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OPINION

SPECIAL ISSUE
CELL BIOLOGY OF MITOCHONDRIA

Mitochondria – the CEO of the cell

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ABSTRACT

As we have learned more about mitochondria over the past decades, including about their essential cellular roles and how altered mitochondrial biology results in disease, it has become apparent that they are not just powerplants pumping out ATP at the whim of the cell. Rather, mitochondria are dynamic information and energy processors that play crucial roles in directing dozens of cellular processes and behaviors. They provide instructions to enact programs that regulate various cellular operations, such as complex metabolic networks, signaling and innate immunity, and even control cell fate, dictating when cells should divide, differentiate or die. To help current and future generations of cell biologists incorporate the dynamic, multifaceted nature of mitochondria and assimilate modern discoveries into their scientific framework, mitochondria need a 21st century 'rebranding'. In this Opinion article, we argue that mitochondria should be considered as the 'Chief Executive Organelle' – the CEO – of the cell.

KEY WORDS: Mitochondria, Organelle, mtDNA

Introduction

All known eukaryotic organisms contain mitochondria or evidence of having housed mitochondria (Roger et al., 2017). Mitochondria are often simplified as 'the powerhouse of the cell'. However, these crucial organelles, descended from once free-living bacteria via endosymbiosis, are integrated into many cellular functions beyond ATP synthesis. Perhaps the strongest evidence of their bacterial ancestry is that most mitochondria retain a highly reduced bacteria-like genome (mtDNA). The human mtDNA encodes 37 genes and is only ∼16.6 kbp (Anderson et al., 1981). However, eukaryotic mitochondrial genomes vary widely in content and size. The most gene-rich mitochondrial genome currently known, that of *Andalucia godoyi*, encodes 100 identified mitochondrial genes and is noted for its strong resemblance to bacterial genomes and the use of a bacterial-like RNA polymerase (Burger et al., 2013). The largest mitochondrial genomes, which can exceed 11 Mbp (most of which is non-coding), are found in plants (Putintseva et al., 2020). In comparison, the smallest natural free-living bacterial genomes are ∼580 kbp and encode ∼500 genes (Fraser et al., 1995). The exact timing of the acquisition of mitochondria in the context of eukaryotic evolution is controversial and is even proposed to have been a key event in the origin of the eukaryotic cell (Gabaldón, 2021; Gray, 2015; Vosseberg et al., 2024). Regardless, it is clear that endosymbiosis was a major driving force in the evolution of all existing eukaryotes.

In contrast to the mtDNA, the human nuclear genome is over 3 billion base pairs (Gbp) in length. The nucleus holds the vast majority of the estimated 20,000 protein-coding genes and numerous non-coding genes (Little, 2005; Salzberg, 2018), and is thus commonly construed as the 'control center' of the cell. The nuclear genome is believed to be descended from an archaeal host, but it has gained a considerable amount of content through duplications (Vosseberg et al., 2021) and acquisition of genes from other sources, including viruses (Quammen, 2018) and the mitochondrial endosymbiont (Timmis et al., 2004). The nuclear genes encode instructions for synthesizing important effectors of cellular processes – proteins and non-coding RNAs. Networks of transcription factors and transcriptional co-activators and co-repressors, many of which are cell type or context specific, can bind and interact with regulatory DNA sequences to induce or impair transcription of certain genes (Lee and Young, 2013). However, focusing solely on what occurs within the nucleus overlooks the numerous other regulatory processes that occur across the cell to direct behavior and that feed into nuclear transcriptional regulation. Moreover, a higher gene content does not necessarily equate to greater control of the cell; rather, it could perhaps imply the opposite, a concept that we explore further using the keychain analogy, discussed in Box 1.

Here, we highlight several ways in which mitochondria play executive roles in the cell, analogous to the CEO of a company (Fig. 1). As we discuss below, even processes that are considered in the wheelhouse of the nucleus, such as transcription factor activity and epigenetic regulation, can be regulated by signals produced by and transmitted from mitochondria. This Opinion article is not intended to be a comprehensive review of mitochondrial biology – the roles of mitochondria in these various cellular activities have been thoroughly reviewed elsewhere (Chakrabarty and Chandel, 2021; Glover et al., 2024; Marchi et al., 2023; Picard and Shirihai, 2022; Suomalainen and Nunnari, 2024) – but rather a holistic introduction to better appreciating the roles mitochondria play in directing the cell, and an argument for a rebranding of mitochondria from the 'powerhouse' to the 'CEO'. We add to this discussion by highlighting some recent interesting findings that further support the view of mitochondria as being the CEO of the cell.

Mitochondria – in control of day-to-day operations

Just as companies navigate turbulent economies, cells face changing environments. Mitochondria are capable of integrating a wealth of

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Box 1. The keychain analogy

We propose reconsidering the association between which organelle has the most genes and which has control. As an analogy, imagine that the cell is a company or organization in which the nucleus and mitochondria are employed, and imagine that their genes are keys. In this context, we argue that the more 'executive' a role an employee plays in the company, the fewer keys they require.

Most people have several keys that they use in their everyday life – a house key, car key, office key, and so forth. Each daily activity requires a key. Similarly, each cellular function requires a set of genes. However, a CEO likely has an administrative assistant, and (if we're being imaginative) a chauffeur and a butler, abolishing their need for an office key, car key and house key. In other words, the CEO contracts out hands-on tasks to focus resources and attention on their main responsibility – running the organization. In contrast, the keychains of a custodian or a security guard are replete with keys. Their roles are crucial to the workings of the company; however, the leader of the company is still the CEO, who, in their executive role, holds fewer keys – or genes, in the case of the cell. Using the keychain analogy, one could argue that the nucleus provides the infrastructure and maintenance of the cell, whereas the mitochondria are in charge of decision making.

Notably, although the mitochondria hold onto fewer distinct 'keys', they are far from insignificant. The mtDNA can still certainly play a role in directing cellular behaviors. Throughout this article, we cover some examples of this control, including how mtDNA itself acts as a signaling molecule (West et al., 2015), how certain RNA and peptide products of mtDNA modulate nuclear activity (Blumental-Perry et al., 2020; Kim et al., 2018; Sriram et al., 2024), and how mtDNA mutations or deletions can impact mitochondrial outputs, thus influencing epigenetics and intercellular signalling (Forsström et al., 2019; Kopinski et al., 2019).

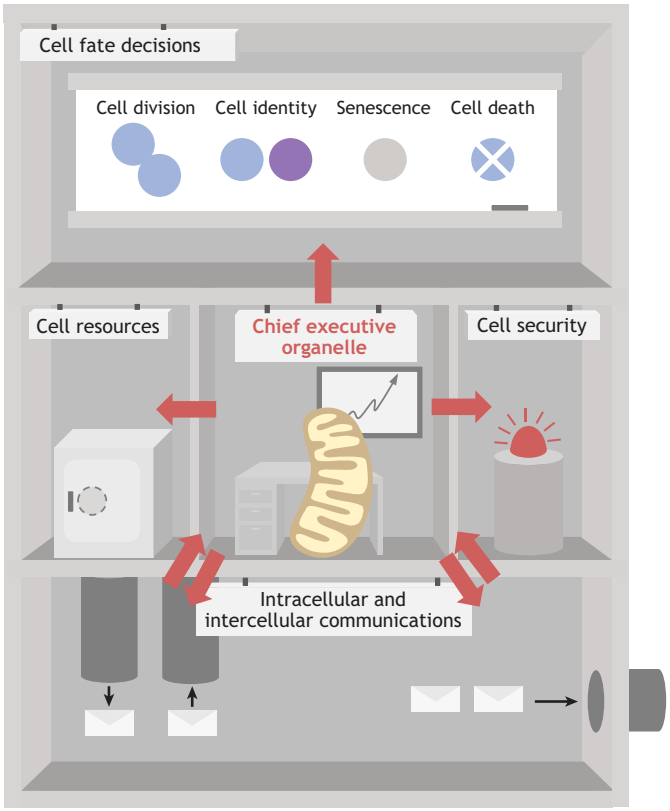

Fig. 1. Mitochondria can be understood as the 'Chief Executive Organelle' of the cell. Mitochondria play key roles in determining cell fate, including regulation of cell division, stem cell differentiation, senescence and cell death, akin to decisions a CEO makes about the growth, diversification or closure of a company. Mitochondria also control key cell resources, including ATP and a variety of other metabolites. Furthermore, mitochondria act as signaling hubs, mediating both intracellular and intercellular signaling, much like communication lines within and between organizations, and regulate innate immune pathways that act as the security system of the cell. Given the many instructive roles mitochondria carry out, we argue that they should be considered the CEO of the cell. This figure was partly generated using Servier Medical Art, provided by Servier, licensed under a CC-BY 3.0 Unported license.

sensory inputs to make decisions (Box 2). Using this information, mitochondria oversee and adapt many aspects of the day-to-day operations needed to maintain the cell. These include regulation of resources through catabolic processes to generate energy and biosynthesis of cellular components, both intracellular and intercellular signaling pathways, and innate immunity (Fig. 2).

Overseeing resources – regulation of metabolism

Much like a CEO needs to approve the budget of an organization, if one equates ATP and other energy intermediates [e.g. GTP and NAD(P)H] to the currency of the cell, the coffers of the cell are primarily under the control of the mitochondrion. Additionally, mitochondria trade in a number of other 'commodities' via their involvement in the synthesis of numerous cellular building blocks and in transforming energy and cellular intermediates from one form into another ('currency exchange') (Spinelli and Haigis, 2018).

Sourcing 'funding' for cellular activities largely falls to the tricarboxylic acid (TCA) cycle and the electron transport chain (ETC), both of which take place within mitochondria. The TCA cycle is a common entry point for cellular fuels (Arnold and Finley, 2023). Breakdown of glucose, fatty acids or amino acids into acetyl-CoA allows entry into the TCA cycle, which produces NADH and $FADH_2$. These molecules donate their electrons to drive the ETC. The TCA cycle also contributes to biosynthetic pathways for fundamental lipid, protein and nucleic acids components that make up the cell. For example, citrate can be exported to the cytosol and converted into acetyl-CoA for synthesis of fatty acids or cholesterol, or as a source for acetylation reactions (Spinelli and Haigis, 2018). Other TCA cycle intermediates, such as oxaloacetate and α-ketoglutarate, can feed into amino acid (Li and Hoppe, 2023) and nucleotide (Lane and Fan, 2015) synthesis pathways. Altogether, these pathways position the TCA cycle as the 'currency exchanger' at the intersection of catabolic and anabolic processes.

Additionally, mitochondria house folate metabolism processes, which support one-carbon metabolism across the mitochondria, cytosol and nucleus, and are used to generate one-carbon units for nucleotide synthesis and methylation reactions (Xiu and Field, 2020). Key steps in the synthesis of the essential co-factors heme (Yien and Perfetto, 2022) and iron-sulfur clusters (Braymer and Lill, 2017) also occur within the mitochondria. By sitting at the confluence of these metabolic pathways, mitochondria hold a unique degree of regulatory control and adapt to the changing circumstances of the cell environment by adjusting to changes in nutrient availability, ensuring metabolite homeostasis and preventing excess buildup of toxic products (Liu and Birsoy, 2023).

Managing communication and collaborations – intracellular and intercellular signaling

A CEO communicates important decisions to the company; similarly, mitochondria are crucial regulators of intracellular signaling (Picard and Shirihai, 2022). A number of mitochondrial products are not only energy and biosynthetic intermediates but also

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Box 2. Mitochondria as sensing organelles

Effective leadership must take into account both company status and the condition of the broader environment. Likewise, mitochondria are capable of recognizing numerous inputs from the cell and extracellular environment. A wide range of mitochondrial sensing pathways have been reviewed elsewhere (Delgado and Pernas, 2024; Eckl et al., 2021; Kaye et al., 2024; Liu and Birsoy, 2023; Picard and Shirihai, 2022; Wu et al., 2021); here, we will highlight a few key sensory inputs.

Many metabolic pathways within the cell pass through the mitochondria (described under 'Overseeing resources – regulation of metabolism'). Given this integration, mitochondria act as sensors of metabolites (Abdullah et al., 2022; Liu and Birsoy, 2023), the levels of which can reflect both cellular status and the extracellular environment. Additionally, a surprising number of receptors localize in part to the mitochondria and have been implicated in regulating mitochondrial transcription or mediating non-genomic effects (Pan et al., 2025; Psarra and Sekeris, 2008). These include receptors for glucocorticoids (Du et al., 2009), estrogen (Pedram et al., 2006), thyroid hormone (Sandra Chocron et al., 2012), angiotensin II (Abadir et al., 2011) and serotonin (Wang et al., 2016), among others (Picard and Shirihai, 2022).

More recently, mitochondria are becoming appreciated for their role in sensing mechanical forces (Phuyal et al., 2023). The shape of the mitochondrial network has been observed to change in response to external forces (Helle et al., 2017) and tension levels in the actomyosin cytoskeleton (Ke et al., 2023; Romani et al., 2022, 2024). Exciting recent work has demonstrated that mitochondria are crucial in transmitting mechanical signals to the cell to activate a broader cellular response (Romani et al., 2024), confirming mitochondria as key 'mechanosensors' (Oliver-De La Cruz and Roca-Cusachs, 2025). Finally, mitochondria are also closely attuned to their own functional status, discussed under 'With great power comes great responsibility – mitochondrial quality control'.

Taken together, mitochondria are central 'information processors' (Picard and Shirihai, 2022), able to integrate numerous inputs. In this article, we discuss how mitochondria use this information to regulate key processes, including coordination of cellular activities and decisions around cell fate.

function as signaling molecules. A considerable body of work has established roles for ATP, ADP and AMP, NADH/NAD^+, reactive oxygen species (ROS), TCA cycle intermediates and mitochondrial Ca^{2+} in signaling (Brillo et al., 2021; Herzig and Shaw, 2018; Martínez-Reyes and Chandel, 2020; Mottis et al., 2019; Shen et al., 2022; Tan and Finkel, 2020). Mitochondria can also communicate through relocation of mitochondrial peptides and proteins, and even through release of mtDNA – the latter of which is of particular relevance to immune signaling and will be further discussed in a later section.

Many of these modalities enable mitochondria-to-nucleus signaling, which is also known as 'retrograde' signaling (versus 'anterograde' nucleus-to-mitochondria signaling) (English et al., 2020). Notably, this concept presupposes the primacy of the nucleus, implying that the canonical or 'forward' signaling axis is from nucleus to mitochondria, an assumption that we question given the significance of mitochondrial input. Signals such as mitochondrial Ca^{2+} and ROS can alter the activity of nuclear transcription factors. Mitochondrial Ca^{2+} release can activate the phosphatase calcineurin and Ca^{2+}-sensitive kinases, including protein kinase C (PKC), calcium/calmodulin-dependent protein kinase type IV (CamK4), c-Jun N-terminal kinases (JNKs) and mitogen-activated protein kinases (MAPKs), which influence transcriptional activities of the cell (Butow and Avadhani, 2004). Mitochondrial ROS activates transcription factor NF-E2-related factor 2 (NRF2) to promote an antioxidant response (Kasai et al., 2020). In other cases, proteins or peptides (Cardamone et al., 2018; Kim et al., 2018; Monaghan et al., 2015) can relocate from the mitochondria to the nucleus under certain conditions to directly regulate nuclear transcription. Recent reports have also implicated mitochondrial RNA species (Blumental-Perry et al., 2020; Sriram et al., 2024) and a mitochondrial transfer RNA (Rouya et al., 2023 preprint) in retrograde signaling. Mitochondria can also direct nuclear gene expression by influencing epigenetics (English et al., 2020; Schvartzman et al., 2018). Certain DNA- and histone-modifying enzymes depend on mitochondrial metabolism for activity. Histone acetyltransferases use acetyl-CoA for acetylation, a major source of which is citrate produced by the TCA cycle. Jumonji C domain-containing (JMJD) histone demethylases and ten-eleven translocation (TET) enzymes involved in DNA demethylation use α-ketoglutarate as a co-substrate. Furthermore, JMJD and TET enzymes can be inhibited by other TCA cycle intermediates, such as succinate and fumarate, as well as 2-hydroxyglutarate, a metabolite of α-ketoglutarate. Mitochondria can thus communicate states such as low nutrient availability (Wellen et al., 2009) or mtDNA defects (Kopinski et al., 2019; Lozoya et al., 2019) to the nucleus via reduced TCA cycle activity, thus decreasing acetyl-CoA availability and histone acetylation. As we will explore further in later sections, this communication channel also facilitates mitochondrial regulation of cell fate.

Unlike the nucleus, which is restricted to one area of the cell, the mitochondrial network extends to every corner of the cell – including down the long axonal and dendritic processes of neurons (Pekkurnaz and Wang, 2022). Much like the CEO must have a finger on the pulse of everything that is happening in the company, mitochondria are in direct contact with the entire cellular organization, including via organelle contact sites (Scorrano et al., 2019), such as with the endoplasmic reticulum (ER), lysosomes, lipid droplets and peroxisomes (Harper et al., 2020; Zung and Schuldiner, 2020). These interactions help coordinate metabolic activities across the cell and allow bi-directional communication between organelles. Organelle contacts also mediate retrograde signaling – mitochondrial–ER contact sites are crucial for Ca^{2+} signaling (Loncke et al., 2021) and can help amplify mitochondrial ROS signaling (Booth et al., 2021). Recent work has uncovered direct mitochondrial–nuclear contact sites that allow for exchange of lipids and proteins to influence nuclear transcription (Desai et al., 2020; Zervopoulos et al., 2022). These examples, among many others, demonstrate the numerous ways that mitochondrial signaling coordinates cellular activities.

To sustain the health of a multicellular organism, cells must collaborate. Beyond managing signaling within the cell, mitochondria can also manage communications with other cells, the same way a CEO might collaborate or interact with other companies. Mitochondria control key metabolic steps in the production of cell non-autonomous or paracrine signaling factors, such as steroid hormones (Miller, 2013) and melatonin (Suofu et al., 2017), allowing mitochondria to influence local tissue or even the entire organism. Another way in which mitochondria can exert distant influence is through 'mitokines' or 'metabokines'. First described in the model organism *Caenorhabditis elegans* (Durieux et al., 2011), mitokines are signaling molecules that communicate mitochondrial stress occurring in one subset of cells to distant tissues, where they enact adaptive processes. In mammalian cells, these include fibroblast growth factor 21 (FGF21) (Forsström et al., 2019; Kim et al., 2013) and growth/differentiation factor 15 (GDF15) (Chung et al., 2017). Mitochondrial metabolic dysfunction in muscle, liver or adipose tissue triggers synthesis and release of FGF21 and GDF15 into the systemic circulation to

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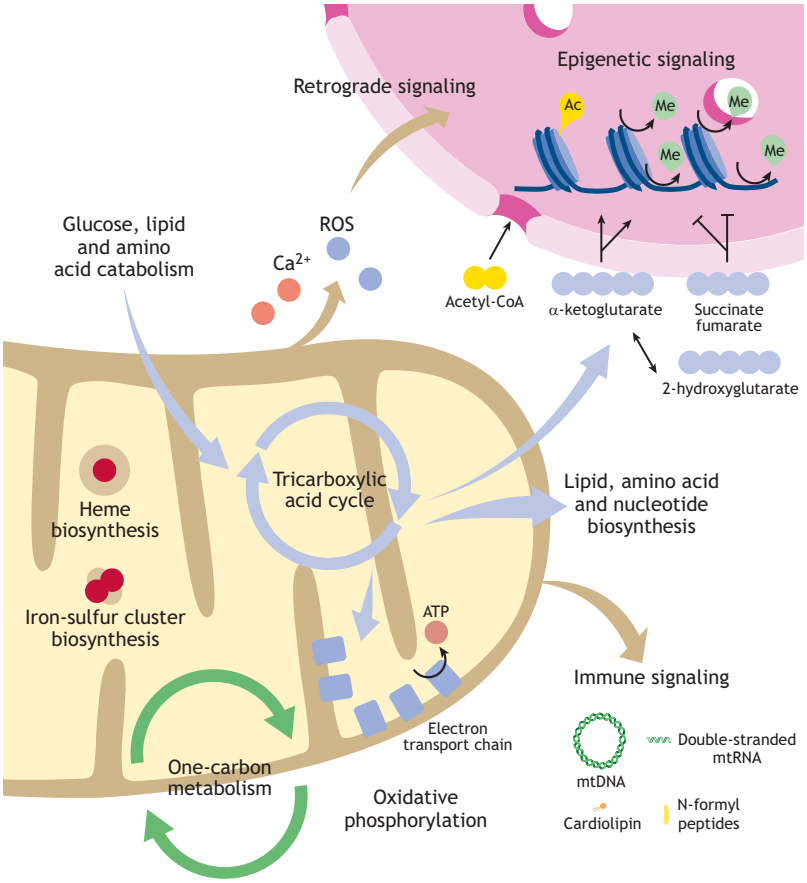

Fig. 2. Mitochondria regulate many key pathways that help the cell adapt to their changing environment. Mitochondria sit at the confluence of biosynthesis and signaling. Mitochondria are involved in energy production through catabolic processes and in production of intermediates needed for biosynthesis of cellular building blocks, including lipids, amino acids and nucleotides, as well as citrate used in production of acetyl-CoA, through processes such as the tricarboxylic acid (TCA) cycle and one-carbon metabolism. Mitochondria can release numerous signals, such as Ca^{2+} and reactive oxygen species (ROS), to other parts of the cell, including the nucleus (known as 'retrograde signaling'), as well as modulate epigenetics. For example, acetyl-CoA and TCA cycle intermediates produced in mitochondria, such as succinate, fumarate and 2-hydroxyglutarate, can influence histone acetylation, histone demethylation and DNA demethylation. Finally, mitochondria also control immune signaling, in part because they are a major endogenous source of immune-activating molecules like mtDNA and mtRNA, among others. This figure was partly generated using Servier Medical Art, provided by Servier, licensed under a CC-BY 3.0 Unported license.

promote metabolic adaptations in unaffected tissues (Jena et al., 2023). In this manner, mitokine signaling coordinates responses across different tissues to ensure homeostasis of the entire organism.

Directing the security system of the cell – innate immunity

Mitochondria are also hubs of innate immune signaling (Bahat et al., 2021; Chen et al., 2023; Faas and de Vos, 2020; Marchi et al., 2023; Newman and Shadel, 2023), the 'security system' that surveils the cell. Pattern recognition receptors (PRRs) are sensors that patrol the cytosol, endosomal compartment and extracellular space for evidence of bacteria or viruses or for signs of cellular damage. Given their numerous links to mitochondria, this network of sensors acts like an alarm system that ensures the office of the CEO is notified of any threats to the cell, and it is attuned to both external threats (e.g. bacteria or viruses attempting to initiate a hostile takeover) and internal dangers such as mitochondrial dysfunction. Indeed, mitochondria form a platform for assembly of certain PRR complexes, which can be regulated by metabolic status and the connectivity of the mitochondrial network (Bahat et al., 2021; Billingham et al., 2022; Hanada et al., 2020).

In addition, mitochondria themselves can activate immune signaling. Owing to their proteobacterial origins, mitochondria are major endogenous sources of immunogenic material that can be recognized by PRRs, including mtDNA (Shimada et al., 2012; West et al., 2015; White et al., 2014; Zhang et al., 2010), mtRNA (Dhir et al., 2018; Tigano et al., 2021), cardiolipin (Iyer et al., 2013) and N-formyl peptides (Zhang et al., 2010). Although mitochondrial contents are typically sequestered away from cytosolic or extracellular immune sensors, numerous mitochondrial and cellular stressors can trigger release of mitochondrial contents to activate immune signaling (Irazoki et al., 2023; Newman and Shadel, 2023; Newman et al., 2024; Próchnicki et al., 2023; Sprenger et al., 2021; Willemsen et al., 2021; Wu et al., 2019). Furthermore, some bacteria and viruses also trigger release of mtDNA, which can help prime the innate immune systems of the cell to take on the intruders (Delgado and Pernas, 2024; Domizio et al., 2022; Moriyama et al., 2019; Newman and Shadel, 2023; Xu et al., 2022). Given the immunogenicity of mitochondrial contents, mitochondria also carefully regulate disposal processes to prevent excess immune activation (Liu et al., 2024; Moehlman and Youle, 2020; Sliter et al., 2018; Todkar et al., 2021). These mechanisms include mitophagy and mitochondria-derived vesicles, both of which are discussed further in a subsequent section. In summary, mitochondria not only hold the keys to the alarm system of the cell but are often the ones regulating its activation.

Making organizational decisions – directing cell fate

So far, we have discussed some of the many tools at the disposal of mitochondria to regulate processes occurring within the cell. With these tools, mitochondria also exert control over cell fate, analogous to a CEO strategizing the expansion, diversification or termination of a company (Fig. 3).

Cell division

Similar to the expansion of a company, cell division is a large undertaking and an intricately coordinated process carried out by a network of cell cycle factors (Engeland, 2022; Fischer et al., 2022). Mitochondria are important participants and regulators of cell

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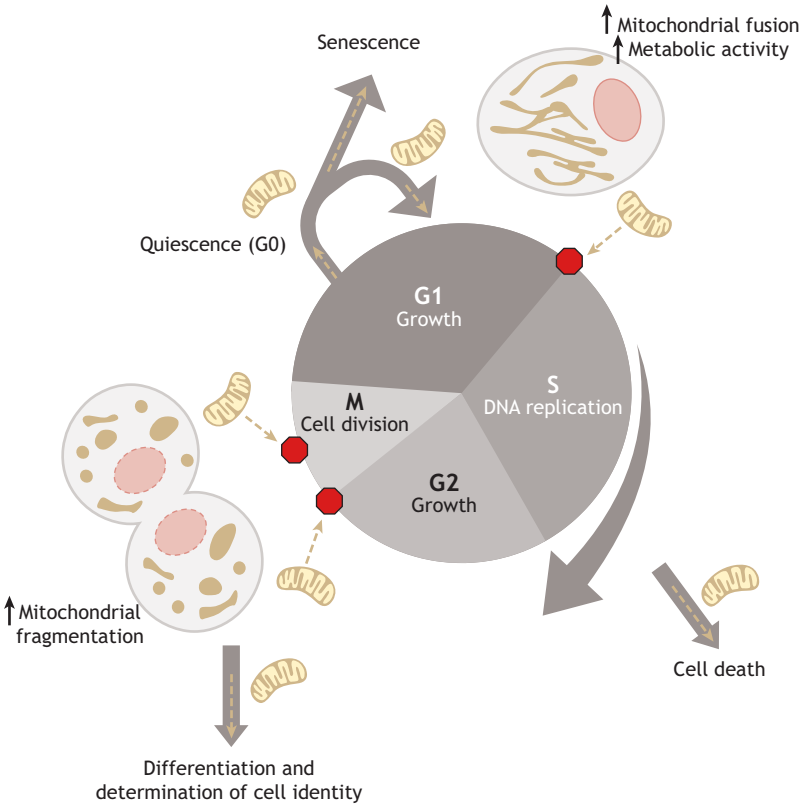

Fig. 3. Mitochondria can determine cell fate. Mitochondria exert influence throughout the life cycle of the cell, as indicated by the dashed yellow lines. During the process of cell division, mitochondria can control whether the cell proceeds through cell cycle checkpoints, depicted as red octagonal stop signs. Furthermore, mitochondria are involved in decisions around entering the cell cycle or leaving the cell cycle to enter quiescent or senescent states, the determination of cell identity during differentiation, and even in the decision to undergo programmed cell death. Key changes in mitochondrial morphology and metabolism during the cell cycle are also illustrated. In G1 phase, increased mitochondrial fusion and interconnectivity supports higher mitochondrial metabolism during growth. In M phase, fragmentation of the mitochondrial network ensures equal distribution of mitochondrial between daughter cells. Disruption of fusion or fission at these stages can also affect cell cycle progression. This figure was partly generated using Servier Medical Art, provided by Servier, licensed under a CC-BY 3.0 Unported license.

division (Diehl et al., 2024; Pangou and Sumara, 2021; Salazar-Roa and Malumbres, 2017). Mitochondria not only oversee key metabolic pathways making energy, nucleotides and lipids required for cell division (Spinelli and Haigis, 2018) but can also exert influence over the progression of the cell cycle.

Mitochondrial metabolism and the shape of the mitochondrial network change throughout the cell cycle (Pangou and Sumara, 2021; Salazar-Roa and Malumbres, 2017) – the mitochondrial network shifts from hyperfused and interconnected during G1 phase, supporting elevated respiration and mitochondrial metabolism, to fragmented during M phase, facilitating even segregation of mitochondria between the two daughter cells. These changes are not a result of one-way instruction from the cell cycle machinery, as mitochondria themselves regulate cell cycle checkpoints that determine whether the cell cycle can proceed.

Mitochondrial metabolism provides an important source of acetyl-CoA to sustain histone acetylation needed to enter the cell cycle (Morrish et al., 2010; Wellen et al., 2009). Inducing mitochondrial fusion promotes entry into the cell cycle (Mitra et al., 2009), whereas impairing mitochondrial fusion prevents G1/S progression (Koval et al., 2019). Later on in the cell cycle, disruption of mitochondrial fragmentation at the G2/M phase halts progression and can even disrupt proper chromosome orientation and segregation (Pangou and Sumara, 2021; Pangou et al., 2021; Qian et al., 2012). Altered mitochondrial respiration (Gemin et al., 2005; Zheng et al., 2023), biosynthetic processes (Birsoy et al., 2015; Sullivan et al., 2015) and even mitochondrial ROS signaling (Kirova et al., 2022) can also impair or drive cell cycle progression. Activation of the PTEN-induced kinase 1 (PINK1)–Parkin mitophagy pathway, which senses and removes dysfunctional mitochondria, can also delay the cell cycle by depleting the cell cycle regulator cyclin E (Taslim et al., 2023) and sequestering Tank-binding kinase 1 (TBK1) away from centrosomes, where it mediates cell division (Sarraf et al., 2019). Sufficient levels of mitochondrial dysfunction can trigger cell cycle arrest, just as a company would avoid undergoing major expansion during a period of shaky leadership. Altogether, these findings suggest mitochondria play a CEO-like role as they regulate the cell cycle.

Cell identity

When stem cells divide, they have the capacity either to become new stem cells (proliferation) or to change and specialize into specific cell types (differentiation), akin to deciding whether it is the right time to diversify a company. Differentiation involves extensive genetic reprogramming through signaling, networks of transcription factors and epigenetics (Rauch and Mandrup, 2021; Sun et al., 2021). Mitochondria have emerged as crucial regulators of this decision, which is important to maintain a stable pool of stem cells and (re)generate specific cell types (Bahat and Gross, 2019; Chakrabarty and Chandel, 2021; Kumar Sharma et al., 2022; Wang et al., 2024). Shifts in mitochondrial metabolism, dynamics and signaling through TCA intermediates, ROS and NADH/NAD^+ support the transition from quiescent to activated stem cells or differentiated cells. An emerging theme suggests that changes to mitochondrial activity are not merely induced by cellular reprogramming, but that they can occur prior to cell fate decisions and in fact drive commitment to proliferation or differentiation (Bahat and Gross, 2019).

Many stem cells rely more heavily on glycolysis than on oxidative phosphorylation (OXPHOS) (Chakrabarty and Chandel, 2021), which might be in part to minimize ROS exposure (Wang et al., 2024). Manipulating metabolism can affect cell identity; for instance, impairing OXPHOS activity has been found to prevent differentiation and promote stemness in hematopoietic stem cells (Vannini et al., 2016). Similarly, modifying the reliance of mouse intestinal stem cells on OXPHOS can either facilitate or impair stem

cell proliferation (Schell et al., 2017). In some cases, a certain mitochondrial metabolic program is necessary to generate cellular acetyl-CoA or α-ketoglutarate levels required for the genome acetylation or demethylation required to maintain stemness or drive differentiation (Carey et al., 2015; Das et al., 2017; Yucel et al., 2019). Mitochondria can also set the agenda in response to environmental cues. For example, mitochondria in bone-derived mesenchymal stem cells adjust metabolite export, required for osteocyte differentiation, based on local oxygen levels (Pouikli et al., 2022).

Mitochondria inherited during cell division can also drive cell fate decisions. Some stem cell populations, such as in human mammary epithelial stem cells, undergo asymmetric mitochondrial division, in which cells that inherit older mitochondria undergo differentiation whereas cells that inherit younger mitochondria retain stem cell identity (Katajisto et al., 2015). The older mitochondrial population more actively respire compared to the younger 'immature' mitochondria, thus establishing distinct metabolic states that determine the identity of the daughter cells; indeed, impairing respiration results in homogenized daughter cell identity (Döhla et al., 2022). In another fascinating example, the fate of mouse and human neural stem cell progenitor daughter cells can be determined post-mitosis based on mitochondrial morphology (Iwata et al., 2020). Daughter cells that adopt a more elongated mitochondrial morphology in the hours after division maintained stemness, whereas daughter cells with fragmented networks differentiated into neurons. Furthermore, manipulation of mitochondrial morphology after cell division is sufficient to drive daughter cell identity, revealing a remarkable degree of mitochondrial control over cell fate.

Cell death and senescence

Just as mitochondria are necessary for the life and health of the cell, they are also involved as cells reach their end. Mitochondrial alterations contribute to senescence, when cells undergo (generally irreversible) cell cycle arrest (Martini and Passos, 2023; Miwa et al., 2022). In the same way, a suboptimal CEO can lead a company to stagnate or deteriorate over time. Conversely, mitochondria can also play a vital role in the process of cell death (Bock and Tait, 2019; Glover et al., 2024), similar to a CEO that makes the decision to merge or downsize, in essence destroying the company or cell.

Mitochondria can both cause and sustain senescence (Martini and Passos, 2023; Miwa et al., 2022). Cells enter senescence following exposure to damage or stress, such as mitochondrial dysfunction, to prevent dysfunctional cells from replicating further. Senescent cells are characterized by a lack of proliferation and secretion of pro-inflammatory molecules (the senescence-associated secretory phenotype; SASP). In particular, the SASP is of growing interest for its roles in aging and age-related diseases (Zhang et al., 2022). Mitochondria can drive SASP through retrograde signaling (Vizioli et al., 2020) and cytoplasmic release of mtDNA and double-stranded (ds)RNA to activate inflammatory signaling (López-Polo et al., 2024; Victorelli et al., 2023). As impaired mitochondrial OXPHOS capacity and senescence-associated stress responses are energetically costly, SASP might be a conduit through which impaired cells communicate their energetic status with the rest of the organism (Shaulson et al., 2024).

In extreme cases, when cells have been exposed to excessive damage or dysfunction, or are unnecessary for the organism, they undergo programmed cell death, or apoptosis. In the intrinsic apoptosis pathway (also called mitochondrial apoptosis), pro- and anti-apoptotic signals converge on the mitochondria to determine cell fate (Bock and Tait, 2019; Glover et al., 2024). When the pro-apoptotic factors dominate, the activated apoptotic effectors Bcl-2-like protein 4 (BAX) and Bcl-2 homologous antagonist/killer (BAK; also known as BAK1) form pores in the outer mitochondrial membrane, causing mitochondrial outer membrane permeabilization (MOMP). Widespread MOMP is considered the tipping point for apoptosis, as it causes a catastrophic loss of mitochondrial function that the cell typically cannot survive. However, to finish the job tidily and efficiently, permeabilized mitochondria release proteins such as cytochrome *c* from the intermembrane space to activate an apoptotic signaling cascade. Activation of effector caspases 3 and 7 rapidly destroys the cell and prevents release of inflammatory material to the extracellular space. In addition to apoptosis, mitochondria are implicated in other forms of cell death, including pyroptosis, ferroptosis and necroptosis (Bock and Tait, 2019; Glover et al., 2024).

Mitochondria provide input on and modulate the decision to undergo apoptosis in numerous ways. For instance, to help the cell survive under stressors, such as starvation, the mitochondrial network becomes highly interconnected to enhance mitochondrial function (Tondera et al., 2009). Mitochondrial elongation safeguards the mitochondrial network from being degraded by cellular autophagy machinery (Gomes et al., 2011; Rambold et al., 2011) and protects the cell from apoptosis (Youle and Karbowski, 2005). Mitophagy, the selective autophagic removal of mitochondrial fragments, is another dynamic mitochondrial process relevant to apoptosis. Mitophagy can be compared to closing down a division of the company that is draining resources to save the overall company from folding. In some cases, mitophagy can help protect the cell from undergoing apoptosis by eliminating damaged mitochondria (Li et al., 2021; Quarato et al., 2023; Yang et al., 2024). Conversely, excessive mitophagy can also lead the entire cell to 'fold' (Li et al., 2021; Yang et al., 2024). Mitochondrial stress signaling proteins, including PINK1, Parkin, mitochondrial elongation factor Tu (TUFM) (Choi et al., 2022) and NLR family member X1 (NLRX1) (Bi et al., 2023; Li et al., 2016; Stokman et al., 2017), can also influence apoptosis independently of their role in mitophagy. PINK1–Parkin-mediated ubiquitylation of different targets can either inhibit apoptosis (Bernardini et al., 2019; Ham et al., 2020) or, presumably under more severe dysfunction and apoptotic stimuli, activate apoptosis (Carroll et al., 2014; Zhang et al., 2014). It is likely that the cellular and mitochondrial context directs PINK1–Parkin signaling to distinct targets to mediate either anti-apoptotic or pro-apoptotic signaling. Situated at the center of these essential pathways and signaling modalities, mitochondria are likely best positioned to make the most informed decisions on whether the cell should live or die.

With great power comes great responsibility – mitochondrial quality control

If the CEO is unwell and unable to orchestrate activities between different components of their organization, the ability of the company to thrive or survive can be compromised, even if the other components of the company are functional. Similarly, altered mitochondrial biology poses a significant threat to the cell and is associated with the development of numerous diseases (Sedlackova and Korolchuk, 2019). As such, mitochondria have numerous exquisite quality control mechanisms to keep them fit (Eckl et al., 2021; Ng et al., 2021).

These mechanisms can respond to different degrees of impaired mitochondrial biology. For instance, given that most proteins within the mitochondria are nuclear-encoded and thus must be imported,

protein import translocases (the ‘gates’ to the mitochondria) experience heavy traffic and must be carefully monitored by mechanisms to degrade misfolded or unimported proteins or to mitigate congestion at the gates (Hsu et al., 2025; Itakura et al., 2016; Kim et al., 2023; Kim et al., 2024; Krakowczyk et al., 2024; Song et al., 2021). Sometimes, dysfunctional mitochondria must recruit help from the rest of the cell. Mitochondria can signal to the nucleus to activate stress-responsive transcription programs, such as the mitochondrial unfolded protein response (Katiyar et al., 2020; Münch, 2018; Sutandy et al., 2023) and the integrated stress response (Fessler et al., 2020, 2022; Fu et al., 2023; Guo et al., 2020), among others (Cardamone et al., 2018; Kim et al., 2018).

If damage is sufficiently severe, mitochondria might need to eliminate damaged components. Mitochondria can expel mitochondria-derived vesicles (MDVs) carrying damaged proteins to lysosomes for turnover (König et al., 2021; McLelland et al., 2014; Soubannier et al., 2012). Damaged mtDNA can be segregated for degradation through various mechanisms (Sen et al., 2022; Tábara et al., 2024). Removal of entire damaged mitochondria can be carried out by mitophagy, which is mediated by diverse proteins that respond to different stressors, such as impaired mitochondrial protein import or oxidative stress (Ganley and Simonsen, 2022; Killackey et al., 2022; Lee-Glover and Shutt, 2024; Liu et al., 2012; Matsuda et al., 2010; Michaelis et al., 2022; Wei et al., 2017).

Finally, cells might even need to look for outside help to reestablish effective leadership. Mitochondria can be transferred between cells, both to eliminate damaged mitochondria and to provide fresh functional mitochondria (Borcherding and Brestoff, 2023; Hayakawa et al., 2016; Nicolás-Ávila et al., 2020; Rosina et al., 2022), similar to how an inefficient CEO can be replaced if they are not functioning effectively.

Conclusion

Unlike the overly reductionist ‘powerhouse’ analogy, reframing mitochondria as the CEO of the cell creates an opportunity to assimilate the rich discoveries of the past two decades that have revealed mitochondria to be a diverse, dynamic and multifaceted family of organelles (Monzel et al., 2023). As we have described, although the ‘Chief Executive Organelle’ certainly energizes the cellular organization, it also does much more – from integration of multiple cellular information streams, to communication, coordination and decision-making regarding the very fate of the cell and organism in which it resides.

Going forward, considering the key roles of mitochondria in cellular leadership will help us better understand normal mitochondrial biology as well as the impacts of mitochondrial dysregulation in disease. Different manifestations of impaired mitochondrial biology are increasingly recognized to be central, upstream processes in the pathogenesis of numerous diseases. For instance, impaired mitochondrial quality control contributes to neurodegenerative diseases by rendering neurons more susceptible to cell death (Franco-Iborra et al., 2018). However, more recent understanding of how mitochondria control inflammation has revealed that mitochondria can also contribute to neurodegeneration through neuroinflammation (Magalhães and Cardoso, 2023). Impaired mitochondrial biology and inflammatory signaling are further implicated in cardiovascular conditions (Ding et al., 2024; Yang et al., 2022), chronic obstructive pulmonary disease (Aghapour et al., 2020; Ryter et al., 2018), systemic lupus erythematous (Al Khatib et al., 2023; Li et al., 2024) and irritable bowel disease (Ho and Theiss, 2022). Mitochondria in cancer perhaps best exemplifies their many roles in regulating cell fate – altered mitochondrial metabolism supports proliferation, epigenetic reprogramming by ‘oncometabolites’ (e.g. succinate, fumarate and 2-hydroxyglutarate) facilitates malignant transformation, regulation of inflammatory signaling and SASP helps create a pro-tumorigenic environment, and altered mitochondrial function aids in evasion of cell death (Marchi et al., 2023; Porporato et al., 2017; Wang et al., 2023).

As technologies develop, we will undoubtedly learn more about how mitochondria control cellular functions and behaviors. Using the CEO analogy, we note that effective leaders must be adaptive and flexible. Mitochondria have numerous resources available to fulfill this executive quality. Multi-omics studies using time-resolved transcriptomics, proteomics and metabolomics profiling (Schäfer et al., 2023) will likely continue to reveal how mitochondria adapt to different circumstances or within different tissues, as well as the intricacies of mitochondrial–nuclear genome coordination (McShane and Churchman, 2024; McShane et al., 2024). Successful leaders must also build relationships. Mitochondria maintain numerous multifunctional organelle contact sites, and the growing appreciation of inter-organelle interactions has challenged and transformed our view of independently functioning organelles (Voeltz et al., 2024). Finally, another essential quality to leadership is communication. Mitochondria mediate communication both within and between cells, from organelle to organism. Increasingly, we need to study the impact of mitochondrial activities in their complex natural, multicellular environment. That can include studying mitochondria in organoids (or ‘mini organs’) (Liput et al., 2021), exploring how mitokines coordinate responses across different tissues (Zhang et al., 2023), or investigating how intercellular mitochondrial transfer might contribute to organizational harmony at the organismal scale (Borcherding and Brestoff, 2023).

In summary, mitochondria are not passive servants of the cell. They not only transform energy to keep the lights on but also make executive decisions shaping strategic cellular behaviors. Considering the mitochondrion as the Chief Executive Organelle (CEO) of the cell might help us usher ourselves and the next generation of cell biologists into an increasingly accurate 21st century perspective of biology.

Competing interests

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