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Decoding the Rosetta Stone of Mitonuclear Communication

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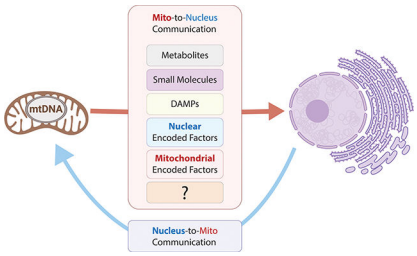
Abstract

Cellular homeostasis in eukaryotic cells requires synchronized coordination of multiple organelles. A key role in this stage is played by mitochondria, which have recently emerged as highly interconnected and multifunctional hubs that process and coordinate diverse cellular functions. Beyond producing ATP, mitochondria generate key metabolites and are central to apoptotic and metabolic signaling pathways. Because most mitochondrial proteins are encoded in the nuclear genome, the biogenesis of new mitochondria and the maintenance of mitochondrial functions and flexibility critically depend upon effective mitonuclear communication. This review addresses the complex network of signaling molecules and pathways allowing mitochondria-nuclear communication and coordinated regulation of their independent but interconnected genomes, and discusses the extent to which dynamic communication between the two organelles has evolved for mutual benefit and for the overall maintenance of cellular and organismal fitness.

Graphical Abstract



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Keywords

Mitonuclear Communication; Mitochondrial Retrograde Signaling; Integrated Stress Response; Epigenetics

Compounds:

Nicotinamide riboside; Superoxide anion; Acetyl-Coenzyme A; S-adenosylmethionine (SAM); Carbonyl cyanide m-chlorophenylhydrazone (CCCP); Oligoymycin; Antimycin; Humanin; alpha-Ketoglutarate

1 - Introduction

Eukaryotic cells presumably evolved from the union of a primordial ancestral cell and bacteria that each brought their independent genomes {Roger, 2017 #2333;Martijn, 2018 #2504}. The endosymbiotic bacteria gave rise to mitochondria, which, due to their bacterial origin, possess a unique circular genome. The mitochondrial and nuclear genomes together constitute a bi-genomic genetic system-Over time, much of the bacterial genome relocated to the host nucleus-through lateral gene transfer (Dyall et al., 2004)(Timmis et al., 2004) (Adams and Palmer, 2003; Burger et al., 2003; Gray, 2012). The transfer of genetic information represents an ongoing evolutionary process. Degenerate mitochondrial DNA segments or sequence insertions into the nuclear genome, referred to as nuclear mitochondrial DNAs (NUMTs) (Lopez et al., 1994), constitute genetic markers of the ongoing lateral gene transfer process (Caro-Quintero et al., 2011; Dayama et al., 2014; Lang et al., 2012; Thomas and Nielsen, 2005) and provide genetic material for gene regulation (Goldin et al., 2004; Schon et al., 2012; Turner et al., 2003; Willett-Brozick et al., 2001). NUMTs are present across species and exist in fragments of varying lengths and homology that are dispersed throughout the genome and can collectively cover the entire mitochondrial DNA sequence (Calabrese et al., 2017; Pereira and Baker, 2004; Richly and Leister, 2004; Simone et al., 2011). Although the evolutionary benefits of maintaining a bi-genomic system in the cell are not fully understood, a strong selection force appears to have favored it as the cost and complexity of maintaining two genomes within a cell is far higher than operating based on a single genome. As we discuss further below, one possible reason behind the dual-genome setup may be to optimize mitochondrial communication. Because mitochondria can exist in the thousands in a given cell, it is plausible that the inherent ability to respond without the need for the nucleus to keep track of all individual mitochondrion would be necessary. Nonetheless, mitochondria and the nucleus have co-evolved at multiple levels. As the two previously independent organisms integrated to generate a unified organism with two interdependent genomes, novel pathways evolved to promote communication between organelles and allow for coordinated and cross-regulated gene expression (Kim et al., 2018; Mottis et al., 2019), thus resulting in a unified genetic network that is built on and regulated by information contributed by both genomes.

Mitochondrial-nuclear coordination is mediated by a robust and sophisticated communication system, which includes a range of signaling factors that are increasingly being identified. Proper mitonuclear coordination is achieved through bi-directional

transmission channels, traditionally referred to as anterograde (nucleus to mitochondria) and retrograde (mitochondria to nucleus) signaling. While much of the early work on mitonuclear communication focused on the nucleus-to-mitochondria direction, it is now well appreciated that mitochondria-to-nucleus signaling is also critical to regulating cellular homeostasis and specific processes, such as metabolism, proliferation, differentiation, and stress adaptation. For detailed discussion of the nuclear network of transcription factors and associated cofactors that regulate nucleus-to-mitochondria signaling through the expression of nuclear-encoded mitochondrial genes, we refer to other reviews (Fang et al., 2016; Hock and Kralli, 2009; Scarpulla et al., 2012; Whelan and Zuckerbraun, 2013; Wu et al., 1999). Here, we will provide a review of the mechanisms supporting mitochondria-to-nucleus signaling, including the exchange of mitochondrial- and nuclear-encoded factors, damaged mitochondrial components that elicit immune responses, and metabolic intermediates with important ties to epigenetic modifications, and discuss how these functional signaling networks are required for maintaining essential cellular communication, homeostatic balance, and prevention of disease through coordinated reprogramming of nuclear gene expression programs.

2- Mitochondrial-derived signaling molecules

Advances in mitochondrial research in recent years have significantly expanded our view of their roles, from semi-independent organelles responsible for metabolic and apoptotic processes to key signaling hubs that are well integrated in multiple signal transduction pathways (Abate et al., 2020; Chandel, 2015; Rath et al., 2018). For excellent coverage of the many ways mitochondrial-derived signals contribute to regulate a variety of cellular functions, we refer to other recent reviews (Bohovych and Khalimonchuk, 2016; Mottis et al., 2019). Here, we will focus on discussing the many intricate mechanisms by which mitochondrial-derived signaling molecules contribute to the communication between mitochondria and nucleus, either directly through intraorganellar translocation, or indirectly by providing cofactors/substrates that provide the metabolic context for transcriptional and epigenetic regulation (Figure 1).

2.1 Peptides

Human mitochondrial DNA (mtDNA) has been traditionally described to encode for 13 proteins, all of which are components of the electron transport chain (ETC). More recently, short open reading frames (sORFs) encoding for bioactive peptides, collectively referred to as mitochondrial-derived peptides (MDPs), have been identified in the mtDNA. MDPs appear to play a significant protective role in mitochondrial health and cell viability in a number of disease contexts including oxidative stress, atherosclerosis, and age-related macular degeneration (Nashine and Kenney, 2020). To date eight MDPs have been reported, including humanin {Hashimoto, 2001 #117;Guo, 2003 #133;Ikonen, 2003 #132}, six small humanin-like peptides (SHLP1–6)(Cobb et al., 2016), and mitochondrial ORF of the 12S ribosomal RNA type-c (MOTS-c)(Lee et al., 2015).

MOTS-c is a peptide encoded within the mitochondrial 12S ribosomal RNA. MOTS-c regulates metabolism, in part, via AMP-activated protein kinase (AMPK) and sirtuin 1

(SIRT1) and promotes cellular homeostasis. In mice, MOTS-c treatment prevented diet-induced obesity and insulin-resistance and reversed age-dependent insulin resistance (Lee et al., 2015). MOTS-c regulates adaptive nuclear gene expression by translocating to the nucleus in response to metabolic stress and interacting with transcriptional factors, including nuclear factor erythroid 2-related factor 2 (Nrf2) and activating transcription factor-1 (ATF1) (Kim et al., 2018). While the details of the nuclear actions of MOTS-c is a topic of active investigation, its identification as the first mitochondrial-encoded factor that directly regulates the nuclear genome reveals cross-regulation between the two genomes. This adds an unprecedented layer to the complexity of mitonuclear communication and raises the question whether other MDPs may facilitate communication between the two genomes. Notably, MOTS-c levels are induced in response to exercise stress in humans and its treatment in mice significantly improves physical performance at all age groups (Reynolds et al., 2019). RNA-seq analyses on aged mouse muscle and myoblasts indicate that MOTS-c regulates proteostasis under stress conditions (Reynolds et al., 2019), which is of special interest considering that MOTS-c is itself encoded within a ribosomal gene. Meanwhile, Tar1p, a small peptide encoded in the nuclear 25S ribosomal RNA gene in *S. Cerevisiae*, functions in mitochondria in response to respiratory demand and dysfunction (Bonawitz et al., 2008), which may reflect a coordinated mitonuclear ribosomal response.

Although it is unclear whether other MDPs directly regulate nuclear function, their diverse cellular functions entail potential interaction with and effect on nuclear gene expression. Humanin, the first reported MDP encoded within the mitochondrial 16S ribosomal RNA, was reported to have protective effects in neurons, brain, eyes, bone, the vascular and the cardiovascular system, (Lee et al., 2013; Tajima et al., 2002; Zarate et al., 2019). Its protective effects have been associated with inhibition of apoptosis and inflammation, oxidation, and regulation of mitochondrial function (Kuliawat et al., 2013; Yen et al., 2013; Zapala et al., 2010). Following humanin, SHLPs were discovered also within mitochondrial 16S ribosomal RNA. Whereas SHLP2 and SHLP3 were reported to have a cytoprotective effect similar to that of humanin, SHLP6 promotes apoptosis (Cobb et al., 2016). SHLPs are also involved in regulation of mitochondrial bioenergetics and chaperone-like function (Nashine et al., 2018; Okada et al., 2017).

2.2 Mitochondrial DNA

Damage-associated molecular patterns (DAMPs) derived from endogenous intracellular components that are released during cellular stress or damage can lead to activation of innate immune responses. In particular, stimulation of pro-inflammatory responses can be triggered by the release of mitochondrial-derived DAMPs (mtDAMPs), including *N*-formylated peptides and mtDNA as discussed in depth in other reviews (Grazioli and Pugin, 2018; West, 2017; West and Shadel, 2017). Relevant to this review is the fact that release of mtDNA in the cytosol indirectly induces signaling to the nucleus and reprogramming of nuclear gene expression to support the innate immune response activation. This is achieved through at least three different receptor-mediated pathways: toll-like receptors (TLRs), NOD-like receptors (NLRs), and interferon stimulatory DNA receptors, with each receptor supporting the regulation of different immune response arms. mtDNA recognition by TLRs, mainly TLR9, promotes gene expression through nuclear factor kappa B (NF-κB) activation (Kawai

and Akira, 2010). mtDNA activation of the NLRP3 inflammasome is responsible for caspase-1 mediated processing and secretion of IL-1β and IL-8 (Kawai and Akira, 2010; Shimada et al., 2012). Furthermore, cytoplasmic mtDNA activates the cGAS-STING-TBK1-IRF3 pathway, resulting in interferon-stimulated gene expression that promotes antiviral immunity (Kwon and Bakhoum, 2020) and acts as a genotoxic stress sentinel that signals the nucleus to enhance DNA repair (Wu et al., 2019). Notably, signaling through mtDNA pattern recognition provides a means not only for intracellular mito-to-nuclear communication, but also for paracrine and organismal signaling, via release of mtDNA in the extracellular space and the circulation. Mitochondrial DNA found in the serum is referred to as circulating cell-free mtDNA (ccf-mtDNA). Several studies reported that ccf-mtDNA contributes to inflammation in type 2 diabetes (Bae et al., 2019) and neuro-immunological disorders (Gambardella et al., 2019). Moreover, not only physical stress but also psychological stress triggers increases of mtDNA in the circulating serum (Trumpff et al., 2019). Further studies are warranted for the understanding of this fine regulation in immune response, which may provide the opportunity for translational therapeutic development in the area of mtDNA signaling. For example, a key aspect of signaling through mtDNA release from damaged mitochondria involves the regulation of mtDNA export, including (i) formation of voltage-dependent anion channel (VDAC) oligomer pores (Kim et al., 2019), (ii) transient (non-lethal) and selective mitochondrial outer membrane permeabilization (MOMP), also referred to as minority MOMP (Brokatzky et al., 2019; Ichim et al., 2015; Xu et al., 2020), and (iii) mitochondrial permeability transition pore (mPTP) (Martinez-Abundis et al., 2007; Nakahira et al., 2011; Patrushev et al., 2004; Szczesny et al., 2018). Excessive interferon (IFN) response increases VDAC1/3 expression (Fernandez et al., 2009; Kim et al., 2019). MOMP has also been suggested to mediate mtDNA release and IFN response, commensurate to mitochondrial stress (Kim et al., 2019). Additionally, mPTP can mediate LPS-induced mtDNA release (Kim et al., 2019; Nakahira et al., 2011). As is the case with mtDNA-stimulated immune responses, mtDNA export mechanisms represent an area of potential therapeutic targets, particularly in the case of pathological conditions associated with uncontrolled inflammation.

2.3 Small Molecules

2.3.1 NAD^+—Nicotinamide adenine dinucleotide (NAD) is present in the cell in two forms: an oxidized (NAD^+) and a reduced (NADH) form. Because the ratio between this redox couple provides an indication of the metabolic status of the mitochondria, NAD serves as an important metabolic sensor or gauge. NAD^+ functions as a key cofactor for multiple metabolic reactions and as a substrate for different classes of enzymes, including some with critical functions in the regulation of nuclear functions and gene expression, such as deacetylases and ADP-ribosyl transferases (ARTs). Thus, NAD^+ levels reflect the cellular energetic status while providing metabolic input to adaptive gene regulation. This is favored by NAD^+ being both tightly regulated and compartmentalized within the cell (Canto et al., 2009; Zhu et al., 2019). Distinct pools of NAD^+ exist in the mitochondria, cytosol, and nucleus respectively, with the cytosolic pool serving as the hub that connects the others (Zhu et al., 2019). Even though the mechanism/s regulating the synthesis, compartmentalization and movement of NAD^+ between the mitochondria and the cytosol/nucleus are not fully characterized, it is clear that each subcellular pool is regulated and utilized differently in

terms of metabolic flux or NAD^+-dependent signaling (Anderson et al., 2017; Davila et al., 2018; Zhu et al., 2019)

Deacetylation is a critical enzymatic process for the regulation of nuclear gene expression. Removal of an acetyl group from lysine residues on histone tails, as governed by histone deacetylases (HDACs), can directly affect chromatin compaction and result in gene repression (Seto and Yoshida, 2014; Yang and Seto, 2007). Moreover, as HDACs activity is not limited to histones, deacetylation of transcription factors and transcriptional regulators can be used to modulate their function, thus providing further specificity to transcriptional regulation (Choudhary et al., 2009; Park et al., 2015; Sterner and Berger, 2000; Thiagarajan et al., 2016). Among HDACs, sirtuins (Class II HDACs) are unique in that they require NAD^+ as a cofactor. Overall, Sirtuins are well described as key regulators of cellular homeostasis and have been shown to be preventive of multiple diseases (Houtkooper et al., 2012; Kupis et al., 2016; Morigi et al., 2018; Pirinen et al., 2012; Vachharajani and McCall, 2020). The intricacies of the specific mechanism, utilizations, and biochemistry of NAD^+ and its production are covered elsewhere (Anderson et al., 2017; Canto et al., 2015; Houtkooper et al., 2010; Kulkarni and Brookes, 2019; Sauve et al., 2006). Briefly, the NAD^+/sirtuin enzymatic reaction functions such that NAD^+ is consumed and nicotinamide (NAM), *O*-acetyl ADP ribose, and the deacetylated substrate (both histone and non-histone) are released. Given that NAD^+ has a central role in energy metabolism, tricarboxylic acid (TCA) cycle flux, and nutrient sensing, changes in its availability can directly link the metabolic status of mitochondria with chromatin remodeling and nuclear reprogramming, in part, via sirtuin activity (Bosch-Presegue and Vaquero, 2015; North and Verdin, 2004). Phylogenetically, sirtuins have been around since prokaryotes and have emerged as key enzymatic regulators of nutrient and cell cycle stress during evolution (Bosch-Presegue and Vaquero, 2015; Frye, 2000). To date, seven mammalian sirtuins have been identified (SIRT1-SIRT7), each with unique subcellular localizations that allow for the utilization of specific NAD^+ pools and the modulation of specific targets. SIRT3,4, & 5, for example, function as key regulators of metabolism and oxidative stress from within the mitochondria. This is not only based on the deacetylation of target proteins, as profiling of the acetylome regulated by the mitochondrial sirtuins has revealed a number of novel modifications targeted by sirtuins, including succinylation, malonylation and glutarylation (Carrico et al., 2018; Downey et al., 2015; Hirschey and Zhao, 2015; Park et al., 2013; Rardin et al., 2013; Rauh et al., 2013). The balance between spontaneous acylation and NAD-dependent de-acylation of mitochondrial proteins significantly contributes to the regulation of mitochondrial functions and metabolic pathways As a result, mitochondrial sirtuins have been associated with protective effects against aging, insulin resistance and other age-related pathologies. At the same time, the nuclear role of SIRT1 and its relationship with NAD^+ have been widely studied in the context of mammalian physiology, stress response, aging and numerous diseases, including cancer and metabolic disorders (Alves-Fernandes and Jasiulionis, 2019; Haigis and Sinclair, 2010; Rahman and Islam, 2011; Tang, 2016; Xu et al., 2018). In addition to histones, the transcriptional cofactor PGC1α is a key target of NAD^+-dependent deacetylation. Deacetylation of PGC1α by SIRT1 leads to its activation and the induction of downstream pathways that control mitochondrial gene expression, particularly

those related to mitochondrial biogenesis, fatty acid oxidation, and oxidative stress response (Feige et al., 2008).

Other enzymes that utilize NAD^+ as a substrate are ADP-ribosyl transferases. Among them, Poly(ADP-ribose) polymerase 1 (PARP1) plays key roles in transcriptional regulation, chromatin reorganization, nuclear organization and DNA damage repair (Ju and Rosenfeld, 2006; Kraus and Lis, 2003; Krishnakumar and Kraus, 2010). Changes in NAD^+ levels can signal to the nucleus by affecting each of these functions. For example, under basal conditions, PARP-1 binds to nucleosomes and promotes chromatin compaction, which is impaired upon saturating NAD^+ levels, leading to PARP1 auto-PARylation (Kim et al., 2004; Wacker et al., 2007). Notably, the need for NAD^+ by multiple enzymes, including those discussed here and others (Anderson et al., 2017; Audrito et al., 2019; Koch-Nolte et al., 2011; Ma et al., 2012; Ma et al., 2015), sets the stage for crosstalk between them based on competition for NAD^+ availability, as shown by studies with PARP-1 and SIRT1 (Canto et al., 2013; Kim et al., 2005; Luna et al., 2013; Zhang and Kraus, 2010).

2.3.2 ROS—Reactive oxygen species (ROS), including the superoxide anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($OH^{\bullet}$), represent major byproducts of aerobic metabolism (Andreyev et al., 2005; Brieger et al., 2012; Liochev, 2013; Liu et al., 2018), with mitochondria being one of the major production sites in most cells (Brand et al., 2004; Turrens, 2003). Upon their initial discovery, it was immediately noted how excess levels of these superoxide species are damaging and associate with a variety of deleterious conditions including cell death, cancer, and degenerative aging (Balaban et al., 2005; Davalli et al., 2016; Droge, 2002; Evans et al., 2003; Harman, 1981). However, with time, our understanding of the role played by these small molecules in the cell has become more nuanced. Although it is clear that high levels of ROS play a major role in oxidative damage, it is now well appreciated that ROS-dependent redox signaling is physiologically necessary (Droge, 2002; Finkel, 2011; Sarsour et al., 2014; Sena and Chandel, 2012) Some of these include anti-microbial or tumoricidal defense coupled with phagocytic cells (Keisari et al., 1983), modulation of protein kinase cascades in vascular smooth muscle cell growth and migration (Griendling et al., 2000), maintenance of whole body homeostasis and metabolism through neuroendocrine connections (Shadel and Horvath, 2015), regulation of glucose-stimulated insulin secretion in pancreatic beta cells (Pi et al., 2007; Pi et al., 2010), and hormetic regulation of lifespan (Merry and Ristow, 2016; Santos et al., 2018; Schroeder et al., 2013; Scialo et al., 2013). At the molecular level, mitochondrial-derived ROS (mtROS) promote these responses through a variety of signaling pathways, often signaling to the nucleus through stabilization or regulated translocation of DNA-binding transcription factors. Increased ROS level under hypoxic conditions, for example, promote hypoxia-inducible factor 1 (HIF1)-mediated transcriptional regulation through inhibition of prolyl hydroxylases (PHDs) and stabilization of HIF1α (Chandel et al., 2000; Duranteau et al., 1998). Activation of the antioxidant protective response is similarly achieved through stabilization and nuclear translocation of Nrf2 (Kovac et al., 2015; Tonelli et al., 2018). mtROS also impact cell survival/cell death pathways and cytokine production through activation of NF-κB (Hamanaka and Chandel, 2010; Herb et al., 2019; Kuwabara et al., 2008; Morgan and Liu, 2011; Naik and Dixit, 2011). In parallel to specific regulation of

DNA-binding transcription factors, oxidative stress can impact on nuclear gene expression via epigenetic changes induced through modulation of chromatin regulators, such as histone demethylases and deacetylases (Chervona and Costa, 2012; Niu et al., 2015). These examples, selected to highlight how ROS directly and indirectly impact upon nuclear functions and reprogramming of gene expression as signaling mediators, only scratch the surface of the diverse roles played by mtROS in cell signaling and physiology. Comprehensive reviews of mitochondrial-derived ROS outline how these small signaling molecules are crucial components of numerous signaling cascades, the likes of which work towards the maintenance of homeostasis and physiologic balance within the cell (Dan Dunn et al., 2015; Reczek and Chandel, 2015; Ristow and Schmeisser, 2011; Shadel and Horvath, 2015). One particularly intriguing aspect of ROS signaling, as relevant to the focus of this review, is the relationships between mitochondrial dynamics and nuclear functions of mtROS. In pulmonary artery endothelial cells, hypoxia was shown to trigger the increase of nuclear ROS levels and HIF1α-dependent regulation of vascular endothelial growth factor (VEGF) expression through accumulation of mitochondria in close proximity of the nucleus via microtubule-associated movement (Al-Mehdi et al., 2012). This observation suggests that reorganization of the subcellular distribution of mitochondria could play an important role in promoting local signaling to the nucleus, something that warrant additional research for ROS as well as other signaling mediators discussed below.

2.3.3 Calcium—As better discussed elsewhere, calcium (Ca^{2+}) ions serve as signaling molecules in a vast number of cellular processes that are crucial for maintaining cellular homeostasis (Berridge et al., 2003; Bootman, 2012; Clapham, 2007; Islam, 2020). To allow for sensitivity and specificity of signaling, calcium levels and fluxes across cellular and intracellular membranes are tightly controlled by a complex and dynamic system of buffers and pumps, while changes are detected by calcium sensors that activate downstream signaling cascades (Berridge et al., 2003; Clapham, 2007; Park et al., 2019). Mitochondria are integral to this system as they both contribute to Ca^{2+} storage and flux regulation, and respond to changes in cellular Ca^{2+} levels via apoptotic responses and adaptation of mitochondrial metabolism (Contreras et al., 2010; Giorgi et al., 2018). Additionally, it has long been noted that Ca^{2+} is a regulator of TCA cycle dehydrogenase activity (specifically pyruvate dehydrogenase, isocitrate dehydrogenase, and α-ketoglutarate dehydrogenase), thus providing an important link between this small signaling molecule and metabolism (McCormack and Denton, 1980; Traaseth et al., 2004; Wan et al., 1989). In the context of mitochondrial mitochondria-to-nucleus signaling, an important facet of Ca^{2+} signaling is based on the effector protein calcineurin, a Ca^{2+}-dependent serine-threonine phosphatase. Calcium-calcineurin mediated mitochondria-to-nucleus signaling is activated in response to cellular stress-inducing factors, including both genetic and metabolic mitochondrial stressors, that promote alteration in mtDNA copy number, loss of membrane potential and dysfunctional ETC. Signaling results into remodeling of nuclear gene expression either directly through activation of nuclear factor of activated T-cells (NFAT) transcriptional signaling and aspects of the NF-κB and cAMP responsive element binding protein (CREB) pathways, or indirectly via activation of other protein kinases and growth factor-dependent cell survival pathways (Biswas et al., 1999; Guha and Avadhani, 2013; Guha et al., 2007; Hogan, 2017; Park et al., 2019; Srinivasan et al., 2017; Tang et al., 2012). Taken together,

this multifaceted signaling cascade is one that is conserved from yeast to humans, and serves a crucial role in adaptive homeostatic responses as required for organismal health.

2.4 Metabolites

Mitonuclear communication is facilitated not only by the translocation of functional proteins and small molecules, but also by the production and movement of metabolites. Classically, the TCA cycle is known to produce crucial metabolites for cell survival and proliferation, as well as production of bioenergetic intermediates responsible for feeding into the ETC (Chandel, 2015; Martinez-Reyes et al., 2016). Many of these metabolites also participate in mitochondria-to-nucleus signaling, whereby they are co-opted as secondary messengers with their levels providing a direct indication of mitochondrial health and metabolic status (Frezza, 2017). Because they often serve as substrates or regulators of enzymes involved in chromatin remodeling, changes in levels and availability of these metabolites are integrated into epigenetic regulatory strategies that drive transcriptional changes under differing stress conditions and physiologic states (Martinez-Reyes and Chandel, 2020). Two of the more common modifications directly linked to the functionality of mitochondrial metabolites are acetylation and methylation, which are mediated by enzymes responsive to changes in acetyl coenzyme A (acetyl-CoA) and α-ketoglutarate (α-KG)/succinate levels and affect nuclear gene expression through DNA methylation and post-translational modifications of histones that are central to the “histone code” (Allis and Jenuwein, 2016). Metabolite-induced changes to the epigenome or metabolic epigenetics contribute to reprogramming of gene expression under physiological and stress conditions, as well as disease progression (Shaughnessy et al., 2014). Changes in nuclear gene expression in response to accumulation of mtDNA mutations, a condition known as heteroplasmy, for example, are facilitated by abnormal metabolite production promoting specific epigenetic modifications, which in turn contribute to transcriptional regulation via modulation of chromatin dynamics (Fetterman and Ballinger, 2019; Kopinski et al., 2019). Changes in the methylation status of nuclear encoded genes upon defects in mtDNA copy number have been observed in the context of both breast cancer as well as osteosarcoma (Feeley et al., 2015; Smiraglia et al., 2008). These observations underscore the link between metabolite-induced epigenetic changes and transcriptional alterations associated with pathogenic phenotypes and disease progression, thus highlighting the important connection between mitochondrial retrograde signaling, metabolites, and genetics.

2.4.1 Acetyl-CoA—Acetyl-CoA generated by the breakdown of carbohydrates, through glycolysis, and the oxidation of fatty acids provides fuel for TCA cycle flux as well as ATP production in cells under oxygenated conditions. Acetyl-CoA levels are tightly associated with histone acetylation, a reversible process by which acetyl groups are either added or removed to/from histones and other target proteins, via the action of histone acetyltransferases (HATs) and histone deacetylases (HDACs) enzymes (Menzies et al., 2016). Acetyl-CoA is an essential substrate for acetyltransferases and histone acetylation is generally associated with increased chromatin relaxation and gene activation (Kaelin and McKnight, 2013; Mews et al., 2017; Pietrocola et al., 2015; Sivanand et al., 2018). Acetyl-CoA is exported out of the mitochondria in form of citrate, which is then converted back into acetyl-CoA and oxaloacetate, with the former becoming available for HATs utilization in the

nucleus (Wellen et al., 2009). Several examples underscore the importance of acetyl-CoA and its mitochondria-to-nucleus signaling capabilities during instances of stress and nutrient sensing. During the “fed” and/or “growth” state, acetyl-CoA levels are high and found predominantly in the nucleus, where it aids in histone acetylation. In contrast, during the “fasted” and/or “survival” state, acetyl-CoA is directed into the mitochondria and is utilized by the organelle as part of the normal TCA cycle flux to generate ATP (Shi and Tu, 2015). Notably, metabolite-induced changes in the epigenome associate with highly specific transcriptional responses, as driven by the need to reprogram gene expression for adaptation to nutrients availability or environmental conditions (Schvartzman et al., 2018; Shaughnessy et al., 2014). Glucose-induced increase in histone acetylation, for example, is associated with the activation of glucose metabolism genes, whereas an increase in lipid-induced acetyl-CoA is reported to drive the upregulation of lipid metabolic genes (McDonnell et al., 2016; Wellen et al., 2009). In hypoxic cancer cells, acetyl-CoA generated from acetate promote histone acetylation for the upregulation of lipogenic genes (Gao et al., 2016). These tailored responses are likely achieved through integrated actions of nutrient-sensing transcription factors and coregulators driving histone acetylation to specific promoters and other regulatory regions. Local regulation of acetyl-CoA production at the site of utilization could also contribute to the specificity of gene regulation. Translocation of the pyruvate dehydrogenase complex (PDC) from mitochondria to nucleus in situations of mitochondrial stress and growth factor stimulation supports histone acetylation of cell cycle genes through the local production of acetyl-CoA (Sutendra et al., 2014). Local production of acetyl-CoA in the nucleus can also be driven by nuclear ATP-citrate lyase (ACLY), upon DNA damage, and acetyl-CoA synthase 2 (ACCS2), under hypoxic conditions. While a full mechanistic understanding of the relationship between these localized enzymatic activities and the regulation of specific gene programs is still lacking, translocation of the PDC was shown to be crucial for zygotic genome activation in both human and mouse embryos, thus emphasizing the importance of tight coordination in mitochondria-to-nucleus signaling and epigenetic modifications (Nagaraj et al., 2017).

2.4.2 Methyl groups—Methylation represents another well-characterized epigenetic modification that is tightly connected to the utilization of mitochondrial metabolites as enzymatic cofactors. Regulation of histone methylation is achieved through either methyltransferases (adding methyl groups) or demethylases (removing methyl groups), the likes of which more specifically repress or activate transcription by regulating the presence and number of methyl groups attached to specific lysine and/or arginine residues on the tails of histone 3 (H3) and histone 4 (H4) (Teperino et al., 2010). Methylation also occurs on DNA, and regulates chromatin structure and subsequent gene expression through single-nucleotide changes. Methylation mediated by DNA methyltransferases (Dnmt) typically occurs on clustered cytosine-guanine repeats, known as “CpG islands”, and the modification at these sites results in a 5-methylcytosine (5mC) (Moore et al., 2013)(Tajima et al., 2016). Overall, methyltransferases can be divided into three separate classes, all of which use *S*-adenosylmethionine (SAM) for the methyl group transfer process. This establishes a first important link to mitochondrial metabolism, in that although SAM is generated in the cytosol by the methionine-homocysteine cycle, this cycle is fueled by ATP and folate products stemming from mitochondrial metabolism (Ducker and Rabinowitz, 2017).

A more direct link is observed in the context of the reverse process, as removal of methyl groups by demethylation requires mitochondrial-produced cofactors. In the case of DNA methylation, the end result of this epigenetic mechanism is the triggering of base excision repair (BER), which serves to replace the modified cytosine with one devoid of any methyl marks (Moore et al., 2013). Prior to this step, ten-eleven translocation (TET) enzymes oxidize 5mC to 5-hydroxymethylcytosine (5hmC) in a process that requires mitochondrial-produced α-KG, Fe(II), and oxygen (O_2), and can be inhibited by fumarate, succinate, and 2-hydroxyglutarate (2-HG) (Etchegaray and Mostoslavsky, 2016; Pastor et al., 2013; Rasmussen and Helin, 2016; Xu et al., 2011). This dependency on the TCA cycle/mitochondrial substrates establishes a firm connection between DNA methylation and mitonuclear signaling, while also showing similarities in the regulation of TET enzymes and Jumonji domain containing protein (JMJD) histone demethylases, which are discussed below (Matilainen et al., 2017).

Histone demethylases are grouped into two families, each with its own particular reliance upon a specific mitochondrial metabolite. The Lys-specific demethylases (LSDs) are flavin adenine dinucleotide (FAD)-dependent, with FAD being a B12 derived redox cofactor required for the TCA cycle as well as beta-oxidation processes (Matilainen et al., 2017). The second branch of the lysine demethylases are the Jumonji C (JmjC) domain demethylases (JMJDs/KDMs). KDMs are unique in that they use α-KG, an important TCA cycle intermediate, as a cofactor. Conversely, KDMs are inhibited by 2-hydroxyglutarate produced as a result of oncogenic mutations in isocitrate dehydrogenases (IDH1/2) or via non-canonical activity of lactate dehydrogenase (LDH) and malate dehydrogenase (MDH) under hypoxia conditions (Intlekofer et al., 2017; Lu et al., 2012; Turcan et al., 2012). Given this co-factor dependency, the interplay between the TCA cycle/mitochondrial function and the actions of demethylases within the nucleus is abundant across species. In *S. Cerevisiae*, Jumonji demethylase Jhd2-mediated regulation of histone methylation is tightly linked to α-KG/succinate ratio (Soloveychik et al., 2016). In *C. elegans*, the actions of H3K27 demethylases *jmjd-1.2* and *jmjd-3.1* also link mitochondrial stress with the activation of the mitochondrial unfolded protein response (mtUPR), a function conserved by their mammalian orthologs plant homeodomain finger (PHF) 8 and JMJD3 (Merkwirth et al., 2016). In mammals, this is associated with removal of repressive H3K9 methylation by JMJD2A/KDM4 from the promoters of nuclear-encoded mitochondrial genes and stress response genes as needed to support their upregulation upon mitochondria-to-nucleus signaling (Cardamone et al., 2018). The complexity of the roles covered by mammalian demethylases is further increased by the fact that modification of distinct histone residues can lead to opposing effects on gene activation or repression. For example, LSD1 can mediate the removal of both H3K4 and H3K9 methylation with the latter being important for LSD1-mediated regulation of energy expenditure, adaptive thermogenesis and oxidative metabolism in adipose tissue (Duteil et al., 2014; Inagaki, 2018; Nagaoka et al., 2015; Sambeat et al., 2016; Shi and Tu, 2015; Shi et al., 2004; Wang et al., 2020). Conversely, modulation of H3K4 methylation status by LSD1 (KDM1A) was associated with the shift from mitochondrial to glycolytic metabolism in human hepatocellular carcinoma cells (Sakamoto et al., 2015). Overall, the tight and intricate relationship between mitochondria-derived metabolites and histone demethylases provide dynamic and sensitive ways to

integrate signals related to mitochondrial metabolism with the regulation of nuclear gene expression through methylation/demethylation of histones and DNA. Accordingly, α-KG, 2-HG and IDHs play central roles in mitochondrial signaling and their misregulation is linked to a variety of mitochondria-related diseases, including cancer, aging, neuronal dysfunction, autoimmune disease, and metabolic stress disorders (Bayliak et al., 2017; Fujii et al., 2016; Hunt et al., 2019; Raineri and Mellor, 2018; Salminen et al., 2014; Schulze and Harris, 2012; Ward et al., 2012; Weinberg et al., 2019).

3- Nucleus-derived signaling molecules

In the previous section, we discussed how mitochondria contribute to epigenetic control of nuclear gene expression through the production of metabolites used as cofactors by chromatin remodeling enzymes. These processes affect gene expression at the genome-wide level rather than providing a means for the regulation of specific genes. Specificity for the activation/repression of dedicated gene expression programs is provided by the integration of these global changes in metabolites availability with the activity of specific DNA-binding transcription factors. Here, we will introduce the nuclear-encoded transcriptional regulators that contribute to the specificity of adaptive responses through sensing of triggering conditions, mitochondria-to-nucleus signaling and targeting of specific nuclear gene programs, and discuss how their conserved actions are integrated in the overall mitochondria-to-nucleus signaling process.

3.1 Retrograde Signaling in Yeast, Worms, and Flies

Initially described in yeast, the mitochondria-to-nucleus retrograde signaling or RTG pathway regulate the rerouting of carbon and nitrogen metabolism - through remodeling on nuclear gene expression - to counteract mitochondrial dysfunction. Key players in this pathway are the DNA-binding transcription factors RTG1-RTG3, and the regulatory factor RTG2, which drives RTG1-RTG3 translocation to the nucleus in response to changes in ATP availability and mitochondrial membrane potential (MMP) as reviewed in detail elsewhere (Borghouts et al., 2004; Jazwinski, 2005; Jazwinski and Kriete, 2012; Jia et al., 1997; Liu et al., 2003; Sekito et al., 2002; Torelli et al., 2015). Metabolic rerouting of yeast cells in conditions of impaired mitochondrial functions (as modeled by loss of mtDNA in ρ° petite cells) include the activation of nuclear genes to support the metabolism of two-carbon compounds through the glyoxylate cycle, promote the regeneration of NAD^+ to restore oxidative balance in the cell, and ensure that the expression of the first four enzymes of the TCA cycle is preserved as needed to provide metabolic intermediates for anabolic biosynthesis (Chelstowska et al., 1999; Eisenberg-Bord and Schuldiner, 2017; Liao et al., 1991; Liu and Butow, 2006; Liu et al., 2003). Tight regulation of this adaptive pathway is guaranteed by positive and negative regulatory factors, such as Grr1p and Mks1p, and feedback regulatory loops, such as the negative regulation of Rtg1/3 by glutamate and glutamine, which production is upregulated by the retrograde response (Liu and Butow, 2006). Despite these common features, it should be noted that the response to different sources of mitochondrial dysfunction promotes the activation of distinct transcriptional programs as shown by genome-wide transcriptional profiling of yeast cells treated with either the mitochondrial uncoupler CCCP, the ATP synthase inhibitor oligomycin or the

complex III inhibitor antimycin (Epstein et al., 2001). Taken together, these selected examples demonstrate the early work done in yeast elucidating a pathway of retrograde signaling, and the significant role it plays in metabolic reprogramming and stress defense under conditions of mitochondrial dysfunction.

Aside from yeast, the mitochondria-to-nucleus response to mitochondrial stress has been widely studied in worms. Most *C. elegans* studies have focused on the mtUPR, an arm of the mitochondrial stress response (MSR) which aims at resolving the stress induced by accumulation of unfolded proteins in the mitochondrial matrix (Mottis et al., 2019). The MSR can be triggered by any number of stimuli, including misfolded protein accumulation, mtDNA depletion and OXPHOS deficiencies, or toxin-induced mitochondrial dysfunctions (Pellegrino et al., 2013). Transcriptional outcomes of the MSR include increased expression of genes involved in restoring proteostasis (proteases and protein folding chaperones), preventing mtDNA damage (anti-oxidant enzymes) and recovering respiration functions (OXPHOS enzymes and assembly factors) (Jovaisaite and Auwerx, 2015; Jovaisaite et al., 2014; Nargund et al., 2015; Wu et al., 2018). The molecular players that mediate mtUPR signaling between the mitochondria and the nucleus have been addressed by a large body of work as discussed in excellent reviews (Anderson and Haynes, 2020; Haynes et al., 2007; Haynes et al., 2010; Liu et al., 2014; Melber and Haynes, 2018; Qureshi et al., 2017). Best characterized is the role of *C. elegans* Activating Transcription Factor associated with Stress-1 (ATFS-1), a DNA-binding transcription factor which kinetics are regulated through the alternative use of either a nuclear localization signal (NLS) or a mitochondrial targeting sequence, both located at the N-terminus of the protein. Under basal conditions, ATFS-1 is imported into the mitochondria and degraded. Conversely, import into the mitochondria is attenuated in conditions of mitochondrial stress, allowing for translocation into the nucleus and regulation of target genes expression along with other factors, such as transcription factors DVE-1 and LIN-65, ubiquitin-like protein UBL-5 and chromatin remodeling enzymes MET2, JMJD-3.1 and JMJD-1.2 (Merkwirth et al., 2016; Nargund et al., 2012; Shpilka and Haynes, 2018; Tian et al., 2016a).

Also important to mention is the work done in flies, which has provided key insights into the mechanism(s) of retrograde signaling, and its impact on organismal health. Early genetic studies in *Drosophila melanogaster* demonstrated that disruption of complex I of the ETC prevented cell cycle cycle progression through a ROS-induced cascade, mediated by ASK-1, JNK, FOXO, and the fly homolog to p27, Dacapo (Owusu-Ansah et al., 2008), thus revealing a pathway of mitochondria-to-nuclear signaling mediated by mitochondrial ROS production. Signaling mediated by JNK and FoxO in response to sublethal ROS levels is also important for promoting hematopoietic differentiation (Owusu-Ansah and Banerjee, 2009), whereas mild complex 1 stress in a model of muscle mitochondrial injury was shown to induce a two-pronged response, including the upregulation of genes controlling the mtUPR and the induction of the Drosophila ortholog of insulin-like growth factor binding protein 7 (IGFBP7), to preserve mitochondrial function, increase lifespan, and prevent muscle degeneration as a function of aging (Owusu-Ansah et al., 2013). Moreover, the mitochondrial retrograde response has been shown to be a crucial facet of *Drosophila* nervous system functionality, with implications for aging and age-related neurodegenerative disorders (Duncan and Bateman, 2016). Mitochondrial stress promotes reprogramming of

gene expression in Drosophila neurons via activation of the UPR stress response ATF4, the Drosophila ortholog of HIFα, Sima, and Ras-ERK-ETS signaling (Cagin et al., 2015; Duncan et al., 2018; Hunt et al., 2019). Notably, in this context, retrograde signaling seems to contribute to neuronal dysfunction rather than playing a protective effect, as shown by the fact that downregulation of Sima was sufficient to restore neuronal function in different genetic models of mitochondrial dysfunction in absence of any impact on the mitochondrial defect per se (Cagin et al., 2015).

3.2 Mitochondria-to-nucleus Signaling in Mammals

Extensive searches for homologs of yeast and *C. elegans* retrograde genes in rodents and humans indicates that while overall goals and regulatory strategies of the MSR are conserved across species, higher organisms rely on more complex communication strategies involving an array of transcriptional regulators. Mammalian transcription factors associated with functions similar to those of Rtg1/Rtg3 or ATFS-1 include ATFs, FOXO, RXR, ETS, NF-κB and Myc (Arnould et al., 2015; Chae et al., 2013; Duncan et al., 2018; Fiorese et al., 2016; Jazwinski, 2013; Quiros et al., 2017; Zhao et al., 2016). This expansion has likely emerged to ensure that specific regulation of distinct subsets of mitochondrial and cellular genes can be achieved through the selective use of specific transcription factors (TFs), which functions are further integrated with a variety of chromatin remodelers that respond to mitochondrial-derived metabolites as discussed in the previous section. Accordingly, the mammalian mtUPR is comprised of different axes including a canonical mtUPR arm mediated by transcription factors ATF4, ATF5, and CHOP, a SIRT3/FOXO3A axis responsible for the activation of the anti-oxidant response and an ERα/NRF1 arm aimed at increasing protein quality control (Fiorese et al., 2016; Germain, 2016; He et al., 2016; Kenny and Germain, 2017; Munch, 2018; Naresh and Haynes, 2019; Papa and Germain, 2011; 2014). In addition to the increased complexity in the number of TFs involved, the mammalian mtUPR is fully integrated in a broader integrated stress response (ISR), which coordinates the response to mitochondrial stress with the regulation of cytosolic protein translation through phosphorylation of eIF2α and selective translation of mRNAs of stress genes, including mtUPR mediators (Costa-Mattioli and Walter, 2020; Garcia-Roves et al., 2008; Wu et al., 2002). As a result, the mammalian mtUPR is coordinately regulated with other growth and damage response pathways (Khan et al., 2017; Nikkanen et al., 2016). Mechanistically, a recent study indicates that activation of ATF4 downstream of mitochondrial stress is achieved through OMA1-dependent cleavage of DELE1 which in turn activates the eIF2α kinase activity of HRI (Fessler et al., 2020; Guo et al., 2020). Moreover, extensive characterization of the mammalian mitochondrial ISR (mtISR) *in vivo* shows that the ISR is not only cell- and stressor-specific, but it also progresses through distinct temporal stages with different ATF factors being involved in subsequent and interdependent waves of gene expression (Forsstrom et al., 2019; Mick et al., 2020; Suomalainen and Battersby, 2018).

As discussed above, integration of these transcription factor-driven responses with metabolite-induced epigenetic changes provides a multi-layered strategy that allows for pairing the metabolic changes occurring at mitochondria level with the activation of specific adaptive gene programs. While this can be achieved through translational regulation, as in

the case of ATF4/5, or protein stabilization, as described for FOXO (Fasano et al., 2019; Lettieri-Barbato et al., 2019), there are also examples of direct mitonuclear communication mediated by actual mitochondria-to-nucleus translocation of nuclear-encoded factors residing on mitochondria (Monaghan et al., 2015a; Monaghan et al., 2015b). The oxidative stress response factor Nrf2, for example, translocates from mitochondria to the nucleus, where it regulates the expression of anti-oxidant genes, upon disruption of the KEAP1-PGAM5 complex that otherwise keeps it sequestered on the outer mitochondrial membrane (OMM) (O'Mealey et al., 2017). FOXO1 translocation from mitochondria to nucleus in response to starvation, instead, is induced by ROS-mediated activation of the mitochondrial phosphatase PTPMT1 (Lettieri-Barbato et al., 2019). Another example of mitochondria-to-nucleus signaling in response to increased ROS levels is provided by CLK-1 (also called COQ7), a mitochondrial monooxygenase playing a critical role in the biosynthesis of the ETC cofactor ubiquinone (Monaghan et al., 2015a). Because its presence in the nucleus, despite being controversial, has been associated with both upregulation of genes involved in ROS metabolism and dampening of the mtUPR, mitochondria-to-nucleus signaling in this case would provide a negative feedback loop to promote ROS homeostasis (Liu et al., 2017; Monaghan et al., 2015b).

To add another layer of increased complexity, direct mitonuclear signaling in mammalian systems is not limited to DNA-binding transcription factors, but rather extends to transcriptional regulators, such as cofactors and chromatin remodeling enzymes, as shown in the case of G-Protein Pathway Suppressor 2 (GPS2) (Cardamone et al., 2018). GPS2 functions as a mediator of mitochondria-to-nucleus signaling, metabolic reprogramming and chromatin remodeling, reminiscent of the yeast regulatory factor Rtg2. Its translocation from the OMM to the nucleus, as triggered by developmental cues or mitochondrial depolarization, is required for the activation of a large transcriptional program that includes nuclear-encoded mitochondrial genes and stress response genes that partially overlap with the programs downstream of the ATF4 and ATF5 mtUPR pathways (Cardamone et al., 2018; Quiros et al., 2017). Notably, recruitment of GPS2 to target promoters serves the purpose of remodeling the chromatin environment through stabilization of the H3K9me2/3 histone demethylase JMJD2A/KDM4A, thus effectively reinforcing the possibility to remove a repressive epigenetic mark only from specific genomic locations (Cardamone et al., 2018) (Figure 2). As discussed above, chromatin remodeling by specific methyltransferases/demethylases is also a key component of the mtUPR response in worms (Merkwirth et al., 2016; Tian et al., 2016b), thus suggesting that spatial regulation of histone methylation/demethylation, via metabolically-regulated enzymes working in cooperation with sequence-specific transcriptional regulators, plays a central role in metabolic adaptive responses across species.

Similar to the regulation of *C. elegans* ATFS-1 described in the previous section, the balance between mitochondria and nuclear pools of nuclear-encoded retrograde factors can be effectively modulated by attenuation of mitochondrial matrix protein import, a step exquisitely sensitive to mitochondrial stress (Monaghan et al., 2015b). Other forms of regulation through post-translational modifications also contribute as in the case of SENP1-mediated de-sumoylation of GPS2 (Cardamone et al., 2018)(Figure 2). The molecular details of SENP1 activation in conditions of stress are not fully elucidated. However, recent

findings indicate that SENP1 levels on the mitochondria fluctuate depending on the nutrition state, with SENP1 accumulation upon fasting driving fatty acid oxidation and energy expenditure via desumoylation of SIRT3 and deacetylation of mitochondrial proteins (Wang et al., 2019). De-sumoylation by SENP1 is also important for promoting the activity of PGC1α, a transcriptional cofactor central to the regulation of mitochondria biogenesis (Cai et al., 2012). Taken together, these observations suggest that SENP1 may be playing a central role as an effector of mitochondria adaptive responses.

4- Mito-nuclear communication and cellular homeostasis

4.1 Genetic compatibility of bi-genomic system

Compatibility between the mitochondria and nuclear genomes is important for cellular fitness in the bi-genomic system. The Bateson-Dobzhansky-Muller model provides a framework for understanding how genes coevolved to stay compatible (Bateson, 1909; Dobzhansky, 1936; Muller, 1942), and recent studies show that delicate nuclear-mitochondrial compatibilities have an important role in optimizing mitochondrial function. Work by Rand and Dowling has shown that interaction of mitochondrial genome and the nucleus affects traits, reproductive success, rate of development, growth, behavior, and aging in fruit flies (Rand et al., 2006; Rand et al., 2004; Wolff et al., 2016). Mice engineered to host mitochondria from distant genetic backgrounds, providing a model of mitonuclear genomic mismatch, exhibit shifted cellular metabolism, mtROS levels, and resistance to cardiovascular burdens (Betancourt et al., 2014; Dunham-Snary and Ballinger, 2015; Fetterman et al., 2013). Moreover, Latorre-Pellicer *et al* compared mouse embryos of C57 strain nuclear background with different mitochondrial DNA haplotypes and found optimized compatibilities of nuclear and mitochondrial genomes affected mitochondrial function such as OXPHOS and mouse embryonic fibroblasts reprogramming efficiency (Latorre-Pellicer et al., 2019).

4.2 Mitonuclear Communication in Physiology and Disease

Given the complex strategies that have evolved to maintain efficient communication between mitochondria and nucleus across species, it is not surprising that their misregulation is involved in a number of pathologies. The disease state can be promoted by the inability to adapt to cellular and environmental stressors or by excessive/uncontrolled oxidative stress. At the same time, activation of mitochondria-to-nucleus signaling and transcriptional reprogramming of cellular functions in response to modest mitochondrial dysfunction can have beneficial effects on the metabolic health and longevity of an organism, through a process defined as “mitohormesis” (Barcena et al., 2018; Yi et al., 2018; Yun and Finkel, 2014). While we refer to other excellent reviews for a detailed summary of this expanding field (Mottis et al., 2014; Tan and Finkel, 2020), here we briefly touch upon the role of mitochondria-to-nucleus signaling within different disease contexts to highlight the importance of finely tuned mitonuclear communication to maintain cellular and organismal homeostasis.

4.2.1 Aging—Across species the aging process is associated with a decline in mitochondrial function and increase in oxidative stress, and mitochondrial dysfunction is

widely regarded as a hallmark of aging (Bratic and Larsson, 2013; Jang et al., 2018; Lopez-Otin et al., 2013; Sun et al., 2016). It was thus surprising to observe that the downregulation of key mitochondrial genes in *C elegans* would promote extended lifespan, albeit associated with decreased respiration and developmental defects (Dillin et al., 2002; Felkai et al., 1999; Feng et al., 2001; Lee et al., 2003). Extensive studies in both worms and flies indicate that the increase in longevity is associated not only with decreased ROS production lowering the oxidative stress burden placed on the organism (Feng et al., 2001), but also with activation of the mtUPR, as triggered by mitochondrial dysfunction or mito-nuclear imbalance (Durieux et al., 2011; Houtkooper et al., 2012; Owusu-Ansah et al., 2013). Knockdown of components of complex IV across *C elegans* developmental stages, in particular, revealed that this is a temporally regulated phenotype whereby tissue-specific activation of the mtUPR during the larval stage triggers beneficial effects on lifespan in adulthood (Dillin et al., 2002; Durieux et al., 2011). The early triggering of a response to mild stress essentially primes the system, through retrograde-dependent reprogramming of gene expression, for improved handling of metabolic insults and oxidative stress throughout the duration of the extended lifespan (Schulz and Haynes, 2015). This is a finely tuned response not only in term of time, but also space. Adaptation is not limited to organ initially insulted, as activation of the mtUPR in one tissue is communicated to other parts of the organism through “mitokine” signaling (Zhang et al., 2018). In mammals, this role is at least partly played by the cytokine FGF21 which was shown to contribute to inter-organ communication in human patients with mitochondrial myopathies as well as mice models of mitochondrial dysfunction (Kim et al., 2013; Suomalainen et al., 2011). However, it is worth noting that mtUPR activation per se has not been observed in tissues other than those primarily affected by mtDNA deletions, despite the essential role played by FGF21 in mediating whole-body metabolic adaptation to muscle mitochondrial defects (Forsstrom et al., 2019). Mitochondrial-derived peptides (MDPs) may also have a role in aging. The levels of MDPs in certain tissues and blood have been shown to be age-dependent (Cobb et al., 2016; Kim and Koh, 2017; Lee et al., 2015; Muzumdar et al., 2009). Humanin is connected to the growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis, a prominent endocrine longevity regulator. Blood humanin levels are higher in GH-deficient Ames mice, whereas the short-lived GH-transgenic mice had lower humanin levels compared to their wild-type counterparts (Lee et al., 2014). MOTS-c treatment significantly reversed age-dependent physical decline in old mice (22 mo.), allowing them to run twice as long on a treadmill and outcompete their middle-aged counterparts (Reynolds et al., 2019). Late-life initiated (23.5 mo.) intermittent MOTS-c treatment (3x/week) improved health- and life-span in mice (Reynolds et al., 2019). These studies suggest that aging is regulated by factors from both mitochondrial and nuclear genomes.

4.2.2 Obesity & Type 2 Diabetes—Given the high level of importance placed upon mitochondria in the maintenance of energy homeostasis and the balance between nutrient storage and utilization, both mitochondria-to-nucleus and nucleus-to-mitochondria signaling are widely implicated in metabolic diseases, such as obesity and type 2 diabetes. Moreover, the above discussion about the mitohormetic response to mild stress promoting cellular and organismal reprogramming towards extended lifespan directly ties into this discussion as improved metabolic performance represents a key aspect of increased longevity. Because of

limited space we cannot discuss in details the numerous and complex interactions that link mitochondrial dysfunctions across different tissues to the development and progression of metabolic disorders, and refer to other reviews for a detailed discussion on these topics (Lin et al., 2005; Patti and Corvera, 2010; Sivitz and Yorek, 2010; Theurey and Rieusset, 2017; Wanet et al., 2015; Xu et al., 2019; Yi et al., 2018; Zorzano et al., 2009).

Here, we only mention a few examples relevant to our understanding of the role played by mitonuclear communication, or lack of thereof, in the development of obesity and associated metabolic diseases. Retrograde signaling by MOTS-c, one of the mitochondria-encoded peptides discussed above, regulates insulin sensitivity and metabolic homeostasis in skeletal muscle. An additional finding from this study shows that systemic treatment of high-fat diet (HFD)-fed mice with MOTS-c prevents age-dependent and diet-induced insulin resistance and obesity (Lee et al., 2015). Also in mice, adipose-specific deletion of the mammalian retrograde factor GPS2 leads to whitening of the brown adipose tissue (BAT), as associated with a significant reduction in mitochondrial content, and development of obesity (Cardamone et al., 2018; Cederquist et al., 2017). Notably, in chow-fed mice GPS2-AKO mice, obesity is uncoupled from inflammation and metabolic dysfunction, highly resembling a human condition known as “metabolically healthy” obesity (Bluher, 2010; Loos and Kilpelainen, 2018). However, work from us and others indicates that the protective effect is lost in condition of diet-induced obesity and that cold-induced browning of the tissue is impaired in absence of GPS2 (Cardamone et al., 2018; Drareni et al., 2018; Fan et al., 2016), suggesting that GPS2-mediated mitochondria-to-nucleus signaling may be critical for adapting to the stress imposed by cold or nutrients overload. Independent studies also show that the mammalian mtISR is induced in the BAT upon cold stimulation to promote ATF4-dependent expression of FGF21 and GD15 (Flicker et al., 2019).

Another area of significant interest in the context of metabolic disorders is mitochondrial lipid signaling. Excessive accumulation of long and medium chain acylcarnitines, as resulting from incomplete beta oxidation in presence of excess nutrients intake, for example is recognized as a driving factor in the development of insulin resistance (Koves et al., 2008; Muoio et al., 2012; Sarparanta et al., 2017; Yazici and Sezer, 2017). Carnitine lipid species have been proposed to impact upon insulin responsiveness, through retrograde signaling, in a similar manner to that increased cytosolic Ca^{2+} or increased ROS production alter nuclear-encoded mitochondrial gene expression under conditions of stress (Devarshi et al., 2017). Moreover, as discussed above, changes to the epigenome driven by metabolite-induced regulation of epigenetic modifiers (HDACs and methyltransferases) are emerging as important underlying events to the development of a variety of diseases, including metabolic disorders (Emamgholipour et al., 2020). According to this model, incomplete fatty acid oxidation could promote insulin resistance by modulating nuclear gene expression through regulation of acetyl-CoA availability and associated changes to the epigenome (Shi and Tu, 2015). Lastly, mitochondrial dysfunctions have been shown to affect not only nutrient handling but also obesity-associated inflammation via cytosolic release of mtDNA triggering mitochondria-to-nucleus signaling through TLR9 and/or cGAS/STING pathways (Bai et al., 2017; Kanneganti et al., 2015; Liu et al., 2016 Mao et al., 2017; Yuan et al., 2017; Zhong et al., 2019).

4.2.3 Cancer—Nutrient sensing is an essential cellular and overall life process heavily governed by mitochondrial signaling networks and epigenetic modifications, the likes of which need to be tightly regulated. In the context of cancer, metabolic flexibility provides transformed cells with a critical advantage for surviving in a nutrient-limited tumor microenvironment. Therefore, there are many instances in which cancer cells can co-opt metabolic and mitochondrial signaling pathways for their own benefit. Many of the metabolites highlighted in this review have been both conceptually and mechanistically shown to be involved in cancer development and progression, through participation in epigenetic modifications. Many of these modifications result in the upregulation of cell proliferation and survival, differential utilization of nutrient substrates based upon availability, and overall oncogenic reprogramming which altogether work for the benefit of the cancer cells. Specific examples of mitochondrial metabolites, their connection to chromatin modifications, and the resulting impact on malignancies through mitonuclear communication were recently reviewed by others (Campbell and Wellen, 2018; Deng and Haynes, 2017; Hirschey et al., 2015).

4.2.4 Neurological Disorders—Mitochondrial dysfunction is well regarded as a hallmark of many neurodegenerative and brain developmental disorders, but the actual characterization of retrograde signaling pathways in these disease contexts has just started to be explored within the last few years. Both inhibition of OXPHOS components, as well as mitochondrial dynamics in neurodegeneration are interconnected to retrograde mechanisms, with several different disease models in both Drosophila and rodent highlighting these signaling networks (Cagin et al., 2015; Celardo et al., 2016; Duncan et al., 2018; Kim et al., 2016; Krug et al., 2014; Meurers et al., 2009; Requejo-Aguilar et al., 2014; Ryu et al., 2002; Wu et al., 2014; Yap et al., 2013). Studies like these place a particular emphasis on the importance of understanding the connectivity of these networks at a basal level, and translating this into further research in neuro-mitochondrial disease treatment. Recent reviews have detailed mitochondrial retrograde signaling in neurological disease, as well as considerations for targeted therapies, and should be referred to for more insight and specifics (Granat et al., 2020; Hunt and Bateman, 2018).

5. Discussion and Future Directions

These are exciting times for mitochondrial research. Mitochondria are recognized as key signaling organelles playing a prominent role in the regulation of cellular homeostasis. This requires that their interaction with a variety of other cellular structures and organelles, including - but not limited to - the nucleus, is addressed as a whole and investigated through innovative approaches. In this review, we have discussed the emerging themes in the area of mitonuclear communication by specifically focusing on mitochondria-to-nucleus signaling. However, the pathways and signaling events described here are to be considered within a more holistic view of mitochondria contribution to whole cell signaling as recently done by others (Boos et al., 2020; Mottis et al., 2019).

One topic specific to mitochondria-nuclear communication is the interplay between metabolism and epigenetics, currently a very active area of investigation. As discussed above, a growing literature addresses how changes in cell metabolism are paired to

epigenetic regulation of nuclear gene expression through the availability of metabolites serving as cofactors for chromatin remodeling enzymes. Intriguingly, conserved strategies for metabolic regulation of chromatin remodeling through the use of matching sets of metabolites/chromatin modifiers are revealed, with α-KG and histone demethylases emerging as a key regulatory dyad in mitochondria-to-nucleus signaling. However, it is still incompletely understood how metabolic metabolite-driven changes to the epigenome impinge upon the regulation of specific gene programs, rather than transcription at large. While we have highlighted a few examples where integration of mitochondria- and nuclear-encoded signals allows for the regulation of specific target genes, we expect that more will follow in coming years. It is also likely, that current studies have only scratched the surface of how changes in cellular metabolic pathways impact upon nuclear regulation through known and possibly uncharacterized metabolites. More examples may emerge as untargeted metabolomic approaches and use of isotope tracing become more widely employed.

Other open questions, more specifically related to the mechanistic aspect of mitochondria-to-nucleus signaling, include: first, how is the stress sensed and transmitted to the nucleus? Mitochondria-to-nucleus signaling is triggered by mitochondrial signals that are relayed to retrograde factors translocating to the nucleus to modulate gene expression. While the mechanistic details of the RTG pathway have been well elucidated in yeast, triggers and sensors of the mammalian mtISR are not fully defined. Also, is mitochondria-to-nucleus signaling mediated by translocation of isolated factors across the cytosol - and if so is the movement regulated? Or is mitochondria mobility and perinuclear clustering required for facilitating the translocation, possibly via the establishment of nucleus-mitochondria contact sites similar to those described for mitochondria tethering to the ER? As we answer these questions and others, new opportunities may become available for harnessing the beneficial effects of mitohormetic responses and developing novel therapeutics towards diseases with impaired mitochondrial functions.

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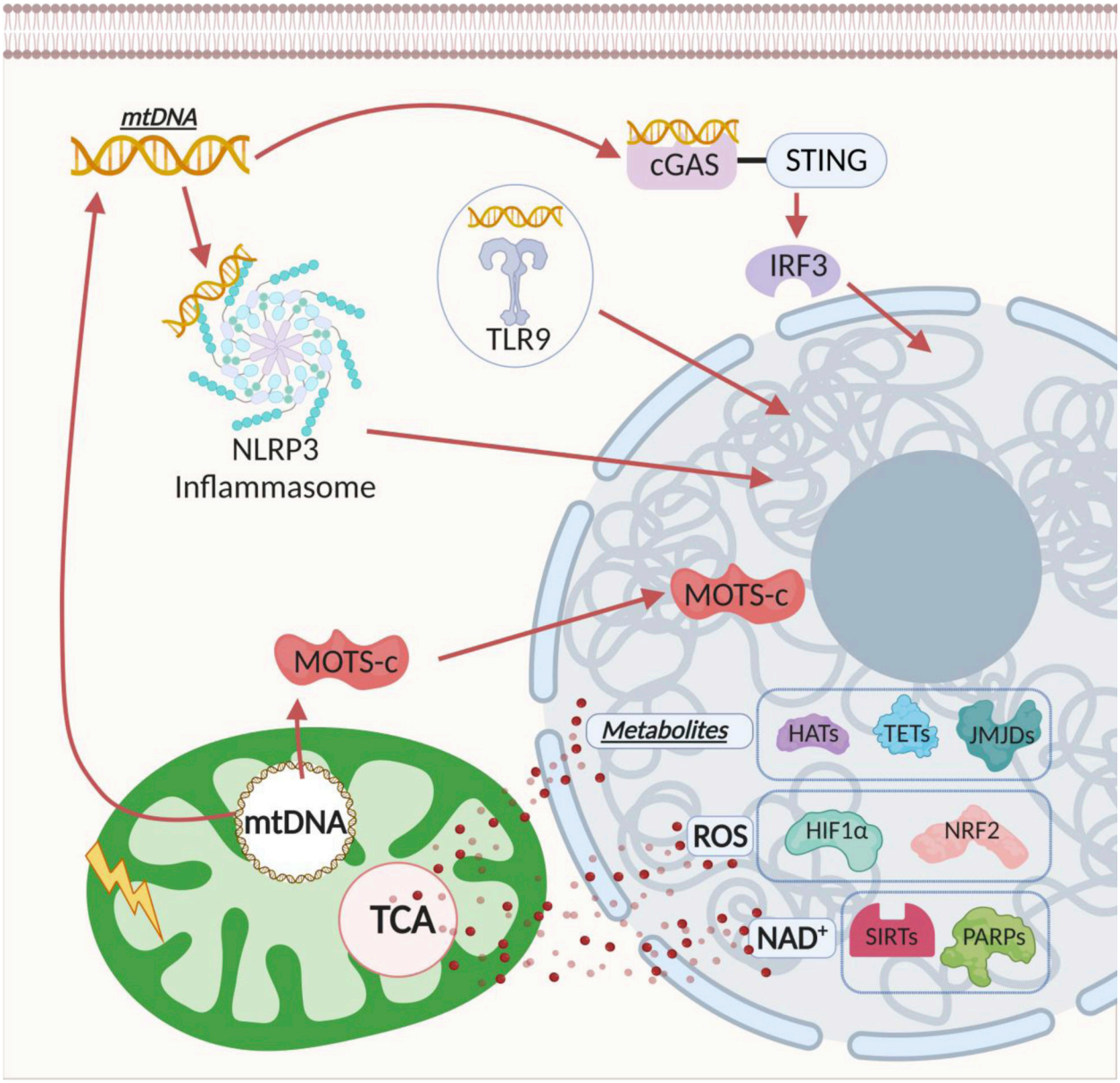

Figure 1.

Mitochondrial-derived signaling molecules promoting mitonuclear communication. Mitochondria-derived signaling molecules promote signaling to the nucleus through both direct and indirect actions. They can be classified in three broad categories as discussed in the text: *1)Peptides, 2)mtDNA*, and *3)Small molecules & Metabolites* such as ROS, NAD^+, Ca^+, Acetyl-CoA, α-KG, 2-HG, succinate, fumarate.

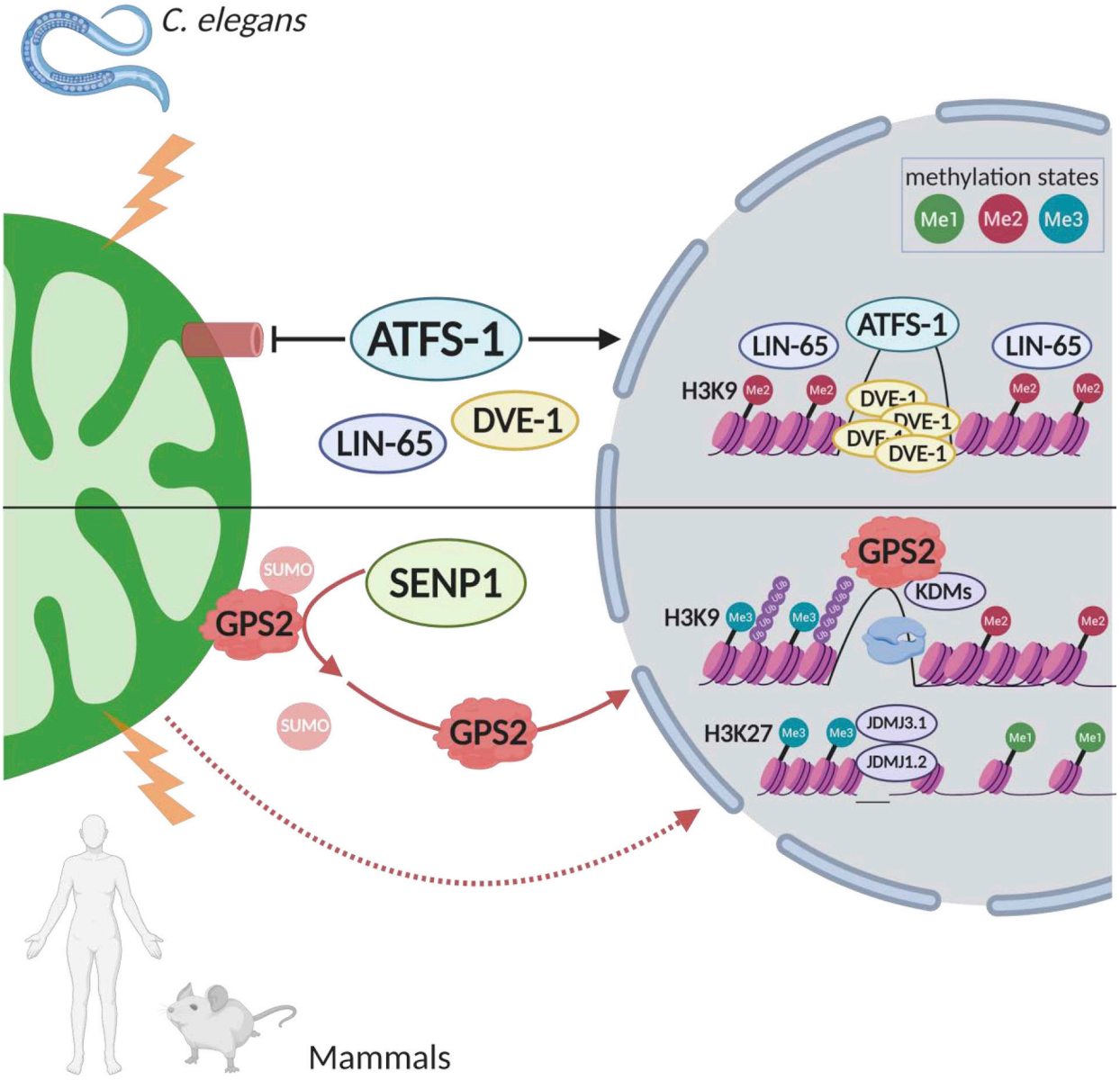

Figure 2.

Mitochondria stress response (MSR) and remodeling on nuclear chromatin via histone methylation and demethylation. Chromatin remodeling through methylation/demethylation of histone tails supports the reprogramming of nuclear gene expression in response to mitochondria dysfunctions across species. In the top panel, it is outlined the mtUPR arm of the MSR in *C. elegans*. Nuclear translocation of transcription factors ATFS-1 and DVE-1 promotes the expression of stress response genes that are excluded from chromatin condensation mediated by H3K9 methyltransferase MET-2 and nuclear cofactor LIN-65. Accessibility of stress responsive promoters is guaranteed by the action of histone H3K9 and H3K27 demethylases, respectively KDM4A or jMJD1.2/PHF8 and JMJD3.1/JMJD3 as shown in mammals in the bottom panel. Mitochondria-to-nucleus translocation of GPS2, upon mitochondrial stress-induced de-sumoylation by SENP1, promotes demethylation of

target promoters by stabilizing KDM4A through inhibition of Ubc13-dependent ubiquitination.