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Mitochondria as Cellular and Organismal Signaling Hubs

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Abstract

Mitochondria are traditionally known as the powerhouse of the cell, but their functions extend far beyond energy production. They are vital in cellular and organismal pathways that direct metabolism, stress responses, immunity, and cellular fate. To accomplish these tasks, mitochondria have established networks of both intra- and extracellular communication. Intracellularly, these communication routes comprise direct contacts between mitochondria and other subcellular components as well as indirect vesicle transport of ions, metabolites, and other intracellular messengers. Extracellularly, mitochondria can induce stress responses or other cellular changes that secrete mitochondrial cytokine (mitokine) factors that can travel between tissues as well as respond to immune challenges from extracellular sources. Here we provide a current perspective on the major routes of communication for mitochondrial signaling, including their mechanisms and physiological impact. We also review the major diseases and age-related disorders associated with defects in these signaling pathways. An understanding of how mitochondrial signaling controls cellular homeostasis will bring greater insight into how dysfunctional mitochondria affect health in disease and aging.

Contents

INTRODUCTION

Over a billion years ago, eukaryotic cells engulfed the mitochondria-like α-proteobacterium ancestor, which beget the mitochondrial organelle as we know it today. Since this engulfment, the fates of mitochondria and the rest of the eukaryotic cell have become intricately intertwined. In

becoming a major component of the eukaryotic cell, mitochondria have been tasked with its most famous role as the cell's powerhouse, providing most of the energy to the cell through oxidative phosphorylation (OXPHOS). However, mitochondria are also involved in and actively influence many other key cellular pathways such as synthesizing and degrading energy and nutrient components as well as directing cellular stress responses involved in metabolic or proteostatic health. Finally, mitochondria also play a key role in cellular fate decisions, such as differentiation and cell survival or death. Altogether, these tasks ensure the health of the mitochondrial organelle itself as well as those of the cell and organism.

To carry out these diverse tasks, mitochondria have established communication routes within the mitochondrial network as well as with many other cellular components. These modes of communication have emerged out of both efficiency and necessity, as during the evolutionary engulfment process of endosymbiosis, mitochondria have given up most of their encoded genes into the nuclear genome, tying their fate to the central eukaryotic organelle. The idea of mitochondria as signaling organelles is not new, starting with the discovery of the mitochondrial release of cytochrome *c* as being pivotal for the induction of apoptosis and cell death decision-making. Since then, the world of mitochondrial signaling has expanded to include the transport of metabolites or small molecule messengers as well as the budding of vesicles carrying mitochondrial cargo to other cellular locations. The array of mitochondrial signaling has also expanded to include physical contact sites with other organelles and subcellular compartments and mitochondria-driven transcriptional responses to rewire cellular metabolism and stress responses. These mitochondrial-to-nuclear transcriptional programs direct the activity of nutrient sensors such as mTORC1 and AMPK and protein homeostasis machinery such as lysosomes, as well as the proteasome, chaperones, and small heat shock factors. Importantly, the mechanisms that govern these processes are numerous and have been discovered to be conserved in many organisms, from yeast through *Caenorhabditis elegans*, *Drosophila melanogaster*, mice, and humans. Beyond the individual cell, mitochondria also signal across tissues during stress to coordinate organismal stress responses and mediate systemic metabolic changes, as well as function as hubs of immune signaling.

The role of mitochondrial signaling in maintaining cellular health is also particularly relevant in the context of disease and aging, in which mitochondria play a key role. The fate of cellular health in aging is well established to be intricately tied to the fate of mitochondrial health. Additionally, modulating mitochondrial health and signaling processes has been shown to influence the course of aging in many model organisms. In aging and age-related disorders such as neurodegenerative diseases, defects have been observed in many of the molecular components known to be essential in mitochondrial signaling pathways, suggesting that molecular deterioration may occur when mitochondrial signaling goes awry. Furthermore, the vast number and diversity of human mitochondrial disorders point to the fundamental importance of understanding how mitochondria operate within themselves and with other cellular and organismal components to maintain health. Here, we review the fundamental areas in which mitochondria communicate and coordinate cellular health pathways. We cover the many conserved molecular model systems in which these pathways exist as well as illuminate the diseases and disorders associated with defective mitochondrial signaling pathways.

MITOCHONDRIAL SIGNALING IN STRESS RESPONSES AND PROTEIN HOMEOSTASIS

Mitochondria have adopted many signaling pathways to maintain protein homeostasis (**Figure 1**). This necessity for their communication with other cellular components likely stems from their endosymbiotic origin. For instance, only 13 of the over 1,000 mitochondrial proteins are encoded

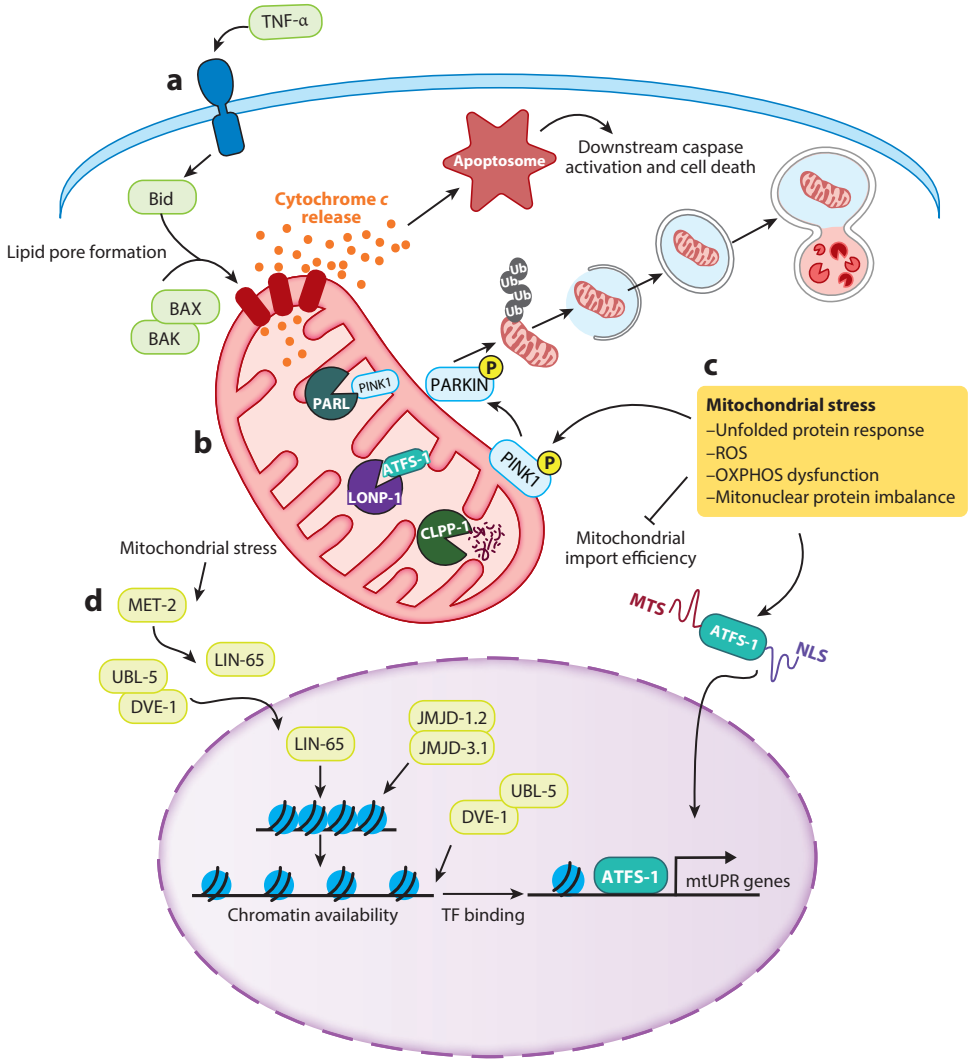

Figure 1

Mitochondrial signaling in stress responses. (*a*) Extracellular pro-apoptotic signaling converges on mitochondria through TNF-α, Bid, and the BAX/BAK complex, which promote lipid pore formation and cytochrome *c* release. (*b*) PINK1 and ATFS-1 are imported into the mitochondria and degraded under basal, nonstress conditions. Accumulated misfolded proteins are digested by proteases such as PARL, LONP-1, and CLPP-1; the resulting peptides can trigger a stress response when exported to the cytosol. (*c*) During mitochondrial stress, mitochondrial import efficiency decreases. This results in PINK1 accumulation at the outer mitochondrial membrane, triggering the recruitment of autophagy machinery for mitophagy degradation as well as increased localization of ATFS-1 into the nucleus, where it activates the expression of mtUPR genes. (*d*) Under mitochondrial stress conditions, MET-2/LIN-65 and JMJD-1.2/JMJD-3.1 mediate chromatin remodeling, promoting the expression of mtUPR genes. Changes in chromatin structure allow for DVE-1/UBL-5 binding and improvement of mtUPR activation mediated by ATFS-1.
Abbreviations: ATFS-1, activating transcription factor associated with stress 1; Bid, Bcl2-interacting protein; JMJD, Jumonji C domain–containing histone demethylase; MTS, mitochondrial targeting sequence; mtUPR, mitochondrial unfolded protein response; NLS, nuclear localization sequence; OXPHOS, oxidative phosphorylation; PINK1, PTEN-induced putative kinase 1; ROS, reactive oxygen species; TNF-α, tumor necrosis factor alpha; Ub, ubiquitin.

within the mitochondrial DNA (mtDNA) (Calvo & Mootha 2010). The majority of mitochondrial proteins are encoded in the nucleus and must be imported into the mitochondria and subsequently folded into their functional form. Further, many mitochondrial protein complexes (e.g., electron transport chain complexes) rely on subunits encoded by both nuclear and mitochondrial genomes (Calvo & Mootha 2010). Strict coordination of expression between mitochondrial and nuclear genes is therefore essential to organelle homeostasis. Imbalances disrupt protein stoichiometry, leading to orphaned protein subunits that trigger mitochondrial stress (Couvillion et al. 2016, Houtkooper et al. 2013). Additionally, because of their double-membrane enclosure, mitochondria also rely on protein machinery outside of the organelle to fulfill all protein homeostasis function. Finally, the mitochondrial OXPHOS activity also produces reactive oxygen species (ROS) that can damage biomolecules in their vicinity at mitochondria and other cellular compartments (Balaban et al. 2005). Thus, mitochondria employ many routes of communication with other cellular components to help with their unique forms of protein stress.

Apoptosis

A classic example of mitochondrial signaling to regulate cellular stress is apoptosis, a conserved process of programmed cell death required for normal development and tissue homeostasis, and one that is centrally regulated by mitochondria (Elmore 2007, Saelens et al. 2004) (**Figure 1*a***). In the mammalian intrinsic apoptotic pathway, pro-apoptotic stimuli, including developmental cues or cytotoxic insults, activate pro-apoptotic BH3-only proteins, which promote the activation and oligomerization of the pro-apoptotic BCL2 homologs BAX and BAK. Oligomerized BAX and BAK form lipid pores in the outer mitochondrial membrane (OMM) through which pro-apoptotic factors, most notably cytochrome *c*, are released from the mitochondrial intermembrane space into the cytosol (Antonsson et al. 2001, Nechushtan et al. 2001, Tait & Green 2010). Cytochrome *c* then activates Apaf-1 and procaspase-9 to form the apoptosome, which in turn cleaves and activates downstream effector caspases (Chinnaiyan 1999, Hill et al. 2004). Through the cleavage of hundreds of downstream targets, these executioner caspases drive the biochemical and morphological changes associated with apoptotic cell death (Julien & Wells 2017). A second, cell-extrinsic signaling pathway is initiated by tumor necrosis factor (TNF)-family cell death receptors and, in some cell types, converges on the mitochondria through cleavage of the pro-apoptotic BCL2 protein Bid and subsequent BAX/BAK activation, though other cells can signal independently of mitochondria through the direct activation of effector caspases (Li et al. 1998, Luo et al. 1998, Scaffidi et al. 1998). Mitochondria are also thought to regulate nonapoptotic cell death mechanisms, including necroptosis, ferroptosis, and pyroptosis, suggesting an even broader function for mitochondria in regulated cell death (Bock & Tait 2020).

Mitophagy

Mitochondrial stress can also be alleviated via mitochondrial autophagy (mitophagy), a process by which defective mitochondria are degraded through the autophagy-lysosomal pathway (Lemasters 2005) (**Figure 1*b***). In addition to degrading defective mitochondrial organelles, mitophagy also serves other functions, such as the elimination of paternal mtDNA during fertilization (Rojansky et al. 2016, Sato & Sato 2011) or the loss of mitochondria during the maturation of reticulocytes in terminal erythroid differentiation (Schweers et al. 2007). To initiate mitophagy, mitochondria cooperate with canonical machinery involved in the autophagy-lysosomal pathway as well as specialized proteins involved in the recognition of defective mitochondria for degradation. One such recognition mechanism is the PINK1/Parkin pathway, mediated by the PTEN-induced putative kinase 1 (PINK1) and a cytosolic ubiquitin E3 ligase Parkin (Narendra et al. 2008).

Under nonstressed conditions, PINK1 is readily imported into the mitochondria and inserted into the inner mitochondrial membrane (IMM), where it is then cleaved by the inner membrane protease PARL (Jin et al. 2010) and subsequently degraded via the proteasome (Yamano & Youle 2013). Upon mitochondrial stress, the mitochondrial import of PINK1 decreases, and PINK1 accumulates on the OMM. Accumulated PINK1 then phosphorylates Parkin and ubiquitin, which further recruits Parkin and more ubiquitin molecules to the mitochondrial surface, ultimately resulting in autophagosome recognition and engulfment (Pickles et al. 2018). Autophagosome recognition of ubiquitinated mitochondria relies on several autophagy receptor proteins, which in mammalian cells include p62, NBR1, NDP52, optineurin, and TAX1BP1 (Lazarou et al. 2015, Pickles et al. 2018). Other mechanisms may also exist for mitochondrial targeting in mitophagy beyond the PINK1/Parkin pathway. While this pathway relies on mitochondrial membrane depolarization and compromised protein import, many forms of mitophagy exist that do not explicitly involve the loss of mitochondrial depolarization for degradation (Pickles et al. 2018). What other mechanisms may exist from ubiquitinated or damaged mitochondria to signal for autophagic degradation requires further exploration.

The Mitochondrial Unfolded Protein Response: Mitochondrial-to-Nuclear Signaling

Another well-studied pathway of mitochondrial proteostasis is the mitochondrial unfolded protein response (mtUPR), a pathway focused on rehabilitating mitochondrial function instead of degradation (**Figure 1*b*,*c***). The mtUPR comprises a stress-signaling cascade between the mitochondria and the nucleus in which mitochondrial stress induces nuclear transcriptional upregulation of gene programs designed to stabilize and improve mitochondrial function. The mtUPR was originally discovered in mammalian cells by expressing an aggregation-prone mutant of the mitochondrial matrix protein ornithine transcarbamylase (Zhao et al. 2002). Expression of this mutant protein induced a transcriptional upregulation of the mitochondrial chaperones Hsp60 and mtHsp70 as well as the proteases ClpP and Lon (Zhao et al. 2002). Since then, the mtUPR has also been found to be activated by numerous sources of mitochondrial stress beyond protein misfolding, such as loss of mtDNA, defects in the electron transport chain, knockdown of mitochondrial protein translation and proteases, mitochondrial fusion/fission dynamics, and others in many model organisms including *D. melanogaster* and *C. elegans* (Houtkooper et al. 2013, Nargund et al. 2012, Pimenta De Castro et al. 2012, Yoneda et al. 2004).

In *C. elegans*, the main nuclear transcription factor conducting the mtUPR is ATFS-1, a bZip transcription factor with both mitochondrial targeting and nuclear localization sequences (Nargund et al. 2012). Under basal conditions with low stress, mitochondria have intact membrane potential, and ATFS-1 is imported into the mitochondria and readily degraded by proteases such as LONP-1 (Nargund et al. 2012). However, under conditions of mitochondrial stress, mitochondrial protein import is decreased, and ATFS-1 is preferentially imported into the nucleus, where it acts as a transcription factor to upregulate protective factors such as mitochondrial chaperones and proteases (Nargund et al. 2012, Soo & Van Raamsdonk 2021). Activation of the mtUPR also promotes the expression of glycolysis genes and limits the transcription of OXPHOS genes, thus shifting the burden of energy production away from mitochondria and toward glycolysis in the cytoplasm (Nargund et al. 2015). Activated ATFS-1 has also been shown to regulate other cellular pathways such as the mevalonate pathway, mitochondrial network expansion, and mtDNA maintenance (Lin et al. 2016, Rauthan et al. 2013, Shpilka et al. 2021). Thus, the mtUPR represents a form of mitochondrial-to-nuclear retrograde signaling and overall cellular metabolism rewiring driven by mitochondrial stress. The mtUPR also plays an active role in chromatin remodeling

through several pathways, such as the histone methyltransferase MET-2 and the nuclear cofactor LIN-65 as well as the histone lysine demethylases Jumonji C domain–containing histone demethylase (JMJD)-1.2 and JMJD-3.1 (**Figure 1*d***). Importantly, the mammalian orthologs of JMJD-1.2 and JMJD-3.1, PHF8 and JMJD3, respectively, show strong correlation with core mtUPR genes in BXD mice, suggesting their role in mitochondrial stress may be conserved (Merkwirth et al. 2016). mtUPR activation has also been shown to increase longevity, demonstrating the prowess of mitochondrial signaling in the organism (Durieux et al. 2011, Mouchiroud et al. 2013, Wu et al. 2018).

While the mtUPR induces the transcription of about 700 genes, only approximately 400 of these appear to be dependent on ATFS-1 for their upregulation (Nargund et al. 2012, 2015). Several other proteins and complexes have been shown to induce mtUPR activity through mitochondrial-to-nuclear retrograde signaling independent of ATFS-1. The ubiquitin-like protein UBL-5 works in concert with DVE-1, a homeobox transcription factor, to activate the mtUPR upon mitochondrial stress (Haynes et al. 2007). In another mtUPR-activating mechanism, the mitochondrial matrix protease CLPP-1 degrades misfolded proteins, generating peptides that are exported through the peptide transporter HAF-1, a transporter located at the IMM, and serve as a signal for mitochondrial perturbation once in the cytosol (Benedetti et al. 2006; Haynes et al. 2010, 2007).

The Mitochondrial Unfolded Protein Response in Mammals

In mammals, initial studies identified the bZip transcription factor ATF5 as being analogous to ATFS-1 in *C. elegans* for the activation of the mtUPR (Fiorese et al. 2016). In HEK293T cells, ATF5 was required for the transcriptional upregulation of mitochondrial chaperones and proteases due to mitochondrial stress, and ATF5 expression itself was also upregulated upon mitochondrial stress (Fiorese et al. 2016). Several molecular factors in addition to ATF5 have also been attributed to activation of the mammalian mtUPR, such as CHOP and C/EBPβ (Aldridge et al. 2007, Zhao et al. 2002). Many mtUPR-responsive genes in mammalian systems have a CHOP-binding site in their promoter (Aldridge et al. 2007). In addition, G-protein pathway suppressor 2 (GPS2), a transcriptional cofactor, has also been shown to regulate mtUPR activation in mammals (Cardamone et al. 2018). GPS2 translocates to the nucleus in response to mitochondrial depolarization and facilitates active transcription through regulating the H3K9 methylation status, leading to the transcription of mitochondrial stress response–related genes (Cardamone et al. 2018).

In contrast to that of *C. elegans*, in which mitochondrial-to-nuclear retrograde signaling seems to be a predominant form of mitochondrial quality control, the picture of mitochondrial homeostasis may be more complicated in mammalian cells. In addition to the mtUPR, the integrated stress response (ISR) has been shown to be important for mitochondrial homeostasis in mammals. Cells treated with various mitochondrial stressors were shown to activate the ISR, with activating transcription factor 4 (ATF4) being the key regulator of this response (Quirós et al. 2017). ATF4 activation also reestablished metabolic homeostasis disrupted by mtDNA depletion or inhibition of the tricarboxylic acid (TCA) cycle (Bao et al. 2016, Ryan et al. 2021).

Regardless of whether the mtUPR or ISR is more essential for mitochondrial homeostasis, there seems to be substantial evidence for a mitochondria-driven transcriptional program in response to stress in mammals. In human Alzheimer's disease (AD) patients as well as transgenic AD *C. elegans* and mouse models, there is a transcriptional upregulation of genes involved in the mtUPR and mitophagy (Sorrentino et al. 2017). These transcriptional changes can be considered as an overall conserved mitochondrial stress response (MSR) transcriptional signature (Sorrentino et al. 2017). Indeed, boosting this MSR via the inhibition of mitochondrial translation

or pharmacological treatment was protective against amyloid-β proteotoxicity and aggregation in *C. elegans* and an SH-SY5Y neuroblastoma cell line, demonstrating the importance of an MSR across multiple species (Sorrentino et al. 2017).

Coordination of the Mitochondrial Unfolded Protein Response with Other Cellular Stress Responses

The identification of communication networks between the various stress response programs has led to new theories of how cellular behavior is coordinated. One prime example of this is communication between the mtUPR and the heat shock response (HSR). Knockdown of mitochondrial HSP70 leads to the activation of the cytosolic HSR, a pathway termed the mitochondrial-to-cytosolic stress response (MCSR). Notably, the MCSR responds to not only mitochondrial chaperone knockdown but also shifts in lipid metabolism (Kim et al. 2016). Increased fatty acid synthesis is both necessary and sufficient for MCSR activation. In addition, accumulation of the mitochondrial lipid cardiolipin is particularly important in MCSR activation through its blockage of ceramide synthesis. Together, these data suggest that mitochondrial stress can lead to shifts in metabolism or lipid accumulation that then activate a cytosolic stress response for overall cellular and organismal protection.

MITOKINES AND MITOCHONDRIA-REGULATED INTERTISSUE SIGNALING

In addition to their role as signaling hubs at the cellular level, mitochondria also coordinate signaling at the intercellular and intertissue levels (**Figure 2**). In this sense, mitochondria can coordinate both cell autonomous and non–cell autonomous cellular responses. In this section, we review intertissue or intercellular signaling as it has been described in *C. elegans* and mouse model systems. Finally, we comment on the emerging evidence that mitochondrial intertissue signaling is relevant in human disease.

Mitokine Signaling in *Caenorhabditis elegans*

Much of the work illuminating how mitochondria coordinate non–cell autonomous signaling, otherwise known as intertissue or intercellular signaling, has been done in the nematode *C. elegans* (**Figure 2*a***). Using *C. elegans*, researchers have discovered many of the genetic mechanisms for how the mitochondria of one tissue can signal to distal cells of another tissue during stress conditions. In one of the initial findings, a *C. elegans* model with mitochondrial stress solely in neurons, performed via neuronal knockdown of subunits of electron transport chain complexes or neuronal expression of a mutant polyglutamine protein, exhibits mtUPR activation in the intestinal tissue, a tissue that had never directly experienced this mitochondrial stress (Durieux et al. 2011). This work led to the hypothesis that stressed mitochondria may secrete signals, called mitokines, that transmit information between tissues and induce mitochondria-related stress responses in distal cells. Note that multiple mitokines exist, and the identity of the mitochondrial perturbation, the cell of origin, and the destination of the mitokine may dictate the identity of the mitokine secreted and its effects. Thus, organisms house a complex mitokine network, and the interactions between the different nodes in this network remain unexplored. Importantly, the concept of intercellular communication from a subcellular organelle is not unique to mitochondria but is a common feature of other protective cellular pathways such as the cytosolic HSR or endoplasmic reticulum (ER)-driven UPR (Douglas et al. 2015, Taylor & Dillin 2013). It remains to be seen what mechanisms work to regulate or coordinate these complex intercellular signaling networks.

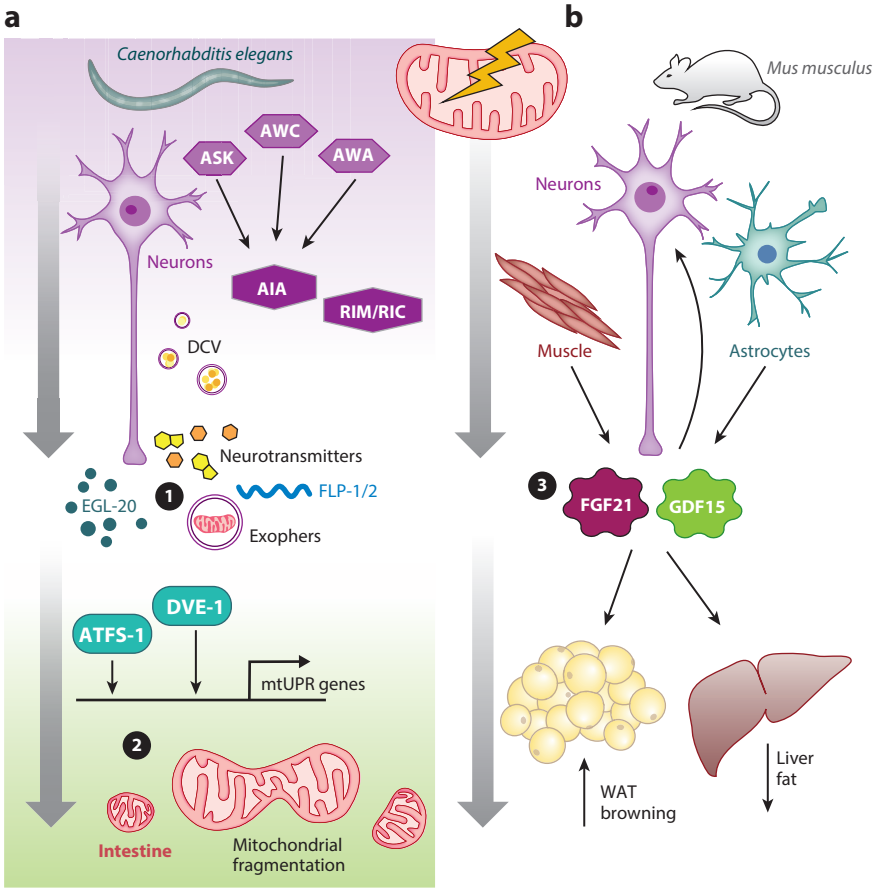

Figure 2

Intertissue communication of mitochondrial stress across model organisms. (*a*) Genetic studies in the nematode *Caenorhabditis elegans* defined the neuronal circuits and the secreted signals (mitokines) that participate in the communication from neurons to the major metabolic organ of nematodes, the intestine. (❶) The ASK, AWA, and AWC sensory neurons and the AIA interneuron are used as part of this signaling. Secreted mitokines can be communicated through DCVs and be composed of neurotransmitters, Wnt ligands (EGL-20), and neuropeptides (FLP-1/2). Recent evidence has also suggested that mitochondria can be physically extruded from neurons in large vesicular membrane-surrounded vesicles called exophers. (❷) These signals trigger the activation of the mtUPR in the intestine and affect mitochondrial dynamics. (*b*) In mammals, two major mitokine signals have been defined, FGF21 and GDF15, to be (❸) secreted from several tissues, which affect the liver and WATs. Abbreviations: ATFS-1, activating transcription factor associated with stress 1; DCV, dense core vesicle; FGF21, fibroblast growth factor 21; GDF15, growth differentiation factor 15; mtUPR, mitochondrial unfolded protein response; WAT, white adipose tissue.

Studies of the underlying mechanisms of mitochondrial intercellular communication have focused on identifying mitokines and the underlying neurons involved in neuronal mitochondrial stress signaling in *C. elegans*. At the cellular level, the nervous system employs the ASK, AWA, and AWC sensory neurons and the AIA interneuron as part of this signaling (Shao et al. 2016). At the molecular level, several molecules have been shown to be involved in the mitochondrial communication between tissues. Acetylcholine, tyramine, glutamate (L.-T. Chen et al. 2021), serotonin,

dense core vesicles (DCVs) (Berendzen et al. 2016), and the Wnt ligand EGL-20 (Zhang et al. 2018) have all been shown to be involved in the intercellular mitochondrial signaling originating from many different sources of mitochondrial stress. The neuropeptides FLP-1 (Jia & Sieburth 2021) and FLP-2 (Shao et al. 2016) have also been postulated to be involved in the signaling. However, increased mitochondrial ROS was also shown to inhibit neuropeptide secretion, emphasizing that different types of mitochondrial stress may lead to opposing effects (Zhao et al. 2018). Intriguingly, mitochondria can also be physically extruded, particularly under mitochondrial stress, from neurons, in large vesicular membrane-surrounded vesicles called exophers (Melentijevic et al. 2017), suggesting that the mitochondria organelle itself may also serve as an intercellular signal. Beyond the identification of the mitokine molecule, many other molecular players and pathways have also been identified as required for the mechanics of mitokine signaling, such as the retromer complex (Zhang et al. 2018), the G-protein coupled receptor (GPCR) FSHR-1 (Kim & Sieburth 2020), β-catenin (Zhang et al. 2018), and the sphingosine kinase SPHK-1 (Kim & Sieburth 2020).

Nonneuronal tissues have also been shown to be able to secrete mitokines. For example, germline cells can secrete an unknown mitokine that activates AMPK and the mtUPR in the intestine (Lan et al. 2019) and affect mitochondrial content in somatic cells via EGL-20 (Calculli et al. 2021). In *Drosophila*, muscle tissue can secrete the insulin-antagonizing peptide ImpL2 (Owusu-Ansah et al. 2013) and the TGF-β ligand Act β (Song et al. 2017) to signal to fat tissues in response to mitochondrial stress. Interestingly, EGL-20 has recently been shown to also be required for communicating mitochondrial stress from neurons to the germline, underlying a possible method of transgenerational inheritance of mitochondrial states (Zhang et al. 2021).

In a physiological context, changes to neuronal mitochondrial function may be triggered by environmental conditions, such as through sensory activity such as touch or smell (Fluegge et al. 2012, Jiang et al. 2015). These could trigger non–cell autonomous responses similar to those induced by tissue-specific mitochondrial perturbations, which are associated with organismal outcomes. In fact, modulating mitochondrial function in different tissues can have opposing effects on the entire organism. For example, triggering the mitochondrial stress response in muscle decreases life span, while when induced in neurons leads to increased life span (Durieux et al. 2011) and resistance to pathogens and stress (Berry et al. 2020, L.-T. Chen et al. 2021).

Mitokine Signaling in Mammalian Models

Recent work in mammalian models has sought to determine whether intertissue mitochondrial stress signaling is conserved and has identified several putative mitokines with systemic effects. Much of the focus of intertissue mitochondrial signaling in mammals has been on mitochondrial dysfunction in muscle, a tissue that is particularly dependent on mitochondrial activity and efficient energy expenditure. Fibroblast growth factor 21 (FGF21) has emerged as a major muscle-secreted factor, or myokine, related to mitochondrial stress signaling in mammals (**Figure 2*b***). While FGF21 is normally expressed in the liver, under stress conditions it can be expressed and secreted from other tissues (Salminen et al. 2017). For example, the skeletal muscle–specific deletion of the autophagy gene *Atg7* induces mitochondrial dysfunction and secretion of FGF21 (Kim et al. 2013). This induction of FGF21 promotes systemic metabolic health with increased resistance to high-fat diet–induced obesity, enhanced glucose tolerance, and increased insulin sensitivity. The induction of FGF21 by autophagy deficiency depends on ATF4, a regulator of the ISR that responds to mitochondrial stress in mammals (Quirós et al. 2017). Other forms of mitochondrial stress such as inhibition of OXPHOS, skeletal muscle–specific knockout of mitofusin 1 and

mitofusin 2, or ectopic expression of uncoupling protein 1 (UCP1) in skeletal muscle similarly induce FGF21 through ATF4 (Keipert et al. 2014, Kim et al. 2013, Ost et al. 2016).

However, not all mitochondrial perturbations that result in FGF21 induction have beneficial effects. While in one study (Pereira et al. 2017), skeletal muscle–specific deletion of the mitochondrial fusion protein Opa1 in 4-week-old mice led to FGF21 secretion, protection against diet-induced obesity, and improved insulin sensitivity, others (Rodríguez-Nuevo et al. 2018, Tezze et al. 2017) have shown that loss of muscle Opa1 at 3–5 months induced inflammation and muscle atrophy and led to premature aging and death. However, some beneficial effects resulting from ISR activation might not depend on FGF21. In mice ectopically expressing UCP1 in skeletal muscle, FGF21 is required for the browning of white adipose tissue and the reduction of blood triglyceride and cholesterol levels but is dispensable for other metabolic changes associated with mitochondrial function, including obesity resistance, glycemic control, and hepatic lipid homeostasis. Additionally, the activation of the mtUPR resulted in subsequent improvement in muscle proteostasis and the induction of amino acid biosynthetic pathways independent of FGF21 (Ost et al. 2016). The nature of the systemic effects resulting from tissue-specific mitochondrial disruption, including whether they are beneficial or detrimental as well as their dependence on Fgf21, may thus depend on the timing, duration, and type of mitochondrial perturbation.

Another mammalian mitokine is growth differentiation factor 15 (GDF15) (**Figure 2*b***). Skeletal muscle knockdown of the mitoribosomal subunit Crif1 promotes the secretion of GDF15 in a CHOP-dependent manner, resulting in improved insulin sensitivity and obesity resistance (Chung et al. 2017). Exogenous administration of GDF15 to *ob/ob* mice or high-fat diet–fed mice decreased body weight and improved peripheral insulin and glucose tolerance (Chung et al. 2017, Tsai et al. 2018). GDF15 overexpression reduces adiposity, improves insulin sensitivity, and extends the life span of mice fed either a low- or a high-fat diet (Wang et al. 2014), suggesting that GDF15 broadly affects metabolic health.

Non–cell autonomous mitochondrial signaling in mammals has also been observed in cell types beyond muscle, such as those in the central nervous system. For example, knockdown of the mitochondrial fission protein Drp1 in neurons also induces the ISR and the expression of FGF21 (Restelli et al. 2018). Most strikingly, recent work showed that causing mild mitochondrial stress in proopiomelanocortin (POMC) neurons leads to high metabolic turnover, increasing thermogenesis in white adipose tissues through secreted molecules (Kang et al. 2021). Similarly, deleting the glucagon-like peptide receptor (GLP-1R) in astrocytes caused defects to mitochondrial integrity and resulted in the secretion of FGF21 and enhanced memory formation (Timper et al. 2020). However, this was not observed when knocking out the mtDNA helicase Twinkle in astrocytes (Ignatenko et al. 2022), highlighting that there may be tissue- and trigger-specific programs induced upon different mitochondrial stresses. In addition, cells within the nervous system were shown to respond to FGF21, creating a potential signaling feedback loop (Jensen-Cody et al. 2020). As the induction of neuron-derived FGF21 is similarly observed in mouse models for tauopathies and prion diseases, measuring FGF21 levels might serve as an early detection biomarker for these types of pathologies (Restelli et al. 2018).

Some of the intertissue mitochondria-related signaling that has been discovered in murine models is now being explored in humans. A recent study in humans assessing mitokine levels across a 92-year age range (21 to 113 years old) found that levels of FGF21 and GDF15, as well as the mitochondria-encoded peptide humanin (HN), were all correlated with age; the highest levels were in subjects over 100 years of age (Conte et al. 2019). For patients of similar biological age, high mitokine levels were associated with poorer health based on parameters such as handgrip strength, insulin sensitivity, and triglyceride levels. Among the older patients, those who survived

the longest had the lowest mitokine levels. These findings suggest that FGF21, GDF15, and HN are likely acting hormetically to promote metabolic health and indicate that they might serve as reliable markers of biological aging (Conte et al. 2019).

MITOCHONDRIA-REGULATED INTERORGANELLAR SIGNALING

As a central hub for cellular metabolism and activity, mitochondria interface with other organelles and subcellular compartments, as well as the extracellular matrix (ECM) (**Figure 3*a***). These modes of communication are essential to maintaining overall cellular health.

The Endoplasmic Reticulum

One of the most well-established interorganellar relationships is that between mitochondria and the ER. This relationship has been mostly described with regard to the extensive physical contacts between the two organelles in the form of mitochondria-associated ER membranes (MAMs) or mitochondria-ER contacts (MERCs), which have been shown to be important sites for lipid and calcium exchange, mtDNA replication, and mitochondrial division (Herrera-Cruz & Simmen 2017). In yeast, these mitochondria-ER contact sites consist of the ERMES (ER-mitochondria encounter structure) complex, composed of protein partners Mmm1p, Mdm10p, Mdm12p, and Mdm34p that reside on both the ER and the OMMs (Kornmann et al. 2009) (**Figure 3*b***). While there seems to be no direct ortholog of this ERMES complex in mammalian cells, several other molecular tethers have been described (Elbaz & Schuldiner 2011, Herrera-Cruz & Simmen 2017) (**Figure 3*b***).

Across model systems, direct physical contacts between the ER and mitochondria have been shown to be important for various aspects of mitochondrial and cell physiology. In both yeast and mammalian systems, ER-mitochondrial contact sites have been observed to mark sites for mitochondrial division (Friedman et al. 2011). At these sites, termed ER-associated mitochondrial division (ERMD) sites, the ER tubules wrap around mitochondria to mark the positions of mitochondrial division, after which MFF, a mitochondrial fission factor in mammals, and Drp1/Dnm1, a dynamin-related protein conserved in both yeast and mammals, are recruited to complete mitochondrial fission (Friedman et al. 2011, Wu et al. 2016) (**Figure 3*b***). These ER-mitochondrial contact sites coordinate mitochondrial morphology and biogenesis, as actively replicating nucleoids are enriched at these sites of tubular ER-mitochondrial contact for the initiation of mtDNA replication (Lewis et al. 2016, Murley et al. 2013). In this way, ER-mitochondrial contact sites actively segregate and distribute mtDNA nucleoids during mitochondrial division (**Figure 3*b***). This role in proper mtDNA segregation is especially important for elongated cells such as neurons, which require proper segregation and spacing of mtDNA to maintain mitochondrial function throughout their long processes.

MAMs have been documented as important sites for metabolite exchange, such as of lipids, cholesterol, and calcium ions, between the ER and mitochondria (**Figure 3*a***). One major lipid transfer pathway that occurs within these contact sites is for phosphatidylserine (PS) (Vance 1990, Voelker 1989). PS is generated from phosphatidylcholine (PC) in the ER and is then transferred to mitochondria, where it is further converted to phosphatidylethanolamine (PE) by PS decarboxylase at the IMM (Schuiki & Daum 2009, Tatsuta & Langer 2017). PS transfer from the ER to mitochondria is controlled by the oxysterol-binding protein (OSBP)-related proteins ORP5 and ORP8 located at mitochondria-ER contact sites (Galmes et al. 2016) in mammalian cells. Loss of these OSBP-related proteins leads to defects in mitochondrial morphology and function, presumably due to the loss of proper lipid trafficking and membrane composition (Galmes et al. 2016). Ca^{2+} transfer between the two organelles through mitochondria-ER contact sites is also

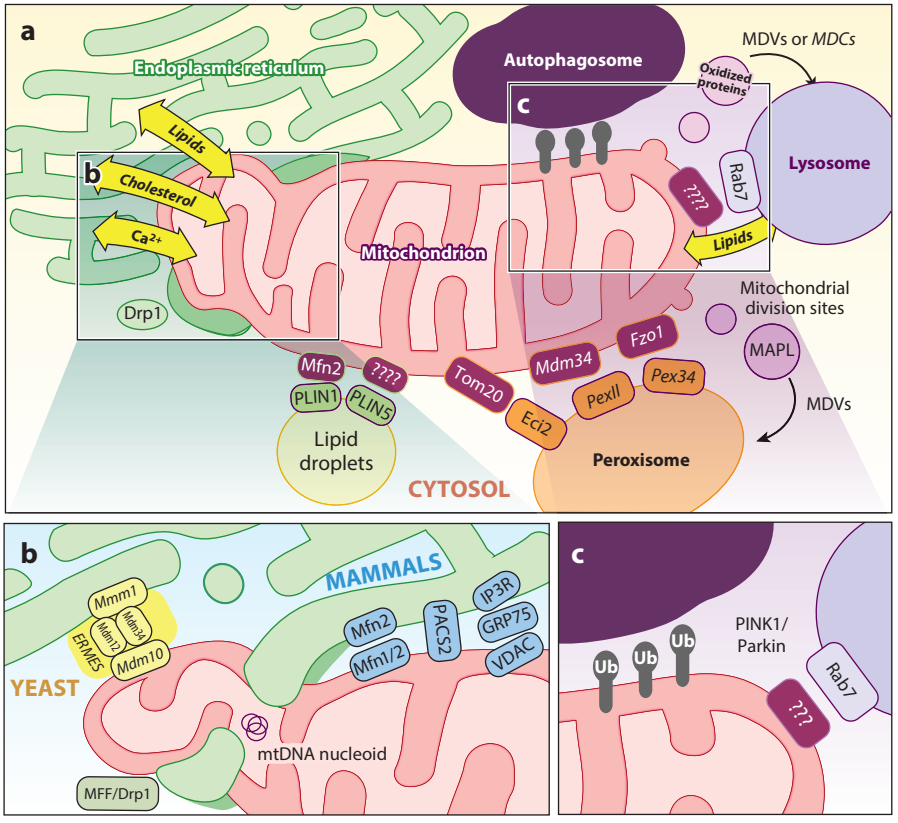

Figure 3

Mitochondrial communication and contacts with other subcellular organelles. Organellar interactions have been described in both mammalian and yeast systems; those so far identified only in yeast are italicized. (*a*) Cellular view of mitochondrial interactions with other subcellular organelles, such as direct physical contacts, vesicular budding, or transfer of metabolites such as lipids, cholesterol, or ions. (*b*) Schematic view of MERCs. In yeast, the ERMES complex is the major identified contact site between mitochondria and the ER (*yellow*), whereas in mammals there are more identified players (*blue*). In both yeast and mammals, ER tubules wrap around mitochondria, and MFF/Drp1 and mtDNA nucleoids cluster around these sites to promote mitochondrial division and the distribution of mtDNA. (*c*) Mitochondrial interactions with the lysosome (or vacuole in yeast) and autophagy system. The PINK1/Parkin mitophagy pathway involves autophagosome recognition of ubiquitinated proteins on the outer mitochondrial membrane surface. Mitochondria also contact lysosomes, where the lysosomal tether is Rab7, but the mitochondrial tether is so far unidentified. Abbreviations: ER, endoplasmic reticulum; ERMES, ER-mitochondria encounter structure; IP3R, inositol-1,4,5-trisphosphate receptor; MERC, mitochondria-ER contact site; MFF, mitochondrial fission factor; mtDNA, mitochondrial DNA; PINK1, PTEN-induced putative kinase 1; Ub, ubiquitin; VDAC, voltage-dependent anion channel.

important, as the ER is a major storage site of Ca^{2+}, and mitochondrial function is regulated by Ca^{2+} levels (Rizzuto et al. 2012). MAMs are a fundamental platform for ER-mitochondrial Ca^{2+} exchange, which occurs mainly through the release of Ca^{2+} by the inositol-1,4,5-trisphosphate receptor (IP3R) and the subsequent transport of Ca^{2+} through the voltage-dependent anion channel (VDAC) at the OMM—the interaction of which is mediated by the GRP75 chaperone—and uptake into the intermembrane space through the mitochondrial Ca^{2+} uniporter (Rizzuto et al. 2012). Perturbations to ER-mitochondrial tether sites have been shown to alter Ca^{2+} trafficking

between the two organelles (Wu et al. 2017). Interestingly, the levels of Ca^{2+} import into mitochondria from ER transfer can control and be influenced by ROS levels (Booth et al. 2016, Dong et al. 2017). Because mitochondrial OXPHOS activity can also release ROS, this suggests a mechanism for regulating mitochondrial activity through Ca^{2+} transport from the ER and cellular oxidative stress levels.

ER-mitochondrial contacts are also dynamic and respond to metabolite and nutrient states of the cell. Mice under high-fat or diabetic conditions have altered contact sites between the ER and mitochondria (Arruda et al. 2014, Thivolet et al. 2017, Tubbs et al. 2014). As obesity from high-fat or high-nutrition diets has been shown to induce ER stress (Fu et al. 2011), changing ER-mitochondrial contacts could be a way to regulate ER health through mitochondrial interaction. Perturbations in PACS-2, a protein involved in ER-mitochondrial contact sites, have also been shown to induce hepatic FGF21 expression and resistance to diet-induced obesity (Krzysiak et al. 2018), suggesting a possible mechanism by which ER-mitochondrial contacts could also regulate organismal metabolic health.

Lysosomes

In recent years, interest has risen in the interaction of mitochondria with lysosomes, as both organelles have crucial roles in nutrient signaling and energy sensing (**Figure 3*a***). Mitophagy, the selective degradation of mitochondria by lysosomes, has been the best-described mechanism of interaction (Pickles et al. 2018) (**Figure 3*c***). However, there are increasing reports of more dynamic interactions between the two organelles in mitophagy-independent ways.

Direct physical contacts between mitochondria and lysosomes have been observed in mammalian cells as well as in yeast between mitochondria and the vacuole, a lysosome-like organelle (Elbaz-Alon et al. 2014, Han et al. 2017, Hönscher et al. 2014, Valm et al. 2017). In mammalian cells, high-resolution live cell imaging and electron microscopy revealed a direct physical interaction between mitochondria and lysosomes regulated by Rab7, a small GTPase that typically associates with late endosomal-lysosomal membranes and directs endosomal-to-lysosomal trafficking (Hutagalung & Novick 2011, Wong et al. 2018) (**Figure 3*c***). A GTP-bound form of Rab7 on the lysosomal membrane promotes physical tethering between mitochondria and lysosomes, and the two organelles are untethered by Rab7 GTP hydrolysis driven by the GTPase-activating protein TBC1D15 recruited to the tethering site by the mitochondrial fission protein FIS1 (Wong et al. 2018). The corresponding mitochondrial binding partner is still unclear. Like ER-mitochondrial contact sites, these mitochondrial-lysosomal contact sites also mark sites of mitochondrial fission, as the loss of Rab7, TBC1D15, or FIS1 leads to defects in both mitochondrial and lysosomal morphology (Wong et al. 2018). Interestingly, ER tubules and Drp1 also associate with the Rab7-mediated mitochondrial-lysosomal contacts at mitochondrial fission sites (Wong et al. 2018), suggesting that there may be important interorganellar communication among the ER, mitochondria, and lysosomes to maintain mitochondrial and cellular homeostasis. Contact sites in mammalian cells have also been observed between mitochondria and melanosomes, a lysosome-like organelle found in pigment cells, driven by Mfn2 (Daniele et al. 2014). Defects in the mitochondrial-melanosomal contact sites result in increased mitochondrial fragmentation and decreased melanosome biogenesis (Daniele et al. 2014).

In yeast, contact sites between mitochondria and the vacuole are orchestrated by the vCLAMP (vacuole and mitochondria patch) complex. This complex comprises the HOPS tethering complex protein Vps39 and the Rab GTPase Ypt7 on the vacuolar surface, while the proteins on the mitochondrial side are as yet unidentified (Elbaz-Alon et al. 2014, Hönscher et al. 2014). The vCLAMP is also an important contact site for lipid trafficking between the endolysosomal system and mitochondria (Elbaz-Alon et al. 2014). Although the vCLAMP does not share

molecular partners with the ERMES complex, mitochondria were shown to rely on either one of the ERMES or vCLAMP tethers to be intact, and deletion of both tethering sites is lethal (Elbaz-Alon et al. 2014, Hönscher et al. 2014). Altogether, these data suggest that there may be important tri-organellar communication among ER, mitochondria, and lysosomes.

The physiological consequences of these contacts are still under exploration, especially in mammalian systems. Like MERCs, mitochondrial-lysosomal contacts may also be subject to the nutrient states of the cell. Glucose levels in yeast have been reported to affect mitochondrial-vacuolar contacts (Hönscher et al. 2014). In mammalian systems, insulin and amino acid levels have been shown to influence lysosomal mTORC1 activation as well as mitochondrial OXPHOS and mtDNA biogenesis pathways, suggesting a possible link between the cell's metabolic state and mitochondrial-lysosomal interaction (Norambuena et al. 2018). In addition, disturbances to mitochondrial-lysosomal contact sites have also been observed in diseases such as Charcot-Marie-Tooth (Wong et al. 2019).

Indirect contact sites between mitochondria and lysosomes have also been observed, mostly in the form of vesicular budding pathways. In yeast, this interaction has been described via mitochondrial-derived compartments (MDCs), which selectively remove damaged components of mitochondria to the vacuole for degradation (Hughes et al. 2016). MDCs are released from mitochondria via mitochondrial fission and eliminated in the lysosome through autophagic mechanisms (Hughes et al. 2016). Suppressing MDC formation increases mitochondrial stress in aged yeast cells, likely from the accumulation of these damaged components during the aging process or from other forms of cellular stress such as elevated amino acid levels (Schuler et al. 2021). In mammalian systems, these vesicular contacts have been described via mitochondrial-derived vesicles (MDVs) (Soubannier et al. 2012, Sugiura et al. 2014). Like MDCs, MDVs also selectively transport phospholipid- or protein-comprising cargo from mitochondria to lysosomes (Sugiura et al. 2014). However, MDCs and MDVs seem to differ in their machinery for formation and degradation. While the formation of MDCs requires mitochondrial fission machinery such as Drp1 and autophagy for degradation, MDVs require PINK1 and Parkin but not autophagy machinery (Soubannier et al. 2012, Sugiura et al. 2014). Interestingly, the budding of MDVs is triggered by an increase in ROS, suggesting that this may be a stress coping mechanism for mitochondria to selectively degrade oxidatively damaged components without sacrificing the entire organelle (Soubannier et al. 2012).

Peroxisomes

While less studied, mitochondrial-peroxisomal interactions have emerged as important in cell physiology (Fan et al. 2016, Islinger et al. 2018, Valm et al. 2017) (**Figure 3*a***). This is especially relevant given that both mitochondria and peroxisomes share much of the same machinery that regulates their morphology dynamics as well as many of the same metabolite pools and pathways, such as β-oxidation of fatty acids and ROS metabolism (Schrader et al. 2015). In mammalian cells, indirect vesicular transport between the two organelles has been described through similar MDVs as those between mitochondria and lysosomes. Although some groups of MDVs are destined for lysosomes, other MDVs transfer vesicles from mitochondria to peroxisomes (Neuspiel et al. 2008). Although the cargo of interest for peroxisome-destined MDVs is less clear, they seem to specifically contain mitochondria-anchored protein ligase (MAPL) (Neuspiel et al. 2008, Sugiura et al. 2014). Regarding physical tethering, a split fluorophore screen for organelle contact sites essential in yeast revealed an important tethering between peroxisomes and mitochondria via the peroxisomal protein Pex34 and mitochondrial Fzo1 (Shai et al. 2018). Interestingly, the human homolog of Fzo1 is mitofusins (Mfn1 and Mfn2), mitochondrial proteins essential for the tethering of mitochondria to other organelles (Elbaz & Schuldiner 2011). In yeast, contact sites have been observed

between the peroxisomal Pex11 protein and the mitochondrial Mdm34 protein, also known to be involved in the ERMES complex (Ušaj et al. 2015). In mammalian cells, peroxisomes and mitochondria may physically tether via a Tom20 and ECI2 interaction, which has been demonstrated to be important for steroid biosynthesis (Fan et al. 2016).

Lipid Droplets

Finally, increasing evidence points to an important metabolic connection between mitochondria and lipid droplets (LDs) (Benador et al. 2018, Yu et al. 2015). Communication between mitochondria and LDs seems to be especially relevant to lipid levels and biosynthesis. Mitochondria and LD contact sites have been documented through several tethering sites such as through Mfn2 and the LD-associated proteins perilipin 1 and 5 (PLIN1 and PLIN5) as well as the SNARE protein Snap23 (Boutant et al. 2017, Jägerström et al. 2009, Wang et al. 2013) (**Figure 3*a***). Contacts between mitochondria and LDs may be important for promoting triacylglyceride synthesis (Benador et al. 2018). Disrupting mitochondrial-LD contacts changes fatty acid levels and leads to stress conditions and the expression of FGF21, a stress mitokine (Boutant et al. 2017). Interestingly, a high-fat diet in mice has been shown to upregulate PLIN5 (Laurens et al. 2016), highlighting the close ties between LDs, mitochondria, and overall metabolic homeostasis.

The Extracellular Matrix

The ECM is a dynamic niche of cells that regulates cell–cell communication and basic cellular behaviors. Mitochondria can sense and actively remodel the ECM depending on cellular states. For instance, cells treated with various mitochondrial stress stimuli show significant changes in the expression of ECM genes (Sun et al. 2019, van Waveren et al. 2006). Mechanistically, increased ROS production is associated with these stress stimuli, and treatment with the ROS scavenger N-acetyl-L-cysteine (NAC) suppressed the expression of ECM genes, indicating that mitochondria-derived ROS may signal to control ECM remodeling at the transcriptional level (Sun et al. 2019).

Mitochondria can also respond to the integrity of the ECM, mostly via integrin-mediated mechanical stress sensing. Anoikis, a Greek word meaning without a home, is a mitochondria-mediated form of cell death induced by cell detachment from the ECM that is mostly observed in epithelial cells. During cell detachment, integrin-mediated focal adhesion kinase signaling is suppressed, which leads to mitochondrial dysfunction such as reduced oxygen consumption, loss of mitochondrial membrane potential, and increased ROS generation via inhibiting the STAT3 pathway (Visavadiya et al. 2016). Integrins can also sense the stiffness of the ECM, a key biophysical property of tissues that may also regulate mitochondrial homeostasis. K. Chen et al. (2021) reported that ECM stiffening (40 kPa) reduces DRP1 expression in an integrin-dependent manner and promotes mitochondrial elongation, whereas ECM softening (0.35 kPa) induces mitochondrial fragmentation. In contrast, Tharp et al. (2021) found that in human mammary epithelial cells, ECM stiffening (60 kPa) induced mitochondrial fragmentation and mitochondrial stress via increased integrin signaling. Overall, changes in ECM stiffness may be associated with a series of physiological adaptations with many possible consequences on mitochondria.

NUTRIENTS AND METABOLITE SIGNALING

As mitochondria are the main energy-producing organelle of the cell, it is critical that they communicate with other components of the cell or organism to direct metabolic activity based on energy and nutrient availability (Bohovych & Khalimonchuk 2016). This communication is largely achieved by metabolites, which serve as sensors and messengers in relaying this information. By

responding to the influx and efflux of metabolites, mitochondria can rewire cellular programs and adapt to stress conditions to maintain homeostasis. These roles may stem from the endosymbiont origin of mitochondria: If mitochondria were originally an independent cell engulfed by a eukaryotic cell, they would have needed mechanisms to transfer metabolites to and from the host cell.

TCA Cycle Metabolites

The TCA cycle is a fundamental metabolic pathway central to the mitochondrial task of OXPHOS. The TCA cycle functions to mainly produce NADH as electron donors for the respiratory chain, but it is also a source of many metabolic intermediates that serve additional roles in signaling pathways and act as the building blocks of synthesis for other cellular components. For instance, acetyl coenzyme A (acetyl-CoA) serves as a building block for citrate and other TCA cycle metabolites, as well as for the synthesis of fatty acids, amino acids, and ketone bodies outside of the mitochondria in the cytosol (Frezza 2017). As the name suggests, acetyl-CoA is also an essential substrate for acetylation. Outside the mitochondria, acetyl-CoA acts as a cosubstrate for acetyltransferases that drive histone and protein acetylation, regulating important cellular pathways such as chromatin modification, DNA acetylation and methylation, and posttranslational protein modification (Martínez-Reyes & Chandel 2020, Shi & Tu 2015).

Other TCA intermediates such as succinate, fumarate, and α-ketoglutarate also have signaling functions outside of mitochondria. α-Ketoglutarate is a cosubstrate of demethylases such as the JMJDs, which activate intertissue mitochondrial stress signaling (Merkwirth et al. 2016) as well as regulate the activity of the prolyl hydroxylases that control hypoxia-inducible factor (HIF) activation (Tennant et al. 2009). Succinate can be released from mitochondria under certain stress conditions such as inflammation or other metabolic perturbations (Ariza et al. 2012). Once outside the mitochondria and in the bloodstream, succinate is recognized by a GPCR receptor GPR91 (He et al. 2004) to regulate organismal homeostasis. As with succinate, the accumulation of fumarate outside of mitochondria leads to significant cellular consequences. For example, accumulated fumarate can inhibit DNA demethylases, resulting in hypermethylation and epigenetic suppression, including the suppression of a microRNA miR-200 involved in the epithelial-to-mesenchymal transition associated with metastasis (Sciacovelli et al. 2016). Elevated fumarate levels also lead to the posttranslational modification of cysteine residues, such as for the E3 ubiquitin ligase complex component Keap1, leading to the aberrant activation of the Nrf2-mediated oxidative stress response (Adam et al. 2011, Ooi et al. 2011). Thus, the TCA cycle of mitochondria serves double duty in both contributing to energy production as well as signaling mitochondrial states to other cellular pathways.

AMP-Activated Protein Kinase and Cellular Energy Levels

As the powerhouse of the cell, mitochondria must have a proper sense of cellular ATP levels to regulate how much energy to produce. One of the main sensors of cellular ATP levels is the serine/threonine kinase AMP-activated protein kinase (AMPK). Under conditions of energy or ATP depletion, AMP levels are high in the cell and bind AMPK to activate it (Herzig & Shaw 2018). Activated AMPK then phosphorylates its downstream targets to upregulate energy-producing pathways, such as glucose transport, fatty acid oxidation, and autophagy, and downregulate energy-consuming pathways, such as the inhibition of mTOR as well as lipid and sterol synthesis pathways (Herzig & Shaw 2018, Zong et al. 2002).

Mitochondria and AMPK have a bidirectional regulatory relationship. Many downstream pathways targeted by AMPK relate to the regulation of mitochondrial dynamics and biogenesis.

In rat skeletal muscle, AMPK activation leads to increased mitochondrial enzyme content and biogenesis (Bergeron et al. 2001, Winder et al. 2000), and PGC-1α, an important regulator of mitochondrial biogenesis, is one of the downstream targets of AMPK (Jäger et al. 2007). When AMP levels are high and more ATP is needed, AMPK activation induces mitochondrial biogenesis via PGC-1α to increase OXPHOS levels to meet energy demands (Jäger et al. 2007, Zong et al. 2002). The activation of AMPK phosphorylates PGC-1α, which then acts in a feed-forward loop to induce even more expression of PGC-1α (Jäger et al. 2007). Overall, the induced expression of PGC-1α by AMPK leads to the increased expression of many mitochondrial genes, such as the glucose transporter GLUT4, electron transport chain proteins, cytochrome *c*, and the anion transporters UCP-2 and UCP-3 (Jäger et al. 2007). AMPK activation also leads to the phosphorylation of OMM protein ACC2, an acetyl CoA-carboxylase, to inhibit de novo lipid synthesis as well as activate lipid β-oxidation in mitochondria (Fullerton et al. 2013). The inhibition of mitochondrial activity or mtDNA mutations can also lead to AMPK activation (Herzig & Shaw 2018), highlighting their bidirectional regulatory relationship.

AMPK plays an important role in regulating mitochondrial morphology. AMPK induces mitochondrial fragmentation through the phosphorylation of MFF (Toyama 2016). MFF is a major fission-inducing factor of mitochondria, as it is one of the main receptors for Drp1 to bind to the OMM and induce mitochondrial membrane constriction and fission (Otera et al. 2010, Toyama 2016). AMPK activation phosphorylates MFF both in response to mitochondrial metabolic stressors, such as inhibitors of the electron transport chain, as well as in the absence of stress. AMPK also regulates mitochondrial health by directly phosphorylating autophagy and mitophagy factors such as ULK1 to promote macroautophagy (Egan et al. 2010, Kim et al. 2011). Whether the AMPK-activated ULK1 pathway also specifically activates mitophagy through the PINK1/Parkin pathway is yet to be determined. Overall, these data suggest a model whereby AMPK simultaneously increases new mitochondrial biogenesis and promotes removal of damaged mitochondria. This would ensure high functionality and quality of mitochondrial pools to promote ATP generation and fatty acid β-oxidation to make more energy available.

NAD^+ Metabolism

The nicotinamide adenine dinucleotide (NAD^+)/NADH metabolite serves an important role in maintaining reduction-oxidation (redox) homeostasis as well as in the mitochondrial electron transport chain as an energy transfer intermediate between the cytosol and the mitochondrial matrix. Because the IMM has historically been thought of as impermeable to NADH, several pathways have been elucidated that transfer NADH energy equivalents between the mitochondrial matrix and cytosol; however, recent evidence has suggested that NADH can also be directly transported into the mitochondria (Davila et al. 2018). Thus, NAD^+/NADH shuttling between mitochondria and the cytosol provides a direct pathway for mitochondrial metabolic pathways to communicate with the cell. The importance of NAD^+/NADH shuttling pathways in mitochondrial health and life span regulation highlights the need for this communication (Easlon et al. 2008).

Outside of its role in the electron transport chain, NAD^+ is an important cofactor for many enzymes involved in metabolic and regulatory pathways. One important enzymatic client of NAD^+ is the sirtuin family, a class of enzymes involved in regulating life span that depend on NAD^+ for their protein deacetylase activity (Verdin 2015, Viswanathan & Guarente 2011). While in yeast there is only one major sirtuin, Sir2, there are several orthologs in mammals for different subcellular compartments. In mitochondria, Sirtuin 3 (SIRT3) controls the acetylation state for mitochondrial proteins involved in oxidative stress and metabolic pathways (Hallows et al. 2011, Hirschey et al. 2010, Lombard et al. 2007, Qiu et al. 2010). The expression of SIRT3 changes in response to metabolic stress conditions such as high-fat diet or aging, illuminating mechanisms

by which metabolic states can regulate mitochondrial pathways via NAD^+ (Hirschey et al. 2010). In addition, SIRT1, the major sirtuin acting in the nucleus, can deacetylate and thereby activate PGC-1α to promote mitochondrial biogenesis (Cantó & Auwerx 2009). SIRT1 could be activated in response to elevated NAD^+ levels, thereby linking the metabolic state of cellular NAD^+ levels directly with mitochondrial activity.

NAD^+ levels also vary with metabolic activity and in aging and stress, and sufficient NAD^+ levels are necessary for cellular and mitochondrial health. Many mitochondrial disorders, such as Friedreich ataxia, are associated with reduced NAD^+ levels and mitochondrial SIRT3 activity (Wagner et al. 2012). Depletion of NAD^+ levels in the cell, such as in PARP hyperactivation, also results in decreased SIRT1 activity, mitochondrial dysfunction, and decreased mitophagy (Fang et al. 2014). In addition, decreased nuclear NAD^+ levels led to decreased nuclear SIRT1 activity and the downregulation of TFAM, the major mitochondrial transcription factor, resulting in a Warburg-like pseudohypoxic state with decreased expression of mitochondrially encoded electron transport chain proteins and increased glycolysis (Gomes et al. 2013). Conversely, increasing NAD^+ levels through either PARP inhibitors or supplementation of the NAD^+ precursor nicotinamide riboside (NR) prolongs longevity and enhances stress resistance via the mtUPR in *C. elegans* as well as other health span aspects in other model organisms (Katsyuba & Auwerx 2017, Mouchiroud et al. 2013). In mouse models, increasing NAD^+ levels via NR supplementation enhanced mitochondrial biogenesis and ameliorated diseases associated with mitochondrial electron transport chain defects (Cerutti et al. 2014). NR supplementation also increases mitochondrial oxidative function and protects against metabolic defects associated with diet-induced obesity (Cantó et al. 2012). Thus, regulating NAD^+ levels could be an important method for regulating mitochondrial activity in health and aging.

S-Adenosyl-L-Methionine

S-Adenosyl-L-methionine (SAM) is an essential one-carbon metabolite synthesized in the cytosol that serves as a methyl donor for many fundamental biological pathways, such as the methylation of proteins, nucleic acids, glutathione synthesis for redox homeostasis, and polyamine synthesis. SAM is also critical in energy metabolism and plays an important role in mitochondria: An estimated 30% of the SAM in the cell resides within mitochondria (Farooqui et al. 1983). Cytosolic SAM is imported into mitochondria by a SAM carrier (encoded by *SLC25A26* in humans), where it is then converted into *S*-adenosylhomocysteine for mitochondrial metabolic reactions (Agrimi et al. 2004). However, the levels of SAM within mitochondria are thought to mostly follow cytosolic availability rather than being a result of active transport into the organelle (Schober et al. 2021).

One of the functional links between SAM and mitochondrial functions was suggested by the observation that studies in mice defective in SAM synthesis [by knockout of the methionine adenosyltransferase 1A mutant (*MAT1A−/−*)] exhibit impaired mitochondrial function, possibly through a decrease in the expression levels of prohibitin 1 (Santamaría et al. 2003). Similar results have been reported in flies, wherein a reduction of SAM in mitochondria resulted in reduced OXPHOS and TCA metabolism, potentially due to a requirement of SAM methylation for electron transport chain complex protein stability (Santamaría et al. 2003). Inhibiting SAM production by knockdown of *S*-adenosylmethionine synthetase was shown to increase mitochondrial fission in *C. elegans* and induced the activation of the mtUPR (Wei & Ruvkun 2020), suggesting additional roles for SAM in regulating mitochondrial function and dynamics.

Oxygen and Reactive Oxygen Species

Normal oxidative metabolism of mitochondria through the electron transport chain generates ROS. While detailed mechanisms of how this occurs through mitochondria are unclear, ROS are

typically thought of as being derived from the leakage of electrons through complex I and III in the electron transport chain, which partially reduces oxygen to form a superoxide anion. Superoxide dismutases in mitochondria then react with this superoxide anion to generate hydrogen peroxide; together, superoxide and hydrogen peroxide are collectively thought of as mitochondrial ROS (mtROS) species. Historically, mtROS have been thought of as a toxic reagent or cellular stressor. However, mtROS are also important for regulating many essential cellular homeostasis and protective functions, such as activation of the mtUPR (Papa & Germain 2014) and cellular fate decisions. For instance, mtROS levels are important in determining hematopoietic stem cell differentiation and homeostasis (Bigarella et al. 2014, Ito et al. 2004, Owusu-Ansah & Banerjee 2009). mtROS are also important in regulating induced cell survival fates regulated by the cytokine TNFα (Kamata et al. 2005). Cells stimulated by TNFα generate mtROS, which then inhibits c-Jun N-terminal (JNK)-inactivating phosphatases by oxidizing their catalytic cysteines, leading to sustained JNK activation and pro-apoptotic death signaling (Kamata et al. 2005). However, in the presence of nuclear factor kappa B (NF-κB), this process is stalled, as the activation of NF-κB induces the expression of the mitochondrial superoxide dismutase SOD2, which then decreases cellular ROS levels to deactivate JNK and inhibit the pro-death response. Constitutive expression of SOD2 scavenges superoxide free radical species, thereby rendering cells more resistant to TNFα-mediated cell death (Wong et al. 1989).

Lipids

Lipids are important for maintaining mitochondrial health for several reasons, such as the integrity of the mitochondrial membranes. Cardiolipin serves as an important lipid component of mitochondrial membranes, especially in the IMM, where it ensures the stability of protein complexes such as the respiratory chain (Gebert et al. 2009). Cardiolipin is also a sensor and scavenger of ROS. This lipid becomes oxidized in the presence of ROS and is subsequently degraded, primarily via hydrolysis by the phospholipase A2γ (PLA2γ) (Chao et al. 2018, Tyurina et al. 2014), and is further oxidized and broken down by the 17-β-hydroxysteroid dehydrogenase 10 (HSD10) (Boynton & Shimkets 2015). If not degraded, oxidized cardiolipin is toxic to mitochondria (Paradies et al. 2002), and alterations to the levels of PLA2γ and HSD10 are associated with mitochondrial stress and neurodegenerative disease (Chao et al. 2018).

Mitochondria use lipid reorganization as a means of stress signaling. During mitochondrial stress, oxidized cardiolipin is transported from the IMM to the OMM (Dudek 2017, Paradies et al. 2019). While at the OMM, cardiolipin serves as a signaling antenna for mitochondria to communicate their stress state to the rest of the cell. For instance, cardiolipin at the OMM recruits many pro-apoptotic proteins such as the caspase-8 protease, Bid, and BAX to induce apoptosis by way of mitochondrial membrane permeabilization and cytochrome *c* release (Gonzalvez et al. 2008, Kuwana et al. 2002, Lai et al. 2019). Cardiolipin at the OMM also interacts with the autophagy marker protein LC3 to induce mitophagy (Chu et al. 2013, Hsu et al. 2015). Ceramide, another lipid, can also induce apoptosis and mitophagy upon accumulation in mitochondria (Chipuk et al. 2012, Sentelle et al. 2012). Thus, changes in lipid content levels and mitochondrial membrane localization seem to constitute a general strategy for mitochondrial communication to other cellular pathways to promote the degradation of defective cells or organelles.

PE is another lipid crucial to mitochondrial signaling. The IMM contains a very high concentration of PE, which is directly synthesized from PS derived from the ER (Tamura et al. 2012). PE levels at the IMM can regulate cellular responses to stress through regulating the activity of YME1L, an *i*-AAA protease present in the IMM that typically cleaves the GTPase Opa1 to regulate mitochondrial fission and fusion (Anand et al. 2014). Typically, PE at the IMM limits YME1L activity (MacVicar et al. 2019). However, under stress conditions such as nutrient deprivation or

hypoxia, inactivation of mTORC1 leads to a signaling cascade through the LIPIN1 phosphatase that decreases the level of PE synthesis at the IMM, thereby activating YME1L. Activated YME1L then mediates the proteolysis of mitochondrial proteins and rewires mitochondrial activity, illuminating how mitochondria-mediated PE lipid signaling can change cellular metabolism in response to stress (MacVicar et al. 2019).

Amino Acids

All 20 amino acids are directly associated with metabolic pathways in mitochondria, except for histidine, alanine, and cysteine, which are converted to pyruvate in the cytosol and are eventually consumed by the TCA cycle in mitochondria (Guda et al. 2007). Mitochondria respond to the intracellular levels of amino acids, as they serve as substrates for mitochondrial catabolic pathways, and because elevated amino acid levels can confer cellular toxicity. In yeast, accumulated neutral amino acids or cysteine has been reported to be potentially transported into mitochondria and to cause undue mitochondrial stress and loss of membrane potential (Hughes & Gottschling 2012, Hughes et al. 2020). In response to elevated amino acid levels, mitochondria generate and release MDCs (Schuler et al. 2021). These vesicles then sequester and deplete the SLC25A nutrient carriers and the import receptor Tom70 from mitochondria as well as promote the degradation of branched-chain amino acids through the Ehrlich pathway (Schuler et al. 2021).

MITOCHONDRIA AS HUBS FOR IMMUNE RESPONSES

The innate immune response is triggered by conserved danger signals exhibited by various pathogens and damage. Mitochondria are vital in sensing and sending out signals to trigger the innate immune response. This is likely due to the endosymbiotic origin of mitochondria, resulting in their retaining multiple prokaryotic vestiges. Thus, mitochondria are a rich source of damage-associated molecular patterns (DAMPs) that can be recognized by pattern-recognition receptors (PRRs) to trigger innate immune responses. Eukaryotic cells thus use mitochondria as sentinel organelles that can evaluate potential disturbances by these pathogens or molecular damage and elicit the corresponding innate immune response.

Mitochondria-Derived Damage-Associated Molecular Patterns as a Platform for the Innate Immune Response

The molecular mechanisms underlying how mitochondrial DAMPs activate innate immune responses have been comprehensively summarized by multiple reviews (Moehlman & Youle 2020, West & Shadel 2017). In brief, mitochondria contain many structural and molecular components that are shared from their bacterial origin but are distinct from the rest of the eukaryotic cell (except for chloroplasts) and can serve as DAMPs. These components include cardiolipin, circular mtDNA with hypomethylated CpG motifs, double-stranded mitochondrial RNA (mtRNA), the start codon N-formylmethionine, and mtROS (Kepp et al. 2011, Shimada et al. 2012) (**Figure 4**). When triggered by pathogen invasion or other sources of damage, these structural or signaling components are released into the cytosol and/or accumulate in endosomal compartments, where they can function as DAMPs to trigger antibacterial or antiviral immune responses. These immune responses include the cyclic GMP-AMP synthase (cGAS)–stimulator of interferon genes (STING) DNA-sensing pathway, the MDA5 and RIG-1 RNA-sensing pathway, the NLRP3/NLRC4/AIM2 inflammasome pathways, and the endosomal TLR9 DNA-sensing pathway (Moehlman & Youle 2020, West & Shadel 2017) (**Figure 4**).

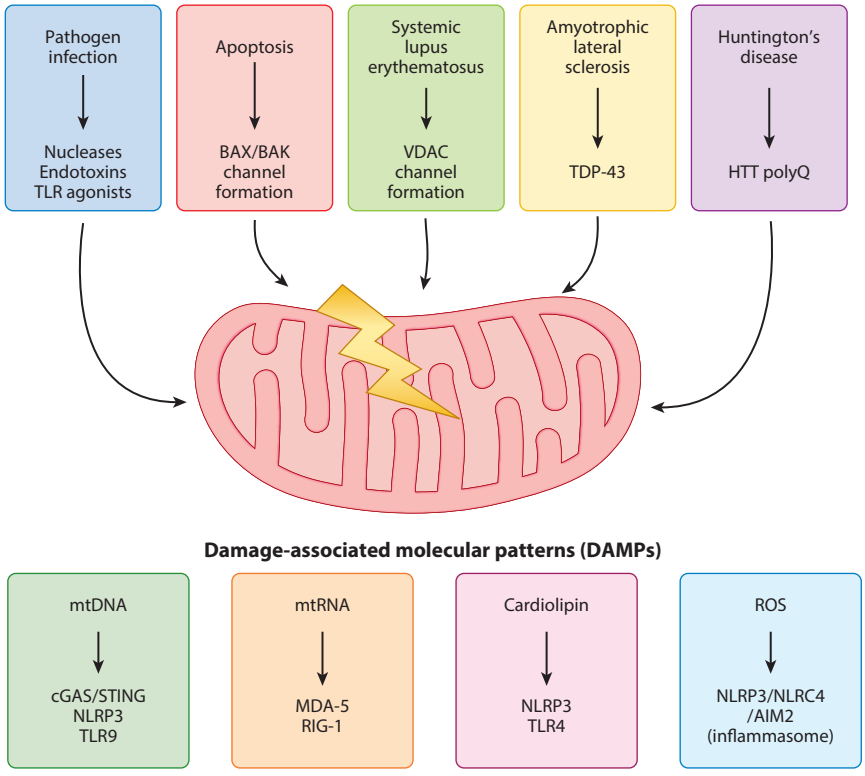

Figure 4

Mitochondria as hubs for immune signaling. (*Top*) Triggers for the mitochondrial release of DAMPs during infection or other stress. Mitochondrial damage and increased membrane permeability downstream of the indicated molecular players allow DAMPs to enter the cytosol. (*Bottom*) Major mitochondrial DAMPs. Release of these mitochondrial components into the cytosol initiates the indicated downstream immune pathways. Abbreviations: cGAS, cyclic GMP-AMP synthase; DAMP, damage-associated molecular pattern; HTT, huntingtin; mtDNA, mitochondrial DNA; mtRNA, mitochondrial RNA; polyQ, polyglutamine; ROS, reactive oxygen species; STING, stimulator of interferon genes; VDAC, voltage-dependent anion channel.

Physiological Triggers of Mitochondrial Damage-Associated Molecular Patterns and Their Disease Relevance

Once released into the cytosol, mtDNA can function as a DAMP to trigger the cGAS-STING immune pathway. For example, intracellular pathogens express mitochondria-intervening proteins to impose direct stress on mitochondria and cause mitochondrial DAMP release. Herpes simplex viruses (HSV-1 and HSV-2) encode the alkaline nuclease UL12.5 that localizes to mitochondria and promotes mtDNA depletion in mouse embryonic fibroblasts (Saffran et al. 2007, West et al. 2015). mtDNA depletion leads to aberrant mtDNA packaging, including uneven distribution and enlargement of mtDNA nucleoids (West et al. 2015). This mtDNA stress may cause the escape of mtDNA into the cytosol and promotes the efficient priming of cellular antiviral type I interferon responses via the cGAS-STING pathway (West et al. 2015). As another example, *Mycobacterium tuberculosis* infection induces production of the cytokine interferon β (INF β) via the cGAS-STING pathway in macrophages. The INF β induction efficiency is mycobacterial strain dependent, and those that can induce more mitochondrial stress and mtDNA release trigger more INF β production (Wiens & Ernst 2016).

In addition to external pathogen infections, endogenous cellular signaling events can also actively regulate mitochondria-related innate immune signaling. In apoptotic cells, the formation of the BAX/BAK channel leads to mitochondrial outer membrane permeabilization (MOMP) that allows the IMM and mtDNA to reach the cytosol, thus triggering the cGAS-STING–type I interferon pathway (McArthur et al. 2018). An alternative mediator of MOMP is the VDAC. VDAC proteins localize on the OMM and may directly interact with mtDNA to form oligomeric pores for releasing mtDNA into the cytosol when triggered by molecular damage (Kim et al. 2019). VDAC oligomerization is associated with the induction of apoptosis by a variety of stressors such as oxidants (Keinan et al. 2010). Increased expression of VDAC, but not BAX/BAK, was observed in systemic lupus erythematosus (SLE) patients. Importantly, pharmaceutically inhibiting VDAC oligomerization using the compound VBIT-4 reduces mtDNA release and IFN signaling and alleviates the disease severity in an SLE mouse model (Kim et al. 2019). This result suggests a key role for mtDNA release–mediated autoimmune responses in SLE.

DAMPs may also be released during mitochondrial stress resulting from the mislocalization of proteins from other cellular compartments to mitochondria. Indeed, this is a mitochondrial stress phenomenon found in multiple neurodegenerative diseases, including amyloid lateral sclerosis (ALS) and Huntington's disease (HD). In sporadic and familial ALS, mutations in the nuclear DNA-/RNA-binding protein TDP-43 result in its mislocalization to mitochondria (Kabashi et al. 2008, Sreedharan et al. 2008). This in turn induces mitochondrial stress, including increased mtROS generation, loss of membrane potential, and the subsequent release of mtDNA into the cytosol via opening of the mitochondrial permeability transition pore (Yu et al. 2020). HD, caused by an abnormal expansion of CAG repeats encoding polyglutamine (polyQ) in the huntingtin (*HTT*) gene, is also associated with increased mitochondrial stress and neuroinflammation. In an R6/2 HD mouse model, mutant HTT protein interacts with the mitochondrial import complex and inhibits mitochondrial protein import both in isolated mitochondria and in primary neurons isolated from an R6/2 HD mouse model (Yano et al. 2014). Overall, mutant HTT expression is associated with increased mitochondrial fragmentation (Wang et al. 2009), increased cytosolic mtDNA, and mtDNA-induced inflammatory responses mediated by cGAS (Jauhari et al. 2020). Interestingly, exogenous melatonin treatment inhibits mtDNA release and inflammation in R6/2 mice (Jauhari et al. 2020), potentially due to its ability to scavenge ROS and thereby protect mitochondrial health. As melatonin levels are known to generally decrease with aging, that melatonin-deficient mice also show increased mtDNA release and neuroinflammation suggests that DAMP release may be generally associated with age-related mitochondrial stress beyond mutation-associated neurodegenerative diseases (Jauhari et al. 2020).

In addition to aberrant damage-induced mitochondrial DAMP release, cells may also actively stress mitochondria to potentiate immune responses. In macrophages, the activation of the TLR-1/2/4 signaling by bacterial or viral TLR agonists induces the translocation of TRAF6 to mitochondria and polyubiquitinates the complex I assembly factor ECSIT (evolutionarily conserved signaling intermediate in Toll pathway), which in turn disrupts the integrity of the electron transport chain and generates mtROS (West et al. 2011). This induction of mtROS is required for optimal immune reactions, as macrophages from catalase-overexpressing mice, in which mtROS are suppressed, are less efficient in controlling intracellular bacterial replication (West et al. 2011).

Mitophagy Limits Damage-Associated Molecular Pattern Release to Control Immune Responses

While mitochondria can be damaged by multiple pathways to release DAMPs, counteractive quality control mechanisms exist to limit mitochondrial stress-induced immune responses. The most

extensively studied such response in mammalian cells is mitophagy. Efficient mitophagy requires the engulfment of damaged mitochondria by autophagosomes and their degradation in lysosomes, and each step of the mitophagy pathway may elicit distinct immune responses. For instance, inhibiting autophagosome formation by depleting the essential autophagic proteins LC3B and Beclin 1 leads to deficient mitochondrial clearance and mtDNA release into the cytosol, which in turn enhances caspase-1 activation and the secretion of interleukin-1 β (IL-1 β) and IL-18 in murine macrophages upon lipopolysaccharide (LPS) and ATP stimulation (Nakahira et al. 2011). This suggests that mitophagy may remove damaged mitochondria that would otherwise trigger an immune response under stress conditions such as LPS challenge. Another example is the case of the PINK1/Parkin pathway, two mitophagy mediators that are found mutated in many early-onset familial Parkinson's disease cases. However, despite the key role of PINK1 and Parkin in inducing mitophagy, Pink1−/− and Parkin−/− mice do not exhibit robust signs of parkinsonism such as loss of dopaminergic neurons and impaired motor ability (Goldberg et al. 2003, Kitada et al. 2009, Oliveras-Salvá et al. 2011, Perez & Palmiter 2005). Later work clarified the in vivo roles of PINK1 and Parkin, showing that certain types of stress such as exhaustive exercise may induce mitochondrial damage in muscle and subsequent STING-mediated inflammation in Pink1−/− and Parkin−/− mice but not in wild-type mice (Sliter et al. 2018). This suggests that mitophagy levels might be very low under physiological conditions, so additional mitochondrial stress inducers may be required for the onset of inflammation and neuronal loss in Parkinson's disease.

Defective lysosomal degradation of mitochondrial components may also trigger cGAS-STING-independent immune responses. Lysosomes overloaded with mtDNA activate TLR-9, a sensor of CpG-enriched DNA that is localized in endosomal compartments. Mice with cardiac-specific deletion of lysosomal deoxyribonuclease II are more prone to pressure overload–induced mortality, myocarditis, and dilated cardiomyopathy due to activated TLR-9 signaling (Oka et al. 2012). The accumulation of nondegraded mtDNA in autolysosomes was observed in these mice, which might be the trigger of these pathological consequences (Oka et al. 2012).

Mitochondrial Immune Signaling Through Mitochondrial Antiviral Signaling

In addition to serving as a source of DAMPs, mitochondria also function as a platform for the innate immune response to infection by RNA viruses. This process relies on the mitochondrial antiviral signaling (MAVS) proteins localized on the OMM. Upon entry into the cell, viral RNA binds the RIG-1-like (RLR) PRRs RIG-1, MDA-5, and LGP2 and initiates a conformational change in those receptors that results in their tetramerization and polyubiquitination (Peisley et al. 2014). The modified receptors then bind MAVS via the shared CARD domains in both the RLR and MAVS proteins. This drives aggregation of MAVS on the OMM surface, forming a MAVS supercomplex that can recruit the TRAF family proteins to initiate a downstream innate immunity signaling response (Hou et al. 2011). These downstream signaling cascades elicit the expression of proinflammatory cytokines by NF-κB and type I interferons by IRF3/7, resulting in the inhibition of viral replication to provide pathogen protection to the host cell (Seth et al. 2005). The role of LGP2, which does not have a CARD domain, in activating MAVS-related innate immune signaling is less clear but is thought to perhaps work through a concentration-dependent mechanism (Bruns & Horvath 2015).

Numerous mitochondria-resident proteins have been identified as MAVS regulators. The outer membrane translocase Tom70 physically interacts with MAVS and potentiates the induction of IFN β by Sendai virus infection or poly(I:C) immune stimulation, possibly through the recruitment of IRF3 via the chaperone Hsp90 (Liu et al. 2010). Mitochondrial proteins that are induced downstream of antiviral signaling might also regulate MAVS, thus creating a feedback loop in the antiviral response; for example, the antiviral interferon-induced protein IFIT3 localizes to the

mitochondria and interacts with MAVS, and increasing or decreasing IFIT3 activity potentiates or abrogates MAVS activity, respectively (Liu et al. 2011). Interestingly, MAVS activity is also responsive to mitochondria-derived signals independent of viral RNA; mtROS production or translocation of cardiolipin from the IMM to the OMM during membrane depolarization causes MAVS oligomerization and NLRP3 inflammasome activation at the OMM (Buskiewicz et al. 2016, Groß et al. 2016, Iyer et al. 2013). Other aspects of mitochondrial biology and dynamics, including mitochondrial fission/fusion and membrane potential, are also modulated by viral infection or immune stimulation and impact MAVS-mediated antiviral signaling (Castanier et al. 2010, Koshiba et al. 2011). Cells deficient in mitochondrial fusion due to the loss of mitofusins 1 and 2 are defective in their induction of interferons and proinflammatory cytokines during infection, as are cells treated with a drug that dissipates the mitochondrial membrane potential (Koshiba et al. 2011). Taken together, these findings and others place mitochondrially localized MAVS at the center of a signaling network that integrates the detection of viral infection with other inputs from the mitochondria to generate a protective antiviral immune response.

Mitochondria and the Adaptive Immune Response

While understudied, the role of mitochondrial signaling in the adaptive immune responses has gained recent traction. One such role in the adaptive immune response is antigen presentation for T cell recognition by mitochondria, otherwise known as mitochondrial antigen presentation (MitAP). MitAP is important in presenting mitochondrial antigens on major histocompatibility complex (MHC) class I molecules upon various stimuli (Matheoud et al. 2016). In a murine macrophage cell line, this presentation was shown to be achieved via the mitochondria-derived vesicle (MDV) route rather than by mitophagy or autophagy, as is more typical for MHC class I or II presentation. Interestingly, the generation of MDVs for MitAP is suppressed by PINK1 and Parkin, which actively suppress the recruitment of MDV sorting factors such as Rab9 and Snx9. In the absence of PINK1 or Parkin, MDVs and MitAP accumulate. This raises the interesting possibility that in Parkinson's disease patients in which PINK1 or Parkin is compromised, increased mitochondrial antigen presentation in the central nervous system may lead to aggravated autoimmune mechanisms that contribute to disease pathology. This has been important in the consideration of conflicting evidence that Pink1−/− and Parkin−/− mice do not show Parkinson's-like pathological defects (Goldberg et al. 2003, Kitada et al. 2009, Oliveras-Salvá et al. 2011, Perez & Palmiter 2005). Interestingly, infection with gram-negative bacteria (LPS+) triggers mitochondrial antigen presentation in Pink1−/− mice in vivo and results in mitochondria-derived peptide-specific $CD8^+$ T cells in the central nervous system. Thus, bacterial infection and Pink1−/− show a synergistic effect, leading to transient dopaminergic neuron defects and motor impairment in mice. Overall, this suggests that Pink1 or Parkin defects themselves are not sufficient to generate a pathological phenotype, but rather that infection could be a triggering factor in combination with the loss of mitochondrial quality control factors that lead to pathophysiology (Matheoud et al. 2019, 2016).

The Mitochondrial Unfolded Protein Response and Immunity

The mtUPR also functions as an important hub in pathogen detection and response; infection by pathogenic bacteria drives the activation of the mtUPR, which in turn promotes a protective immune response. A study of mtUPR activation by bacteria isolated from wild *C. elegans* habitats found that 18% of the 560 bacterial strains tested induced expression of the mitochondrial Hsp70 chaperone in *C. elegans* HSP-6, suggesting a significant role for the mtUPR in the response of *C. elegans* to microbes in its natural environment (Liu et al. 2014). Numerous bacteria-derived

toxins, including electron transport inhibitors (e.g., antimycin A, cyanide, and pyocyanin) and iron-chelating siderophores (pyoverdins) similarly induce the mtUPR (Liu et al. 2014, Melo & Ruvkun 2012, Pellegrino et al. 2014, Runkel et al. 2013). Mitochondria thus play an important role in sensing pathogens and inducing stress signals that warn of an imminent infection.

In *C. elegans*, the immune response program initiated downstream of mitochondrial dysfunction is coordinated by the major mtUPR-regulatory transcription factor ATFS-1 (Pellegrino et al. 2014). In addition to activating canonical targets associated with improving mitochondrial proteostasis, such as the chaperones HSP-6 and HSP-60, ATFS-1 also induces the expression of genes more directly associated with infection clearance, such as secreted lysozymes, antimicrobial peptides, and C-type lectins, as well as enzymes involved in detoxification, such as cytochrome P450 and glucuronosyltransferases (Liu et al. 2014, Pellegrino et al. 2014). The loss of ATFS-1 or other positive regulators of the mtUPR including DVE-1 in *C. elegans* decreases survival on infection with pathogens such as *Pseudomonas aeruginosa*, while the hyperactivation of ATFS-1 enhances infection survival, indicating that this branch of the immune response is functionally important (Pellegrino et al. 2014, Shao et al. 2020).

Interestingly, some pathogens have mechanisms to disrupt the mtUPR, thus partially evading this aspect of the immune response and promoting their own virulence. For example, *P. aeruginosa* cocultured with *C. elegans* suppresses natural host mtUPR activation, resulting in only transient activation of the mtUPR during infection, and blocks mtUPR activation upon treatment with other mitochondrial inhibitors such as antimycin (Liu et al. 2014, Mahmud et al. 2020). Recent work has begun to elucidate the mechanisms of this immune evasion. Loss of the branched-chain amino acid catabolic enzyme acyl-CoA dehydrogenase FadE2 in *P. aeruginosa* impairs the ability of the pathogen to block host mtUPR activation and affects host metabolism (Mahmud et al. 2020), and the host protein ZIP-3, a negative regulator of ATFS-1 activity in *C. elegans*, is required for the *P. aeruginosa*–mediated inhibition of the mtUPR (Deng et al. 2019). Whether these mechanisms function in the same or parallel pathways to repress *C. elegans* mtUPR by *P. aeruginosa* remains unclear.

Though the connection between the mtUPR and the immune response has been studied most extensively in *C. elegans*, there is also evidence of mtUPR activation or mitochondrial stress signaling during infection in other animal models. In mammalian cells, mitochondrial stress results in the induction of anti-microbial peptides (Pellegrino et al. 2014), and mtUPR components such as HSP60 and ATF5/ATFS-1 are upregulated during pathogenic infection of a diversity of organisms, including fish, reef-building coral, and whiteleg shrimp (Chen et al. 2016, Dimos et al. 2019, Song et al. 2018). Whether mitochondrial stress may lead to a specific mtUPR-like transcriptional program that induces the expression of certain immune genes remains to be fully understood in mammals.

CONCLUSION

As a central organelle of the cell, mitochondria are responsible for many essential pathways beyond energy production. Rather than an isolated cellular powerhouse, mitochondria should be thought of as a central signaling hub. Akin to a control center in an airport tower, mitochondria continually receive information about nutrient and health states beyond the organelle and, in return, send out molecular messengers to either rewire cellular transcriptional, metabolic, or proteomic states or perform the activities themselves. These active listening and acting roles that mitochondria play likely stem from their endosymbiotic origin. As previously autonomous proteobacterial organisms, mitochondria were initially self-contained in their cellular functions. However, as they were engulfed by eukaryotic cells and became more entwined in cellular function and fate, they

evolved a need and ability to exchange signals with the rest of the eukaryotic cell, and eventually other tissues within the organism.

Many open questions remain in the field of mitochondrial signaling, and continual study only begets more questions. At this time, the list of molecular components, organelles, and tissues regulated by mitochondrial signaling pathways only continues to grow. However, in many cases, questions remain: To what extent do mitochondria play a direct role in these signaling pathways? How centrally controlled are each of these signaling mechanisms by the mitochondria, versus more indirectly influenced by the more central roles of mitochondria in energy or metabolic production? Moreover, many of these signaling mechanisms clearly become perturbed in aging and disease. Because of the intricate involvement of mitochondria in so many diverse cellular pathways, the question remains: How can we target specific activities of these mitochondria to reduce pathophysiology in these diseases? The clear role that mitochondria play in determining health during aging only makes this question more important. Depending on the physiological context, the upregulation or slight downregulation of mitochondrial activity can both have beneficial effects on longevity. Much work remains to be done to understand the detailed roles of mitochondrial signaling in aging and disease and how to leverage this understanding for therapeutic design.

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