DNA Damage Related Crosstalk Between the Nucleus and Mitochondria

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Abstract

The electron transport chain is the primary pathway by which a cell generates energy in the form of ATP. Byproducts of this process produce reactive oxygen species that can cause damage to mitochondrial DNA. If not properly repaired, the accumulation of DNA damage can lead to mitochondrial dysfunction linked to several human disorders including neurodegenerative diseases and cancer. Mitochondria are able to combat oxidative DNA damage via repair mechanisms that are analogous to those found in the nucleus. Of the repair pathways currently reported in the mitochondria, the base excision repair pathway is the most comprehensively described. Proteins that are involved with the maintenance of mtDNA are encoded by nuclear genes and translocate to the mitochondria making signaling between the nucleus and mitochondria imperative. In this review, we discuss the current understanding of mitochondrial DNA repair mechanisms and also highlight the sensors and signaling pathways that mediate crosstalk between the nucleus and mitochondria in the event of mitochondrial stress.

Keywords

Reactive oxygen species; mitochondrial DNA damage; mitochondrial DNA repair; mito-nuclear signaling; oxidative phosphorylation; mitochondrial dysfunction; REDOX signaling

Introduction

A few decades after the nucleus was discovered in the 1830s [1], another granular-looking organelle termed "bioblasts" by Richard Altmann was discovered [2]. In 1898, the term mitochondria was coined by Carl Benda who named this organelle after the Greek words "*mitos*" meaning thread and "*chondros*" meaning granule [2]. The discovery that mitochondria contained nucleic acids was made in the 1960s and the development of cloning and sequencing techniques aided in a much better understanding of these organelles [3, 4]. Despite their primary role in ATP generation, mitochondria also play critical roles in aspects of cellular signaling, fatty acid oxidation, calcium signaling, heme biosynthesis, and the assembly of iron-sulfur clusters in proteins [5–7]. These essential functions make

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Conflict of Interest

None

mitochondria indispensible for cellular function; however, the first example of a eukaryotic microorganism that lacks mitochondria was recently reported [8]

The circular ~16.5 kb human mitochondrial DNA (mtDNA) is maternally inherited and encodes for 13 polypeptides, 22 tRNAs, and 2 rRNAs that participate in oxidative phosphorylation (OXPHOS) via the electron transport chain (ETC) [9]. Unlike nuclear DNA, which is packaged into nucleosomes, mtDNA molecules are tightly associated with the mitochondrial matrix and form compact structures called nucleoids [10]. Nucleoids are composed of mtDNA-protein complexes that include proteins involved in replication and transcription such as mitochondrial single-strand binding protein (mtSSB), DNA polymerase gamma (POLG), and mitochondrial transcription factor A (TFAM) [11].

Just like its nuclear counterpart, mtDNA is subjected to genotoxic assaults from exogenous sources such as exposure to chemotherapeutic drugs as well as from endogenous sources including reactive oxygen species (ROS) that form as byproducts of mitochondrial respiration [12]. While evidence suggests that mtDNA molecules are likely to be more susceptible to oxidized DNA damage than nuclear DNA owing to their proximity to sites of oxidative phosphorylation, our current knowledge on the extent of mtDNA damage is limited owing to the lack of experimental approaches to accurately detect oxidatively generated mtDNA damage [7, 12]. Several DNA repair mechanisms exist within a cell to restore DNA integrity and while these pathways have been extensively studied in the nucleus (reviewed in [13, 14]), the base excision repair (BER) pathway has been established as the primary repair pathway in the mitochondrion [15]. Evidence for DNA repair pathways occurring in the mitochondria has been presented where mtDNA repair enzymes are encoded by nuclear genes and translocate to the mitochondria [15, 16]. With the exception of the 13 mtDNA encoded polypeptides, the mitochondrial proteome comprises an estimated >1,500 proteins encoded by nuclear genes that are exported to the mitochondria for mtDNA maintenance [17, 18]. Multiple mitochondrial protein import pathways participate in protein translocation to the mitochondria [19]. For instance, many proteins possess a mitochondrial targeting signal (MTS) that enables the protein to be transported via translocases of the outer and inner membranes (TOM and TIM), while others rely on the redox-mediated MIA pathway for import into the mitochondria [18–20]. Web servers like MitoProt, MitoFates, and TPpred2 that predict mitochondrial localization by analysis of the primary amino acid sequence, are becoming useful tools to theoretically evaluate the probability of mitochondrial targeting of a protein [21–23].

Mitochondria are unique in their genome organization in that they can contain multiple copies of mtDNA molecules within a single mitochondrion. Therefore, mtDNA damage if left unrepaired can lead to mutations that could result in heteroplasmy, a condition where both undamaged and damaged mtDNA molecules co-exist within the same mitochondrion [24]. Mitochondrial mutations can cause coding errors in the 13 polypeptides involved in ATP generation via the ETC and in the 22 tRNA molecules encoded by the mitochondrial genome [25, 26]. Depending on the extent of DNA damage, heteroplasmy can lead to mitochondrial dysfunction and the fine threshold between normal mitochondria and those that develop into a disease state remains intriguing [27]. Several chronic human diseases including diabetes, aging, neurodegenerative disorders (such as Alzheimer's and Parkinson's

disease), and cancer are believed to be associated with mitochondrial dysfunction [17, 26, 28–30]. Mitochondria signal and communicate with the rest of the cell through numerous signaling pathways in response to dysfunction caused by physiological stimuli, stresses, and biological events [31–33]. In this review, we discuss our current knowledge of mtDNA repair and highlight some of the signaling pathways that coordinate stress responses between the nucleus and mitochondria in the event of DNA damage.

Mitochondrial DNA genome maintenance

Mitochondrial antioxidant pathways present the first line of defense that protects mitochondrial genome integrity (reviewed in [34, 35]). These include superoxide dysmutases (SODs), and the glutathione (GSH) peroxidase, thioredoxin (Trx), and peroxiredoxin (Prx) pathways [36–39]. Manganese SOD, an example of a member of this family, is present in the mitochondrial matrix and converts superoxide ($O_2^{•−}$) to hydrogen peroxide (H_2O_2) [40]. The H_2O_2 generated can be neutralized to water by either GSH or the thiol-specific peroxidases, Prx [39]. If the H_2O_2 generated in the mitochondria is not neutralized to water, it can be readily converted to the hydroxyl radical ($^•OH$), a strong oxidant, in the presence of Fe^{2+} via the Haber-Weiss Fenton reaction [41]. Since the mitochondria play a critical role in FeS cluster biogenesis and in iron homeostasis, these organelles are likely to be more susceptible to damage by H_2O_2 [12].

Oxidative stress results when the equilibrium between the antioxidant systems and ROS production is perturbed. Guanine has the lowest redox potential of the four DNA bases and is prone to oxidatively generated DNA damage produced by one-electron oxidants or singlet oxygen species [42–44]. The most common base modification that results from oxidation of guanine is 8-oxo-7,8-dihydroxyguanine (or 8-oxoG, Figure 1) [45, 46]. Thymine on the other hand is susceptible to $^•OH$-mediated damage resulting in lesions such as 5,6-dihydroxy-5,6-dihydrothymine [43]. Other modifications including alkylation, bulky adducts, and deamination also occur within mtDNA (Figure 1). To combat DNA damage, like the nucleus, mammalian mitochondria also possess DNA repair pathways, which involve repair proteins encoded by nuclear genes that are transported to the mitochondria (see Table 1). Whether these repair enzymes pre-exist in mitochondria at the time of damage or translocate into the mitochondria in response to damage signals is still not clear. The DNA repair pathways in mammalian mitochondria include base excision repair (BER), direct reversal (DR), mismatch repair (MMR), translesion synthesis (TLS), and possibly double-strand break repair (DSBR) [16, 47–49]. Thus far, there is no evidence for the repair of helix-distorting bulky adducts and ultraviolet-induced photodimers by the nucleotide excision repair (NER) pathway in mitochondria [50]. However, in one study, XPD, an NER protein was seen to protect mtDNA from oxidative DNA damage [51]. These data need to be further clarified and substantiated [52]. Furthermore, bulky adducts such as benzo[a] pyrene diol epoxide that are also formed within mtDNA (Figure 1) have no known mechanism of repair within the mitochondria, and are susceptible to destruction by autophagy [17, 53]. Overall, of the DNA repair pathways available in the mitochondria, BER appears to be the major pathway for eliminating ROS-induced oxidative damage.

Base excision repair (BER)

The BER pathway is a well-characterized, tightly-coordinated process that is carried out in a step-wise manner and includes: recognition and excision of the damaged DNA base, removal of the resulting abasic (apurinic/apyrimidinc or AP) site, end processing, gap filling, and ligation (summarized in Figure 2) [16, 48, 54]. BER can proceed via three sub-pathways, short-patch repair (SP-BER, 1-nt), long patch repair (LP-BER, 2 or more nt), and single-stranded break repair (SSBR) (extensively reviewed in [55–57]).

The initiation step of BER is carried out by DNA glycosylases, specialized enzymes, which recognize the damaged base and catalyze the cleavage of the N-glycosyl bond between the damaged base and its 2-deoxyribose resulting in an AP site [58, 59]. Glycosylases are either monofunctional or bifunctional, depending on whether they possess an intrinsic lyase activity. Seven of the eleven known mammalian DNA glycosylases contain an MTS that allows them to translocate to the mitochondria (summarized in Table 1 and Figure 2) [54]. The translocation of some DNA glycosylases to their respective nuclear and mitochondrial compartments is enabled by mechanisms of alternative splicing and different transcription start sites as observed with the uracil-DNA glycosylase (UDG), 8-oxoG DNA glycosylase 1 (OGG1), and MUTYH DNA glycosylase [60–62]. Monofunctional glycosylases excise non-oxidized damaged bases and rely on AP endonuclease (APE1) to complete the lyase elimination reaction whereas bifunctional DNA glycosylases are involved in the removal of oxidized DNA bases and nick the DNA backbone 3' to the lesion [63, 64]. End processing following base excision and backbone cleavage by bifunctional glycosylases either involves APE1 as is seen in the case of OGG1 and NTHL1 (Nth-like 1) or polynucleotide kinase phosphate (PNKP) that processes the ends generated by the NEIL (Nei-like) enzymes [64, 65]. Both APE1 and PNKP have been identified in the mitochondria and play critical roles in mitochondrial BER [66–69]. DNA POLG, the primary polymerase in the mitochondrion, is responsible for the gap-filling synthesis step in the mitochondria [70, 71]. During SP-BER, POLGA, the catalytic subunit of heterotrimeric POLG, possesses lyase activity and is able to excise the 5'-phosphodeoxyribose (dRP) moiety generated by APE1 and fills the 1-nt gap [72]. During LP-BER, the strand displacement synthesis activity of POLGA is utilized, which generates flaps of 2–6 nt that are good substrates for the flap endonuclease 1 (FEN1) [73–75]. Although early reports suggested that SP-BER was the primary mitochondrial BER pathway, the choice between LP-BER and SP-BER is determined by several factors that are present in both the nucleus and mitochondria [64, 74]. For instance, certain types of oxidized abasic sites (such as 2-deoxyribonolactone) that are not suitable substrates for POLG undergo FEN1-dependent LP-BER [75]. Another enzyme DNA2, also found in mitochondrial extracts, assists in the FEN1-mediated cleavage of the DNA flaps by maintaining the length of single-stranded flap so that it is not immediately coated by mtSSB [76]. In contrast, another study demonstrates that 5'-exo/endonuclease (EXOG) removes 5' flaps during mitochondrial LP-BER independently of FEN1 and DNA2 [77]. The final ligation step in the mitochondria, which is common in all BER sub-pathways, is carried out by DNA ligase III (LigIII) [78, 79].

The SSBR pathway is considered to be a form of SP-BER that involves detection of SSBs, end processing, gap filling, and ligation where the later two steps follow the same path as

SP-BER [48, 80, 81]. The SSBR pathway in the nucleus is initiated by the detection of SSBs by enzymes of the poly (ADP ribose) polymerase family such as PARP1 that has been shown in some studies to localize to the mitochondria [82]. The exact role of PARP1 in mtDNA SSBR remains unknown partly due to conflicting reports describing the effects of PARP1 depletion on the accumulation and repair of mtDNA damage [82–84]. Although the BER enzymes APE1, and PNKP, discussed above, can perform end processing, tyrosyl-DNA phosphodiesterase 1 (TDP1), and aprataxin (APTX) have also been implicated in the end processing steps of mitochondrial SSBR (Table 1) [85–87]. TDP1 activity in the mitochondria is required to hydrolyze the bond between a tyrosyl moiety and a 3' DNA end as well as for hydrolyzing other 3'-end alterations such as 3'-phosphoglycolate that are poor substrates for APE1 [87]. ATPX catalyzes the removal of chemically adducted 5'-AMP moieties generated by aborted DNA ligation reactions and its importance is highlighted in human neuroblastoma cells where depletion of APTX resulted in mitochondrial dysfunction and an increase in mtDNA damage [85, 86].

Factors other than the core BER enzymes also play a role in mitochondrial BER. For instance, mitochondrial TFAM possesses a greater affinity for oxidized lesions like 8-oxoG and inhibits the activity of OGG1, uracil-DNA glycosylase (UNG), and APE1 [88]. Furthermore, the tumor suppressor p53 is able to bind to TFAM and alter its DNA-binding so that the BER glycosylases are no longer inhibited. OGG1 also interacts with the Cockayne Syndrome A and B proteins (CSA and CSB), which may localize to the mitochondria under oxidative stress [89]. Given that BER is the major repair pathway in the mitochondria, disease states associated with mutations and deletions in the BER machinery result in aging-related neurodegenerative disorders, ataxia, diabetes, and cardiomyopathy reviewed elsewhere [13, 80, 90–92].

Direct reversal (DR)

The DR pathway is a simple one-step repair pathway that is responsible for the repair of lesions such as cyclobutane pyrimidine dimers and O^6-alkylguanines. In bacteria, the enzyme photolyase is responsible for the removal of cyclobutane pyrimidine dimers and while this enzyme has been identified in plant and yeast mitochondria, no evidence for mammalian homologs has been presented [93, 94]. In mammalian cells, direct reversal of O^6-methylguanine to guanine is carried out by methylguanine DNA methyltransferase (MGMT; Table 1) [95–97]. It has been suggested that a methyltransferase with a similar molecular weight as nuclear MGMT may exist in mitochondria, but these results have yet to be further substantiated [16, 95, 98–100].

Mismatch repair pathway (MMR)

The MMR pathway is a highly conserved repair process involved with the recognition and removal of mismatched bases and slippage errors caused by DNA polymerase during replication (reviewed in [101, 102]). The eukaryotic MSH (MSH2-6) or MutS homolog, and MUTL (MLH1,3) or MutL homolog proteins, are key components of this pathway in the nucleus where MMR ensues with the recognition of DNA mispairs by the MSH proteins followed by recruitment of the MLHs and activation of downstream molecules to repair the mismatch [102, 103]. Mitochondrial MMR appears to occur independently of the MSH and

MLH proteins but relies instead on the Y-box binding protein (YB-1; Table 1) [104, 105]. While there is precedence for the presence of MLH1 in the mitochondria, further evidence is warranted to fully understand the role of these enzymes in the mitochondria [106].

Translesion synthesis (TLS)

TLS is an error-prone DNA damage tolerance pathway that utilizes a group of specialized DNA polymerases that can bypass DNA lesions and allow DNA replication to proceed [107, 108]. In eukaryotic nuclei, five polymerases perform TLS including Rev1, polymerases kappa, eta, and iota (Polκ, Polη, and Polι) that belong to the Y-family of polymerases and polymerase zeta (Polζ), which is a B-family polymerase [108]. The recruitment of these polymerases to the site of a lesion is described by two well-supported models, where one model proposes a "polymerase switching" mechanism whereas the other involves a "gap-filling" model (reviewed in [107–110]. Yet, how cells decide which TLS polymerase to use remains one of the most perplexing questions in this field.

In the mitochondria, POLG exhibits TLS activity and is able to bypass lesions such as cyclobutane pyrimidine dimers by incorporating purines opposite the lesion [111]. POLG is also able to bypass 8-oxoG and exocyclic DNA adducts that gives rise to increased mutagenicity [112, 113]. Both Polζ and Rev1 have been identified to have a role in yeast mitochondrial genome maintenance where overexpression of these enzymes led to a reduction in point mutations in the mtDNA [114, 115]. More recently, Polζ was detected in the mitochondria of mammalian cells and elevated expression of the enzyme in breast tumors was associated with cell migration and invasion [116]. PrimPol, a DNA primase-polymerase, was identified in the mammalian mitochondria [117] and evidence for its ability to bypass DNA lesions such as 8-oxoG was presented [118]. A conflicting report suggests that while PrimPol is unable to promote DNA damage bypass at a replication fork, its interactions with proteins involved in mtDNA replication, such as the Twinkle helicase, may be important for mtDNA metabolism [119].

Double-strand break repair (DSBR)

DNA double-strand breaks (DSBs) that occur in nuclear DNA are repaired by homologous recombination (HR), microhomology-mediated end-joining (MMEJ), and non-homologous end joining (NHEJ) pathways (reviewed elsewhere [48, 120]). While HR-mediated repair of mtDNA has been reported in plants and yeast, the occurrence of a bonafide HR repair mechanism in mammalian mitochondria has been debated and remains to be elucidated [121–125]. Some evidence for HR occurring within mammalian mitochondria was presented in studies using mitochondrial extracts where a recombinase RecA-mediated recombination event was observed [126]. The presence of recombination intermediates in mtDNA from human heart muscle were reported and suggest that an HR-like mechanism may occur in these cells [127]. Other studies revealed that if recombination events do occur, they do so at a low frequency, primarily under conditions where mtDNA is first depleted by treatment with either ethidium bromide or restriction endonucleases [128, 129].

NHEJ and MMEJ are relatively more error-prone when compared with the HR pathway and result in large deletions in the DNA. In yeast, direct-repeat-mediated deletions were seen to

accumulate in mtDNA thereby implicating the existence of the DSB repair pathways in the mitochondria [130, 131]. Another report in yeast also indicated that NHEJ proteins such as the MRX (Mre11p, Rad50p, Xrs2p) and Ku70/80 (Ku70p, Ku80p) complexes were observed in the mitochondria at the site of induced DSBs [132]. End-joining activity of linearized mtDNA substrates was observed using mammalian mitochondrial protein extracts where most of the molecules were end joined accurately, but regions containing direct repeat sequences displayed deletions [133]. While some mammalian DSB proteins have been observed in the mitochondria (Table 1), overall, it appears as though DSB repair in mammalian mitochondria may exist as a minor pathway under certain conditions, and further evidence is required to support the existence of these pathways within this organelle.

Signaling between the nucleus and mitochondria

For efficient DNA repair to take place in the mitochondria, DNA repair proteins are first transcribed in the nucleus, synthesized as precursors in the cytosol, and then imported through the outer mitochondrial membrane aided by the TOM translocase complex [19]. Further transport into the inner membrane of the mitochondria is aided by the translocase of the inner membrane (or TIM23 complex) [19]. Since a majority of the mitochondrial proteome comprises genes synthesized by the nuclear machinery, the flow of information from the nucleus to the mitochondria can be described as a way for the nucleus to inform the mitochondria about changes in the cellular environment, energetic requirements, and to signal stress responses [134, 135]. The stream of information from the nucleus to the mitochondria is termed anterograde signaling and the reverse process is called retrograde signaling or mitochondrial stress signaling (summarized in Figure 3) [136–138]. Gene expression of mitochondrial-targeted proteins drives mtDNA replication, maintenance, and energy homeostasis [135, 137, 139]. In return, mitochondrial dysfunction resulting from loss of mtDNA, damage accumulation, and oxidative stress trigger signals (such as elevated Ca^{2+} and NAD^+ levels) that then orchestrate a nuclear gene expression response to mitigate the defect [138]. In mammalian cells, the first report of inter-organellar signaling between the nucleus and the mitochondria was described by differential expression of respiratory chain complexes between wild-type and mtDNA depleted fibroblasts [139, 140]. Signaling between the two organelles is essential for deciding cellular fate and for the remainder of this review, we will discuss some of the damage sensors, metabolite signals, and pathway cascades that are triggered upon DNA damage.

Ca^{2+} signaling

The importance of calcium (Ca^{2+}) uptake by mitochondria is known to have critical functions in metabolism, stress signaling, and cell survival (reviewed in [141, 142]). Stressors such as depletion of mtDNA and treatment with ionophores result in perturbation of membrane potential (Ψ_m) thereby causing a change in Ca^{2+} efflux [143, 144]. This was observed in work performed in mouse myocytes where elevated cytosolic Ca^{2+} levels prompted a nuclear response that included reduced levels of nuclear factor-κB (NF-κB) and activation of the calcineurin dependent nuclear factor of activated T-cells (NF-AT) [144]. These responses in turn stimulate other transcription factors that drive nuclear transcription of genes involved in Ca^{2+}metabolism and glycolysis. Notably, restoration of mtDNA resulted in the reversal of these signals, thereby strengthening the relationship between

mtDNA stress and nuclear transcription [144, 145]. Elevated calcium levels resulting from mtDNA damage can also directly influence pathway activation including protein kinase C (PKC), and c-Jun N-terminal kinase (JNK)/p38 as well as activation of Ca^{2+}/calmodulin-dependent protein kinases (CAMKIV) that modulates phosphorylation of the cAMP-responsive element-binding protein (CREB) [146, 147]. Both NF-κB and the JNK signaling pathways have been linked to the DNA damage response and are involved with the post-translational modifications of DNA repair proteins [148, 149]. It still remains to be elucidated whether activation of these pathways influences import of DNA repair genes into the mitochondria.

Signaling mediated by NAD⁺/ NADH

Nicotinamide adenine dinucleotide (NAD) in its oxidized (NAD⁺, electron acceptor) and reduced (NADH, electron donor) forms is an essential metabolite and coenzyme that is involved in the regulation of pathways such as glycolysis, the ETC, and the tricarboxylic acid (TCA) cycle [150–152]. NAD⁺ content appears to be unevenly distributed throughout the cell with the lowest concentrations observed in the nucleus in comparison to the mitochondria and cytosol [151, 152]. NAD⁺ is a substrate for two families of enzymes that serve critical roles in the DNA repair response: the PARP family and the sirtuin family of NAD⁺-dependent deacetylases (SIRTs) [7, 153–155]. Three of the 17-membered PARP family of enzymes (PARPs1–3) have known roles in DNA repair where PARP1 and PARP2 play a role in BER, while PARP3 senses DSBs and is involved in DSBR [81, 156–159]. The PARP enzymes synthesize poly(ADP-ribose) or PAR by utilizing NAD⁺ as a substrate to transfer the ADP-ribose moiety of NAD⁺ to acceptor proteins. This type of post-translational modification occurs when nuclear DNA damage in the form of DNA strand breaks (SSBs and DSBs) is sensed. Both PARP1 and PARP2 auto PARylate themselves, interact with the DNA, and further recruit and PARylate other repair enzymes [157]. This consumption of NAD⁺ drives NAD⁺ synthesis presumably by either the *de novo* synthesis pathway or the salvage pathway to keep up with cellular demand [160]. Localization of PARP1 to the mitochondria has been reported but its function in this organelle is still a matter of debate [82]. PARP1 appears to have an inhibitory negative role in the mitochondria where it interacts with and PARylates POLG, and EXOG and inhibits BER, a function that is opposite to its roles in the nucleus [83].

The sirtuin family of proteins use NAD⁺ as a substrate to deacetylate proteins by the removal of acetyl groups from lysine residues [161]. Of the 7 sirtuin family members, SIRT1, SIRT6, and SIRT7 are localized in the nucleus, SIRT2 is mainly present in the cytoplasm and SIRT3, SIRT4, and SIRT5 are mitochondrial proteins [153, 161]. Despite this compartmental segregation, these enzymes can shuttle between the two organelles and the cytosol in response to cellular stimuli. SIRT1, the most studied sirtuin enzyme, plays a role in mitochondrial biogenesis, where it deacetylates key proteins such as peroxisome proliferator-activated receptor-γ co-activator 1α (PGC-1α), and in DNA repair via DSBR by deacetylating and activating proteins such as Ku70 [162–164]. Another target of SIRT1 deacetylation is the hypoxia inducible factor 1 alpha (HIF-1α), which belongs to the hypoxia-inducible transcription factor family of proteins that are regulators of cellular responses to oxygen deprivation [165, 166]. This SIRT1-mediated deacetylation event

inactivates HIF-1α signaling under normal conditions, but allows for activation of this pathway when SIRT1 levels are low and under hypoxic conditions where NAD^+ levels are also diminished [166]. Since both PARP1 and SIRT1 are involved in DNA repair and use NAD^+ as a substrate for their respective activities, they compete for NAD^+ in an interplay that is not completely understood. Furthermore, the rivalry between SIRT1 and PARP1 is also observed in NF-κB regulation where SIRT1 deacetylates the transcription factor and inhibits its activity whereas PARP1 activates and stimulates NF-κB activity [167]. Recent evidence presented in pulmonary artery endothelial cells indicates that an increase in Ca^{2+} levels in the mitochondria influences the NAD^+/NADH ratio in the cytoplasm by causing an efflux of NADH from the mitochondria to the cytosol [168]. This change influences the NAD^+ consuming SIRT family of enzymes, and provides a link between Ca^{2+} fluctuations, NAD^+ levels, DNA damage, and mitochondrial dysfunction [168].

Energy homeostasis mediated by AMP-activated protein kinase signaling

AMP-activated protein kinase, AMPK, is referred to as the energy sensor of the cell as it is highly sensitive to changes in intracellular energy levels (or the ATP:AMP ratio) [169]. AMPK is a serine/threonine kinase that is activated in response to increased levels of AMP and ADP and triggers a cascade of orchestrated responses that are able to restore ATP levels and maintain energy balance [169, 170]. To mention two examples, both p53 and the oxidative stress/ DNA damage sensor protein, ataxia telangiectasia mutated (ATM), can phosphorylate and activate AMPK (Figure 4) [171–173]. AMPK is activated by the Sestrin 1 and 2 proteins, which are targets of p53 activation upon genotoxic stress [172]. Incidentally, p53 is also a target of AMPK phosphorylation where this phosphorylation event triggers several outcomes including cell cycle-dependent checkpoint activation, and accumulation of mitochondrial p53 that promotes apoptosis via the Bak-Bcl-xL complex [174, 175]. ATM can phosphorylate AMPK in response to oxidative stress via the liver kinase B1 tumor suppressor protein [173, 176]. Phosphorylated AMPK in turn can phosphorylate a number of factors involved in nuclear-mitochondrial signaling responses including SIRT1, PGC-1α, and HIF-1α (Figure 4) [177–179]. Additionally, the mitochondrial SIRT4 protein regulates cellular ATP levels thereby contributing to mito-nuclear crosstalk via AMPK-mediated signaling [180]. These studies coupled with reports describing the role of redox molecules in triggering AMPK response mechanisms, further strengthens the importance of this signaling pathway in the maintenance of cellular homeostasis [169].

Redox signaling: Reactive oxygen, nitrogen species, and APE1

Both ROS and reactive nitrogen species (RNS) are highly reactive and are generated during normal cellular metabolism as byproducts of processes such as respiration, and by enzymatic processes involving nitric oxide synthases (NOS), and NADPH oxidase [181]. Some forms of ROS including •OH and singlet oxygen species are highly reactive and are able to react with and damage DNA bases whereas H_2O_2 in the presence of metals (such as Fe^{2+}) generates •OH via the Fenton reaction [43, 182]. Several antioxidant mechanisms (discussed above) exist to combat ROS including natural antioxidants such as vitamins A, E, and C obtained from the diet and endogenous enzymes like glutathione peroxidases and superoxide dismutases, which reduce free H_2O_2 to H_2O and cause the dismutation of $O2^{•-}$ to H_2O_2 and O_2, respectively [183, 184]. Increased levels of ROS can overwhelm the antioxidant

responses and trigger the activation of transcription factors including NF-κB, HIF-1α, p53, and nuclear factor E2-related factor 2 (NRF2) [185–189]. An example of signaling between the mitochondria and nucleus under conditions of high levels of ROS is witnessed by the stimulation of over 100 target genes such as glutathione S-transferases mediated by the binding of NRF2 to antioxidant response elements [189]. Furthermore, the triggering of TFAM expression for driving mitochondrial transcription by NRF1 occurs in response to increased levels of ROS [190].

RNS such as nitric oxide (NO), which is biosynthesized by NOS readily diffuse across cell membranes and function as signaling molecules between the nucleus and mitochondria [191, 192]. Mitochondria also possess NOS (mtNOS) that is capable of generating NO in the inner mitochondrial membrane and modulates diffusion of NO from the mitochondria to the cytosol [193, 194]. NO can impart toxicity in a cell via its oxidation products that damage DNA as well as by the inhibition of mitochondrial respiration [195]. NO reacts with $O_2^{\bullet-}$ to produce peroxynitrite ($ONOO^-$), which can lead to the nitrosative deamination of DNA bases, nitrated DNA bases (8-nitroguanine), and the nitration of tyrosine residues that blocks signaling cascades [195]. Mitochondrial NO binds to and inhibits cytochrome C oxidase (Complex IV) thereby modulating respiration by directly competing with intracellular O_2 [196, 197]. One way that NO mediates mito-nuclear signaling under conditions of oxygen deprivation, is by destabilizing HIF-1α, which inhibits its transcriptional activity [198]. Furthermore, an increase in NO signaling correlates with an elevated number of mitochondria and is consistent with an upregulation in the levels of the mitochondrial biogenesis master regulator, PGC-1α that mediates downstream activation of factors such as TFAM [199, 200]. This increase in PGC-1α regulation by NO can also be influenced by the binding of NO to AMPK (Figure 4) [201] and is particularly useful for scrutinizing mitochondria-rich tumors such as thyroid oncocytoma [202]. While increased RNS levels can elicit harmful effects in a cell, their role in immune responses and as anti-tumor agents has been previously described [203].

Redox activities are not limited to ROS and RNS. Incidentally, the only known DNA repair protein that is able to regulate other proteins via a redox mechanism is APE1 [204, 205]. As a DNA repair protein, APE1 functions in the BER pathway (discussed above), and as a redox regulator, it plays roles in processes such as immune inflammatory responses, angiogenesis, and in tumor progression [206]. Cysteine residues 65, 93, and 99 have been implicated in mediating the redox activities of APE1 [207–209]. Cys 65 and 93 are not solvent exposed residues based on the crystal structure of APE1, implicating that a conformational change has to occur within APE1 in order for these cysteine residues to serve as nucleophiles during the redox process [210]. APE1 maintains downstream targets such as HIF-1α [211], NF-κB [212], and p53 [213] in their reduced forms to promote stabilization and enhanced DNA binding. APE1 can also negatively regulate the activity of the NRF2 protein that is involved in the oxidative stress response, thereby serving a critical role as a regulator in DNA repair, transcriptional control, and genome maintenance [214]. Thioredoxin, the antioxidant enzyme interacts with APE1 and mediates its redox activities by reducing the oxidized form of APE1 [215]. The importance of APE1 as an essential regulator of cellular processes is evidenced by the fact that knockdown of APE1 in mice leads to embryonic lethality [216]. Although the mitochondrial translocation of APE1 has

been documented previously, recent evidence suggests that APE1 translocates to the mitochondria in a redox-dependent manner via interaction with Mia40, the mitochondrial import protein that is also used by p53 to translocate to the mitochondria [217, 218].

Mitochondrial unfolded protein response-like pathway

The maintenance of protein homeostasis via the unfolded protein response (or UPR) is tightly controlled in the cytosol, endoplasmic reticulum, as well as in the mitochondria and involves crosstalk between these organelles and the nucleus [219–221]. Mutations and deletions in mtDNA yield misfolded or mutant proteins that are unable to form stoichiometric complexes with the nuclear encoded proteins being transported to the mitochondria for OXPHOS. This can place a large amount of stress on the protein folding machinery in the mitochondria [220]. The UPR in mitochondria (UPR^mt) has been studied extensively in yeast and in *C. elegans* and is reviewed in [219, 222, 223]. In *C. elegans*, UPR^mt is triggered when ROS levels increase and involves expression of nuclear genes such as the heat shock proteins (hsp) *hsp-6* and *hsp-60*, which encode for chaperone proteins [224]. In mammalian cells there are two modes of UPR^mt that have been proposed in order to understand the key players involved in this process. The first pathway described by Hoogenraad and colleagues describes a UPR^mt where unfolded proteins accumulate in the mitochondrial matrix and result in the expression of nuclear encoded proteins including HSP60 (chaperone 60), and the ClpP mitochondrial protease [225]. This process is mediated by activation of the CHOP (C/EBP homology protein) transcription factor [226]. The second CHOP-independent UPR^mt model was described by Germain and colleagues in MCF-7 mammalian cells where protein aggregates accumulate in the inter-membrane space and trigger a response involving estrogen receptor α [227, 228].

Another level of regulation that occurs with the accumulation of misfolded proteins, depletion of mitochondrial chaperone proteins, or disruption of mitochondrial membrane potential, is mitochondrial autophagy (or mitophagy) [229]. In normal mitochondria, the multifunctional PINK1 kinase that regulates mitophagy is imported into the mitochondrial matrix via an MTS and is degraded by proteases [230, 231]. However, under conditions of inner membrane stress, PINK1 cannot cross the inner membrane and instead is integrated into the outer membrane where it recruits the ubiquitin ligase Parkin [232]. Parkin is phosphorylated and activated by PINK1 and is able to ubiquitilate multiple mitochondrial proteins that further leads to mitophagy [233]. However, while much is known about the unfolded protein response and mitophagy, the precise mechanisms of these processes still need to be resolved since many disease states have been attributed to a malfunction in UPR^mt signaling and mitophagy including neurodegenerative disorders such as Parkinson's disease, aging, and Friedreich's ataxia [30, 222, 234].

Concluding remarks and unanswered questions

In this review, we have summarized the current knowledge of the DNA repair mechanisms that exist in the mitochondria and highlighted some of the signals that connect the two organelles during stress responses. Despite the vast body of literature on this subject, numerous questions still remain to be answered [7]. In terms of DNA repair, although we

know that nuclear genes are responsible for the maintenance of the mitochondrial genome, how and when these proteins are targeted to the mitochondria remains unclear. Furthermore, the chaperone proteins responsible for the proper folding and further processing of these enzymes are still largely unknown. The role of post-translational modifications of DNA repair proteins either within the mitochondria, or in the cytosol that enables mitochondrial targeting, also remains an area of interest.

From our current understanding of mitochondrial biology, it is evident that numerous factors are responsible for the well-being and proper functioning of mitochondria. As presented here by us and in reports by other groups, the signaling cascades that occur between the mitochondria and the rest of the cellular milieu, represent a "*web*" of interactions that are interconnected and influence each other. When one of these pathways is disrupted, in the case of mitochondrial stress, we can easily fathom progression of a disease state or the triggering of pathways that lead to apoptosis. The recent development of mitochondrial-nuclear exchange (MNX) mice has helped us cultivate a better understanding of the contribution of damaged, mutated, and variant mtDNA to disease progression [235]. In these mice, the nuclear and mitochondrial genomes from different mice strains were interchanged, and from these animal models, and subsequent studies, it was evident that mtDNA contributes to increased levels of ROS, vulnerability to cardiovascular stress, and changes in lipid metabolism in chronic liver disease, independently of nuclear DNA [235, 236]. Furthermore, the importance of mtDNA repair is highlighted in studies that indicate that some repair enzymes are transported to the mitochondria not only to maintain mitochondrial genome integrity, but also to protect against tissue injury such as ventilator induced lung injury in mice [237–239]. In other animal models, a neuroprotective role was suggested for mitochondrial BER enzymes where increased levels these enzymes protected against ischemic brain injury [240]. It is therefore apparent that mtDNA serves a protective role in controlling cell fate in response to a variety of oxidative stresses and is essential for proper cellular maintenance and function. Unfortunately, in this review, we were unable to cover the all facets of mitochondrial signaling including mitophagy, apoptosis, mitochondrial fusion and fission, and mitochondrial diseases that result from dysfunction. In summary, despite the wealth of knowledge that exists in the fields of DNA repair and mito-nuclear signaling, much is left to be determined to deconvolute the complex array of interactions that maintain cellular homeostasis.

Acknowledgments

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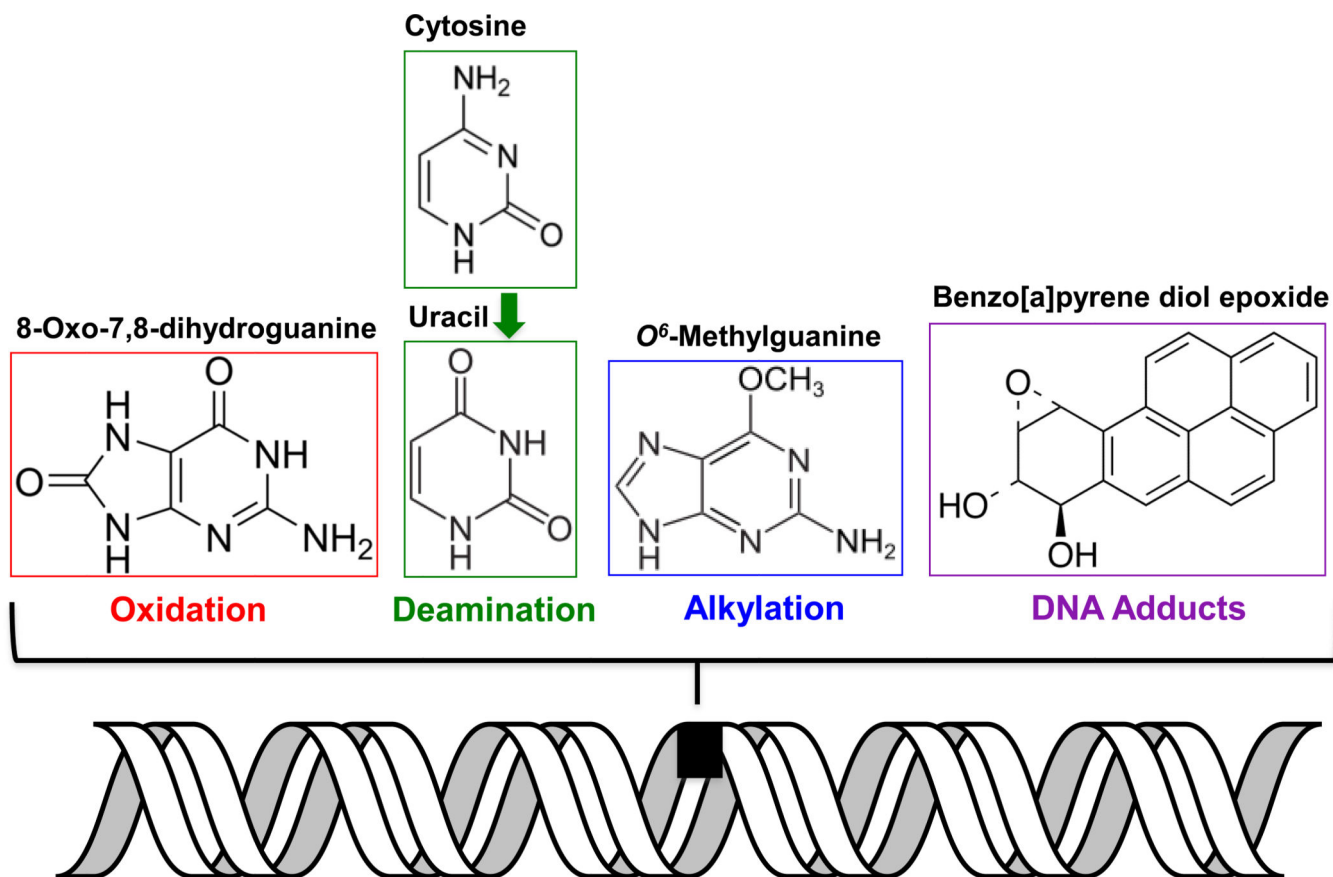
Figure 1. Types of DNA lesions found in the mitochondria

Damage to mtDNA can occur in the form of alkylation, oxidation, spontaneous deamination, and bulky adducts. Examples of lesions from each of these categories are shown.
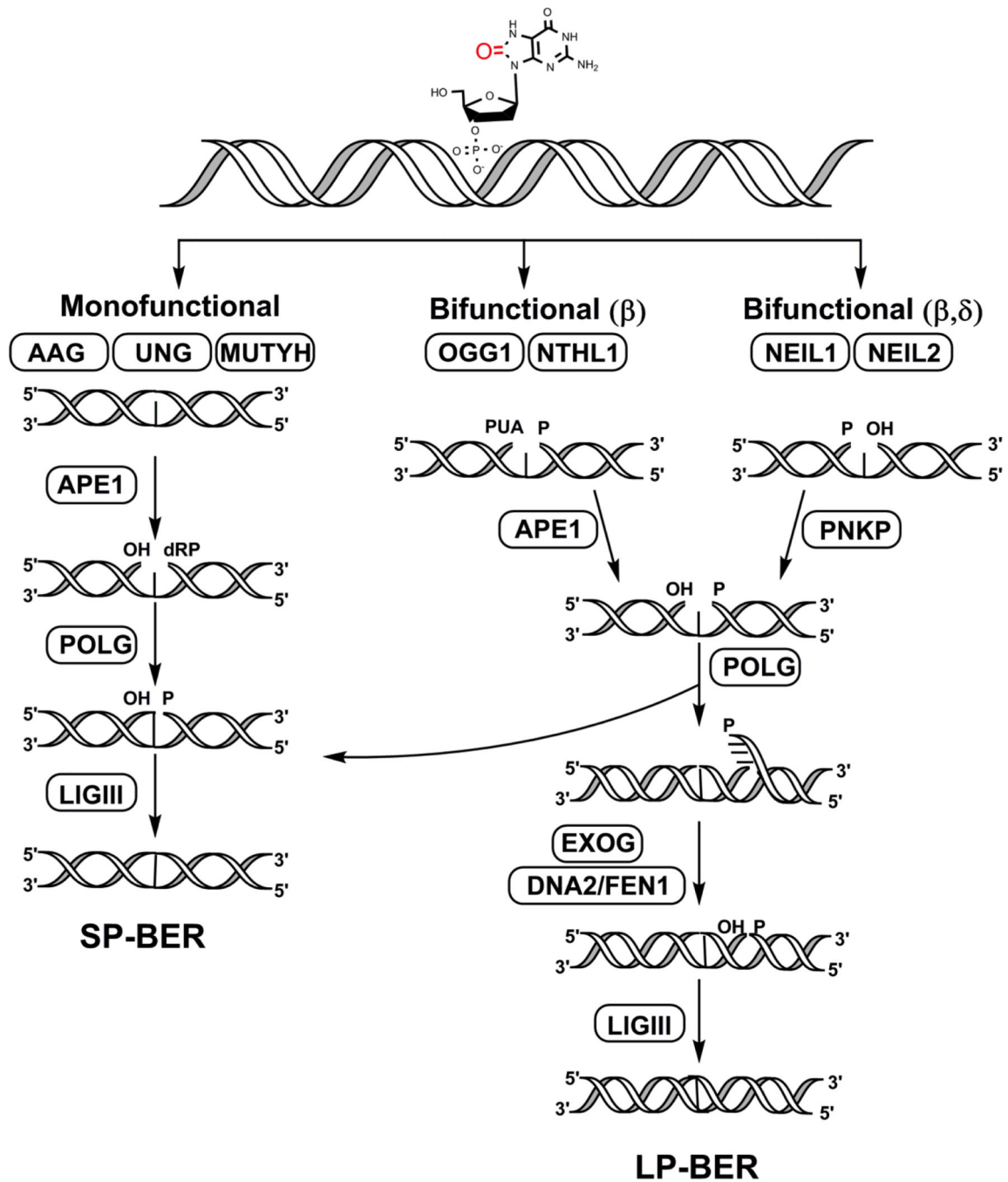
**Figure 2. Overview of base excision repair in the mitochondria**

This figure displays the step-wise repair of DNA base damage via the BER pathway by enzymes identified in the mitochondria. Initially, the lesion is recognized by either mono or bifunctional DNA glycosylases depending on the type of damage. Of the eleven known mammalian DNA glycosylases, only seven have been identified in the mitochondria. These include: the monofunctional glycosylases AAG (alkyladenine DNA glycosylase), UNG (uracil N-glycosyalse), and MUTYH (MutY glycosylase homolog) as well as the bifunctional glycosylases OGG1 (8-oxoG DNA glycosylase 1), NTHL1 (Nth-Like 1),

NEIL1 (Nei-like 1), and NEIL2 (Nei-like 2). The resulting AP sites are further processed either by APE1 in case of the monofunctional, OGG1, and NTHL1 glycosylases or by PNKP that processes the ends after the NEIL enzymes, thereby leaving suitable ends for gap-filling by POLG. Ligase III then seals the DNA nick and completes the process in SP-BER. In the long-patch (or LP, >2 or more nt) repair pathway, a 2–6 nt flap is generated by POLG that is further processed by DNA2/FEN1. Alternatively, EXOG may function as the major 5' flap-processing enzyme in the mitochondria in both SP- and LP-BER. The final ligation step is carried out by LIGIII.
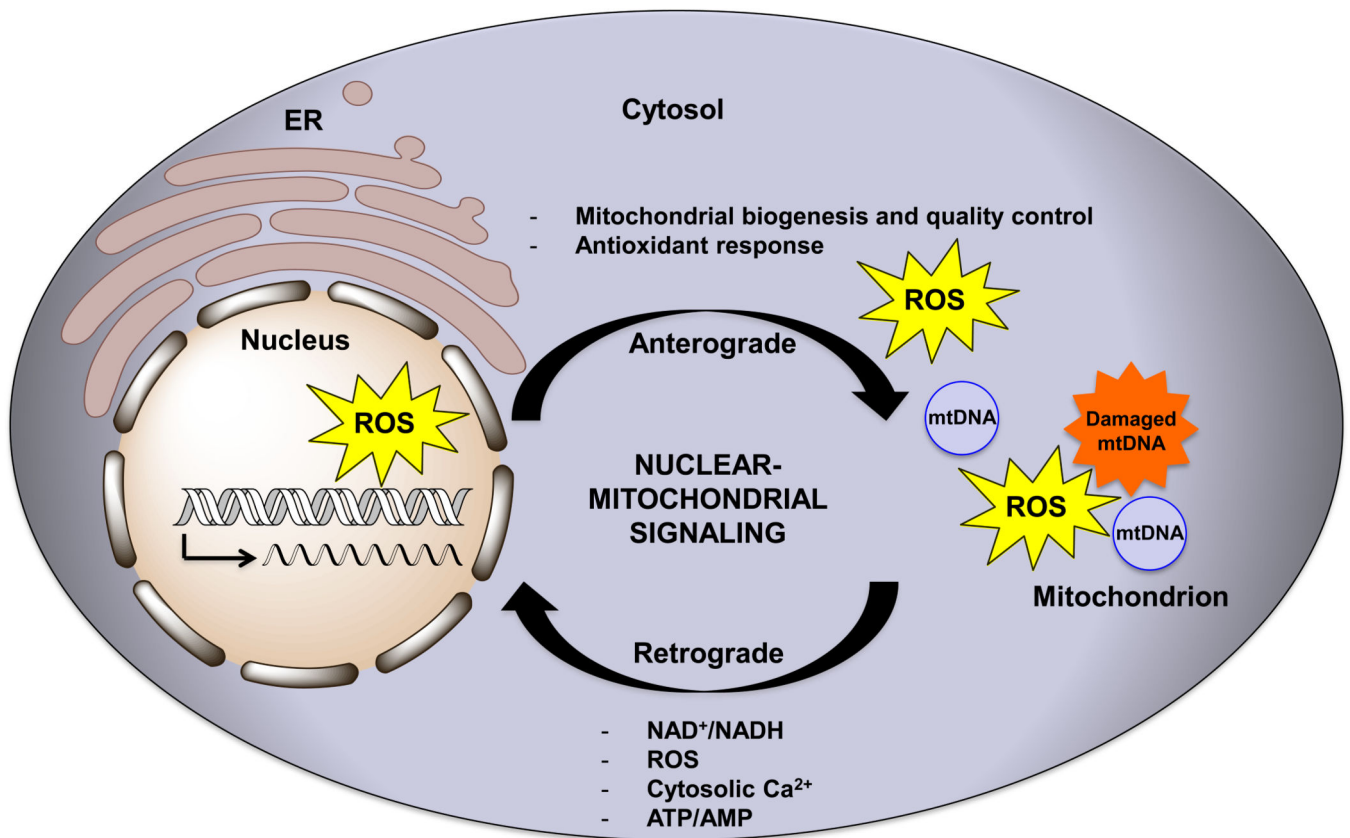
Figure 3. Signaling between the nucleus and mitochondria

Crosstalk between the nucleus and mitochondria occurs not only to signal oxidative stress, DNA damage, and mitochondrial dysfunction but also occurs during normal cellular metabolism. The flow of information from the nucleus to the mitochondria (termed anterograde signaling) involves the transcription and translocation of genes involved with mitochondrial biogenesis. Anterograde regulation also includes responses to stressors that trigger an antioxidant response by regulating the expression of genes involved with Ca^{2+} metabolism and glycolysis. Mitochondria can signal to the nucleus (in a process called retrograde signaling) in times of stress via signals such as changes in the levels of NAD^+/NADH, ROS, cytosolic Ca^{2+}, and ATP/AMP as well as changes in membrane potential. ER stands for endoplasmic reticulum. The arrow within the nucleus signifies the transcriptional activation of nuclear genes either during normal conditions, or upon stress induced signaling.
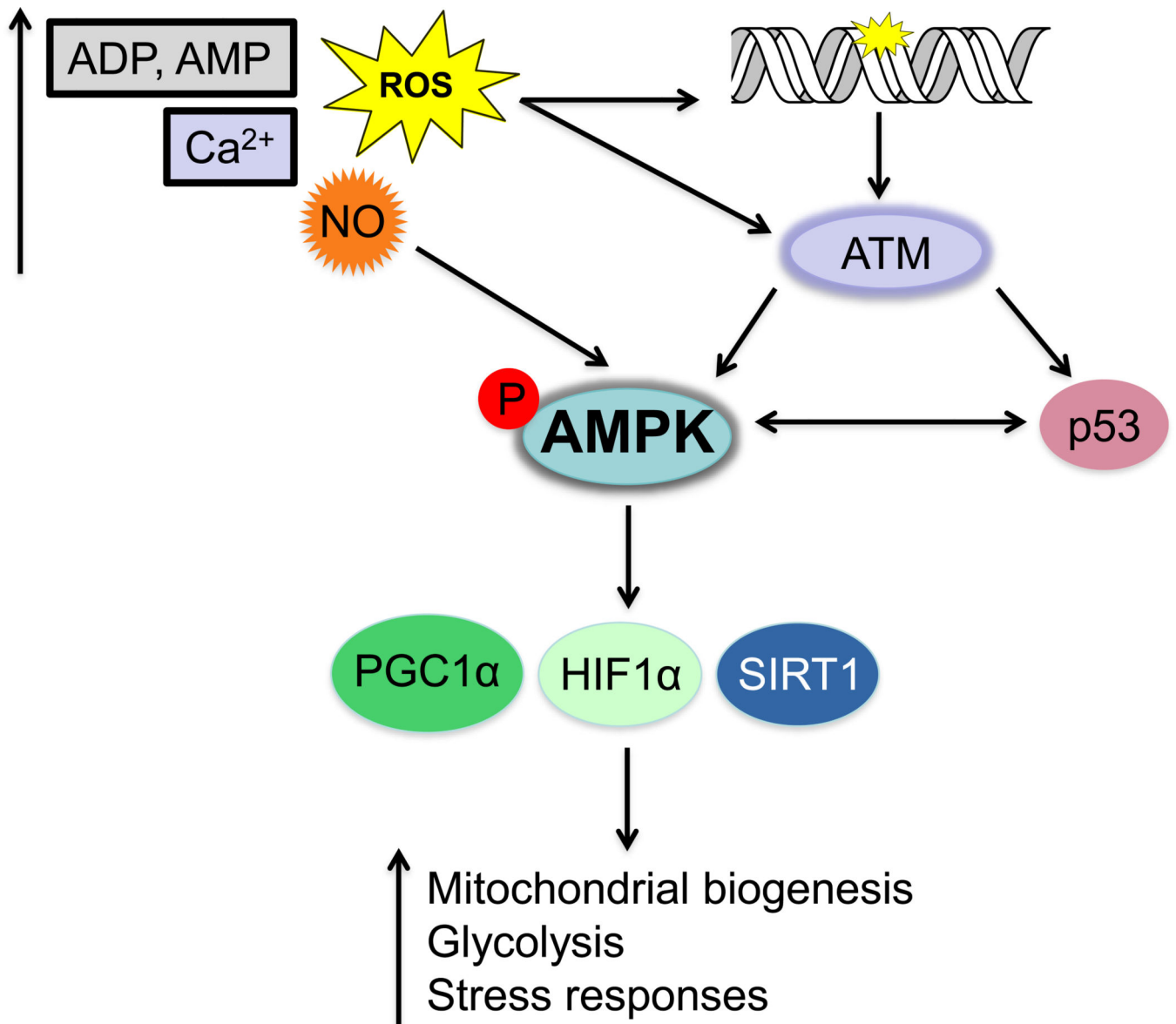
Figure 4. Schematic of AMP-activated kinase (AMPK) signaling triggered by changes in cellular metabolites and DNA damage

AMPK is activated upon increased levels of AMP/ADP, ROS, and cytosolic calcium. Activation of AMPK can be triggered by the ataxia telangiectasia mutated (ATM) kinase that is activated upon oxidative stress or DNA damage. ATM triggers a DNA damage response that activates other factors such as p53 that can also directly activate AMPK. The activation of AMPK elicits downstream responses regulated by proteins including PGC-1α, SIRT1 and HIF-1α. These responses manifest in an upregulation of mitochondrial processes such as glycolysis, fatty acid oxidation, and responses to hypoxia.

Table 1

Mammalian proteins and enzymes involved in the repair of mtDNA

Pathway	Protein/Enzyme	Function	Reference
BER	NEIL1	DNA glycosylase (Bifunctional)	[241]
	NEIL2	DNA glycosylase (Bifunctional)	[69]
	OGG1	DNA glycosylase (Bifunctional)	[242, 243]
	NTH1	DNA glycosylase (Bifunctional)	[242]
	MUTYH	DNA glycosylase (Monofuctional)	[242]
	AAG	DNA glycosylase (Monofuctional)	[244]
	UNG	DNA glycosylase (Monofuctional)	[60, 245]
	TFAM	Mitochondrial transcription factor A stimulates glycosylase activity	[88]
	TDP1	DNA end processing	[87]
	PARP1	Senses SSBs, PARylates itself and other proteins	[82, 84]
	APE1	DNA end processing endonuclease	[68]
	PNKP	DNA end processing	[67, 69]
	APTX	DNA end processing	[85]
	POLG	Mitochondrial DNA polymerase	[246]
	FEN1	Flap endonuclease, flap processing	[75]
	EXOG	Flap processing	[77]
	LIGIII	DNA ligase	[133]
DR	MGMT	Methytransferase	[98, 100]
MMR	YB-1	Mismatch binding and repair	[104, 105]
	MLH1	Mismatch binding and recruitment of downstream proteins	[106]
TLS	PrimPol	DNA primase-polymerase	[117]
	Polymerase zeta	Error-prone B family DNA polymerase	[116]
DSBR	RAD51	Central catalyst of HR	[247]
	XRCC3	Participates in HR and maintains chromosome stability	[247]
	BRCA1	DNA binding and protein interactions	[248]
	Ku70/80	DSB binding during NHEJ	[249, 250]
	MRE11	mtDNA binding and end processing	[251]
NER	NONE to DATE		