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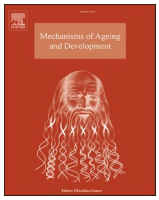

The role of mitochondria in cytokine and chemokine signalling during ageing

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ABSTRACT

Ageing is accompanied by a persistent, low-level inflammation, termed "inflammageing", which contributes to the pathogenesis of age-related diseases. Mitochondria fulfil multiple roles in host immune responses, while mitochondrial dysfunction, a hallmark of ageing, has been shown to promote chronic inflammatory states by regulating the production of cytokines and chemokines. In this review, we aim to disentangle the molecular mechanisms underlying this process. We describe the role of mitochondrial signalling components such as mitochondrial DNA, mitochondrial RNA, N-formylated peptides, ROS, cardiolipin, cytochrome c, mitochondrial metabolites, potassium efflux and mitochondrial calcium in the age-related immune system activation. Furthermore, we discuss the effect of age-related decline in mitochondrial quality control mechanisms, including mitochondrial biogenesis, dynamics, mitophagy and UPR^{mt}, in inflammatory states upon ageing. In addition, we focus on the dynamic relationship between mitochondrial dysfunction and cellular senescence and its role in regulating the secretion of pro-inflammatory molecules by senescent cells. Finally, we review the existing literature regarding mitochondrial dysfunction and inflammation in specific age-related pathological conditions, including neurodegenerative diseases (Alzheimer's and Parkinson's disease, and amyotrophic lateral sclerosis), osteoarthritis and sarcopenia.

1. Introduction

Ageing is the progressive functional decline that occurs in most organisms over time and is associated with increased risk for multimorbidity and mortality (Vetrano et al., 2018). Ageing in different organisms shares several common denominators, referred to as the hallmarks of ageing, with chronic inflammation being one of these factors (Lopez-Otin et al., 2023). Indeed, levels of the pro-inflammatory cytokines, interleukin-1 beta (IL-1β), tumour necrosis factor (TNF) α, IL-6, and the chemokine (C-C motif) ligand (CCL) 2 have been shown to

Abbreviations: AD, Alzheimer's disease; ALS, Amyotrophic lateral sclerosis; AMPK, AMP-activated protein kinase; APP, Amyloid precursor protein; ATF5, Activating Transcription Factor 5; BNIP, BCL2 interacting protein; CCL, Chemokine (C-C motif ligand); CCR, C-C chemokine receptor; CGAS, cyclic GMP–AMP synthase; CLPP, Caseinolytic Peptidase P; CXCL, Chemokine (C-X-C motif ligand); CXCR, C-X-C chemokine receptor; DAMP, Damage-associated molecular pattern; DRP, Dynamin-related Protein; EIF2α, Eukaryotic translation initiation factor 2 subunit 1; ETC, electron transport chain; FIS, Mitochondrial fission protein; HIF-1α, Hypoxia-inducible factor 1α; IFN, Interferon; IKK (, inhibitor of NF-κB kinases; IκB, Inhibitor of NF-κB; IL, interleukin; IRF, Interferon regulatory factor; JNK, c-Jun N-terminal kinase; KO, Knock out; MAVS, Mitochondrial antiviral-signaling protein; MDA, Melanoma differentiation gene; MDVs, Mitochondrial-derived vesicles; MFF, Mitochondrial fission factor; MFN, Mitofusin; MiDAS, Mitochondrial dysfunction-induced senescence; MiMOMP, minority mitochondrial outer membrane permeabilization; MQC, Mitochondrial quality control; Mt, mitochondrial; NADH, Nicotinamide adenine dinucleotide; NAMPT, Nicotinamide phosphoribosyltransferase; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP, NLR family pyrin domain containing; NRF, Nuclear respiratory factor; OA, Osteoarthritis; OPA, Optic atrophy; OXPHOS, Oxidative phosphorylation; PAMP, Pathogen-associated molecular patterns; PD, Parkinson's disease; PGC-1α, Peroxisome proliferator-activated receptor-γ coactivator 1-alpha; PINK, PTEN-induced kinase 1; PNPase, Polynucleotide Phosphorylase; PRR, Pattern recognition receptor; PSN, Presenilin; RIG, retinoic acid inducible gene-I; RLR, RIG-I-like receptors; ROS, Reactive oxygen species; SASP, Senescence-associated secretory phenotype; SOD, Superoxide dismutase; STING, stimulator of interferon genes; TDP, TAR DNA-binding protein; TFAM, Mitochondrial transcription factor A; TLR, Toll-like receptors; TNF, Tumour necrosis factor; TOM40, translocase of the outer mitochondrial membrane; UPR^{mt}, Mitochondrial Unfolded Protein Response; VDAC, Voltage-Dependent Anion Channel.

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significantly increase upon ageing (Alvarez-Rodriguez et al., 2012; Gerli et al., 2000; Zembron-Lacny et al., 2019). Interestingly, IL-6 has been characterized as the "gerontologist's cytokine" due to its influential role in modulating ageing-related pathology (Ershler, 1993). It has been hypothesized that the inflammatory state observed during ageing can be partially attributed to the accumulation of cell debris and misplaced or damaged self-macromolecules over time due to the age-associated decline in organismal quality control mechanisms (Franceschi et al., 2017). Self-molecules are able to trigger inflammatory responses due to the degeneracy of pattern recognition receptors (PRRs), which are responsible for integrating and transducing cellular responses following the exposure to inflammatory stimuli (Franceschi et al., 2018). Particularly, a limited number PRRs recognize both self-molecules called damage-associated molecular patterns (DAMPs) and bacterial or viral molecules called pathogen-associated molecular patterns (PAMPs), and, in both cases, they elicit inflammatory responses and mediate a plethora of ageing-related pathologies. This chronic, sterile (in the absence of infection), low-grade inflammation accompanying ageing and resulting in aberrant immune system responses has been termed inflammageing (Franceschi et al., 2000).

Emerging evidence suggests an interplay between chronic inflammation and the hallmarks of ageing (Baechle et al., 2023). Mitochondria have been found to both influence the progression of age-associated inflammation and to be negatively affected by it (Conte et al., 2020). These organelles have evolutionary derived from α-proteobacteria and, therefore, harbour multiple molecules also present in bacteria (Sagan, 1967). This renders mitochondria an important signalling hub for immune pathways since the mitochondrial release of immune-stimulating molecules can result in inflammatory signalling. Therefore, the dysregulation of mitochondrial homeostasis may lead to inflammation-related pathology (Chandel, 2015; Wein and Sorek, 2022). Indeed, the cytosolic or extracellular release of mitochondrial components triggers the production of pro-inflammatory mediators, while mitochondrial quality control mechanisms have been shown to decline during ageing, which further exacerbates mitochondrial-related inflammation (Krysko et al., 2011; Picca, Calvani, et al., 2020). Mitochondria also play a key role in cellular senescence-related inflammation and influence the onset of age-related pathologies characterized by chronic inflammation (Amorim et al., 2022; Gallage and Gil, 2016).

In this Review, we report on findings concerning the role of mitochondrial signalling components in the release of pro-inflammatory molecules. We continue by examining the effect of ageing on mitochondrial quality control mechanisms and how this is related to cytokine and chemokine production, and we summarize the current literature concerning the role of mitochondria in regulating the senescence-associated cytokine and chemokine secretion. Finally, we discuss the role of mitochondria-regulated inflammation in the progression of age-associated diseases.

2. Mitochondrial control of inflammageing

Due to their endosymbiotic origin, mitochondria retain several bacterial traits that distinguish them from other cellular compartments. Nevertheless, the sequestered nature of the organelle prevents these traits from gaining physical access to the cellular PRRs and triggering inflammatory responses in physiological conditions (Krysko et al., 2011; Roger et al., 2017; Sagan, 1967). However, the "garb-ageing" theory, proposed by Franceschi in 2017, suggests that age-related mitochondrial impairment could be a significant source of misplaced self-molecules that initiate and sustain inflammageing (Franceschi et al., 2017).

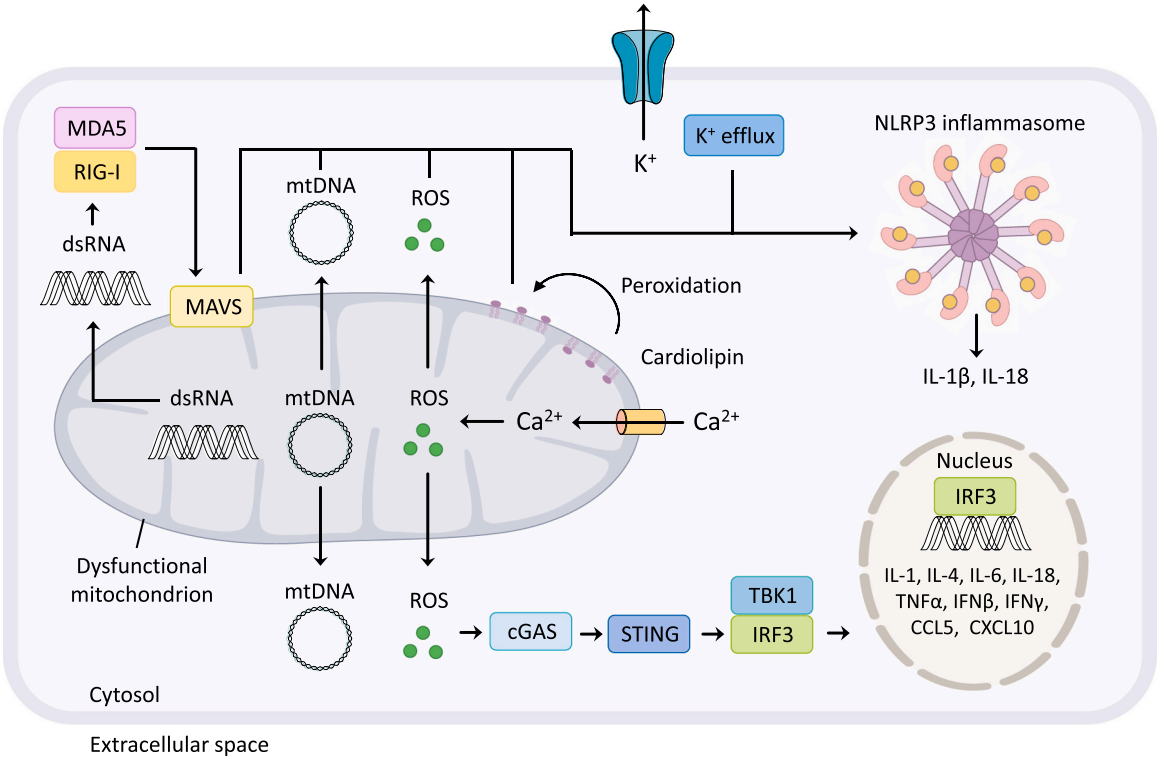

Fig. 1. The role of intracellular mitochondrial signals in cytokine and chemokine production. Multiple mitochondrial constituents are released from mitochondria during organelle dysfunction and are able to drive inflammatory responses via specific sensors. mtDNA and mitochondrial ROS can be sensed by the cGAS-STING pathway and therefore trigger the production of pro-inflammatory mediators. Furthermore, multiple mitochondrial components, as well as ions, are able to trigger the activation of the NLRP3 inflammasome and the subsequent production of IL-1β and IL-18. In particular, multiple NLRP3 agonists activate NLRP3 through upstream signalling events including K^+ efflux, mitochondrial Ca^{2+} uptake, release of mtDNA and mitochondrial ROS into the cytoplasm and translocation of cardiolipin to the outer mitochondrial membrane upon lipid perodxidation. Mitochondrial dsRNA can also activate similar pathways in coordination with MDA-5, RIG-I and MAVS.

Therefore, understanding the molecular mechanisms underlying the contribution of mitochondrial constituents to immune activation is essential in the context of ageing. The main mitochondrial signalling components implicated in this process are mtDNA, mtRNA, N-formylated peptides, ROS, cardiolipin, cytochrome c, mitochondrial metabolites and ion homeostasis (Fig. 1).

2.1. Mitochondrial DNA (mtDNA)

Owning to its bacterial ancestry, mitochondrial DNA (mtDNA) exists in many copies, and, unlike nuclear DNA, it lacks CpG methylation (Liu et al., 2016). Therefore, when located outside mitochondria, mtDNA is recognized as a danger stimulus and drives inflammatory responses upon its accumulation in the cytosol or extracellular space (West and Shadel, 2017). Particularly, cell-free mtDNA can trigger toll-like receptor (TLR) 9 signalling in circulating leukocytes, which leads to activation of the NF-κB transcription factor and subsequent expression of pro-inflammatory mediators such as TNF, IL-6, and IL-8 (Kawai and Akira, 2007). Furthermore, mtDNA located in the extracellular milieu participates in the formation of neutrophil extracellular traps, which are implicated in the type I IFN-mediated pathology observed in sterile inflammatory diseases such as systemic lupus erythematosus (McIlroy et al., 2014; H. Wang et al., 2015). However, mtDNA can also trigger intracellular immune signalling by acting as an endogenous agonist of inflammasomes. mtDNA molecules, when released into the cytoplasm, can interact with the NLR family pyrin domain containing NLRP3 inflammasome, which induces caspase-1 stimulation and, therefore, the processing of the pro-inflammatory cytokines IL-1β and IL-18, ultimately leading to a specific type of cell death called pyroptosis (Nakahira et al., 2011). Moreover, when released intracellularly, mtDNA can also serve as a cell-intrinsic cyclic GMP–AMP synthase (cGAS) ligand. Released mtDNA can engage cGAS-STING-IRF3 signalling and trigger the expression of pro-inflammatory interferons IFN-β and IFN-γ (Rongvaux et al., 2014; White et al., 2014). Interestingly, several studies have implicated mtDNA mutations in the ageing process since mice that carry increased mtDNA mutations age at an accelerated rate and have reduced lifespan (Kujoth et al., 2005; Ross et al., 2013; Trifunovic et al., 2004). Notably, levels of circulating mtDNA rise gradually with age following the fifth decade of life, correlate with pro-inflammatory cytokine levels, and therefore may contribute to the inflammageing phenotype (Pinti et al., 2014).

2.2. Mitochondrial RNA (mtRNA)

The mitochondrial genome encodes for 11 mRNAs that are translated into 13 polypeptides since two of the mtRNAs are bicistronic (Bogenhagen and Yoza, 1986). Indeed, mitochondria are a rich source of dsRNA within the cell due to the bidirectional transcription of the mtDNA. In physiological conditions, the mitochondrial dsRNA levels are modulated by the mitochondrial RNA degradosome (Chen and Hur, 2022). The exonuclease polynucleotide phosphorylase (PNPase) degrades mitochondrial mtRNAs upon their accumulation. Accordingly, patients with mutations in the gene encoding for PNPase experience a chronic type I interferon response due to the accumulation of mtRNA that is ultimately released into the cytosol (Dhir et al., 2018). During mitochondrial dysregulation, mitochondrial dsRNA can accumulate in the cytosol and gain access to nucleic acid sensors, thereby activating pro-inflammatory pathways. Specifically, upon detecting mitochondrial dsRNAs in the cytosol, receptors such as RIG-I or MDA5, known as RIG-I-like receptors (RLRs), assemble the mitochondrial antiviral signalling protein (MAVS) (Seth et al., 2005). MAVS is located on the outer membrane of mitochondria and serves as a central point for innate immune defence against viruses, and once activated, it triggers an antiviral response via NF-κB and the expression of interferon regulatory factor IRF3 and IRF7 (Liu et al., 2015; Pichlmair et al., 2006). Furthermore, mitochondrial dsRNA has been implicated in autoimmune and inflammatory disease progression. A recent study shows that the RNA editing process responsible for suppressing dsRNA sensing by MDA5 plays an essential role in the genetic risk for multiple autoimmune diseases (Li et al., 2022).

2.3. N-formylated peptides

Initiation of intra-mitochondrial protein translation, similarly to protein translation in bacteria, requires the N-formylation of the first methionine-charged tRNA (Dela Cruz and Kang, 2018; Sinha et al., 2014). Thus, the 13 polypeptides encoded by the mitochondrial genome contain an N-formylated methionine in their N-terminal, which is retained in 12 out of 13 polypeptides, with the only exception being the CoxIII protein (Walker et al., 2009). Upon cell death, N-formylated peptides are released from mitochondria into the extracellular milieu and can act as chemo-attractants for neutrophils and monocytes and trigger immune activation by binding to N-formyl peptide receptors (Dahlgren et al., 2016; Schiffmann et al., 1975). Indeed, stimulation with an N-formylated peptide in an in vitro model of Schwann cells resulted in increased levels of the C-C chemokine receptor (CCR) 2 and CXCR4 (Korimova and Dubovy, 2020). Furthermore, the interaction between N-formylated peptides and their receptor significantly increases the release of IL-8 from monocytes in the presence of TFAM (Crouser et al., 2009). Importantly, N-formylated peptides play an influential role in the progression of sterile lung inflammation of patients with acute respiratory distress syndrome, while mitochondrial N-formylmethionine formation has been associated with common age-related disorders such as ischemic stroke (Cai et al., 2021; Dorward et al., 2017).

2.4. Reactive Oxygen Species (ROS)

ROS is an umbrella term that describes an array of chemical species derived from the incomplete reduction of molecular oxygen and includes the superoxide anion radical ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2) and the hydroxyl radical ($^{\cdot}OH$). Despite the existence of many sources of ROS inside the cell, the mitochondrial Electron Transport Chain (ETC) is one of the major contributors of intracellular ROS production. ROS are known to fulfil a dual role in cell biology (Holmstrom and Finkel, 2014). Supraphysiological concentrations of ROS can lead to non-specific protein oxidation and to deleterious effects on biomolecules, whereas low physiological levels of H_2O_2 and $O_2^{\cdot-}$ can act as signaling agents in many cellular processes, such as immune system function (Sies and Jones, 2020). It has been reported that generation of mitochondrial ROS upon mitophagy inhibition triggers the activation of the NLRP3 inflammasome, subsequent caspase-1 activation and cleavage of pro-IL-1β and pro-IL-18 (Zhou et al., 2011). Furthermore, ROS can also affect inflammatory signaling through NF-κB, which is a redox-sensitive transcription factor. H_2O_2 can oxidize and therefore activate the inhibitor of NF-κB kinases (IKK) which in turn destabilizes the inhibitor of NF-κB (IκB), ultimately leading to the translocation of NF-κB to the nucleus and the initiation of an inflammatory response (Schreck et al., 1991). Moreover, in addition to its indirect redox regulation, NF-κB can be directly oxidized in the cysteines of its DNA-binding region and this modification decreases its transcriptional activity (Halvey et al., 2007). Finally, mitochondrial ROS can also have immunomodulatory roles through the lipid oxidation of polyunsaturated fatty acid side chains of phospholipids. In particular, oxidized lipids can transcriptionally activate the NLRP3 inflammasome and therefore contribute to an atherogenic phenotype of endothelial cells (Hitzel et al., 2018).

2.5. Cardiolipin

Cardiolipin is a phospholipid found predominantly in bacteria but also within the inner mitochondrial membranes of eukaryotic cells (Tian et al., 2012). It performs both structural and functional roles within

mitochondrial membranes as it affects the curvature of mitochondrial cristae and directly binds to complexes of the ETC, aiding their configuration and proper function (Jiang et al., 2000; Joshi et al., 2009; Koshkin and Greenberg, 2002; Zhang et al., 2005). However, in cases of mitochondrial stress or dysfunction, cardiolipin can undergo lipid peroxidation and be released outside of mitochondria, where its distinctive structure marks it apart from other cellular components and triggers various signaling pathways (Claypool and Koehler, 2012; Dudek, 2017). When translocated to the outer mitochondrial membrane, cardiolipin can mark the organelle for mitophagy, or it can directly bind and activate the NLRP3 inflammasome, leading to the production of pro-inflammatory cytokines IL-1β and IL-18, thereby leading to innate immune response (Chu et al., 2013; Iyer et al., 2013). Cardiolipin has also been shown to have a net pro-inflammatory effect during bacterial pneumonia since it downregulates the expression of the anti-inflammatory cytokine IL-10 and promotes the production of TNF and IL-6 (Chakraborty et al., 2017). Similarly, cardiolipin promotes the secretion of CCL2 and the Chemokine (C-X-C motif) ligand (CXCL) 10 from microglial cells and is required for IL-6 and IL-1α production by LPS-induced macrophages (Pointer et al., 2019; Reynolds et al., 2023). Moreover, cardiolipin found in the extracellular environment induces the overexpression of the lipid antigen-presenting molecule CD1 on dendritic cells and directly binds to CD1d of antigen-presenting cells, which presents cardiolipin to T cells and activates them (Dieude et al., 2011; Leslie et al., 2008). However, the role of cardiolipin in modulating inflammation remains controversial since there are a few studies reporting on its anti-inflammatory effects (Balasubramanian et al., 2015; Pointer et al., 2019).

2.6. Cytochrome c

Cytochrome c is a small, heme-containing protein that is loosely associated with the inner mitochondrial membrane under physiological conditions. It plays a critical role in the ETC, and its release from mitochondria can trigger cell death and immune signalling (Eleftheriadis et al., 2016; Kuhlbrandt, 2015). While the presence of cytochrome c in the cytoplasm triggers the non-inflammatory process of cell death, when cytochrome c is translocated to the extracellular milieu, it can act as a DAMP and trigger inflammation (Li et al., 1997). In vitro studies have shown that extracellular cytochrome c can trigger inflammatory responses in microglial cells via TLR4 signaling, and stimulation of mouse spleen cells with exogenous cytochrome c leads to NF-κB activation along with the increased secretion of pro-inflammatory cytokines and chemokines (Gouveia et al., 2017). Moreover, injection of exogenous cytochrome c increases the levels of CCL2, CCL3, CCL5, CXCL2, TNFα and IL-6 via NF-κB and promotes arthritis in mice via a neutrophil and monocyte-dependent mechanism (Pullerits et al., 2005).

2.7. Mitochondrial metabolites

The tricarboxylic acid metabolites produced through mitochondrial metabolism may be capable of influencing the sterile inflammation observed upon ageing. Succinate is a metabolite with pro-inflammatory properties. It accumulates during macrophage activation because of the dysregulated activity of succinate dehydrogenase enzyme (complex II of the ETC), which is responsible for converting succinate to fumarate (Mills and O'Neill, 2014). Succinate accumulation stabilizes HIF (hypoxia-inducible factor) 1α, which enhances IL-1β production during inflammation (Tannahill et al., 2013). Moreover, succinate released from activated macrophages has been found in inflamed joints, where it also induces the production of IL-1β and exacerbates rheumatoid arthritis via the GPR91 receptor (Littlewood-Evans et al., 2016). Furthermore, succinate has chemotactic potential on dendritic cells and induces the release of TNF, IL-1β, CCL2 and CXCL8 (Rubic et al., 2008). When succinate is oxidized by succinate dehydrogenase, there is an increase of reverse electron transport in complex I of the ETC, ultimately driving mitochondrial Reactive oxygen species (ROS) production and, therefore, a pro-inflammatory response (E. L. Mills et al., 2016). Interestingly, reverse electron transport increases with age and extends fly lifespan through a ROS-mediated mechanism (Scialo et al., 2016).

Fumarate, an intermediate metabolite in the citric acid cycle, has been shown to have anti-inflammatory effects. Exogenous fumarate supplementation limits pro-inflammatory cytokine and chemokine secretion by immune cells and reduces oxidative stress in conditions marked by systemic inflammation (Brennan et al., 2015; Loewe et al., 2002; McGuire et al., 2016; Stoof et al., 2001; Timpani and Rybalka, 2020; Zhang et al., 2023; Zinger et al., 2022). Several studies have also made a link between fumarate synthesis and mitochondrial nucleic acid release (Hooftman et al., 2023; Zecchini et al., 2023).

Furthermore, in physiological conditions, mitochondria are the main suppliers of ATP. ATP can have chemotactic and immunostimulatory effects upon release into the extracellular environment, where it binds to purinergic receptors PYRY2 and PYRX7 expressed on myeloid cells (Elliott et al., 2009; Ghiringhelli et al., 2009). It has been shown that ATP released by cancer cells in the context of immunogenic cell death can recruit antigen-presenting cell to the tumor microenvironment and activate them via P2RX7 binding, leading to inflammasome activation and the consequent synthesis of the pro-inflammatory cytokine IL-1β (Kroemer et al., 2022; Ma et al., 2013).

Finally, studies have shown that itaconate, an immunometabolite recently identified as a regulator of macrophage function, has an overall anti-inflammatory effect as it restricts inflammation and regulates type I interferons via Nrf2 activation (Day and O'Neill, 2022; Lampropoulou et al., 2016; McGettrick and O'Neill, 2023; Mills et al., 2018). Interestingly, itaconate has been implicated in the ageing process as it extends the lifespan of *Caenorhabditis elegans* in a mitochondria-dependent manner (Wang et al., 2022).

2.8. Ion homeostasis

Although not a mitochondrial constituent, cellular ion homeostasis is a key upstream event for the activation of the NLRP3 inflammasome. Thus, the disruption of ion homeostasis within cells plays a regulatory role during inflammatory responses.

Potassium (K^+) efflux is important for the activation of the NLRP3 inflammasome since many NLRP3 activators act by lowering the intracellular potassium levels (Xu et al., 2020). However, although mitochondrial dysfunction has also been implicated in NLRP3 inflammasome activation, the exact mechanism underlying the regulation of NLRP3 activation by both upstream events has not been fully elucidated yet (Jo et al., 2016). It has been reported that mitochondrial perturbation and ROS production are dispensable for the activation of the NLRP3 inflammasome while a drop in cytosolic K^+ is required for this process (Munoz-Planillo et al., 2013). However, it has also been found that imiquimod, a TLR7 ligand, can induce NLRP3 inflammasome activation in a K^+ efflux-independent manner via inhibition of the quinone oxidoreductases NQO2 and mitochondrial Complex I and the subsequent burst of ROS (Gross et al., 2016). Interestingly, a study published in 2017 showed that NLRP3 agonist-induced K^+ efflux and mitochondrial ROS activate NLRP3 through chloride (Cl^-) efflux (Tang et al., 2017). Indeed, NLRP3 agonists promote K^+ efflux, which in turn leads to mitochondrial damage and ROS generation. Then, Cl^- intracellular channels translocate to the plasma membrane and induce Cl^- efflux, resulting in inflammasome assembly. Furthermore, the mitochondrial apoptotic effectors BAX-BAK have been shown to activate effector caspase-3 and −7, which in turn cause K^+ efflux and NLRP3 activation (Vince et al., 2018). Interestingly, curcumin has been found to exert its anti-inflammatory effects by preventing the NLRP3 inflammasome activation via inhibition of K^+ efflux and of the downstream subcellular rearrangement of mitochondrial (Yin et al., 2018).

Calcium (Ca^{2+}) signaling and mitochondrial destabilization have both been indicated to have an important role in the activation of the

NLRP3 inflammasome, although a consensus model has not been found (Horng, 2014). Released pancreatic mtDNA in type 1 diabetes induces Ca^{2+} influx and generation of mitochondrial ROS in endothelial cells, which leads to NLRP3 inflammasome activation and therefore to the endothelial dysfunction that is associated with diabetes (Pereira et al., 2019). Interestingly, recent studies have demonstrated that Ca^{2+} uptake leads to the exit of mtDNA from mitochondria and the activation of cGAS-STING and the NLRP3 inflammasome by triggering the oligomerization of the voltage-dependent anion channel (VDAC) of the inner mitochondrial membrane (Xian et al., 2022) (Baik et al., 2023). Notably, mtDNA-induced NLRP3 activation can also occur as a consequence of mitochondrial damage, ROS production and loss of membrane potential triggered by Ca^{2+} influx (Murakami et al., 2012). Elliott and colleagues have shown that, during NLRP3 activation, the association of the caspase recruitment domain ASC with NLRP3 on the mitochondrial surface is calcium dependent (Elliott et al., 2018). Interestingly, liposomes and oxidized phosphatidylcholine both act as NLRP3 activators in a Ca^{2+} influx and mitochondrial ROS dependent mechanism (Zhong et al., 2013) (Yeon et al., 2017). Finally, it has been reported that the formation of the complement membrane attack complex, beyond its role in lysing cells, also leads to influx of Ca^{2+}, which then enters the mitochondria, resulting in a loss of mitochondrial membrane potential and the consequent NLRP3 activation (Triantafilou et al., 2013).

3. Mitochondrial Quality Control mechanisms (MQC) in inflammageing

Mitochondria are intimately linked to the ageing process (Sun et al., 2016). Mitochondrial damage accumulates over time, and the proper function of the organelle depends on mitochondrial quality control (MQC) mechanisms (Amorim et al., 2022). MQC ensures cell homeostasis through a network of pathways that are highly coordinated (Fischer et al., 2012). Mitochondrial biogenesis maintains a proper number of mitochondria within the cell, fusion facilitates the diffusion of damaged mitochondrial contents, fission isolates damaged parts to be degraded through mitophagy and UPR^{mt} mitigates the accumulation of misfolded proteins within mitochondria. Mitochondrial dysfunction plays a pivotal role in the development of the inflammageing phenotype, and therefore, it is essential to examine the role of the MQC system in this process (Picca et al., 2017) (Fig. 2).

3.1. Mitochondrial biogenesis

Mitochondrial biogenesis is the process by which cells increase their mitochondrial mass and copy number, and it is tightly regulated by endogenous and extracellular stimuli (Popov, 2020). Peroxisome proliferator-activated receptor-γ coactivator 1-alpha (PGC-1α) is a master regulator of mitochondrial biogenesis and function and interacts with multiple transcriptional regulators, such as NRF1/2, leading to the expression of genes responsible for mitochondrial biogenesis and function (Fernandez-Marcos and Auwerx, 2011; Gleyzer et al., 2005). Besides PGC-1α, the mitochondrial transcription factor A (TFAM) is also a modulator of mitochondrial biogenesis through its binding to mtDNA (Picca and Lezza, 2015). It is unclear how the ageing process affects the number of mitochondria within cells; while many studies report a decrease in mitochondria during ageing (Burns et al., 1979; Chabi et al., 2008; Corsetti et al., 2008; Genova et al., 1997; Gureev et al., 2016; Kerner et al., 2001; Ojaimi et al., 1999; Tate and Herbener, 1976), other research groups have not identified any age-related changes in mitochondrial number (Callahan et al., 2014; Hepple, 2014; Mathieu-Costello et al., 2005; Schmucker and Sachs, 1985). Interestingly, a few studies have reported a link between chronic inflammation (a hallmark of ageing) and the regulators of mitochondrial biogenesis. Mice with TFAM-deficient T cells exhibit a premature ageing phenotype and reduced lifespan compared to wild-type mice (Desdin-Mico et al., 2020). The TFAM-deficient T cells of young mice recapitulate the mitochondrial dysfunction observed in wild-type aged T cells and instigate the secretion of pro-inflammatory cytokines IFNγ and TNFα, thereby initiating premature inflammageing. Furthermore, in a mouse model for Type II diabetes, temporary induction of PGC-1α in aged mice leads to a reduction in plasma levels of the pro-inflammatory cytokines IL-1α, IL-6, and TNFα and the chemokines CCL2, CXCL2 and CXCL10, which are involved in monocyte and macrophage trafficking (Botta et al., 2013). Finally, it has recently been reported that inhibition of mitochondrial biogenesis with chloramphenicol decreases the ABT-734 and QVD-induced accumulation of cytoplasmic mtDNA in ARPE-19 cells, which may have an anti-inflammatory effect, given the role of mtDNA as a cell-intrinsic cGAS ligand (Jimenez-Loygorri et al., 2024).

3.2. Mitochondrial dynamics

Mitochondria are dynamic organelles whose size and morphology are highly variable and regulated by mitochondrial fusion and fission, collectively termed mitochondrial dynamics (Bereiter-Hahn, 1990). Mitochondrial fusion leads to the formation of an interconnected mitochondrial network that facilitates the exchange of contents between mitochondria and the buffering of mtDNA mutations and oxidized proteins (Ni et al., 2015; Santel et al., 2003; Wai and Langer, 2016). Mitochondrial fission, on the other hand, results in many mitochondrial fragments and serves mitochondrial distribution and isolation of defective parts for autophagic degradation (Brooks et al., 2009; Burman et al., 2017). The role of mitochondrial dynamics in regulating sterile inflammatory responses has been extensively studied. Mitochondrial fragmentation induced by repression of mitofusins Mfn1 or Mfn2 results in the binding of mislocalized mtDNA to TLR9 and, therefore, in NF-κB-mediated inflammation, while mitochondrial elongation induced by repression of dynamin-1-like protein Drp-1 leads to both NF-κB-induced inflammation and type I interferon (IFN) inflammatory responses (Irazoki et al., 2023). In adult mice, hepatocyte-specific knockdown of mitochondrial fission protein Drp1 results in liver inflammation and fibrosis (Steffen et al., 2022). Furthermore, a recent study also shows that a decrease in mitochondrial fission results in the escape of mtDNA–protein complexes called nucleoids from mitochondria, which then enter the endolysosomal pathway and ultimately activate cGAS-STING (Newman et al., 2024). Finally, in the context of ageing, it has recently been reported that metformin exerts its neuroprotective effects by reducing mtDNA release and the consequent cGAS-STING activation via Mfn2, which leads to suppression of astrocyte senescence and age-related neurodegeneration (Wang et al., 2024).

3.3. Mitophagy

Macroautophagy (hereafter referred to as autophagy) is a catabolic pathway that eliminates long-lived or defective cellular components via lysosomal degradation to promote cell homeostasis (Dikic and Elazar, 2018). Mitophagy, a subtype of autophagy in which the targeted cargo is mitochondria, fine-tunes mitochondrial number and prevents the accumulation of faulty or superfluous mitochondria (Ashrafi and Schwarz, 2013). Many studies have highlighted an intricate crosstalk between mitophagy and inflammatory responses. Mitophagy prevents the cytosolic release of mtDAMPs, such as mitochondrial ROS and mtDNA, thereby inhibiting inflammasome activation and the production of pro-inflammatory cytokines IL-1β and IL-18 (Nakahira et al., 2011; Saitoh et al., 2008; Zhong et al., 2016; Zhou et al., 2011). In the context of antiviral signalling, mitochondria act as a platform for MAVS oligomerization, which leads to IRF3 and IRF7 activation and type I IFN expression. Thus, mitophagy inhibits the expression of type I interferons and other pro-inflammatory molecules, such as CXCL10, by removing the platform necessary for host antiviral responses (Lei et al., 2012; Xia et al., 2014; Zhao et al., 2012). Therefore, not surprisingly, the physiological ageing-related decline in mitophagy contributes to the establishment of chronic inflammation. Alzheimer's disease pathogenesis is

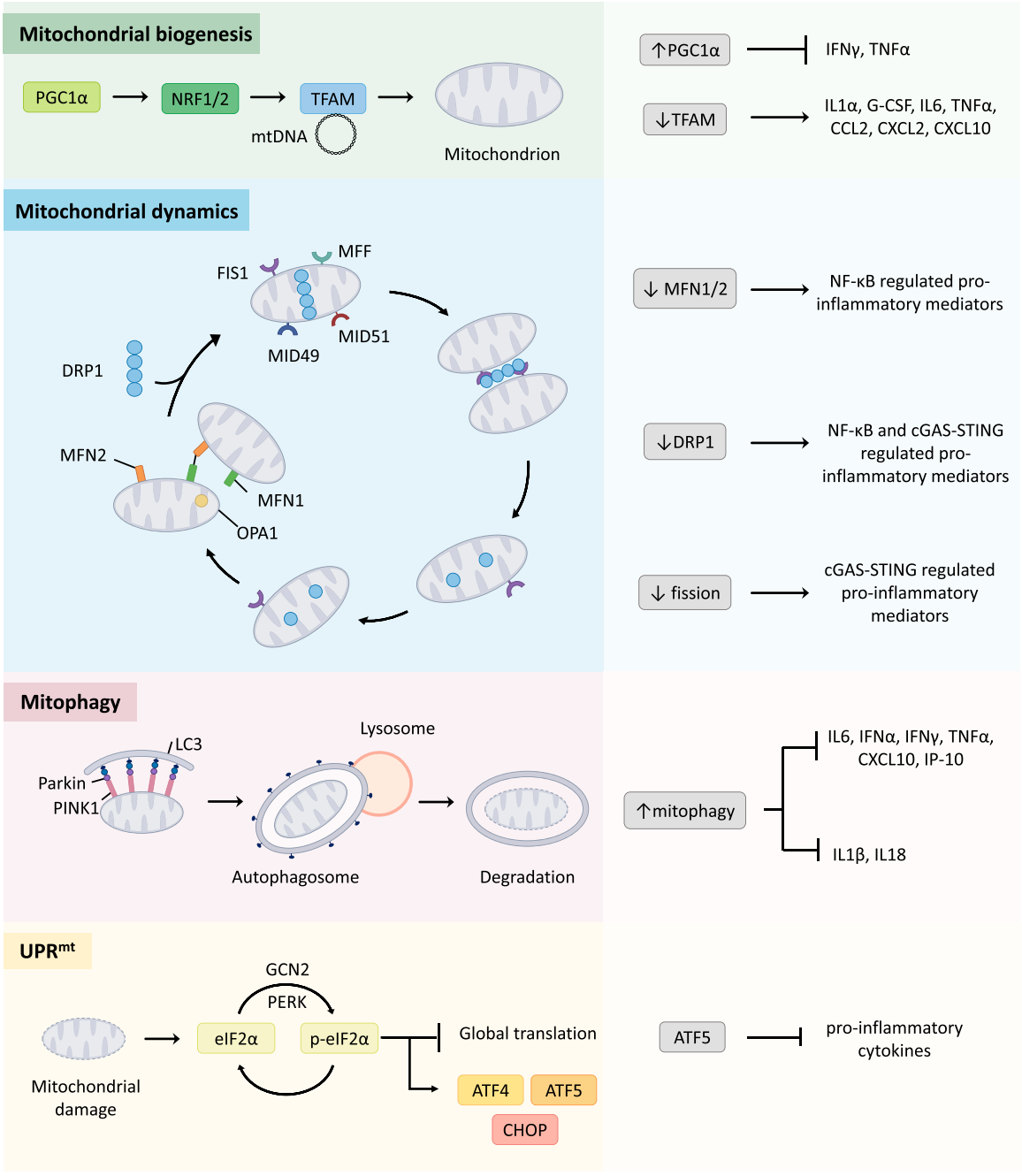

Fig. 2. Mitochondrial quality control mechanisms and their role in inflammageing. Mitochondrial homeostasis is ensured through the coordination of mitochondrial biogenesis, mitochondrial dynamics, mitophagy and the UPR^{mt}. Mitochondrial biogenesis is transcriptionally controlled by the transcription coactivator PGC-1α and the transcription factors NRF1/2 and TFAM through its binding to mtDNA. Induction of PGC-1α leads to reduced plasma levels of pro-inflammatory mediators and TFAM-deficient T-cells instigate pro-inflammatory cytokine and chemokine production. After organelle biogenesis, mitochondrial morphology is regulated by fusion and fission events. Activation of fusion proteins, such as MFN1, MFN2 and OPA1, results in an interconnected mitochondrial network, while fission proteins, such as DRP1, FIS1, MFF, MID49 and MID51, induce fragmentation of dysfunctional mitochondria. MFN1/2 repression activates the transcription of NF-κB-related mediators while DRP1 repression induces both NF-κB and cGAS-STING-regulated transcription. Moreover, fission attenuation leads to cGAS-STING activation via cytosolic release of mtDNA. Dysfunctional mitochondria are degraded by mitophagy through the functions of PINK1, Parkin, and LC3, and ubiquitination. These components of the autophagic machinery aid the engulfment of the dysfunctional mitochondria by a double-membrane structure, called autophagosome, which then fuses with lysosomes and thereby facilitates mitochondrial degradation. Mitophagy induction has a protective role during inflammageing, since it mitigates the production of pro-inflammatory mediators. During mitochondrial stress, the accumulation of irreversibly misfolded proteins triggers the phosphorylation of eukaryotic translation initiation factor 2 subunit 1 (eIF2α) by GCN2 and PERK. Following eIF2α phosphorylation, there is attenuation of protein translation and the translation of CHOP, ATF4 and ATF5 encoding mRNAs, which will then be involved in the UPR^{mt} ATF5 has been reported to mitigate the production of pro-inflammatory cytokines.

severely affected by mitophagy defects. Induction of mitophagy in APP/PS1 mice improves the efficiency of microglial phagocytosis of Aβ plaques. It also mitigates neuroinflammation by reducing the levels of pro-inflammatory cytokines IL-6 and TNFα, typically produced by activated microglia in mice with Alzheimer's disease (Fang et al., 2019). Furthermore, the mitophagy receptor BNIP3 (BCL2 interacting protein 3) is upregulated in skeletal muscle during ageing to mitigate age-related muscle inflammation and atrophy, while downregulation of BNIP3 leads to TLR-9 and NLRP3 inflammasome-triggered inflammation (Irazoki et al., 2022). Recent studies also indicate that mitophagy attenuates the cGAS-STING-induced release of pro-inflammatory mediators IFNα, IFNγ, and TNFα that occurs during ageing (Jimenez-Loygorri et al., 2024; Zhong et al., 2022). Along similar lines, NAD^+ supplementation has been reported to exert anti-inflammatory effects in age-related pathologies via mitophagy induction (Hou et al., 2021; Yang et al., 2021; Ye et al., 2024). Taken together, these observations emphasize the therapeutic potential of mitophagy modulators in alleviating age-related inflammation.

3.4. Mitochondrial Unfolded Protein Response (UPR^{mt})

In higher eukaryotes, mitochondrial dysfunction activates the UPR^{mt}, a transcriptional program that functions to alleviate the accumulation of irreversibly misfolded proteins within mitochondria that occurs during impairment of mitochondrial integrity (Shpilka and Haynes, 2018). Several studies in *Caenorhabditis elegans* have shown that, during pathogen infection, UPR^{mt} can act as a sensor for pathogens that cause mitochondrial dysfunction and initiates a protective innate response via the activation of detoxification and immune responses and the production of lysozyme and anti-microbial peptides (Pellegrino et al., 2014) (Gao et al., 2019) (Sapkota et al., 2021). However, UPR^{mt} components do not only trigger innate immune responses during infection but may also modulate inflammatory responses during various pathological conditions. Loss of the caseinolytic peptidase P (CLPP), a mitochondrial peptidase relevant for UPR^{mt}, induces infertility and hearing loss via the accumulation of mtDNA and other inflammatory factors (Gispert et al., 2013). Furthermore, in the case of neuroinflammation, overexpression of sirtuin-3 protects neuronal mitochondria during ischemic injury by activating UPR^{mt} (Xiaowei et al., 2023). Along similar lines, the UPR^{mt} activating transcription factor 5 (ATF5) has been shown to mitigate pro-inflammatory cytokine secretion in activated microglia and can therefore be an amenable target for therapies attenuating neuroinflammation (Zhu et al., 2023). Interestingly, induction of UPR^{mt} has also been observed in the articular cartilage of patients with osteoarthritis and is accompanied by decreased inflammation levels in the synovial fluid (Zhou et al., 2022). However, despite the protective role of UPR^{mt} in many pathological conditions, it has also been reported that UPR^{mt} induction negatively affects mitochondrial function and therefore disease progression in the case of osteoporosis and pulmonary disorders (Gao et al., 2021) (Jiang et al., 2020).

4. Mitochondria in senescence-associated secretory phenotype (SASP) production

Cellular senescence, first described by Hayflick in the 1960s, is a cell state of (almost) irreversible growth arrest that occurs in response to various triggers. It is considered a hallmark of ageing, being causally related to the ageing process and the onset of age-related pathology (Di Micco et al., 2021; Hayflick and Moorhead, 1961; Lopez-Otin et al., 2023). It is often accompanied by a senescence-associated secretory phenotype (SASP) that includes many inflammatory mediators such as cytokines, chemokines, growth factors, and proteases and, therefore, the accumulation of senescent cells in multiple tissues has been speculated to be a possible driver of inflammageing (Freund et al., 2010; Kuilman and Peeper, 2009; X. Li et al., 2023). As mitochondria are major regulators of the ageing process, it is not surprising that several studies have reported that mitochondrial homeostasis and cellular senescence are intimately linked (Ghosh-Choudhary et al., 2021; Martini and Passos, 2023; Miwa et al., 2022). Mitochondrial dysfunction can drive cellular senescence both in vitro and in vivo, but the exact mechanism controlling this effect remains elusive (Dai et al., 2010; Kang et al., 2013; Moiseeva et al., 2009; Wang et al., 2003). Nevertheless, there are several detailed studies that provide more insights into the role of mitochondria in this process (Fig. 3**)**.

4.1. Iron-Lipofuscin accumulation in cellular senescence

Mounting evidence suggests that mitochondrial and lysosomal dysfunction influence the age-related functional decline that is observed in post-mitotic cells. Dysfunctional mitochondria are known to accrue with age, while the mechanisms responsible for mitochondrial turnover also decline in an age-dependent manner (Luo et al., 2013). According to the mitochondrial-lysosomal axis theory of ageing, oxidatively damaged mitochondria undergo enlargement and they cannot be autophagocytosed because of the lipofuscin-induced lysosomal impairment (Brunk and Terman, 2002b). Lipofuscin is an undegradable fluorescent mixture of cross-linked macromolecules that is associated with ageing and is therefore named the "age pigment" (Brunk and Terman, 2002a) (Munnell and Getty, 1968). Lipofuscin is known to accumulate in lysosomes, thereby decreasing their degradative capacity, ultimately resulting in impaired mitochondrial turnover (Brunk and Terman, 2002b). Interestingly, because of oxidative stress, lipofuscin is known to aggregate in senescent cells and to increase their levels of autofluorescence (Rattan et al., 1982). Notably, the formation of lipofuscin is promoted by iron, likely through lipid peroxidation (Ashraf et al., 2018). Iron overload facilitates the generation of hydroxyl radicals ($^{\cdot}OH$), which initiate lipid peroxidation, leading to oxidative stress and cellular damage (Galaris et al., 2019). Emerging evidence also suggests that iron accumulation plays an important role in fueling cellular senescence and the formation of the SASP. Excessive iron accumulation has been implicated in mitochondrial dysfunction and in initiating lipid peroxidation, therefore contributing to oxidative stress and cellular damage. A recent study showed that iron accumulation leads to mitochondrial dysfunction and to the cytoplasmic release of mtDNA (H. Y. Li et al., 2023). In the cytoplasm, mtDNA activates the cGAS-STING pathway, resulting in SASP formation and induction of senescence. Furthermore, it has recently been shown that iron accumulation also fuels the SASP via generation of ROS and that the plant-derived compound cardamonin protects against iron accumulation by decreasing ROS production and inhibiting the activation of the NLRP3 inflammasome (Maus et al., 2023) (S. Li et al., 2023). However, it has also been shown that iron deficiency induced by impaired lysosomal acidification leads to instability of mtDNA and to inflammatory signaling (Yambire et al., 2019).

4.2. Mitochondrial ROS in cellular senescence

Mitochondrial ROS produced by senescent cells mediate the production and secretion of SASP. ROS produced because of the senescence-associated mitochondrial dysfunction are sufficient to activate the transcription factor NF-κB, which in turn mediates the secretion of pro-inflammatory mediators IL-6 and IL-8 from senescent fibroblasts, but conversely, NF-κB activation does not affect ROS production (Nelson et al., 2018). Furthermore, complete ablation of mitochondria in senescent cells protects against senescence and abrogates the development of pro-inflammatory SASP, indicating that mitochondrial dysfunction is a prerequisite for the pro-inflammatory SASP (Correia-Melo et al., 2016). It has also been reported that depletion of the mitochondrial superoxide dismutase (SOD2) causes nuclear DNA damage and induction of cellular senescence (Velarde et al., 2012). Along similar lines, ROS produced because of mitochondrial dysfunction have been shown to activate the JNK kinase, ultimately leading to the formation of cytoplasmic chromatin fragments and, therefore, to SASP (Vizioli et al.,

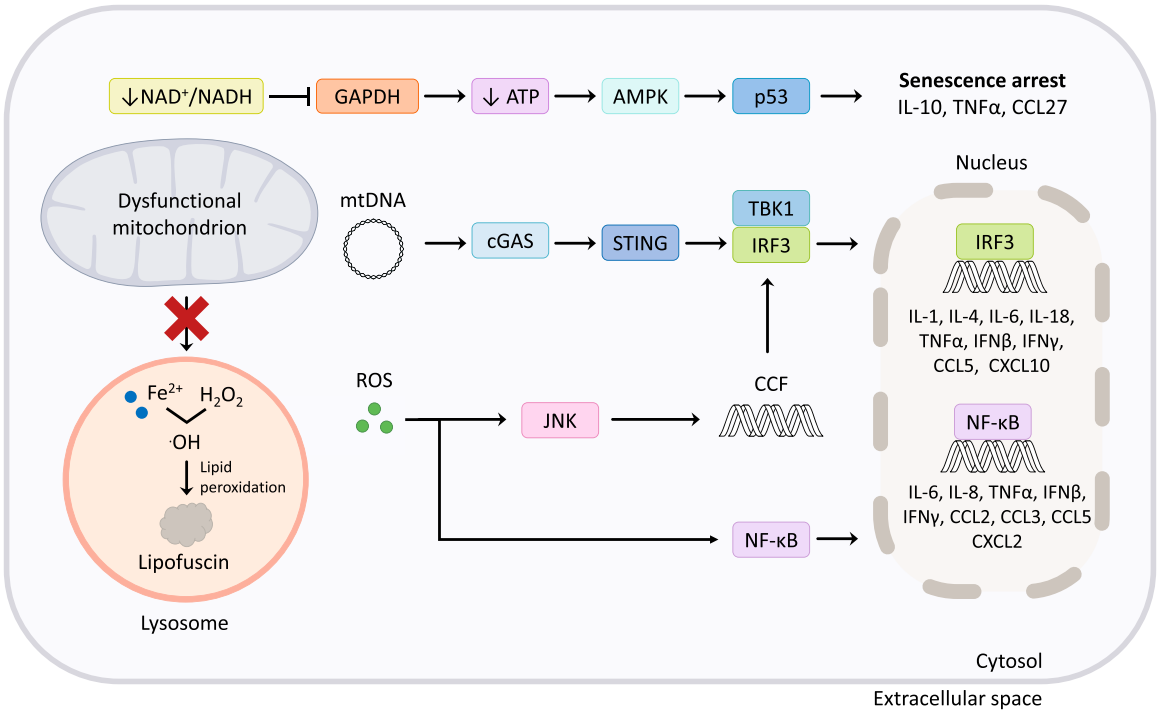

Fig. 3. Involvement of mitochondria in regulation of senescence-associated secretory phenotype (SASP) and mitochondrial dysfunction-induced senescence (MiDAS). Mitochondrial dysfunction can affect cellular senescence through multiple pathways. Senescent cells accumulate lipofuscin in their lysosomes as a result of iron-induced lipid peroxidation. The aggregation of this non-degradable mixture decreases lysosomal degradative capacity and therefore mitochondrial turnover, leading to accumulation of dysfunctional mitochondria. Additionally, in senescent cells, mitochondrial ROS and mtDNA are released in the cytosol. Upon their release, ROS activate the both the NF-κB transcription factor and the JNK kinase, which then enters the nucleus and triggers the formation of cytoplasmic chromatin fragments (CCFs). Both CCFs and mtDNA bind to cGAS and drive SASP formation. In addition to its contribution to the regular SASP, mitochondrial dysfunction can also induce a distinct state of senescence, termed MiDAS, during which, the decreased NAD+/NADH ratio inhibits the glycolytic enzyme GAPDH, provoking ATP depletion. This activates AMPK which in turn triggers p53-mediated senescence arrest and the secretion of MiDAS SASP.

2020).

4.3. mtDNA in cellular senescence

The release of mtDNA in the cytoplasm and the following activation of the cGAS-STING pathway might also be one of the mechanisms that explain why mitochondria are major regulators of the SASP. A 2021 study showed that, in a mouse model for ataxia telangiectasia, disturbed mitochondrial homeostasis leads to the release of mtDNA in the cytoplasm, the subsequent activation of STING, and the initiation of a robust pro-inflammatory response, and senescence (Yang et al., 2021). It has also been demonstrated that NAD^+ supplementation prevents SASP formation via PINK1-dependent activation of mitophagy. Furthermore, a recent study demonstrated a connection between cGAS-STING-mediated SASP formation and minority mitochondrial outer membrane permeabilization (miMOMP). miMOMP-induced cGAS-STING-mediated SASP formation occurs in a subset of mitochondria without inducing apoptosis (Bock and Tait, 2020; Ichim et al., 2015; Victorelli et al., 2023). It was also found that miMOMP is a feature of cellular senescence that enables the release of mtDNA in the cytoplasm and the subsequent cGAS-STING pathway activation and SASP formation. Interestingly, pharmacological inhibition of miMOMP in vivo decreased the levels of several circulating SASP factors and improved health span in aged mice.

4.4. Mitochondrial dysfunction-associated senescence

Notably, a study by Wiley and colleagues shows that mitochondrial dysfunction induces a senescence state called mitochondrial dysfunction-associated senescence (MiDAS) and a distinct secretion profile that lacks the IL-1 signaling arm of the SASP but includes IL-10, TNF-α, and CCL27 (Wiley et al., 2016). MiDAS results from the accumulation of NADH in the cytosol, which leads to a decreased NAD^+/NADH ratio and ultimately to growth arrest while preventing the formation of IL-1-dependent SASP factors. Within this framework, supplementation with NAD^+ precursors has been shown to alleviate age-associated decline (Garten et al., 2015; K. F. Mills et al., 2016; Verdin, 2015; Zhang et al., 2016). Moreover, a study published in 2019 showed that NAD^+ metabolism regulates SASP by upregulating nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting enzyme of the NAD+ salvage pathway (Nacarelli et al., 2019). It has also been demonstrated that the decline in NAD^+ levels that is observed during ageing can be partially attributed to the inflammageing-induced accumulation of $CD38^+$ inflammatory cells (Chini et al., 2020).

5. Mitochondria and inflammation in age-related diseases

In addition to their influential role in ageing-related decline, inflammation and mitochondrial dysfunction are also implicated in the progression of age-related diseases such as Alzheimer's and Parkinson's disease, amyotrophic lateral sclerosis, osteoarthritis, and sarcopenia (Table 1).

5.1. Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative disease worldwide, and AD patients display symptoms of memory and learning deficits and behavioural issues (Shin, 2022). Distinct features of the disease are senile plaques that consist of β-amyloid aggregates and the accumulation of hyperphosphorylated microtubule-associated protein Tau into intracellular neurofibrillary tangles within the brains of elderly individuals. These pathophysiological features drive the

Table 1
Summary of studies on the role of mitochondria and inflammation in age-related diseases.

Disease	Model	Effects	References
Alzheimer's disease (AD)	GFAP-Cre:Tfam$^{flox/flox}$ mice (model of astrocyte-specific OxPhos deficiency)	Mitochondrial dysfunction in astrocytes triggered neuroinflammation via a mechanism involving lipid droplet accumulation and decreased fatty acid degradation	(Mi et al., 2023)
	5XFAD mice (AD model expressing human amyloid-β precursor protein APP)	Release of fragmented mitochondria in the neuronal milieu by microglia propagated an inflammatory response with increased pro-inflammatory cytokine production and neuronal cell death	(Joshi et al., 2019)
	Prkn$^{-/-}$;STING$^{gt/gt}$ and Pink1$^{-/-}$; STING$^{gt/gt}$ mice	Mitophagy decreased the risk of AD by mitigating inflammation	(Sliter et al., 2018)
	APP/PS1 mice (AD model)	Pharmacological induction of mitophagy reduced microglia-induced inflammation	(Fang et al., 2019)
Parkinson's disease (PD)	Patients with PD	Dysregulation of MQC and release of mitochondrial-derived vesicles (MDVs) resulted in PD-related neuroinflammation	(Picca, Guerra, et al., 2020)
	Mice overexpressing human wild type α-Synuclein	Decreased levels of TOM40 triggered the binding of misfolded α-synuclein with mitochondria, resulting in the formation of mitochondrial ROS and the release of mtDNA	(Bender et al., 2013)
	COS−7 fibroblasts-like and RAW macrophage cell lines, PINK1 and Parkin KO mice and primary bone-marrow-derived macrophages isolated from these mice	PINK1 and Parkin prevented MDV formation and mitochondrial antigen presentation, while loss of PINK1 or Parkin fuelled inflammation	(Matheoud et al., 2016)
	gba KO zebrafish (PD model)	Cytosolic mtDNA induced neurodegeneration in PD zebrafish	(Matsui et al., 2021)
	PINK1 KO mice	Loss of PINK1 lowered dopamine levels and induced mitochondrial dysfunction	(Zhi et al., 2019)
	Primary mesencephalic neuronal cultures from naive mice	Exposure to an environmental proteobacterium drove inflammation in mesencephalic neurons via TLR4 and NLRP3 signalling, resulting in α-synuclein aggregation inside mitochondria, mitophagy induction, although it was not sufficient to prevent DAMP release, and inflammation	(Magalhaes et al., 2023)
Amyotrophic lateral sclerosis (ALS)	TDP−43-overexpressing THP−1 monocyte and HEK293T epithelial-like cell lines, TDP−43$^{Tg/+}$Sting$^{-/-}$) (mice overexpressing human TDP−43 and STING KO)	TDP−43 can enter the mitochondria and trigger mtDNA release and cGAS/STING activation	(Yu et al., 2020)
	SOD1-G85R mice (ALS model)	Aggregates of misfolded SOD1 induced mitochondrial damage and release of mtDNA and a mtRNA:DNA hybrid, which resulted in cGAS-STING induced expression of type I interferon genes and neuroinflammation	(Tan et al., 2022)
	SOD1^{G93A} mice (ALS model)	Nicotinamide riboside and pterostilbene ameliorated neuroinflammation-associated gliosis that is present in ALS, possibly by inhibiting the formation of the mitochondrial permeability transition pore complex	(Obrador et al., 2021)
Osteoarthritis (OA)	Human knee chondrocytes and human and mouse knee cartilage	Reduced activity of ETC complexes I, II, III and V resulted in decreased OXPHOS, which could trigger the secretion of pro-inflammatory cytokine IL−1β and sustain inflammation	(Y. Wang et al., 2015)
	Human chondrocytes	TNFα and IL−1β were sufficient to drive mitochondrial dysfunction and decreased activity of ETC complex I, ultimately leading to OA cartilage pathology	(Lopez-Armada et al., 2006)
	Mouse bone marrow-derived macrophages, peripheral blood monocyte-derived human macrophages	Mitochondrial dysfunction prevented the repolarization of M1 inflammatory macrophages to the M2 anti-inflammatory phenotype and aggravated pro-inflammatory cytokine secretion, which could	(Van den Bossche et al., 2016)

(continued on next page)

Table 1 (*continued*)

Disease	Model	Effects	References
		influence OA progression	
	Human chondrocytes	Elimination of damaged or depolarized mitochondria via mitophagy alleviated cytokine-induced chondrocyte pathology	(Ansari et al., 2018)
	Chondrocyte cell line C28/I2, Rat chondrocytes	Interventions that include mitochondrial transfer to chondrocytes mitigated OA-related inflammation and pathology	(Kim et al., 2023; Yu et al., 2022)
Sarcopenia	Elderly patients with sarcopenia	Circulating mtDNA levels were positively correlated with plasma levels of cytokines IL−6 and IL−8 in elderly individuals with sarcopenia, highlighting the involvement of mtDNA in driving sarcopenia-related inflammation	(Fan et al., 2022)
	NLRP3$^{-/-}$ mice,	NLRP3 activation induced sarcopenia progression	(McBride et al., 2017; Sayed et al., 2019)
	Wild type C57BL/6 J mice treated with 5,7-dimethoxyflavone	5,7-dimethoxyflavone mediated its anti-sarcopenic effects by reducing serum levels of the pro-inflammatory cytokines TNF and IL−6 and by improving mitochondrial function	(Kim and Hwang, 2020)

activation of glial cells, defined as neuroinflammation, and ultimately the secretion of pro-inflammatory cytokines and chemokines in the surrounding area (Heneka et al., 2015; Querfurth and LaFerla, 2010). Many factors have been speculated to be causally linked to AD initiation, with one of them being mitochondrial dysfunction (Oliver and Reddy, 2019). Mounting evidence suggests that chronic low-grade inflammation (a prominent AD feature) results in enhanced glucose uptake and a shift towards aerobic glycolysis, further exacerbating the secretion of pro-inflammatory mediators (Cloonan and Choi, 2012; Lartigue and Faustin, 2013). Mi and collaborators demonstrated that, in an AD mouse model, mitochondrial dysfunction in astrocytes triggers neuroinflammation via a mechanism involving lipid droplet accumulation and decreased fatty acid degradation (Mi et al., 2023). Furthermore, in cellular and animal models of neurodegeneration, the release of fragmented mitochondria in the neuronal milieu by microglia propagates inflammatory responses with increased cytokine production and neuronal cell death (Joshi et al., 2019). It is well known that AD is accompanied by a decline in mitophagy and the subsequent accumulation of dysfunctional mitochondria (Kerr et al., 2017) (Pradeepkiran and Reddy, 2020) (Morton et al., 2021). It has been demonstrated that mitophagy decreases the risk of AD by mitigating inflammation, while pharmacological induction of mitophagy reduces microglia-induced inflammation (Fang et al., 2019; Sliter et al., 2018).

5.2. Parkinson's disease

Parkinson's disease (PD) is an age-related neurodegenerative disorder, and its most prominent pathological features are the aggregation of the protein α-synuclein into Lewy bodies within neurons and the consequent irreversible loss of dopaminergic neurons in substantia nigra (Jankovic and Tan, 2020). Picca and collaborators have demonstrated that PD patients have higher serum levels of pro-inflammatory mediators TNFα and CCL4 and that dysregulation of MQC mechanisms and the release of mitochondrial-derived vesicles (MDVs) fuel PD-related neuroinflammation (Picca, Guerra, et al., 2020). In the degenerating neurons of PD patients, mitochondrial dysfunction has also been shown to promote aggregation of α-synuclein (Rocha et al., 2018). Intriguingly, decreased levels of TOM40 (translocase of the outer mitochondrial membrane) have been found to trigger the binding of misfolded α-synuclein with mitochondria, which results in the formation of mitochondrial ROS and the release of mtDNA (Bender et al., 2013). This finding may be of particular importance in the context of neuroinflammation, since cytosolic release of mtDNA is known to induce cGAS-STING signalling and interferon production. Furthermore, PINK1 and Parkin, proteins that are implicated in PD pathology, prevent MDV formation and mitochondrial antigen presentation, while loss of PINK1 or Parkin fuels inflammation (Matheoud et al., 2016). Along similar lines, loss of PINK1 or Parkin also interrupts mitophagy and leads to lower dopamine levels, mtDNA leakage, and the release of pro-inflammatory cytokines, such as TNFα and IL-1β by astrocytes and microglia (Matsui et al., 2021; Sliter et al., 2018; Zhi et al., 2019). Finally, a recent study shows that exposure to an environmental proteobacterium drives inflammation in mesencephalic neurons via TLR4 and NLRP3 signalling and IL1β, IL-6 and TNFα production, resulting in α-synuclein aggregation inside mitochondria (Magalhaes et al., 2023). This, in turn, leads to mitophagy induction, although it is not sufficient to prevent DAMP release and inflammation.

5.3. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that results in cell death of upper and lower motor neurons and muscle atrophy (Kiernan et al., 2011). Since motor neurons present high bioenergetic activity and are, therefore, more sensitive to mitochondrial dysfunction, it is not surprising that mitochondrial dysfunction has been identified as a hallmark of ALS. A common feature of ALS is the aggregation of TAR DNA-binding protein 43 (TDP-43), an RNA/DNA binding protein responsible for RNA processing. A recent study has demonstrated that TDP-43 can enter the mitochondria and trigger mtDNA release and cGAS/STING activation (Yu et al., 2020). In the same study, cytoplasmic mtDNA was detected in the cells of ALS patients. Furthermore, ALS has also been linked with mutations in the superoxide dismutase 1 gene (SOD1), which encodes for the enzyme that eliminates ROS in mitochondria. In a mouse model of SOD1-driven ALS, aggregates of misfolded SOD1 drive mitochondrial damage and release of mtDNA and a mtRNA:DNA hybrid, which results in cGAS-STING-induced expression of type I interferon genes and neuroinflammation (Tan et al., 2022). Interestingly, the compounds nicotinamide riboside and pterostilbene ameliorate neuroinflammation-associated gliosis in ALS possibly by inhibiting the formation of the mitochondrial permeability transition pore complex (Obrador et al., 2021).

5.4. Osteoarthritis

Osteoarthritis (OA) is a progressive cartilage degenerative disease that leads to pathological joint tissue changes and is highly prevalent in the elderly population (Habiballa et al., 2019; Martel-Pelletier et al., 2016). OA pathology is speculated to be triggered by an initial injury, which initiates the secretion of pro-inflammatory mediators that

exacerbate cartilage damage, while emerging evidence highlights the importance of low-grade synovial inflammation in OA pain progression. Multiple factors can initiate OA pathology, one of them being mitochondrial damage. In OA chondrocytes, reduced activity of electron transport chain (ETC) complexes I, II, III, and V decreases oxidative phosphorylation, which, in turn, triggers the secretion of pro-inflammatory cytokine IL-1β and sustains inflammation (Blanco et al., 2011; Y. Wang et al., 2015). Conversely, the pro-inflammatory cytokines TNFα and IL-1β are sufficient to drive mitochondrial dysfunction and ETC complex I impairment, ultimately leading to OA cartilage pathology (Lopez-Armada et al., 2006). Moreover, mitochondrial dysfunction prevents the repolarization of M1 inflammatory macrophages to the M2 anti-inflammatory phenotype and aggravates pro-inflammatory cytokine secretion, which may accelerate OA progression (Van den Bossche et al., 2016). Consistently with these findings, eliminating damaged or depolarized mitochondria via mitophagy alleviates cytokine-induced chondrocyte pathology (Ansari et al., 2018). Therapeutic interventions that include mitochondrial transfer to chondrocytes have been shown to mitigate OA-related inflammation and pathology (Kim et al., 2023; Yu et al., 2022).

5.5. Sarcopenia

Sarcopenia, a term first coined in 1989, is the decline in muscle mass that is observed in older individuals and is associated with an increased likelihood of adverse health outcomes (Baumgartner et al., 1998; Chen et al., 2020). Mounting evidence indicates that sarcopenia is intimately linked to age-related inflammation. However, the mechanisms explaining this association remain elusive to a large extent (Bano et al., 2017). Sarcopenia-related pathology has been attributed to a wide range of factors, with mitochondrial dysfunction being particularly relevant among them (Picca et al., 2018). Circulating mtDNA levels have been positively correlated with plasma levels of IL-6 and IL-8 in elderly individuals with sarcopenia, highlighting the role of mtDNA as an inflammatory stimulus in the disease. Importantly, it has also been reported that mtDNA can drive sarcopenia pathology via NLRP3 inflammasome activation (McBride et al., 2017; Sayed et al., 2019). Furthermore, age-related mitochondrial dysfunction increases mitochondrial ROS production, thereby provoking chronic inflammation, impairment of muscle proteostasis, and sarcopenia-related pathology. In turn, disturbances in muscle proteostasis also drive impaired mitochondrial bioenergetics and further exacerbate tissue pathology in a vicious cycle (Chung et al., 2009). Therefore, strategies targeting mitochondria may have therapeutic potential for treating sarcopenia. For example, the natural agent 5,7-dimethoxyflavone has been shown to mediate its anti-sarcopenic effects by reducing serum levels of the pro-inflammatory cytokines TNF and IL-6 and by improving mitochondrial function (Kim and Hwang, 2020). Finally, mitochondrial transplantation from stem cells has been proven to have anti-inflammatory effects and to alleviate sarcopenia-related pathology (Tian et al., 2023).

6. Concluding remarks

Here, we surveyed the key role of mitochondria in inflammation in the context of ageing. We discuss how mitochondrial homeostasis influences the release of pro-inflammatory cytokines and chemokines during ageing and how ageing results in a decline of proper mitochondrial quality control mechanisms. We also describe the mechanisms by which mitochondria regulate senescence-associated cytokine and chemokine secretion during ageing and in specific age-associated pathologies (neurodegenerative conditions such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, and osteoarthritis and sarcopenia). In summary, mounting evidence points to an undoubtable link between mitochondrial dysfunction and cytokine and chemokine production in ageing and age-related diseases. Nevertheless, further research is needed to deeply understand the molecular mechanisms underlying this link and, ultimately, to discover therapeutic approaches targeting these pathways in order to improve organismal life span and health span.

Ethical approval and consent to participate

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CRediT authorship contribution statement

Nektarios Tavernarakis: Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization. **Teresa Rubio-Tomás:** Writing – original draft, Investigation. **Maria Kalykaki:** Writing – original draft, Investigation.

Data Availability

No data was used for the research described in the article.

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Consent for publication

The authors give their consent for the publication of the manuscript.

Competing interests

The authors declare no competing interests.

Author contributions

M.K., T. R-T. and N.T. conceived, wrote and reviewed the manuscript.

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