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Mitohormesis and metabolic health: The interplay between ROS, cAMP and sirtuins

Carlos Marques Palmeira[a,b], **João Soeiro Teodoro**[a,b], **João Alves Amorim**[b,c,d], **Clemens Steegborn**[e], **David A. Sinclair**[d,f], **Anabela Pinto Rolo**[a,b,*]

[a]Department of Life Sciences, University of Coimbra, Portugal

[b]Center for Neurosciences and Cell Biology, University of Coimbra, Portugal

[c]IIIUC – Institute of Interdisciplinary Research, University of Coimbra, Portugal

[d]Department of Genetics, Blavatnik Institute, Paul F. Glenn Center for the Biology of Aging, Harvard Medical School, Boston, MA, USA

[e]Department of Biochemistry, University of Bayreuth, 95440, Bayreuth, Germany

[f]Laboratory for Ageing Research, Department of Pharmacology, School of Medical Sciences, The University of New South Wales, Sydney, NSW, 2052, Australia

Abstract

The key role of mitochondria in oxidative metabolism and redox homeostasis explains the link between mitochondrial dysfunction and the development of metabolic disorders. Mitochondria's highly dynamic nature, based on alterations in biogenesis, mitophagy, fusion and fission, allows adjusting sequential redox reactions of the electron transport chain (ETC) and dissipation of the membrane potential by ATP synthase, to different environmental cues. With reactive oxygen species being an inevitable by-product of oxidative phosphorylation (OXPHOS), alterations on mitochondrial oxidative rate with a consequent excessive load of reactive oxygen species have been traditionally associated with pathological conditions. However, reactive oxygen species have also been suggested as promoters of mitohormesis, a process in which low, non-cytotoxic concentrations of reactive oxygen species promote mitochondrial homeostasis. Therefore, signaling systems involved in the regulation of mitochondrial homeostasis are attractive candidates for drug development for metabolic diseases triggered by mitochondrial dysfunction. Reversible phosphorylation downstream the cyclic AMP (cAMP) signaling cascade and deacetylation mediated by sirtuins are recognized as major mitochondrial regulators.

*Corresponding author. Departamento de Ciências da Vida, Largo Marquês de Pombal, 3004-517, Coimbra, Portugal. anpiro@ci.uc.pt (A.P. Rolo).

Author disclosure statement

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Keywords

Mitochondria; ROS; Mitohormesis; Metabolic diseases; cAMP; Sirtuin

1. Introduction

Mitochondria are known for their key role in cellular energetic metabolism involving oxidative phosphorylation (OXPHOS), β-oxidation of free fatty acids and the tricarboxylic acid cycle (TCA). Also the participation of mitochondria in redox and calcium homeostasis makes mitochondrial signaling pathways regulators of many cellular functions implicated in vital processes [1-3]. Several studies have indicated that the misbalance of energy homeostasis is linked to a compromised mitochondrial function, which appears to be an early event in the development of metabolic disorders. In fact, metabolic disorders are associated with an increase in oxidative damage correlated with a deregulation in mitochondrial dynamics and decreased expression of genes involved in the control of mitochondrial biogenesis [4].

Mitochondrial homeostasis is dependent on dynamic processes such as fusion, fission and removal of irreversibly damaged mitochondria (mitophagy), preventing the accumulation of dysfunctional organelles (Fig. 1A). However, mitophagy must be counter-balanced by mitochondrial biogenesis, allowing tuning mitochondrial function to the cellular needs [5]. Indeed, signaling pathways activated by physiological stimuli such as changes in nutritional availability and energy requirements coordinate adaptive changes in oxidative metabolism mediated by a crosstalk between the nucleus and mitochondrial genomes [6]. Moreover, modification of mitochondrial proteins by reversible phosphorylation downstream of the cAMP-dependent pathway and deacetylation mediated by sirtuins (SIRTs) have emerged as major regulatory mechanisms for rapid modulations of mitochondrial homeostasis [7-9].

Interestingly, mitochondrial adaptive processes may also involve signaling by reactive oxygen species (ROS). Traditionally, increased ROS formation has been associated with numerous diseases and age-related disorders [10]. With ROS being an inevitable by-product of OXPHOS, an imbalance between increased formation of reducing equivalents by the TCA cycle and the capacity of the ETC results in increased ROS formation and oxidative stress, and high concentrations of ROS cause damage to membranes, proteins, carbohydrates, and DNA [11,12]. However, conditions that induce a mild increase in mitochondrial-derived ROS such as caloric restriction (CR) and physical exercise, have a known pro-longevity effect by a process known as mitohormesis [2]. A mitohormetic response is proposed to be triggered by transient mitochondrial stress wherein low, non-cytotoxic concentrations of ROS can serve as signals to mitochondrial and antioxidant signaling pathways promoting changes in the antioxidant defense system and mitochondrial dynamics, therefore resulting in extended lifespan [2,11]. In the present review, we summarize current knowledge concerning the relationship between ROS formation and mitochondrial function, in a hormetic perspective. We also discuss how the crosstalk between cAMP and SIRTs may have a critical impact on mitochondrial homeostasis.

2. The dynamics of mitochondrial function

Mitochondrial quality control mechanisms are necessary to maintain a healthy mitochondrial network within cells, by controlling mitochondrial distribution, mass and activity [13]. As the mitochondrial DNA (mtDNA) accounts for only 13 subunits of the ETC, mitochondrial biogenesis is the process, dependent on coordinated mitochondrial and nuclear gene expression, by which cells increase mitochondrial mass and shape bioenergetic capacity [6]. Among the regulators of this process, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) acts as a co-activator of the nuclear respiratory factors (NRFs) 1 and 2, inducing the expression of nuclear-encoded mitochondrial genes, including subunits of the ETC, mitochondrial ribosomal proteins and key mitochondrial enzymes [14,15]. Additionally, NRFs also regulate the mitochondrial transcription factor A (TFAM), which drives transcription and replication of mtDNA (Fig. 1A) [15]. Since stimulation of mitochondrial biogenesis coordinately increases mitochondrial mass and substrate oxidation, it could be expected that increased rates of electron flow through the ETC could increase ROS generation. However, it has been shown that PGC-1α buffers ROS as demonstrated by a burst in ROS when PGC-1α is downregulated during myogenesis [16] as well as the attenuation of mitochondrial disease in mouse models of disrupted cytochrome *c* oxidase (COX) activity [17].

Mitochondrial network organizational changes also result in crucial alterations in cellular function since it influences mitochondrial homeostasis. These events are governed by a complex molecular machinery that adapts mitochondrial function to the cell metabolic needs and thus alter calcium signaling, OXPHOS rates and ROS generation [6]. On one hand, fusion events result in a more interconnected network, allowing the exchange of DNA and metabolites between neighboring mitochondria, therefore optimizing mitochondrial function. On the other hand, fission events facilitate mitochondrial transport and the elimination of damaged organelles by mitophagy [5,13].

The selective elimination of dysfunctional or damaged mitochondria by mitophagy is also crucial in maintaining mitochondrial homeostasis and cellular metabolism since the major factor driving this process is the mitochondrial membrane potential [18]. In fact, one well-established pathway that regulates mitophagy is the impairment of PINK1 (phosphatase and tensin homolog (PTEN)-induced kinase 1) import system in depolarized mitochondria, resulting in its accumulation on the outer mitochondrial membrane (OMM) and the recruitment of Parkin, which ubiquitinates OMM proteins and triggers mitophagy (Fig. 1B) [19]. It is important to note that mitophagy is a crucial precursor to mitochondrial biogenesis, allowing the expansion of a healthy mitochondrial network, and that biogenesis must balance mitophagy for proper mitochondrial turnover [13], which is supported by the proposed link between PINK1 and regulation of mtDNA content [20]. Since mitophagy primes the elimination of dysfunctional and depolarized mitochondria for degradation, thus preventing oxidative stress, mitophagy has been suggested to be a longevity factor as shown by the extended lifespan involving mitophagy induction upon mild attenuation of mitochondrial function or by dietary restriction [13,18].

3. The dual role of mitochondrial ROS on cellular function

As a major source of ROS generated by the ETC and other mitochondrial enzymes, mitochondria act as regulators of the cellular redox state [21]. Electrons from reducing equivalents such as NADH and $FADH_2$, generated by intermediary metabolism are transferred along a series of carriers, with increased oxidation potentials, in the four complexes of the ETC. This exergonic process is coupled to proton translocation across the inner mitochondrial membrane, generating an electrochemical gradient. The movement of protons back to the matrix through the ATP synthase drives the conversion of ADP and Pi to ATP. The leak of single electrons from the ETC results in one-electron reduction of oxygen originating mitochondrial superoxide anion [22].

The critical role of the reductive power provided by NADH/NADPH for several cellular processes, conditions of reductive stress such as when NADH is supplied to the ETC at a rate higher than the reduction of oxygen takes place, has been pointed as a first insult toward metabolic diseases [23]. Under physiological conditions, antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase detoxify ROS and prevent oxidative stress. Non-enzymatic defenses such as vitamin C and phenolic compounds also act as ROS scavengers. However, conditions of decreased NAD^+/NADH ratio observed in the early phases of hyperglycemic exposure [24] or faulty proteins in the ETC caused by mtDNA defects, overwhelm the endogenous antioxidant capacity. This results in oxidative damage to lipids, proteins and mtDNA with progressive mitochondrial dysfunction further boosting ROS generation and creating a vicious cycle of oxidative damage [11]. In fact, oxidative stress caused by mitochondrial dysfunction has been associated with the development of several pathologies such as diabetes, neurodegenerative and age-related disorders in which a decrease in mitochondrial content could be a quality-control process [11,12,19].

Despite the harmful side of increased ROS generation and its association with disease and aging, ROS are also closely related to human health through their impact on cellular signaling and diverse physiological processes [3]. Regarding mitochondrial function, the cellular redox state has been proposed as a regulatory signal for mitochondrial biogenesis [9,25]. In a model of high-fat induced-obesity, at a state where increased mitochondrial content is observed in skeletal muscle, the inclusion of a mitochondrial-targeted antioxidant in the diet prevented the increase in mitochondrial biogenesis [26]. This suggested that stimulation of mitochondrial biogenesis aims to prevent excessive ROS formation due to the surplus of reducing equivalents to the ETC. Also treatment of mouse embryonic cells with H_2O_2 has been shown to increase PGC-1α and 1β transcription [27] and in C2C12 cells, pretreatment with the antioxidant N-acetyl-L-cysteine (NAC) prevented the increase in PGC-1α mRNA induced by H_2O_2 [28]. In addition, by modulating stress kinases and transcription factors, ROS induce cellular antioxidant defenses that overlap with the regulation by PGC-1α and PGC-1β on the expression of catalase and SOD [29].

ROS may also confer cellular protection by regulating autophagy. In fact, autophagy is induced in conditions of increased ROS formation such as starvation, an event blocked by ROS scavengers [30]. ROS were found to modify a cysteine residue near the catalytic domain of autophagy-related protein 4, a protease that regulates autophagy [8]. Mitophagy is

also triggered by ROS (Fig. 1B). Transient low concentrations of H_2O_2 and rotenone, an inhibitor of the ETC complex I, were shown to trigger fission-dependent mitophagy in the absence of mitochondrial dysfunction [18]. Recently it has been shown that treatment with NAC inhibits PINK1-dependent Parkin translocation to mitochondria [31] and superoxide is the major species of ROS that mediates mitophagy following Parkin translocation to mitochondria, since SOD inhibitors were able to interfere with the progression of Parkin/PINK1-mediated mitophagy [32].

4. Mitohormesis as a gatekeeper of metabolic health

The study of mitochondrial ROS as signaling agents of paramount importance for normal cellular physiology and the concept that cell exposure to mild stressors elicits an adaptive response [33], has expanded the concept of hormesis into a mitochondrial-centric view [34]. Mitohormesis describes various forms of mitochondrial stress that elicit a beneficial retrograde signaling response that includes the modulation of mitochondrial dynamics, the expression of nuclear and mitochondrial-encoded genes and genes related to the antioxidant response, stimulating mitochondrial function and increasing cellular defense mechanisms, that can be either transient metabolic and biochemical alterations or long-lasting cytoprotective mechanisms that increase stress resistance [2,35] (Fig. 2A).

The decline of mitochondrial function with age has pointed to mitochondria as major players in the aging process [36], as major generators of ROS considered as unwanted by-products of oxidative phosphorylation. Being mitochondria a principal target for ROS, this would lead to the gradual loss of cell function overtime due to oxidative stress and accumulated damage. This theory has emerged as a rather untouchable dogma but began to be questioned by studies reporting the negative action of antioxidants [37]. For instance, antioxidants supplemented to the dietary regimen failed in delaying cardiovascular disease and even were reported to increase cancer growth [38,39]. Furthermore, the recognition of increased ROS as a mediator of skeletal muscle adaptation to exercise, associated with improved mitochondrial function [40], and the link between ROS, CR and longevity [34,35], have supported the concept of a mitohormetic adaptive response mediated by ROS (Fig. 3). Indeed, acute exercise stimulates expression of PGC1-α, resulting in increased mitochondrial content and oxidative capacity in skeletal muscle [41] and several reports have brought attention to the fact that oral administration of antioxidants prevent exercise-induced adaptation of muscle mitochondria [42]. In *S. cerevisae*, CR was shown to increase mitochondrial function and, inevitably, ROS formation [35]. The upregulation of genes associated with the endogenous antioxidant defence response has been proposed as a mechanism by which CR and exercise prevent age-related disorders. Nuclear factor erythroid 2-related factor-2 (Nrf2) is a transcription factor that regulates cellular redox status by promoting the antioxidant response elements (ARE) signaling, a pathway that becomes less active with aging [43]. Nrf2 also impacts mitochondrial function since Nrf2 is associated with impaired OXPHOS while activators of Nrf2 promote mitophagy and resistance to oxidative stress [44]. Recently, it has been shown that ablation of Nrf2 impairs mitohormesis in conditions of OXPHOS deficiency due to mitochondrial uncoupling [45].

One of the first findings was in the nematode *Caenorhabditis elegans*, where reduced glucose availability causes an increase in both ROS and catalase activity, ultimately culminating in increased survival rates [46]. Several other studies have further demonstrated that many strategies promoting longevity share a common downstream: increased mitochondrial ROS. Inhibition of the mitochondrial ETC by certain mutations or inactivation of mitochondrial superoxide dismutase extends *C. elegans* lifespan [47]. Also low doses of rotenone, an inhibitor of mitochondrial complex I, has been shown to extend *C. elegans* lifespan [47] as well as to induce hormesis in primary human fibroblasts, an effect not possible in neither older cells nor with higher concentrations of rotenone [48]. Inhibition of the signaling mediated by the autophagy regulator mammalian target of rapamycin complex 1 (mTORC) and consequent induction of autophagy by caloric restriction or by pharmacological agents has also been found to promote longevity in yeast, worms, flies and mice [49].

Regulation of mitophagy and mitochondrial biogenesis by mitohormesis can mediate the positive impact of a mild induction of ROS signaling pathways. Animals with cardiac impaired mitophagy and consequent accumulation of damaged ROS-forming mitochondria develop cardiomyopathy, which can be surprisingly improved by the ROS-dependent activation of compensatory autophagic pathways of mitochondrial quality control, preventing a vicious cycle of ROS formation and mitochondrial dysfunction [50]. Also, double KO-AOX mice with a muscle-specific COX15 knockout and expressing alternative oxidases (AOXs), that bypass respiratory complexes III and IV, transferring electrons directly to oxygen, exhibit decreased ROS generation, PGC-1α signaling and lifespan [25]. Livers from adult mice in which mitochondrial superoxide dismutase 2 was depleted during embryonic development display mitochondrial adaptive responses with increased mitochondrial biogenesis and antioxidant defenses, while exhibiting decreased ROS [51].

5. Modulation of mitochondrial homeostasis by sirtuins and cAMP

Activation of signaling pathways involved in the regulation of mitochondrial homeostasis constitutes an important therapeutic target for metabolic diseases triggered by mitochondrial dysfunction. cAMP signaling and the sirtuins (SIRT1-7), a family of lysine deacylases that regulate the activity of enzymes, transcription factors and chromatin may constitute a central network at the crossroads of energy metabolism, metabolic diseases, and aging. Both these pathways converge into the regulation of mitochondrial function and ultimately maintain cellular energy homeostasis [7,9,52,53].

Sirtuins are activated by conditions of low cellular energy status that result in high NAD^+ levels which SIRTs use as co-substrates to remove acyl moieties from lysines on histones and proteins [52,54]. SIRT1 is predominantly located in the nucleus and its activation stimulates mitochondrial biogenesis, thus preventing metabolic complications [55-59]. By migrating into mitochondria, SIRT 1 also deacetylates and increases SIRT3 activity [60], which localizes at the mitochondrial matrix where it deacetylates and regulates the activity of mitochondrial proteins including intermediary metabolism, fatty acid oxidation, OXPHOS and the oxidative stress response [9,61]. Resveratrol, a known SIRT1 activator that increases PGC-1α activity and prevents metabolic decline [8] has also been shown to stimulate mitophagy [62].

SIRT3 is also a known modulator of mitohormesis. In fact, several studies have demonstrated that the most famous member of the sirtuin family that localizes to mitochondria has a tremendous direct impact on mitochondrial function upon a mild stressing event. For example, when animals are subjected to caloric restriction, SIRT3 is fundamental for the tackling of oxidative stress [92,93], and its expression is upregulated by oxidative stress [94]. This is further supported by the fact that SIRT3 is paramount for the activity of the mitochondrial native manganese superoxide dismutase (MnSOD) [93] and loss of SIRT3 leads to oxidative stress, genomic mutations and elevated cancer proneness [95]. As such, it is unsurprising that SIRT3 leads to the activation of known tumor suppressing gene LKB1 [96], via a pathway that involves the activation of AMPK (strikingly, SIRT1 is also capable of activation of LKB1 [97]). The induction of SIRT3 by oxidative stress has a noticeable effect on mitochondrial metabolism [98,99]. Finally, it appears the unfolded protein response, a defense mechanism heavily involved in mitohormesis has in SIRT3 one of its critical components [100]. Given all of this, it is safe to assume that SIRT3 plays a role in the mitohormetic response.

While SIRT1 and 3 are by far the most studied sirtuin family members, in particular regarding mitochondrial function and the role of oxidative stress, it is not true that there are no known effects of the other family members. In fact, the cytosolic SIRT2 has been shown to regulate mitochondrial OXPHOS, ATP generation, mitochondrial dynamics, oxidative stress and mitochondrial biogenesis in normal and metabolic disease settings [71,72]. SIRT3 is not the only mitochondrial sirtuin, for SIRT4 and 5 are also native to mitochondria. SIRT4, thought to not be a deacetylase like SIRT1-3 but a NAD + -dependent ADP-ribosyltransferase, has a clear effect on mitochondrial quality control, metabolic regulation and ageing processes [73-75], and recent evidences also point to a rather interesting deacetylating activity of lysine residues [75]. SIRT5 is a lysine demalonylase [76] that is involved in mitochondrial dynamics regulation [77,78], ATP generation and metabolic fluxes [78,79], with impact in OXPHOS due to cardiolipin binding [80] and overall mitochondrial metabolic homeostasis [81]. Regarding SIRT6, which is a highly specific lysine deacetylase [82], it has been shown that it can protect mitochondria from ischemia/reperfusion injury by inhibition of inflammatory activity [83], from hyperglycemia through AMPK activation [84], from known mitochondrial toxicant and anticancerous agent doxorubicin [85], while also coordinating with p53 [86] and SIRT1 [87] to protect and boost mitochondrial function. Finally, SIRT 7 has also been shown to be a potent regulator of mitochondrial function, since its deletion leads to a reduction of the expression of nuclearly encoded mitochondrial genes, leading to mitochondrial dysfunction [88], while also playing key roles in metabolic regulation of mitochondrial function and biogenesis [89-91]. As such, it seems that there is a rather large overlap of functionality and targets between the different SIRT family members, which might appear to lead to some redundancy in function, but it is more probable to attribute this to a case of different effectors in various cellular compartments and with somewhat different functions that ultimately result in the same broad goals.

cAMP is a ubiquitous second messenger that in the mitochondria orchestrates mitochondrial fusion/fission, motility and mitophagy and acts as a mediator of metabolic signals regulating mitochondrial homeostasis and ROS generation [7,63]. The adenylyl cyclases (ACs) family comprises ten isoforms that are responsible for the conversion of cAMP [64]. In fact, a

soluble AC (sAC) is described not only in nucleus and cytosol, but also in the mitochondria of cardiac, liver and skeletal muscle cells [65,70]. Since OXPHOS is regulated by cAMP generated inside mitochondria by sAC, the role of this isoform in the mechanisms regulating mitochondrial activity and consequently in the balance between energy storage and energy consumption have been under investigation [66]. Mitochondrial sAC, and thus the sAC/Protein Kinase A (PKA) axis, is stimulated by physiological bicarbonate concentrations, and its presence increases OXPHOS activity while limiting ROS production. In isolated mitochondria, stimulation of the mitochondrial cAMP pathway by bicarbonate has been shown to decrease the susceptibility to calcium-induced mitochondrial permeability transition, an abrupt increase in permeability of the inner membrane to solutes that uncouples OXPHOS [67]. In addition, cAMP levels have been shown to increase by activation of sAC [63]. In fasted mice, the induction of cAMP signaling enhances SIRT3 activity that deacetylates leucine-rich protein 130, resulting in increased mitochondrial transcription and improved OXPHOS efficiency [68]. Therefore, targeting sAC has been shown to improve bioenergetics defects, including COX activity, respiration and mitochondrial biogenesis [66]. Evidence also supports that the stimulation of cAMP signaling pathways with forskolin, an activator for the nine transmembrane members of the AC family, induces mitochondrially encoded genes, and thus that extra-mitochondrial cAMP signaling impacts mitochondrial function [68]. Another important link can also be established between cAMP and SIRT1. Activation of the cAMP signaling pathway has been shown to result in SIRT1 phosphorylation, increasing its deacetylase activity and stimulating fatty acid oxidation [69] (Fig. 2B). Taken together, these data support that the regulation of mitochondrial function is mediated by the activity of several AC isoforms, including cAMP effects on the activity of sirtuins [63,70]. Therefore, it is conceivable that alterations in the AC-SIRTs axis and the associated mitochondrial dysfunction could be linked to metabolic-related diseases (Fig. 4).

6. Conclusions and perspectives

In the last years, the risk associated with the indiscriminate use of antioxidants and the role of ROS as signaling molecules has come under the spotlight. ROS have been proposed as triggers of an adaptive response that strengthens cellular defensive mechanisms, as a strategy to maintain mitochondrial homeostasis and therefore prevent metabolic unbalance. By triggering mitophagy and biogenesis, low, non-toxic concentrations of ROS mediate the expansion of a healthy mitochondrial network able to use the reducing equivalents, generated by intermediary metabolism, thus preventing conditions of reductive stress and a vicious cycle of increased ROS generation and oxidative damage. Better knowledge about the signaling pathways that mediate mitonuclear communication and the mechanisms underlying mitohormesis may help to design therapies more effective in improving metabolic health.

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Abbreviations:

AC	adenylyl cyclase
AOX	alternative oxidase
ARE	antioxidant response element
cAMP	cyclic AMP
COX	cytochrome *c* oxidase
CR	caloric restriction
DRP1	dynamin related protein 1
ETC	electron transport chain
mtDNA	mitochondrial DNA
FIS1	mitochondrial fission 1 protein
HDAC6	histone deacetylase 6
LC3	microtubule-associated protein 1A/1B-light chain 3
MFN	mitofusin
mTORC	mammalian target of rapamycin complex 1
NAC	N-acetyl-L-cysteine
NRF	nuclear respiratory factor
NRF-2	nuclear factor erythroid 2–related factor 2
OMM	outer mitochondrial membrane
OPA1	mitochondrial dynamin-like 120 kDa protein
OXPHOS	oxidative phosphorylation
p62/SQSTM1	p62/ signaling adaptor sequestosome 1
PE	phosphatidylethanolamine
PGC-1α	peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PINK1	PTEN-induced kinase 1

PKA	protein kinase A
PTEN	phosphatase and tensin homolog
ROS	reactive oxygen species
sAC	soluble AC
SIRT	sirtuin
SOD	superoxide dismutase
TCA	tricarboxylic acid cycle
TFAM	mitochondrial transcription factor A
VDAC	voltage-dependent anion channel
ΔΨ	mitochondrial membrane potential

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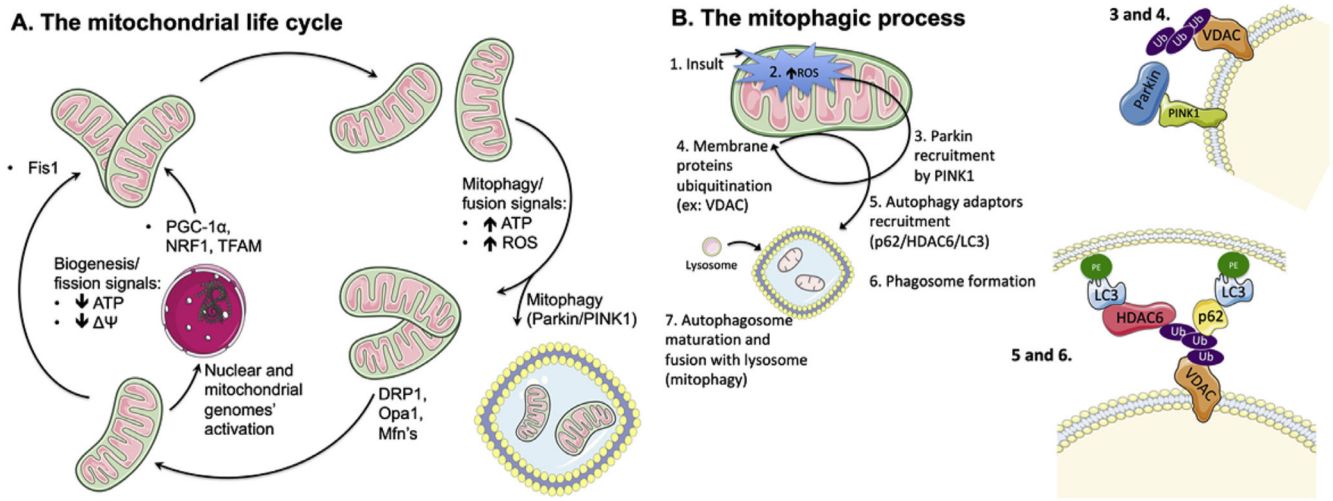

Fig. 1.

A. The mitochondrial life cycle. The mitochondrial population is a highly dynamic and fluid entity within a cell, with organelle units continually being produced or removed, depending on the cell's needs and diverse signals. One of the cell's mechanisms to cope with a decrease in cellular ATP levels, with concomitant fall in mitochondrial membrane potential (ΔΨ), is to generate more mitochondria either by fission of existing ones (which decreases membrane area per organelle, thus elevating ΔΨ) or simply producing newer ones, with resource to the genetic templates within the nucleus and the mitochondrial genome. For the biogenesis process, example of key players are PGC-1α, NRF1 and TFAM, while FIS1 is typically crucial for fission. Conversely, when ATP levels are high, oxidative stress is also elevated. As such, it becomes energetically costly to maintain numerous, unnecessary mitochondria, some of them quite damaged. As such, the cell induces either the removal of damaged mitochondria by mitophagy (which involves, for example, Parkin and PINK1, and is discussed in more detail in Fig. 1B) or fuses unnecessary mitochondria (using effectors such as DRP1, OPA1 or MFN, reducing the number of units but increasing they surface area, effectively decreasing ΔΨ and thus contributing to a lower ATP generation rate as well as decreased oxidative stress. DRP1: dynamin related protein *1*, Fis1: mitochondrial fission 1 protein, Mfn: mitofusin, NRF1: nuclear respiratory factor 1, Opa1: mitochondrial dynamin-like 120 kDa protein, PINK: phosphatase and tensin homolog (PTEN)-induced kinase 1, PGC-1α: peroxisome proliferator-activated receptor gamma coactivator-1α, ROS: reactive oxygen species, TFAM: mitochondrial transcription factor A. **B. Mitochondrial autophagy (mitophagy) dependency on ROS.** When an insult (1) leads to elevation of mitochondrially-generated ROS levels (2), with concomitant loss of membrane potential, the membrane-bound PINK1 protein is stabilized and undergoes autophosphorylation, which triggers the recruitment of Parkin (3), a soluble E3 ubiquitin ligase. Parkin then ubiquitinates (4) other outer mitochondrial membrane proteins (such as VDAC, MFN1, and others), which is a signal for the recruitment of the autophagy adaptors p62/SQSTM1 and HDAC6 (5). These proteins anchor active LC3 units, which are themselves bound to phosphatidylethanolamine, serving as initiator point for phagosome membrane formation and maturation. Finally, the mature autophagosome is fused with hydrolytic-enzymes carrying lysosomes (7), which leads to the degradation of the lysophagosome's contents.

HDAC6: histone deacetylase 6, LC3: microtubule-associated protein 1A/1B-light chain 3, MFN: mitofusin, p62/SQSTM1: p62/signaling adaptor sequestosome 1, PE: phosphatidylethanolamine, PINK1: phosphatase and tensin homolog (PTEN)-induced kinase 1, ROS: reactive oxygen species, VDAC: voltage-dependent anion channel. . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

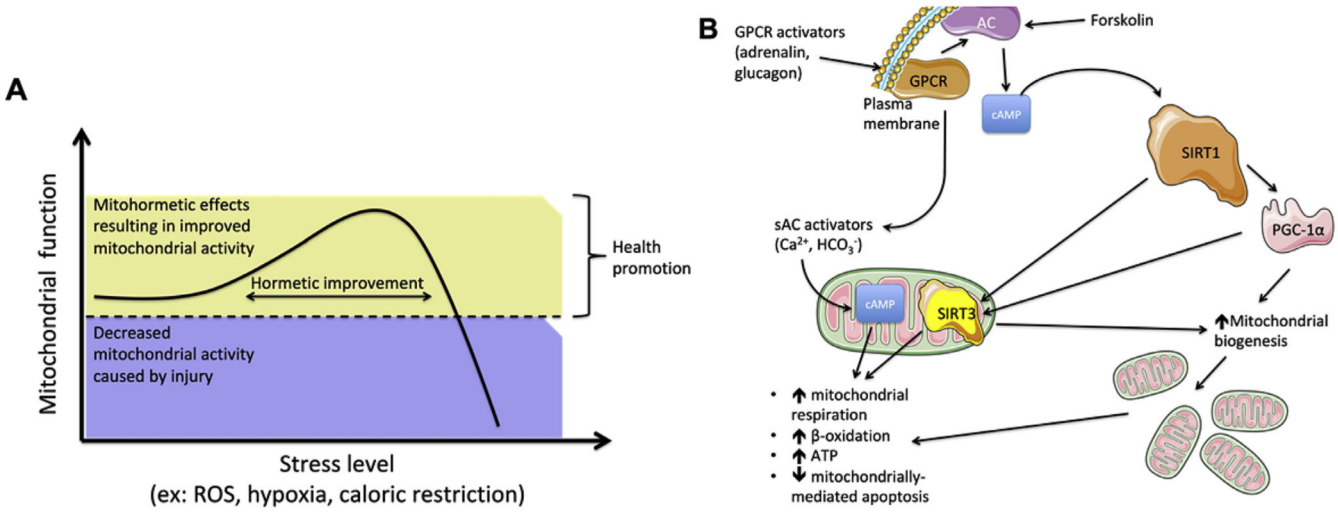

Fig. 2.

A. The mitohormetic response. ROS and other mitochondrial toxicants are well known to cause the development of a mitohormetic response, when presented at low values. In fact, a small harmful effect will boost a response of overdrive, i.e., the cell will try to elevate mitochondrial activity to combat the injury, whether by increasing mitochondrial numbers and active respiratory components, to mitophagic (removing the more damaged units) and fission (increasing the number of mitochondria, while diminishing their overall surface area per unit, thus increasing $\Delta\Psi$ and ATP generation) events. However, this is a tough balancing act to pull through, for the tipping point where activity rapidly decreases can be easily traversed, resulting in the more commonly known toxic effects of ROS and other mitochondrial toxicants. **B. The role of cAMP on mitochondrial metabolism and mitohormesis.** cAMP signaling affects mitochondrial homeostasis and metabolism, for it can result in an increase in NAD^+ and the activation of sirtuin 1 (SIRT1), which deacetylates (and thus hyperactivates) peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), the master regulator of mitochondrial biogenesis, leading to elevated mitochondrial numbers and thus increased overall cellular mitochondrial activity. Similarly, cAMP can lead to the activation of SirT3 within the mitochondrial matrix, leading to the deacetylation of several proteins, resulting in the elevation of mitochondrial activity.

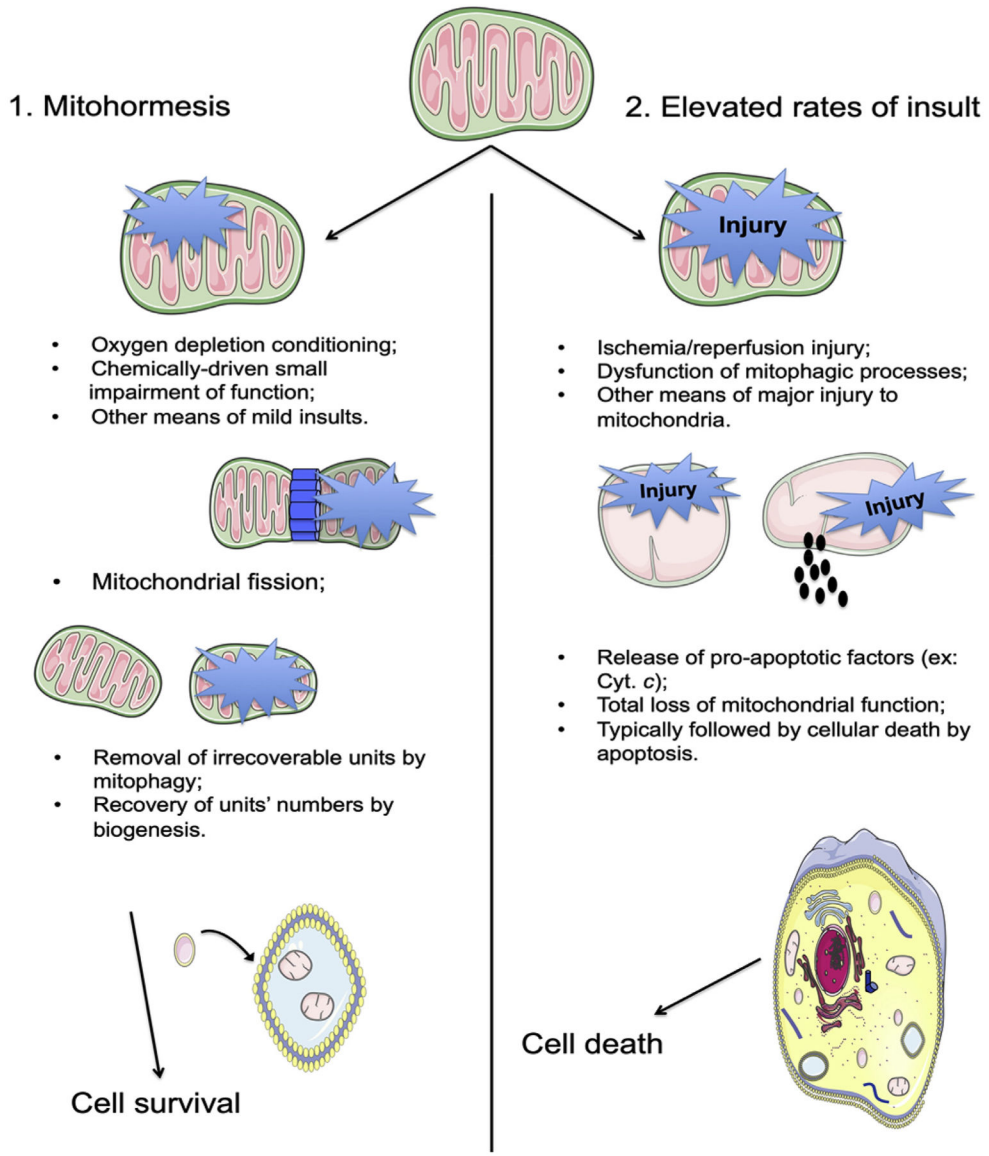

Fig. 3. Comparison between (1) mild, mitohormetic-inducing events and (2) highly injurious phenomena and respective downstream events.

A mild insult to a cell's mitochondrial population (such are, for example, small bursts of oxygen and nutrient deprivation, extremely low doses of mitochondrial inhibitors/toxicants) is a conditioning stimulus for the removal of older, less functional, more susceptible mitochondria from the population pool, allowing it to be repopulated by the generation of new, unharmed (biogenesis) mitochondria (1). However, if this insult is too prolonged or highly harmful, or if the cell has an inherent condition (for example, aged mitochondria with a lower threshold for damage or alterations in the typical players of the mitophagic event, such is the case with Parkin mutations in Parkinson's Disease) that renders it more sensitive to the insult, then ROS generation can be too elevated and widespread for the cell to repopulate the mitochondrial pool (2). In this case, the insult will normally lead to cell death, typically by apoptosis.

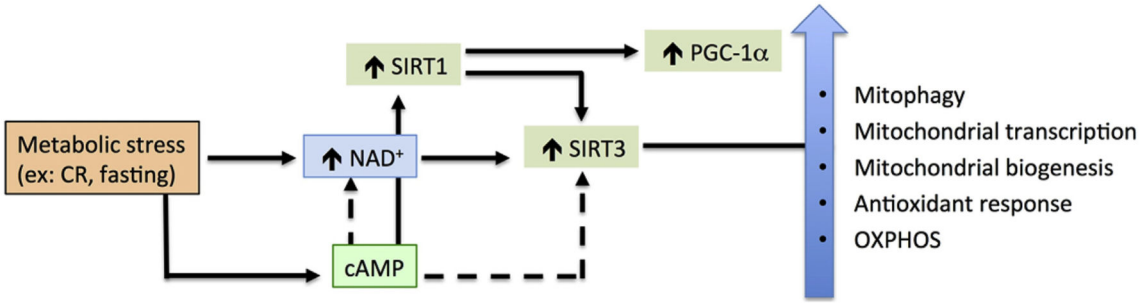

Fig. 4. cAMP-sirtuin crosstalk.

Conditions that increase NAD^+ such as caloric restriction and fasting stimulate sirtuins (SIRT) 1 and 3 activities that converge into enhanced mitochondrial function, through deacetylation of mitochondrial proteins and increased mitochondrial mass. SIRT1 also deacetylates and increases SIRT3 activity, although it is unclear if this happens due to cytosolic or mitochondrial cyclic AMP (cAMP). cAMP signaling, indirectly (dashed lines) by increasing NAD^+ or directly (solid lines) by phosphorylation increases sirtuin activity.