then, specific actin-containing structures called "investment cones" move from the perinuclear area along the tail, collecting mitochondria and other organelles. Then, the tip of the tail with the collected material is cut off, forming spherical structures containing mitochondrial debris as waste. This is a very clear example of a non-exocytotic mechanism (Figure 2).

Apoptosis is undoubtedly one of the important developmental programs, where blebbing of the plasma membrane and following formation of apoptotic bodies accompany the final stages. The early electron microscopic studies revealed the presence of mitochondria in apoptotic bodies both in vitro (Searle et al., 1975) and in vivo. Much later, it was shown that mitochondria are distributed to some, but not all, subclasses of apoptotic bodies (Jiang et al., 2017). Interestingly, if caspases were inhibited during apoptosis, mitochondria were degraded almost entirely within the cell, presumably with help of mitophagy (Xue et al., 2001).

1.2 | Extrusion of dysfunctional mitochondria

In studies of developmental extrusion of mitochondria, it has been suggested that mitochondria targeted to elimination are dysfunctional.

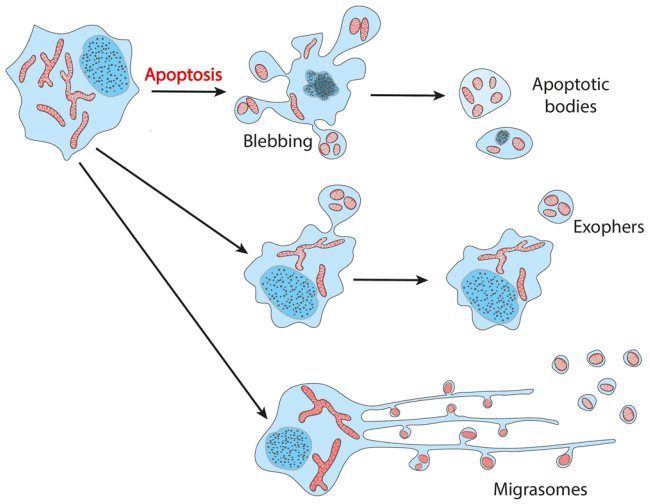

FIGURE 2 Nonexocytotic pathways of mitochondrial extrusion. Mitochondria can be captured by the blebs and then by apoptotic bodies during apoptosis. Some bodies may also contain nuclear material. In living neurons and cardiomyocytes, damaged mitochondria can be released inside large (about 4 μm) vesicles formed by the plasma membrane. These vesicles, called exophers, may also contain protein aggregates. At the rear end of migrating cells, damaged mitochondria can be transported into large (about 0.5–1.2 μm) plasma membrane vesicles (migrasomes) and subsequently removed from the cells in a process called mitocytosis

At the same time, only a few studies have analyzed the extrusion of mitochondria caused by the cessation of oxidative phosphorylation. In 2008, we showed that uncouplers of oxidative phosphorylation induce the massive release of mitochondria from the highly glycolytic tumor cell line HeLa (Lyamzaev et al., 2004, 2008). This effect was stimulated by inhibitors of respiratory chain Complex III, myxothiazol, and antimycin. Uncouplers induced rapid (within 1 h) fragmentation of mitochondria with subsequent formation of dense clusters. Further, these clusters were occluded by a single membrane and expelled from the cell. Some cells died within 72–96 h, and the surviving cells almost completely lost their mitochondria, so this process was described as mitoptosis (for recent review see Lyamzaev et al., 2020). No signs of apoptosis were observed in these cells; in particular, chromatin did not condense, and phosphatidylserine did not undergo externalization (Lyamzaev et al., 2008). Uncouplers strongly stimulate general autophagy and mitophagy, but autophagosomes do not colocalize with mitochondrial clusters. The possible role of autophagy in this model remains unclear, but electron microscopic studies indicate that the endosomal–autophagosomal pathway is responsible for mitochondrial extrusion. Mitochondrial extrusion was accompanied by severe oxidative stress. Unexpectedly, the antioxidants *N*-acetylcysteine or Trolox caused rapid cell death under these conditions (Lyamzaev et al., 2008). Probably, oxidative stress promotes the induction of mitochondrial extrusion, and mitoptosis plays a protective role.

Several models have been described in which the extrusion of mitochondria is induced by physiological ligands. Bacterial wall lipopolysaccharide (LPS), one of the most potent pro-inflammatory agents, induces the extrusion of mitochondria mediated by autophagy in hepatocytes and fibroblasts (Unuma et al., 2015). It has been observed that autophagosomes with mitochondria inside fuse directly with the plasma membrane (not with lysosomes), releasing mitochondria in a process resembling secretory autophagy (Figure 1). It is important to note that this process was not accompanied by apoptosis; moreover, the induction of apoptosis in hepatocytes by the combination of LPS with D-galactosamine prevented the extrusion of both mitochondrial and autophagosomal markers (Unuma et al., 2015).

In vivo, LPS injected intraperitoneally caused the release of mitochondrial proteins from hepatocytes, and this was prevented by an autophagy inhibitor (Unuma et al., 2013). It was shown that mitochondrial components appear in the bloodstream much earlier than a marker of hepatocyte damage (Unuma et al., 2013).

Another pro-inflammatory agent, cytokine tumor necrosis factor (TNF), induced mitochondrial extrusion in combination with apoptosis (Nakajima et al., 2008). In this model, fragmented mitochondria are surrounded by vacuoles formed from the plasma membrane independently of autophagy. These vacuoles fuse with the plasma membrane and release naked mitochondria into the extracellular spaces. This process is fundamentally different from the shedding of apoptotic blebs. Mitochondrial extrusion was specific for TNF-induced apoptosis and was not observed during apoptosis induced by cisplatin (Nakajima et al., 2008). Massive extrusion of mitochondria was observed in cell models of TNF-dependent necroptosis (Maeda & Fadeel, 2014). The authors observed the release of naked mitochondria that "appeared to be morphologically intact" (Maeda & Fadeel, 2014). The last statement raises serious doubts since isolated mitochondria rapidly disintegrate in the medium containing millimolar Ca^{2+} (see Chernyak, 2020 for discussion).

An interesting example of circadian mitochondrial extrusion was recently described in zebrafish cone photoreceptors (Giarmarco et al., 2020). Photoreceptors in various species support their energy demands during the daytime through aerobic glycolysis, but contain the clusters of mitochondria. During the day, mitophagy in zebrafish cone photoreceptors is activated, but at night mitochondrial biogenesis occurs and mitochondria are metabolically activated. Unexpectedly, the extrusion of mitochondria containing matrix deposits was observed at night. It has been suggested that this mechanism mediates the clearance of damaged mitochondria from the cell, but the details remain elusive (Giarmarco et al., 2020).

The annual cycling of mitochondria was described in the retinal cones of ground squirrels (Reme & Young, 1977). During hibernation mitochondria, as well as many other organelles, are degraded due to autophagy, but after awakening, the cellular composition is restored. It should be noted that in some other examples of terminal differentiation, such as lens fiber maturation or keratinocyte cornification during hair development, mitochondria are eliminated without any signs of extrusion.

1.3 | Extrusion of mitochondria from long-lived cells

Some metabolically active long-lived cells have significant problems with the intracellular utilization of damaged mitochondria. In neurons, mitochondria damaged at synapses must be transported very long distances to the cell body for autophagy and lysosomal degradation. An alternative, less energy-consuming mechanism has been described in the optic nerve head (ONH) of the retinal ganglion of mice (Davis et al., 2014). Large (about 3 μm in diameter) protrusions filled with mitochondrial clusters were observed in healthy axons. These protrusions were located specifically at the sites of contact with astrocytes, and their mitochondrial content was detected in the lysosomes of neighboring cells. It was found that most of the mitochondria of axons in ONH are degraded by astrocytes, and this process was called "transmitophagy" (Davis et al., 2014), while it belongs to the category of nonexocytotic mechanisms (Figure 2). The authors observed similar protrusions and clusters of degrading mitochondria in astrocytes located along neurites in the superficial layers of the cerebral cortex.

Similar large protrusions containing mitochondria and protein aggregates were observed in various adult neurons of the nematode *Caenorhabditis elegans* and were named "exophers" (Melentijevic et al., 2017). Inhibition of autophagy or proteasome stimulates exophers' production. Mitochondria captured by exophers contain more oxidized components than mitochondria in the cell body; therefore, both proteostasis impairment and mitochondrial dysfunction can promote exophers' formation. Sometimes the size of the exopher can be similar to the size of the neuron body, but the neurons that ejected exophers remain fully functional. Moreover, genetic interference with the formation of exophers leads to a decrease in neuronal function. In contrast to protrusions from retinal ganglion cells, exophers in nematodes can mediate the transfer of neuronal material for degradation to distant cells (Melentijevic et al., 2017).

Recently, a similar mechanism of mitochondrial extrusion was described in cardiomyocytes (Nicolás-Ávila et al., 2020). In healthy cardiomyocytes, mitochondria with reduced functionality were mainly observed at the cell periphery. Large protrusions reminding exophers often contain aberrant mitochondria with decreased membrane potential. It has been suggested that autophagy is an important mechanism for the extrusion of mitochondria from cardiomyocytes, as markers of autophagy have been found within exophers. Moreover, hemizygous mice with deletion of one allele of Atg7 (an important component of the autophagy machinery) in cardiomyocytes showed a strong decrease in the content of cardiac exophers.

Exophers have been found to be engulfed by specific cardiac macrophages. Depletion of these macrophages or knockout of the phagocytic receptor tyrosine kinase Mer led to impaired cardiac mitochondrial clearance, metabolic alterations, and ventricular dysfunction (Nicolás-Ávila et al., 2020). The discovery of the key role of resident macrophages in the removal of damaged mitochondria from the heart was quite unexpected and ignited a strong resonance. Mammalian heart tissue is postmitotic, with limited abilities for regeneration and renewing. It is very likely that similar mechanisms will soon be described in skeletal muscles and in some other high metabolic tissues.

One more mechanism of extrusion of components of damaged mitochondria involves the formation of small vesicles (mitochondrial-derived vesicles, MDVs) containing mitochondrial proteins and fragments of both mitochondrial membranes (see review Sugiura et al., 2014). It has been shown that PINK1 and Parkin, the important players in mitophagy, are involved in MDV formation (McLelland et al., 2014). MDVs predominantly contain oxidized proteins and phospholipids. It has been suggested that mitochondrial components are first oxidized and then collected in the MDVs. MDVs have been shown to transport mitochondrial components to lysosomes or peroxisomes, but some of them instead fuse with the multivesicular body (MVB) to be released from the cell along with exosomes (Figure 1).

Another important mechanism of extrusion of damaged mitochondria has recently been described in migrating cells (Jiao et al., 2021). It has been found that migrasomes, large vesicles formed on actin retraction fibers and left behind by a moving cell, can be filled with damaged mitochondria (Figure 2). This process, called "mitocytosis" by the authors, is induced by low concentrations of uncouplers, while higher concentrations induce mitophagy and suppress mitocytosis. Various mitochondrial inhibitors, as well as starvation, also enhance mitocytosis. The outward motor KIF5B has been shown to attract mitochondria to the plasma membrane, while the inward motor dynein recruitment is suppressed in damaged mitochondria. In the cortical layer, myosin Myo19, associated with mitochondria, binds mitochondria to cortical actin, and finally, mitochondria undergo fission and are packed into migrasomes. Mitocytosis was observed in differentiating macrophages and in neutrophils, but not in immobile hepatocytes. When mitochondria-containing migrasomes were isolated from blood, it was found that almost 90% of them were derived from neutrophils. Moreover, mitocytosis has been shown to improve the viability of neutrophils in circulation.

1.4 | Extracellular mitochondrial components as DAMPs

Most likely, mitochondria of eukaryotic cells arose from ancient relatives of modern alphaproteobacteria (Gray et al., 1999). This hypothesis is commonly used to explain the function of mitochondrial components as the damage-associated molecular patterns (DAMPs), which are recognized by various cells. The main goal of recognizing DAMPs is to attract immune cells to the sites of injury to fight possible infection and facilitate tissue repair and regeneration. Inflammation stimulates phagocytes to efficiently cleanse cellular debris and dead cells, activates the proliferation and differentiation of epithelial cells and fibroblasts, angiogenesis, and remodeling of the extracellular matrix (Sarhan et al., 2018).

The study of mitochondrial DAMP (mtDAMPs) signaling and their changes in various pathophysiological conditions has an important clinical application since DAMPs may act as predictors of the development of potentially life-threatening conditions in many inflammatory diseases. Undoubtedly, mtDAMPs are not only markers but are also involved in the pathogenesis of various diseases associated with inflammation.

The inflammatory effect of mtDAMPs was demonstrated in 2010 by the group of Prof. C. J. Hauser (Q. Zhang et al., 2010). It was discovered that the content of the mitochondrial matrix stimulated chemotaxis and degranulation of neutrophils in vitro. Intravenous administration of mitochondria to rats caused systemic inflammation and inflammatory damage to the lungs (Q. Zhang et al., 2010). Currently, the mtDAMPs list includes mtDNA, cardiolipin, ATP, and succinate, as well as several mitochondrial proteins. Proteins encoded in the mitochondrial genome and translated in mitochondria have formylated methionine at the N-termini, just like bacterial proteins. Bacterial and mitochondrial N-formylated proteins (NFPs) are recognized via formyl peptide receptors (FPRs) (Carp, 1982). Besides NFPs, some nuclear-encoded mitochondrial proteins may also act as DAMPs. For instance, mtDNA-binding protein transcription factor A and cytochrome *c* are recognized by innate immune cells (Riley & Tait, 2020). Only some of the mitochondrial DAMPs are recognized by the same receptors that recognize bacterial pathogen-associated molecular patterns, while others have specific receptors (Figure 3). The main types of mtDAMPs and their effect on inflammatory signaling will be briefly reviewed below.

mtDNA still possesses some properties typical of ancestral bacterial DNA: a circular genome, as well as unmethylated cytosines in CpG dinucleotides (Hong et al., 2013), which are capable of activating pattern recognition receptors (PRRs) such as TLR9 after phagocytosis (Krysko et al., 2011). The other PRRs, NOD-like receptor family pyrin domain containing 3 (NLRP3), and cytoplasmic cyclic GMP-AMP synthase (cGAS) recognize mtDNA released from endogenous mitochondria. Downstream signaling results in the expression of interleukin-6 (IL-6), IL-8, TNF, IL-1β, IL-18, matrix metalloproteinases, and type I interferons (IFN-1s) (Fang et al., 2016). mtDNA induces inflammatory activation of human preliminary activated (primed) neutrophils (Prikhodko et al., 2016; Q. Zhang et al., 2010), induces neutrophil extracellular traps (NETs) (Itagaki et al., 2015), and increases cytokine expression in macrophages (J.-Z. Zhang et al., 2014). The release of mtDNA is often accompanied by excessive reactive oxygen species (ROS) production resulting in mtDNA oxidation. The pro-inflammatory properties of oxidized mtDNA were shown in a pioneering study in which injection of endogenously oxidized mtDNA-induced arthritis mediated by monocytes/macrophages (Collins et al., 2004). Intracellular oxidized mtDNA acts as a strong DAMP-activating cGAS/STING (stimulator of IFN genes) and NLRP3 inflammasome in the cytosol (Zhong et al., 2018).

The presence of circulating mtDNA in the plasma of trauma patients was found more than a decade ago (Q. Zhang et al., 2010). Since then, many studies have described mtDNA-dependent pathologies including systemic inflammatory response syndrome,

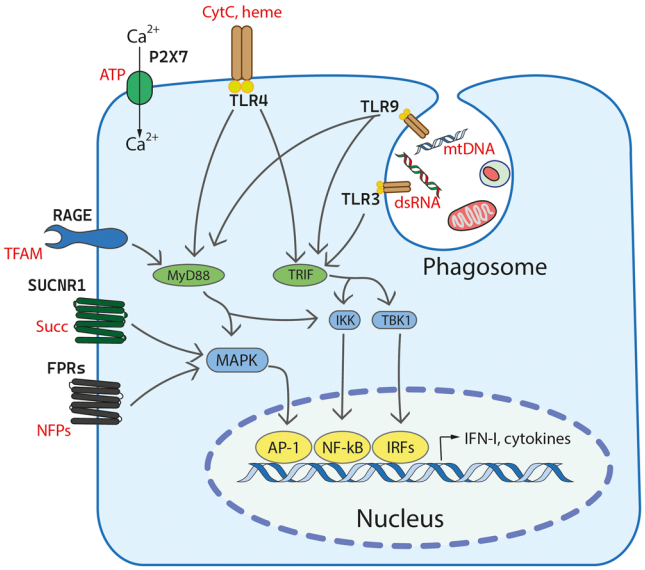

FIGURE 3 Receptors that recognize mitochondrial components (DAMPs) and mediate pro-inflammatory signaling. *Receptors*: Toll-like receptors (TLRs) 3,4, 9, formyl peptide receptors (FPRs) that recognize mitochondrial N-formylated peptides, SUCNR1 receptor of succinate (succ), receptor for advanced glycation end products (RAGE) that recognizes mitochondrial transcription factor A (TFAM), P2X7 purinergic receptor that is a Ca^{2+} channel gated by extracellular ATP. *Adaptor proteins*: MyD88, TRIF (Toll/IL-1R domain-containing adaptor-inducing IFN-β). *Protein kinases*: MAPK (mitogen-activated protein kinases), IKK (kinase of the inhibitor of NFkB, nuclear factor kappa-light-chain-enhancer of activated B cells), TBK1 (TANK-binding kinase-1). *Transcription factors*: AP1, NFkB, IRFs (interferon (IFN) regulatory factors)

acute liver injury and nonalcoholic steatohepatitis, age-related macular degeneration, cardiovascular diseases, and viral and bacterial infections (reviewed in West & Shadel, 2017). Importantly, circulatory mtDNA is now being recognized as a predictor of health-threatening complications and mortality (Harrington et al., 2019). Recent work describes mtDNA release, TLR9 activation, and cytokines release in severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) endothelial cell infection (Costa et al., 2021).

ATP, produced and accumulated in mitochondria, is another important mtDAMP, activating inflammatory reactions through P2 purinergic receptors (Bours et al., 2006). ATP induces multiple pro-inflammatory reactions in neutrophils, monocytes, and lymphocytes (reviewed in Di Virgilio et al., 2020). Importantly, ATP is enzymatically converted to adenosine acting as a strong immunosuppressant for certain cell types (Thiel et al., 2003), thus providing a negative feedback loop restricting uncontrolled inflammation.

More recently, succinate has been recognized as mtDAMP (for a review see Krzak et al., 2021). Succinate is an intermediate in the tricarboxylic acid cycle (TCA), so its concentration in unstressed cells is very low. The content of succinate increases strongly during hypoxia and in pro-inflammatory macrophages, where TCA activity and respiration are reduced. Succinate in macrophages is mainly produced by glutaminolysis via α-ketoglutarate and through the

γ-aminobutyric acid shunt (Tannahill et al., 2013). Intracellular succinate induces the production of ROS in mitochondria and stabilizes hypoxia-inducible factor 1α in the cytoplasm, thereby stimulating the production of pro-inflammatory cytokines (Mills et al., 2016).

The role of extracellular succinate began to be intensively investigated after it was discovered that the orphan G-protein-coupled receptor (GPR91) recognizes succinate (He et al., 2004). This receptor, named SUCNR1, has been found to stimulate both pro-inflammatory and anti-inflammatory responses in macrophages, as well as diverse responses in various cells (Krzak et al., 2021). It should be noted that the effects of extracellular succinate on liver metabolism (Kaminsky et al., 1983) and neuronal responses to acetylcholine (Andreev et al., 1986) were described by Dr. M. N. Kondrashova with colleagues in the 1980s, but did not raise much interest.

Cardiolipin is a phospholipid found in both bacterial and inner mitochondrial membranes. Mitochondrial dysfunction results in the externalization of cardiolipin at the cytoplasmic surface of the outer mitochondrial membrane where it is involved in the assembly and activation of NLRP3 inflammasome leading to IL-1β and IL-18 production (Iyer et al., 2013). Extracellular cardiolipin is recognized by CD1d-restricted T cells, thus contributing to adaptive immunity reactions (Dieudé et al., 2011). Cardiolipin was also shown to inhibit the resolution of inflammation by suppressing the synthesis of anti-inflammatory IL-10 in lung macrophages (Chakraborty et al., 2017). Extracellular mitochondria exhibiting cardiolipin on the surface are highly procoagulant and cause coagulopathy associated with traumatic brain injury (Zhao et al., 2016).

Early work has demonstrated that apoptotic cell death is accompanied by cardiolipin oxidation in cytochrome *c*-catalyzed peroxidase reaction (Kagan et al., 2005). At the same time, recent findings highlight the role of phospholipid oxidation in their function as DAMPs (Di Gioia et al., 2020). It is tempting to speculate that cardiolipin oxidation also modifies its inflammatory functions.

Mitochondrial N-formylated peptides are recognized by G-protein-coupled receptors of the FPR family expressed at leukocytes and many other cell types (Raabe et al., 2019). Interestingly, only 5 out of 13 NFPs can induce pro-inflammatory reactions, and this ability is defined by their similarity to formyl peptides typical of Gram-negative bacteria (Kaczmarek et al., 2018). Moreover, it was also shown that the ligands of FPRs can induce different outcomes while binding to the same receptor (Raabe et al., 2019). Neutrophil activation by NFPs includes calcium influx and mitogen-activated protein kinases activation, resulting in chemotaxis, ROS production, and protease secretion (Wilkins et al., 2017).

The clinical importance of mitochondrial NFPs in the pathogenesis of life-threatening nosocomial (hospital-acquired) lung infections, frequently developed after traumatic injury, is well illustrated by a recent work by C. J. Hauser with coworkers (Kwon et al., 2021). It was found that the high plasma level of mitochondrial NADH dehydrogenase subunit 6 (one of NFPs) was independently associated with the development of secondary infection in septic shock patients. This increased susceptibility to secondary infection is probably due to the suppression of neutrophil chemotaxis by NFP occupancy of FPRs. In this case, circulatory NFPs may distract immune cells from true infectious agents and contribute to immunosuppression typical for sepsis. In addition, circulating mtDNA suppresses neutrophils' chemotaxis in response to bacterial invasion (Konecna et al., 2021). Possibly, most circulatory mtDAMPs act in a similar way making host organisms more susceptible to infections.

The cellular source of circulatory mitochondrial components including mtDAMPs depends on the (patho-)physiological condition of the host organism. A massive release of mitochondrial components into the bloodstream occurs after extensive trauma or surgery, as well as in severe ischemic or toxic damage to the heart, liver, and so on. Pro-inflammatory activation of leukocytes can initiate the programmed necrotic cell death accompanied by the release of mitochondria. In neutrophils, the process called NETosis results in the release of decondensed chromatin forming NETs (Vorobjeva & Chernyak, 2020). The various modes of necrotic death of macrophages (pyroptosis, necroptosis, parthanatos) can be necessary for the release of pro-inflammatory interleukins (Robinson et al., 2019).

The mechanisms of extrusion of mitochondria from cells, described above, can also promote the release of mtDAMPs into the blood. Activated platelets are one of the main sources of free mitochondria and EVs with mitochondria and other cellular components (Boudreau et al., 2014). Mass release of mtDNA was found in live lymphocytes (Ingelsson et al., 2018) and granulocytes (eosinophils, basophils, and neutrophils), where this process was called "vital NETosis" (Yipp & Kubes, 2013). Since there are very few mitochondria in granulocytes, it is difficult to imagine that the release of mtDNA will lead to the formation of functional pathogen traps, but this amount may be important for cell-to-cell signaling. It should be emphasized that the release of mtDAMP in these cases is not associated with cell death.

Low molecular weight mtDAMPs can also be secreted by living cells via specific transporters. ATP can be released through a channel formed by its P2X7 receptor in combination with pannexins (Idzko et al., 2014). Cytosolic succinate can be released via organic anion/dicarboxylate transporters (Anzai et al., 2006) and monocarboxylate transporters (MCTs) (Reddy et al., 2020). It is known that MCTs selectively transport only monocarboxylic acids. It has recently been found that succinate is transported by MCT1 in the monoprotonated form at low pH in the physiological range of exercise muscles. Extracellular succinate during exercise stimulates SUCNR1 expressed in nonmyofibrillar cells and induces muscle remodeling (Reddy et al., 2020).

The active secretion of mtDAMPs can be compared to the release of nuclear DAMPs. Some of the most important and well-characterized DAMPs are high mobility B1 protein (HMGB1) and cold-induced RNA-binding protein (CIRP). HMGB1 is an evolutionarily conserved DNA-binding protein that functions as a chaperone in the nucleus. CIRP in the nucleus regulates the transcription and processing of RNA, while in the cytoplasm it is involved in the translation and turnover of mRNA. Various stressors and inflammatory mediators can induce the expression of HMGB1 and its

acetylation by histone acetylases, which leads to translocation into the cytoplasm (Andersson et al., 2018). The migration of CIRP from the nucleus to the cytoplasm is stimulated by methylation and other posttranslational modifications (Aziz et al., 2019). Secretion of both DAMPs can occur through exocytosis of secretory vesicles similar to endolysosomes (Aziz et al., 2019; Gardella et al., 2002). Another mechanism is realized in activated platelets containing significant amounts of HMGB1 on the cell surface. Vascular damage causes a massive release of HMGB1 with EVs contributing to the pathogenesis of thrombosis (Vogel et al., 2015). The same exocytotic mechanism, as well as the formation of EVs, is involved in the release of mitochondria described above. The active release of mitochondria, as well as nuclear DAMPs, indicates a possible active role of cells producing DAMPs in innate immunity.

1.5 | Intercellular signaling with EVs and mitochondrial transfer

Mitochondrial components can be extruded from cells within two types of EVs (Caicedo et al., 2021). One type of small vesicles (~30–250 nm) called exosomes are formed in the endosomal compartment and are surrounded by the common membrane forming MVBs. Exosomes are extruded from the cell after the fusion of MVBs with the plasma membrane. Another type is larger vesicles (up to several microns), which are formed due to the budding of the plasma membrane. Exosomes and large EVs carrying mitochondrial material can initiate inflammatory signaling due to phagocytosis and delivery of mitochondrial DAMPs into innate immune cells. For example, mitochondrial DAMPs released in EVs from platelets play an important role in the pathogenesis of systemic lupus erythematosus (Linge et al., 2018). MtDNA delivered with EVs from placental explants exposed to antiphospholipid antibodies stimulates the inflammatory response in endothelial cells, possibly contributing to the pathogenesis of preeclampsia (Linge et al., 2018). EVs enriched with mtDNA stimulate alcoholic neutrophilia and hepatotoxicity (Tong et al., 2017). Interestingly, the delivery of double-stranded RNA (dsRNA), which is a novel mitochondrial DAMP, within the EVs, has been described in a similar model of alcoholic hepatotoxicity (Lee et al., 2020). It was shown that in hepatocytes treated with ethanol, dsRNA accumulates in mitochondria (presumably due to the inactivation of polynucleotide phosphorylase, which catalyzes its rapid degradation) and stimulates TLR3-dependent activation of Kupffer cells (liver macrophages). Previously, it was shown that mitochondrial dsRNA accumulated after inhibition of degradation stimulates the IFN-I response (Dhir et al., 2018). MtDNA released within EVs from endothelial cells infected with the Kaposi's sarcoma-associated herpesvirus also induces IFN response in uninfected endothelial cells (Jeon et al., 2019).

Another important example of the pro-inflammatory action of extracellular mitochondria in models of three neurodegenerative diseases (Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis) was recently published (Joshi et al., 2019). It has been shown that the release of fragmented mitochondria from activated microglial cells and their engulfment by astrocytes promotes neuroinflammation. It has been suggested that fragmentation is necessary for the release of dysfunctional mitochondria and that only these mitochondria are responsible for the subsequent neuronal damage. Unfortunately, the authors did not consider the role of EVs containing mitochondria; therefore, their conclusions require further analysis.

A possible anti-inflammatory effect of mitochondrial release has also been observed in the brain. As mentioned above, mitochondria extruded from neurons can be engulfed by astrocytes (Davis et al., 2014). But astrocytes have also been found to secrete large vesicles containing mitochondria and lipid droplets when stimulated with ATP (Falchi et al., 2013). It was later shown that the release of mitochondria from astrocytes is mediated by an important secondary messenger, cyclic ADP-ribose (Hayakawa et al., 2016). Electron microscopy revealed EVs containing mitochondria in conditioned media from rat cortical astrocytes. These vesicles were 300–1100 nm in diameter and contained respiring mitochondria with membrane potential. In this study, astrocyte-derived mitochondria were found in neurons in coculture and in vivo. Moreover, the transfer of mitochondria from astrocytes supported neuronal survival during serum/glucose starvation in vitro and in mice subjected to focal cerebral ischemia (Hayakawa et al., 2016).

It was found that MSCs secrete EVs containing mitochondria, and the role of released mitochondria in the therapeutic anti-inflammatory effect of MSCs was suggested (Phinney et al., 2015). MSCs are located in the bone marrow niche at very low oxygen concentrations. Normoxia causes oxidative stress and excessive production of mtROS, interfering with the functioning of these cells (Boregowda et al., 2012). It was shown (Phinney et al., 2015) that mitophagy is stimulated in MSCs in response to oxidative stress, and then depolarized mitochondria are packed into microvesicles mediated by the arrestin domain-containing protein 1 and released from cells. The resulting exosomes are taken up by macrophages. It was observed that EVs from MSCs (MSC-EVs), but not from fibroblasts, caused a small but statistically significant increase in macrophage respiration and respiratory capacity. The authors suggest that engulfed mitochondria "enhance the bioenergetics" of macrophages. They also uncovered a mechanism for preventing the inflammatory activation of macrophages by mitochondrial transfer. It was shown that MSCs simultaneously release specific exosomes containing microRNA, which inhibits macrophage activation by suppressing Toll-like receptor signaling (Phinney et al., 2015). Later, it was shown that MSC-EVs containing mitochondria suppress the production of inflammatory cytokines and stimulate phagocytosis in alveolar macrophages using LPS or bronchoalveolar lavage fluid from patients with acute respiratory distress syndrome (ARDS). MSC-EV reduced inflammation and lung damage in ARDS mice (Morrison et al., 2017). Recently, it was reported (Dutra Silva et al., 2021) that MSC-EVs improve the integrity of the alveolar–capillary barrier in the ARDS model through mitochondrial transfer. It should be noted that in the cited studies, only a very small (Phinney et al., 2015) or statistically

insignificant (Morrison et al., 2017) increase in the respiratory capacity of macrophages was observed. It is still possible that the effects of trapped mitochondria are mediated by modulation of signaling pathways independent of the effect on bioenergetics.

The transfer of mitochondria between MSCs and various target cells and its role in the therapeutic effects of MSCs is extensively studied. These studies were reviewed recently (Mohammadalipour et al., 2020), so their discussion is outside the scope of this review. We should mention only that in large part of these studies the mechanism of mitochondrial transfer did not include their release to the extracellular medium can be mediated by cellular fusion, gap junctional channels, or tunneling nanotubes.

One more hot topic in the field of mitochondrial transfer is the so-called "mitochondrial transplantation." This term applies to the reported therapeutic effects of isolated mitochondria injected into the problematic organ or in the bloodstream. These studies have recently been critically discussed (Chernyak, 2020). As a rule, studies of "mitochondrial transplantation" do not contain evidence of the transfer of functional mitochondria, but claim to improve the bioenergetics of recipient cells (McCully et al., 2017). Possible therapeutic effects of the limited inflammation induced by mtDAMPs may be responsible for the reported effects. Another possibility is the activation of the Nrf2 pathway in response to mitochondrial administration. For example, a recent article describes the therapeutic effect of mitochondria on chemotherapy-induced cognitive deficits (Alexander et al., 2021). Although the authors assume a direct protective action of the applied mitochondria on the hippocampus of cisplatin-treated mice, they also described an Nrf2-mediated response after intranasal administration of mitochondria. Nrf2 controls the expression of genes involved in antioxidant protection, maintenance of redox homeostasis, detoxification, and mitochondrial biogenesis (Robledinos-Antón et al., 2019). Nrf2 activation at the organismal level results in a generalized anti-inflammatory response (Tu et al., 2019). Moreover, high expression and activity of Nrf2 are typical for the cells with cisplatin resistance (Silva et al., 2019). Thus, activation of Nrf2 by mitochondrial transfer appears to be a good explanation in this and, possibly, some other cases.

2 | CONCLUSION

Studies of the phenomenon of the displacement of mitochondria from the cell have been continued for more than half a century. The current literature contains many examples of mitochondrial extrusion used in developmental processes, in the regulation of inflammation, and for garbage clearance of dysfunctional mitochondria. However, it is still unclear how the cell selects individual mitochondria for extrusion. Early in vitro studies showing the role of mitochondrial uncoupling in this process still awaits experimental verification in vivo. The general mechanisms of mitochondrial extrusion also require further study.

Extruded mitochondria play an important role in intercellular signaling. However, there is an apparent contradiction between the pro-inflammatory properties of extracellular mitochondria containing DAMPs and the reported anti-inflammatory effects of EVs containing mitochondria derived from MSCs. This problem also awaits its solution.

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